Journal of Pharmaceutical Sciences

JULY 1974

VOLUME 63 NUMBER 7

REVIEW ARTICLE

Pharmaceutical Sciences — 1973: Literature Review of Pharmaceutics

ALLEN K. HERD*x and JOHN K. HALEBLIAN‡

Keyphrases □ Pharmaceutical sciences—1973 literature review of pharmaceutics □ Technology, pharmaceutical—sterility, dosage forms, cosmetics, packaging equipment □ Physical pharmacy—dissolution, solubility, permeability, complexation, surface phenomena □ Antibiotics—pharmaceutical aspects □ Radiopharmaceuticals—pharmaceutical aspects □ Biopharmaceutics—drug properties, formulation effects, absorption mechanisms and control □ Pharmacokinetics—literature review □ Literature review—pharmaceutical sciences 1973

CONTENTS

This review of the literature represents a comprehensive cross section of the research and development effort in various selected disciplines of pharmaceutical sciences. As in past years, the scope of this endeavor has been limited to a review of the area of pharmaceutics because annual reviews of the literature related to other areas of pharmaceutical sciences are published elsewhere. This is the 12th annual review in the series (1–12). To compile it, numerous journals, periodicals, and selected sections of *Chemical Abstracts* were abstracted.

The review was prepared to provide a convenient method for pharmaceutical scientists to review the literature of the past year and to supply a source of references to articles of preferred interest. Except for minor changes, the well-accepted format of last year's review was retained.

GENERAL PHARMACY

A review of the chemistry, pharmacology, toxicity, metabolism, specific side effects, and antiallergic properties *in vitro* and *in vivo* of disodium cromoglycate (cromoglycic acid, disodium salt) was presented (13). Other reviews presented during the past year considered the use of dimethyl sulfoxide in dermatology (14); chemistry, biological activity, and therapeutic activity of the prostaglandins (15); and current aspects of pharmaceutics (16). The latter included dissolution, absorption of drugs, physical pharmacy, chemical stability, pharmaceutical microbiology, and tableting technology.

Preservatives—In an investigation of the inhibitory action of 3-phenylpropan-1-ol, 2-phenylethanol, and benzyl alcohol against *Pseudomonas aeruginosa*, 3-phenylpropan-1-ol was the most effective and benzyl alcohol was the least effective, as shown by growth rate, minimum inhibitory concentration (MIC), and determination of sterilization times (17). The three compounds enhanced the bactericidal action of benzalkonium chloride in the same rank order. The effect of polyvalent cations on growth inhibition of *Streptococcus faecalis* was investigated (18). With the exception of chromium, there was a rank-order correlation between the ability of the polyvalent metal salts to reduce the ζ-potential of the bacteria and to inhibit their growth. Suggestions were presented as to how the critical micelle concentration (CMC) of a nonionic surfactant could be increased and thereby lessen the possibility of reducing the activity, or even obtaining synergistic germicidal activity, of a cationic surfactant (19).

Multicomponent preservative systems containing up to six active components were used in cosmetics and pharmaceutical formulations to provide a wider spectrum of antimicrobial activity (20). Each preservative was screened alone and then with one other preservative before proceeding to more complex mixtures. The degradation of 14 commonly used preservatives in a 2% aqueous solution of polyvinylpyrrolidone was determined at 30° for up to 63 days (21). It was shown that the degradation of nonphenolic preservatives in the presence of polyvinylpyrrolidone was no greater than that in aqueous solutions. The effect of polyethylene and polyvinyl chloride granules on the stability of commonly used antimicrobial agents and antioxidants was studied. The potency losses of these agents were mainly attributed to their sorption affinities toward the plastic materials (22).

The effects of 11 different pharmaceutical materials on the bactericidal activities of benzyl alcohol, chlorobutanol, chlorhexidine diacetate, chlorocresol, methyl *p*-hydroxybenzoic acid ester, phenylmercuric nitrate, and benzalkonium chloride were investigated using viable count techniques (23, 24). The most antagonistic agents were colloidal magnesium aluminum silicate (Veegum), magnesium trisilicate, and polysorbate 80. The preservative efficiency of organomercuric compounds, *p*-hydroxybenzoic acid esters, and sorbic and benzoic acids was tested in emulsions containing sunflower oil, castor oil, and paraffin oil (25). Sorbic acid (1%) was the most efficient preservative. In another study of the preservation of oil and water emulsion ointment bases, sorbic acid (0.2%) or dimethyldodecylbenzylammonium chloride (0.01%) was recommended (26). The same type of study, but on anhydrous ointment bases, indicated that hexachlorophene and quaternary ammonium compounds possessed the highest antibacterial activity (27). Phenylethanol and sodium edetate were shown to be excellent preservatives for sulfacetamide eye drops against *P. aeruginosa* (28). The irritating action of some commonly used preservatives in preparation of collyria was studied (29). Of the preservatives tested, the organomercuric compounds, especially thimerosal, proved the best. Exceptional irritation and low bactericidal activity were demonstrated by a mixture of methyl- and propylparaben.

Additional references relative to preservatives can be found in Table I.

Table I—Additional References on Preservatives

Reference	Topic
30	Recommended procedures for conducting challenge tests for pharmaceutical preparations
31	Fundamental concepts for preservation of cosmetic formulations
32	Review of preservatives for cosmetics and some directions for manufacturing cosmetic preparations
33	Effectiveness of furoic acid and ethyl, propyl, and butyl esters against *P. aeruginosa*
34	Antiseptic properties of perfume oils and perfume chemicals
35	Bactericidal properties of aromatic substances and essential oils
36	Review of ophthalmic preservatives and vehicles
37	Review of adsorption, permeation, and chemical reactivity of 27 preservative agents for different types of plastics
38	Review of mode of action and parameters affecting activity of preservatives

Flavor, Aroma, and Color—A series of 2,7-dialkylcarbonate esters of lincomycin was synthesized (39) to enhance the pediatric acceptability of this antibiotic. Four diester derivatives exhibited oral bioactivity comparable to lincomycin. The physiology of bitterness was described (40). Bitter taste could be masked by local anesthesia of the tongue, modification of the chemical structure, or correction of the taste by special galenical preparations such as the addition of sweetness, increased viscosity, or modification of ionic concentration. Procedures to decrease or suppress the bitter taste of quinine hydrochloride as a solution or in a syrup were described (41). The linguistic difficulties in describing specific sensations of taste and smell were discussed (42). Experts in different countries were urged to communicate to work out a uniform terminology.

An encyclopedic evaluation of the literature in the

Table II—Additional References on Flavor, Aroma, and Color

Reference	Topic
55	Review of identification of flavors
56	Use of continuous process for preparing essential oils by steam distillation
57	Review of natural essential oils produced in Yugoslavia and their physicochemical characteristics
58	Essential oils of South America
59	Review of natural and synthetic aromatic elements and their use in the creation of perfumes and flavors
60	Description of method to improve the yield of rose oil
61	Listing of compounds with a jasmine odor
62	State of the art of perfuming aerosol products
63	Review of artificial and natural pineapple compounds
64	Use of ferric oxide as pigment dye for drug forms
65	Recent progress in jasmine research
66	Flower oils of lily-of-the-valley and lilac
67	Degradation of acid dyes by irradiation plus oxidation

perfumery materials field was continued (43). The composition affecting a perfume's fragrance is always distorted by the substrate due to inequality of association between each molecular species in the substrate (44). Suggestions for elimination of this distortion were discussed. A computer was used for routine blending and comparison of olfactory and gustatory components in essences and scents (45). Objective criteria for the actual smell had to be found so that the precise data could be fed into the computer. The smell masking of wax-containing products, foam rubber, textiles, synthetic leather products, and solvents in candles was described (46). A new class of perfumery ingredients, alkoxyalkylpyrazines, was developed, which is of particular interest since changes in the structure of the basic molecule lead to distinct and progressive changes in odor characteristics (47). Some general operative principles for the preparation of aerosol products were reviewed, and perfume dosages for various cosmetic products were given (48). It was pointed out that the perfume in cosmetics should give a distinct and elegant character and should mask the odor of the starting ingredients (49). Two examples of a popular perfume and the necessary modifications for its use in a cosmetic were given. The process of microencapsulation of perfumes and aromas was explained, and the application of this new technique in the cosmetic industry was reviewed (50). Anonis (51) described an experiment attempting to relate four major colors to corresponding odors.

The liquid and solid solution interactions of eight FD&C dyes with pharmaceutical gelatins and the effects of the dyes on disintegration behavior of gelatins were studied (52). All dyes interacted with Type A gelatin, but none interacted with Type B gelatin. In simulated gastric fluid without pepsin, FD&C Red No. 3 dye greatly diminished the average disintegration rate of both gelatins. 4,5-Dinitrofluorescein was discussed as to toxicology and legal aspects as a new coloring substance for cosmetics (53). Data on the properties of 16 common dyes were listed (54). Those properties considered were solubility in different solvents, light fastness, stability to heat, pH, oxidizing and reducing agents, and compatibility with citric and ascorbic acids, glucose, lactose, saccharose, sodium bicarbonate, and gelatin.

Table II lists additional references on flavor, aroma, and color.

Stability—The effect of certain commonly used vehicles on the decomposition of 5 and 20% sodium aminosalicylate solutions was studied (68). In all cases, the 20% solutions degraded more than the 5% solutions, but solutions containing glycerol and propylene glycol were more stable than those containing water. The decomposition of aspirin in a polyethylene glycol base was inhibited by citric and tartaric acids (69). Even when water was added, citric acid tended to slow the decomposition process. Fats of vegetable origin were incorporated into a polyethylene glycol base in an attempt to inhibit the decomposition of aspirin in this type of mixture (70). Degradation was retarded at 26°, but little effect was noted at 4 and 45°. The stability of erythromycin base compounded in lanolin, petrolatum, and their admixtures was determined for a year at room temperature (71). The optimal ointment consisted of 40 parts lanolin and 60 parts petrolatum. Sodium salicylate solutions (10 and 15%) were stabilized after the addition of 0.1% sodium bisulfite and 0.05% sodium edetate (Trilon B); they then could be autoclaved at 120° for 5 min and then stored for 1 year (72).

The decomposition of physostigmine salicylate solution sterilized at 120° for 20 min in the presence of various quantities of ascorbic acid and air or nitrogen was investigated (73). The addition of 50 mg of ascorbic acid to 100 ml of solution prevented oxidation, even when the ampul filling was carried out in air. Air in the presence of 1×10^{-3}% copper (II) caused considerable decomposition of procaine (Novocaine) solutions (74). This decomposition was significantly retarded by 0.01% sodium metabisulfite and 0.05% sodium bisulfite. For solutions of dexamethasone sodium phosphate, an empirical method was developed for determining the proper package size for preserving sodium bisulfite based on the volume of air per volume of product; the method was independent of any loss due to interaction of the preservative with other components of the formulation (75). Degradation of isoproterenol, phenylephrine, and epinephrine was studied by adding these compounds to aqueous oxymix systems and assaying for the remaining parent compound (76). After 30 min, recoveries of isoproterenol and phenylephrine were 89–100 and 89–108%, respectively, while the recovery of epinephrine was 53–79%.

Due to reports of transacetylation of acetaminophen (paracetamol) and codeine by aspirin, Roller (77) investigated the possible acetylation of morphine by aspirin. His conclusion was that this reaction between these two compounds is insignificant. The oxidation of aqueous cholesterol dispersions was studied in the absence and presence of various lecithins at 85° (78). More than half of the cholesterol was oxidized within 8 hr in the absence of phospho-

Table III—Additional References on Stability

Reference	Topic
87	Effect of structure of chelating agents on stability of apomorphine chloride solutions
88	Thermal stability of tocopherol acetate solutions in oil
89	Description of method for testing and preserving dihydroxyacetone
90	Effect of light on stability of aqueous solution of metaproterenol (orciprenaline) sulfate
91	Stability of chlorhexidine during autoclaving
92	Preservation of shark liver with sodium bisulfite
93	Thermal and storage stability of desoxycorticosterone acetate solutions in oil
94	Effect of light on stability of solutions of cardenolides
95	Stability of physostigmine eye drops
96	Influence of reducing agents on oxidation of epinephrine (adrenaline) with potassium iodate
97	Stability testing of sterilized adenosine solutions
98	Determination of decomposition rate of nicotinoyltauraminothiazole
99	Stability of aqueous guanethidine sulfate solutions
100	Degradation of phenylbutazone in aqueous solutions
101	Stability of elixir of diacetylmorphine (diamorphine) and cocaine
102	Chemical stability of homatropine and survival of bacteria in frozen buffered homatropine eye drops
103	Effect of freezing on pH of buffered aqueous solutions
104	Incompatibility of nonionic surfactants with oxidizable drugs
105	Properties of physiological solution of sodium chloride during different storage times
106	Stability and shelflife of drugs in liquid dispersion form
107	Physical and chemical interactions of injectable drugs, particularly antibiotics
108	Influence of various factors on stability of amino acid infusion solutions
109	Stability of casein hydrolyzate preserved at different temperature regimes
110	Chemistry of degradation of drugs in pharmaceutical systems
111	Method for evaluating stability of pharmaceutical products
112	Review of nonisothermal stability studies
113	Stability testing of pharmaceutical preparations
114	Review of methods available for accelerated aging studies
115	Review of cybernetic principles and use of charts as means of controlling drug quality

lipids, but less than 10% oxidation occurred in the presence of the lecithins. Factors involved in the browning of antacid tablets containing glycine were investigated (79). Initial pH was found to be the most important factor, with the greatest discoloration being at high pH. The content uniformity of nitroglycerin tablets was shown to be affected by volatilization and intertablet migration of the active ingredients (80), and the factors influencing these parameters were discussed. The conversion of lanatoside C to digoxin was shown to take place at 37° *in vitro* below pH 3 (81). Thus, moderate hydrolysis of the drug by gastric juices might be expected if taken between meals and substantial hydrolysis might be expected if taken with meals.

The stability of drug substances in solid pharmaceutical systems was discussed and theoretical models for various situations were proposed (82). As indicated by accelerated aging tests of compressed tablets containing eucalyptol, adsorbents with large surface area were the most effective in preserving the volatile agent (83). High humidity and compression force were unfavorable for good preservation. A simplified method for determining the chemical stability of drug substances in pharmaceutical suspensions was described (84), and the value of the method was confirmed experimentally using aspirin. A comparative study of the influence of ultrasound and heat on the hydrolysis of some organic esters was presented (85). The hydrolysis rate of the organic esters was nine times higher when subjected to ultrasound with heat as opposed to heat alone. In a study aimed at developing a stable solution of essential amino acids for parenteral nutrition, tryptophan was the only amino acid that degraded in considerable amounts (86); the use of amber vials and a 6-month expiration date were recommended.

Other papers of interest relating to stability are listed in Table III.

Stability Kinetics—The degradation of prostaglandins E_1 and E_2 was studied at 60° at pH 1–10 (116). A consecutive first-order reaction appeared to be operative above pH 4 for the dehydration and rearrangement reactions, and the data suggested that the *cis*-Δ^5-double bond participated actively in the rearrangement reaction of PGE_2 and was responsible for the greater reactivity of this molecule compared to PGE_1. The kinetics of hydrolysis of the carbamoyl group of 4-benzoylphenyl *N*-methylcarbamate in 50% aqueous ethanol showed that the reaction was first order with respect to both hydroxide ion and carbamate (117). The calculated half-life at pH 7.3 and 37° was 73 min. By studying the kinetics of the hydronium-ion-catalyzed hydrolysis of the ketal group in dexoxadrol hydrochloride, Brown and Forist (118) predicted that 91% of orally ingested dexoxadrol remained intact for a resident time of 60 min at pH 2 in the stomach. Previous investigations suggested that various 1-acyl-3,5-dimethylpyrazoles might owe their hypoglycemic activity to a nonenzymatic hydrolysis *in vivo* to the potent compound 3,5-dimethylpyrazole (119). To test this hypothesis, relative rates of hydrolysis at pH 2 and 6.7 were determined for a representative series of compounds covering a wide range of hypoglycemic potencies but no correlation between hydrolysis rate and activity was observed.

By selective formulation of aqueous solutions of methylprednisolone, it was observed that the stability of this compound could be affected significantly (120). A mechanism of solubilization and stabilization, based on hydrogen bonding and inclusion of the methylprednisolone into the polyoxyethylene exterior of polysorbate 80 micelles, was proposed. The acid degradation of sulfisoxazole in hydrochloric acid solutions in concentrations of 10–24% at 108° was studied (121). Two parallel pathways of molecular degradation, which led simultaneously to the formation of sulfanilic acid and sulfanilamide as final products, were determined and both were shown to be pseudo-

Table IV—Additional References on Stability Kinetics

Reference	Topic
128	Stability of aqueous solutions of aminopyrine (amidopyrine)
129	Autoxidation of drotaverine in aqueous solutions
130	Chemical stability of cyclophosphamide in aromatic elixir
131	Use of viscosimetry in the study of chemical kinetics in aqueous carbomer- (Carbopol) based gels
132	Stability of aspirin in substituted and nonsubstituted polyethylene glycol bases
133	Autoxidation of paverine in aqueous solutions
134	Kinetic behavior of phenylbutazone in four solvent systems
135	Chemical change of pentazocine in aqueous acidic media
136	Stability of 5-allyl-5-(2-hydroxypropyl)barbituric acid in solution
137	Stability of curcuma pigments in solution
138	Incompatibilities with thimerosal

first order. The kinetics of hydrolysis of benoxinate (oxybuprocaine) in aqueous citrate buffer solutions were studied over pH 1–6.5 (122). The pH–rate profile indicated that this molecule is subject to both acid and base catalysis, and the most stable pH was 3.0. An investigation of the decomposition of phenylephrine in buffered solution at pH 6.8 indicated that the major decomposition products, as identified by GLC–mass spectrometry, were 1,2,3,4-tetrahydro-4,6-dihydroxy-2-methylisoquinoline and the 4,8-dihydroxy analog (123). A possible mechanism for the degradation reaction was discussed. A kinetic study was made on norphenylephrine in aqueous solution (124). The decomposition rate depended on the rate constants of three dissociated ionic species. Hydronium ion and hydroxyl ion had no catalytic activity.

Hou and Poole (125) demonstrated that the β-lactamase-catalyzed hydrolysis of several penicillins followed Michaelis–Menton kinetics. Penicillins with a lipophilic side chain had the highest affinity for the enzyme. The introduction of a polar group into the side chain and/or a bulky diester group on the penicillin nucleus drastically lowered the binding. Exposure of dilute solutions of *N*-(2,6-dichloro-*m*-tolyl)anthranilic acid to visible or UV light resulted in fairly rapid decomposition with concurrent formation of approximately equimolar amounts of 8-chloro-7-methylcarbazole-1-carboxylic and 8-chloro-5-methylcarbazole-1-carboxylic acids (126). The kinetics of the hydrolysis of polysorbate 80 in aqueous buffers were studied over pH 1–10 (127). The hydrolysis appeared to be specific acid catalyzed at pH values below 3 and specific base catalyzed at pH values greater than 7.6. Both the acid- and base-catalyzed hydrolyses exhibited an unusual initial micellar surfactant concentration–rate dependence, opposite to that previously reported for the hydrolysis of anionic surfactants of the *n*-alkyl sulfate type.

Other papers related to stability kinetics are listed in Table IV.

Antibiotic Stability—The kinetics of the inactivation of some broad-spectrum antibiotics (tetracycline, chlortetracycline, and demeclocycline) were studied (139). The rate constants, activation energies, reaction half-times, and frequency factors were calculated. The toxic impurities, anhydrotetracycline and 4-epianhydrotetracycline, in commercial tetracycline products were determined spectrophotometrically (140). The storage temperature of tetracycline had a profound effect on the accumulation of these impurities, but temperature had practically no adverse effect on the biological activity or color of the preparations. Schlecht and Frank (141) used NMR to monitor the epimerization of tetracycline, since the dimethylamino resonance of tetracycline and that of its C-4 epimer differ by 0.1 ppm. This method eliminated the need for acidification in the previously reported spectrophotometric method, thereby lessening the possibility of anhydro formation which occurs in the presence of mineral acids. The radiochemical purity of three commercially available tritium-labeled tetracycline products was reported (142). All three products contained, in addition to tetracycline, substantial amounts of radioactively labeled 4-epitetracycline.

Decomposition of benzylpenicillin was measured over 24 hr at 25° in normal saline and in a solution containing one part of a tyloxapol-containing product (Alevaire) with four parts normal saline (143). In normal saline, a satisfactory degree of penicillin activity was retained for 24 hr, but penicillin decomposition was approximately 28% in solutions containing the tyloxapol product and saline. The presence of 10% sodium sulfacetamide had a stabilizing effect on sodium penicillin G eye drop preparations (144). In the formulation of suppositories with penicillin, degradation was enhanced greatly when the antibiotic was associated with antiseptic ingredients (145). Incompatibilities occurred, which led to as much as 95% inactivation of penicillin in the presence of creosote and guaiacol. Nystatin powder, which is known to be relatively unstable in its powder form and particularly sensitive to temperature, was shown to be more temperature stable in suppository bases (146). The stability of solutions containing amphotericin B was studied under the following conditions: exposure to 100 ft-candles of light at 23°, protection from light at 23°, exposure to 35 ft-candles at 4°, and protection from light at 4° (147). There was no appreciable loss of active material during an 8-hr exposure under these conditions. In the presence of phosphate–citrate buffers, nystatin and amphotericin B were optimally stable between pH 5 and 7 (148). Loss of biological activity followed first-order kinetics except under acid conditions. The decomposition rates of cephalosporin C in aqueous buffers and in fermentation broth at 25° were determined and found to obey the rate law $-dC/dt = [0.27(H^+) + 0.005 + 500(OH^-)]C$ mole/liter/hr (149). In a typical fermentation, nonenzymatic hydrolysis destroys about 15% of the product.

The stability of oleandomycin phosphate was determined at pH 2–8 at various storage times and temperatures (150). The decomposition rate was shown to be first order and the compound was most stable at pH 4. The stability of solid α-cycloserine was extremely dependent on moisture content (151).

Table V—Additional References on Antibiotic Stability

Reference	Topic
153	Effect of heat on biological activity of tetracycline and oxytetracycline hydrochloride
154	Effect of insoluble penicillins on stability of sodium penicillin G in aqueous solutions
155	Vacuum evaporation of water–butanol solutions of penicillin in a thin film
156	Stability of penicillin and streptomycin in tissue culture media
157	Influence of various concentrations of polysorbate 80 on stability of chloramphenicol
158	Effect of sodium benzoate and sodium salicylate on stability of chloramphenicol
159	Effect of sodium benzoate and sodium salicylate on solubility of chloramphenicol
160	Hydrolysis of chloramphenicol (levomycetin) esters
161	Alkaline degradation products of cephradine
162	Effect of honey, sugar syrup, and pasteurization methods on activity of kanamycin and benzathine penicillin G (Bicillin)
163	Thermodynamic and structural aspects of antibiotic–surfactant mixtures

At 0.15% moisture, little decomposition occurred; but at 1.3%, a sharp drop in activity was observed at 40°. The stability of antibiotics in infusion solutions was examined, and possible causes of inactivation were discussed (152). There were no general rules for the stability of antibiotics in these systems and specific stability studies are required.

Other references relating to antibiotic stability can be found in Table V.

Vitamin Stability—The effect of addition of 0.015% *p*-butoxytoluene antioxidant on the quality of soybean oil and the stability of vitamin A acetate solutions in soybean oil was studied (164). Although vitamin A was slowly oxidized in systems with and without the antioxidant, the rate was three times faster than that in the soybean oil containing the antioxidant. The stability of vitamin A alcohol, an intermediate product of vitamin A acetate, was determined in aqueous ethanolic solutions (165). The stability of this vitamin in 60–100% alcoholic solutions decreased gradually as water content increased. A photometric and spectrometric study related to the stability of vitamin A in dermatological preparations was presented (166). Vitamin A losses in anionic and nonionic hydrophilic bases and in polyethylene glycol gels were 3–17 and 100%, respectively, after 18 months of storage. In an effort to relate the stability of vitamin A in cod liver oil to filtration at 0–5°, it was determined that the filtration of the oil was not beneficial (167).

McAlpine *et al.* (168) studied the photoxidation of ascorbic acid in water at pH 4.5–11.6 using electron spin resonance spectroscopy. Results were consistent with a primary photochemical step involving the ejection of an electron from the monoanion of ascorbic acid to form the ascorbate. Sixteen commercial liquid multivitamin preparations were stored at 5, 25, and 40° for 1 year, and the contents were assayed for vitamins B_1 and C (169). As might be expected, degradation at 40° was more rapid than at 25°, and considerable difference was found among the commercial preparations. The results of an investigation of microbial contamination in oral vitamin preparations was reported (170). The occurrence of microorganisms in all preparations was higher than the values suggested in the literature, and pathogenic bacteria were found in 11 of 17 investigated preparations.

PHARMACEUTICAL TECHNOLOGY

In vitro test methods were described for the evaluation of antacid preparations (171). By using these procedures, a mixture of 400 mg dihydroxyaluminum L-histadinate and 400 mg magnesium hydroxide was compared with 15 experimental antacid mixtures. Phares and Hramchenko (172) described the advantages of colloidal alumina (Sol-Al; Baymal) and its chemical and physical properties in pharmaceutical applications. The test methods used by several investigators, or recommended by official compendia, for the microbial control of pharmaceutical and cosmetic products were reviewed and discussed (173). Attention was drawn to important factors that could influence test results such as product composition, sample preparation, time and temperature of incubation, and culture media. Fifty pharmaceutical grade samples of lactose were examined for microbial content (174). None showed greater than 6×10^4/g total aerobic colony-forming units. A basic description of the physical principles of accelerated freeze drying and the best methods for practical application were given (175). Methods for determining optimum conditions for freeze drying and for monitoring the progress of the cycle were described. Addition of carboxymethylcellulose, sodium alginate, gum tragacanth, pectin, and gum arabic increased the rate of solution of the lyophilized product (176). Viscosity of the reconstituted solutions was slightly decreased with respect to that of the unlyophilized gums, but viscosity did not decrease after storage.

Application of cation- and anion-exchange resins for the purification of ascorbic acid solutions from heavy metal and anion contamination was described (177). Finished material satisfied all compendial requirements. A paper reviewed the surface forces controlling the properties of dispersions of particles smaller than 1 μm in diameter (178). It was pointed out that distinction must be made between the process of deposition of such particles onto solid surfaces and their subsequent removal. The latter is a more complicated problem because of deformation of the materials at points of contact, the extreme closeness of the surfaces, and the possible formation of chemical bonds. For measurement of the angular intensities of scattered light of an aerosol, a method was devised without the aid of a cell with glass windows (179). This method was compared with the method using the glass cell and the Raleigh ratio. A technique was developed whereby a formulation with optimum properties, according to predetermined criteria, could be selected by computer analysis (180). The results of a statistically designed set of experiments, based on five independent variables, were used as the data input. An example was presented of the selection of an optimum formulation by this procedure and of its preparation in the laboratory.

Table VI—Additional References on Pharmaceutical Technology

Reference	Topic
181	Progress in pharmaceutical technology in 1970 and 1971
182	Use of nonaqueous solvents for preparing solutions of *N*-acetylsarcolycine peptides
183	Use of separate granulations in production of sodium barbital tablets with diphenhydramine hydrochloride (Dimedrol)
184	Fat-soluble vitamins and related compounds
185	Formation of gelatinous aluminum hydroxide and some properties of the derived alumina
186	Production and properties of highly disperse precipitated calcium carbonate for use in the pharmaceutical industry
187	Effect of technology on effervescent strength of piperazinium effervescent preparations
188	Structure and properties of natural hydrocolloids
189	Sulfurous acid salts as pharmaceutically useful antioxidants
190	Review of antioxidants used in pharmacy
191	Experiment planning methods on pilot plant apparatus for crystallization of trichloroacetic acid
192	Review of percutaneous absorption of chemical agents with particular emphasis on toxicity and side effects

Additional references on pharmaceutical technology are listed in Table VI.

Parenterals—Groves presented reviews dealing with the nature, origin, and hazard of particulate material in intravenous fluids (193), the detection of particulate contamination (194), and the existing standards and proposed new standards for particulate contamination in intravenous fluids (195). Efforts to produce solutions to specifications are defeated when the solution becomes contaminated with particulate matter from administration sets and cannulas (196). Therefore, it was suggested that standards be applied to all solution administration equipment. A comparative determination of particulate matter indicated that stable antibiotic solutions and lyophilized antibiotics have the lowest particulate contamination levels (197). In contrast, sterile powder-filled antibiotics have contamination levels two to three times higher.

The current trend toward quantitating trace particulates in parenteral preparations has resulted in an increased emphasis on the membrane filtration technique (198). A simplified method for carrying out this procedure was described. In a comparative study of particulate contamination in ampuls, standards based only on Coulter counter readings were not the whole answer (199). Visual examination was also found to be necessary. Results of a membrane filtration study of particulate matter contamination of intravenous fluids manufactured by four firms were reported (200). Three-year comparative data showed that considerable improvement in particulate matter contamination had taken place and that solutions in flexible plastic containers were the least contaminated. A manual counting method and an electronic scanning method were compared for determining particulate contamination in several small-volume commercial products (201). It was determined that, for large numbers of particles in the 5–25-μm range, the electronic method resulted in higher counts; in general, this method was more precise and more rapid than the manual counting method.

Ryan *et al.* (202) concluded that both the design and utilization of presently available equipment necessary for administering intravenous solutions are apparently deficient. In a study of 100 postoperative patients, the effectiveness of a 0.45-μm membrane filter dramatically minimized acute phlebitis and thrombophlebitis. The influence on flow rates of infusion fluids, when they are used with commercially available final filtration devices, was studied along with their ability to remove particulate matter (203). Commonly used infusion fluids flowed satisfactorily with these devices, and the filters did not significantly influence the pH and were effective in removing particulate matter. Intravenous administration of latex particles in doses of 8×10^6/kg with 0.4–10-μm diameter particles and of 4×10^5/kg with 40-μm diameter particles was well tolerated by rats (204). No histopathological effects, including inflammation, were seen except for infrequent focal myocardial degeneration with 10- and 40-μm particles. Dosage of 8×10^6/kg with 40-μm particles killed acutely. The factors causing drug additive compatibility problems were discussed, with the conclusion that general methods for determining compatibility are limited (205). Until more complete information is available, it was suggested that the health-care professions attempt to limit the number of drugs added to any single large-volume injectable solution. A review of the physical incompatibility of parenteral drugs was presented (206). It included the effects of concentration and temperature, stability of parenteral solutions, pH patterns for intravenous additives, and the presence of two or more drugs in the same parenteral vehicle including carbenicillin and gentamicin, carbenicillin and other drugs, antibiotics and synthetic sweetening agents, cardiovascular and psychotherapeutic agents with sodium ethacrynate, admixtures of two or more preoperative drugs, and penicillin and tetracycline.

The ability of large-volume vacuum-packed parenteral containers to maintain vacuum under adverse conditions of temperature and agitation was studied (207). In all cases, the vacuum seal was maintained under the test conditions; it was concluded that such factors as decomposition of ingredients and faulty glassware should be suspected if vacuum loss is found with these types of containers. The hypothesis that contamination of large-volume parenteral containers may be due to improper handling techniques was examined (208). Statistical evaluation of the results indicated that certain procedures may, indeed, result in contamination in many cases, whereas there was no significant contamination in any system tested when recommended procedures were followed. *In* a similar test, a series of different drug additives was added to intravenous glass bottles of Ringer's solution in a hospital ward (209). None of the bottles became contaminated during this procedure, but the bottles collected from bedside after administration to patients were found to be contaminated at a 3% level with fungi or bacteria. The effectiveness and safety

Table VII—Additional References on Parenterals

Reference	Topic
215	Suspended substances in commercial infusion solutions
216	Review of particulate matter in intravenous infusions
217	Parenteral dosage forms with prolonged action
218	Effect of oil solutions and suspensions for prolongation of vitamin B_{12} action
219	Methods for preparation of prolonged-action injectable preparations
220	Differential thermal analysis as screening technique for adjuvants in parenteral formulation
221	Parenteral incompatibilities in hospital pharmacy
222	Incompatibilities and other problems involved in adding drugs to intravenous solutions
223	Incompatibilities in multicomponent liquids used for injections
224	Interactions between penicillin and aminoglycoside antibiotics in parenteral solutions
225	Growth of microorganisms in parenteral nutritional fluids
226	Use of neutral olive oil for injections
227	Plastic containers for liquid parenteral drugs
228	Method for preparing ethyl oleate, a solvent for parenteral administration
229	Solubilization, emulsification, and dispersion with surfactants in parenteral preparations
230	Preparation of sodium bicarbonate solutions for injection
231	Stable parenteral dosage form of orotic acid
232	Preparation of parenteral dosage forms of trypsin and α-chymotrypsin
233	Preparation of stable injectable solution of *N*-benzyl-*N*-(β-benzoylethyl)piperazine dihydrochloride
234	Development of spasmolytic and analgesic preparation in injectable form
235	Problems in preparation and control of injectables in hospital pharmacy
236	Review of oil emulsions for parenteral administration
237	Problems in preparation of Ringer's injection, lactated Ringer's injection, sodium lactate, Trometanol, and urea solutions for parenteral infusion
238	Influence of siliconization on hydrolytic glass resistance
239	Evaluation of methods for testing of ampuls for undissolved impurities
240	Microbiology training for pharmaceutical production personnel
241	Design, construction, and operation of sterile filling facility

of a plastic two-way transfer needle for aseptically reconstituting parenteral drug powders, or transferring parenteral liquids, were studied, and it was found suitable for these purposes over a broad pH range (210).

In studies to evaluate methods for detecting leaks in glass ampuls, it was concluded that the best dye test is a pressure test (211). However, for routine testing, the pressure used should be the highest possible consistent with no ampul damage. A suggested approach to the selection of an elastomer compound for use with various parenteral solutions was presented (212). Many factors, including type of solvents, solvent pH, and the effect of the sterilization process, must be considered. Since many freeze-dried pharmaceutical preparations contain very small amounts of active medicaments, it is often necessary to add other ingredients to provide a supporting matrix of solids for the dried product (213). A method that measured fracturability of the plug was developed and was shown to give reproducible and meaningful results in evaluating these additive materials. In an effort to produce a long-acting intramuscular injection, trifluoperazine pamoate (trifluoperazine embonate) was microencapsulated by interfacial polymerization techniques (214). The time of duration of suspensions of microencapsulated drug was shown to be approximately double that of the same drug in polyethylene glycol 400 solution.

Other papers of interest in the area of parenterals are listed in Table VII.

Ophthalmics—Drainage of an instilled drug solution away from the eye is responsible for a considerable loss of drug and, hence, affects the biological activity of drugs in the eye (242). The rate of this drainage is related to the volume of drug solution instilled and increases with increasing volume. In a study conducted on anesthetized and unanesthetized rabbit eyes, it was concluded that the drop size of ophthalmic delivery systems should be reduced from its present 50–75-μl size to, at most, 5–10-μl drops. In a review article on ophthalmic preservatives and vehicles, Mullen *et al.* (243) indicated that the most widely used ophthalmic preservatives were benzalkonium chloride, chlorobutanol, and phenylmercuric nitrate or acetate. The most commonly used vehicles were hydroxypropyl methylcellulose and polyvinyl alcohol. Rabbit corneas were denuded of epithelium and the rate of reepithelization was measured to determine the toxicity of various commercially available wetting solutions used for contact lenses (244). Of six commercial solutions, three were inhibitory, but no consistent pattern was revealed as to which components were toxic.

Eighty-four semisolid, water-soluble, anhydrous bases for possible ophthalmic use were formulated and evaluated on the basis of pH and desirable physical spreading characteristics over 0–50° (245). One was selected on the basis of several attributes as the best formulation for ophthalmic use. Pilot plant facilities were designed and built for scale-up activity based on accumulated data from investigations of conventional sterilizing procedures and aseptic techniques for manufacturing sterile anhydrous ophthalmic ointments (246). Because of batch sizes normally made by production, practical means for sterilizing and operating on a large scale under aseptic conditions were evaluated. The detection of metal particles as an impurity in ophthalmic ointments dispensed in collapsible metal tubes was studied (247). A modification of the USP method was given in which the disturbing solid was extracted by a suitable solvent before the final inspection. The dilution effect of drugs introduced as solutions into the conjunctival sac could be minimized by use of a hydrophilic contact lens made of glycol methacrylate polymer (248). Lenses composed of this polymer were immersed in various antibiotic solutions and placed in the eye with no deleterious effects and with prolonged duration of action.

Sterility and Sterilization—A review of the improvements made over recent years in sterilization

procedures and sterility testing methods for the aseptic manufacturing of parenteral products was presented (249). Methods were investigated for isolating and enumerating *Escherichia coli*, inoculated into white, soft petrolatum, by a membrane filtration technique (250). Superior recovery levels were obtained by homogenizing the ointment base with a polysorbate 80–peptone–water mixture, which permitted the estimation of contamination in up to 250 mg of material. Factors influencing the reisolation of inoculated organisms in ointments and creams were also examined employing a membrane filtration technique (251). Ointments were less sensitive to experimental design and had more consistent recovery rates, while creams required more rigid conditions and low levels of contamination could remain undetected because of the difficulty of increasing sample size. Bruch (252) reported that the best proof that a lot of sterilized material has a high probability of being sterile is the destruction of calibrated doses of microorganisms of defined resistance carried by a few samples from the lot. In a study comparing thioglycolate medium with four other medium broths, it was determined that thioglycolate was superior in terms of accuracy and time required (253).

Studies indicated the doses of ethylene oxide injected subcutaneously that would cause tissue reaction (254). Factors that affect the elution of ethylene oxide from medical materials were discussed. To determine the necessary aeration time of materials before they can be determined safe for use, the desorption characteristics of ethylene oxide from three types of silicone polymer were studied (255). Very rapid desorption of gas to low residual levels was observed in two nonreinforced silicone rubbers. The third material, Dacron-reinforced silicone sheeting, lost the gas at a considerably slower rate due to retention by the Dacron reinforcement. An acute ocular toxicity test for ethylene oxide, ethylene glycol, and ethylene chlorohydrin was described (256). In general, the ocular damage was most intense with ethylene oxide and least intense with ethylene glycol. It was reported that the establishment of effective economic ethylene oxide sterilization cycles for medical devices involved three major considerations (257). These were the determination of total microbial load on the product prior to sterilization, the use of the total load information to determine the number of samples to be tested, and a comparison of the resistance to sterilization of the indicator with that of the microorganisms on the product.

Schulman (258) presented a review on the fundamentals of interaction of ionizing radiation with chemical, biochemical, and pharmaceutical systems. Thirteen antibiotics belonging to different groups were exposed to 5, 10, and 15 Mrads of neutron and γ-radiation (259). With γ-radiation, oxytetracycline at 15 Mrads and penicillin G at 5 and 10 Mrads showed a considerable decrease in activity. Other antibiotics did not show significant change in activity by this method. When subjected to γ-radiation at 2.5 Mrads, procaine hydrochloride crystals showed no chemical changes from the nonirradiated material (260). A slight yellow color was attributed to minute traces of chemically nondetectable compounds. Injectable solutions and powders of ephedrine hydrochloride, atropine sulfate, scopolamine hydrobromide, strychnine nitrate, morphine hydrochloride, codeine phosphate, and neostigmine (proserine) were radiation sterilized at low temperature (261). All preparations underwent some decomposition accompanied by changes of color and pH, appearances of foreign impurities, decreases in biological activity, and increases in toxicity. Disposable tube stoppers and adaptors, made of both high and low density polyethylene, were successfully sterilized by γ-radiation (262). No changes between irradiated and nonirradiated material were detected.

A discussion of deep and surface filtration, the design, production, and efficiency of membrane filters, process filtration with membrane filters, cold sterilization with membrane filters, techniques of filtration, and filtration carried out just prior to filling containers was presented (263). Ultrasound of 800 kHz frequency was successfully used in sterilizing a *Bacillus subtilis* spore suspension in 0.9% sodium

Table VIII—Additional References on Sterility and Sterilization

Reference	Topic
269	Laminar flow in the pharmaceutical industry
270	Use of *Bacillus stearothermophilus* as biological indicator
271	Sterility testing of large-volume aqueous pharmaceutical products by the membrane filtration technique
272	Further developments in *Limulus* amebocyte lysate pyrogen testing
273	Membrane filtration tests for sterility
274	Bacteriological control of pharmaceutical emulsions through laser radiation scattering
275	Applicability of Attest indicators for testing sterile solutions
276	Ethylene oxide sterilization of nylon-wrapped materials
277	Sterilization by ethylene oxide and its application to respirators
278	Decontamination of artificial respirators by ethylene oxide
279	Antimicrobial treatment with ethylene oxide and formaldehyde
280	Effect of neutron and γ-radiation on drugs
281	Sterilization of biochemical products by γ-irradiation
282	Effects of γ-radiation on physical and chemical properties of disposable infusion assemblies
283	Radiosterilization of chamomile
284	Effect of ionizing radiation on essential oils
285	Description of sterilization procedure for eye drops
286	Continuous, automatic sterilization system for parenteral solutions
287	Review of sterilizing filtration of liquids
288	Filtration of liquids and gases by calibrated porous membrane
289	Effect of sterilization process on pH of solutions of 6% dextran (Hemodex) and 10% dextran (Reoisodex)
290	Germicidal effect of thimerosal on biological products
291	Review of actions, mechanisms, and uses of formaldehyde as sterilizing agent
292	Review of antimicrobial activity and chemical properties of glutaraldehyde as cold sterilizing agent
293	Peracetic acid as suitable disinfectant for disinfecting rooms
294	Review of sterilization by antiseptic liquids

chloride solution (264). Increased spore sensitivity to ultrasound, in the presence of very small amounts of preservatives, was attributed to changed permeability of the spore membrane. A review discussed the possible applications of β-propiolactone as a sterilizing agent (265). The bactericidal activities of isomeric trifluoromethylphenols against *E. coli* were found to be in the order: *meta* > *para* > *ortho* (266). These activities were related to the partition coefficients of the compounds between polar organic phases and aqueous buffers. The advantages and disadvantages of the application of sodium hypochlorite, potassium hypochlorite, peracetic acid, β-propiolactone, propylene glycol, phenolic agents, and formaldehyde solutions by aerosol spray were discussed (267). The importance of the limiting speed of sprayed droplet collapse, the exposed surface being covered by 1 ml of sprayed liquid, and the vapor pressure of a monodispersed droplet as a function of its diameter was presented. Ceramic and plastic tiles, as well as joint sealing materials, were sprayed with five disinfectants of specific action against Gram-positive and Gram-negative test organisms and fungi (268). Polished and glossy surfaces were more resistant to decontamination than dull or rough surfaces, and spraying left four times as many organisms as scrubbing.

Other papers relating to sterility and sterilization are listed in Table VIII.

Tablets and Capsules—A computer optimization technique was used to indicate the directions necessary to improve various characteristics of a production tablet (295). Data from experimental and production size batches were compared with computer predictions. The relationships of temperature, relative humidity, size of inoculant, and duration of storage on survival of *Staphylococcus aureus* inoculated onto surfaces of 17 commercial tablets and one gelatin capsule were determined (296). Within limits of the experiment, decreased survival was associated with an increase in each variable. Several other articles dealing with the general topic of tablets and capsules concerned identification coding (297), a discussion of hard capsule dosage forms (298), advances in tablet production (299), and quality control of tablet production (300–302).

The other numerous articles dealing with pharmaceutical technology of tablets and capsules have been subdivided into the following classifications to facilitate a search of the literature: comminution, mixing, granulation, and drying; powder characteristics; compression; effects of excipients; and tablet coating. For a thorough review, consideration of the entire section is advised due to the obvious overlap in the subject matter.

Comminution, Mixing, Granulation, and Drying—Jet grinding was evaluated as a method for reducing particle size of several forms of pharmaceuticals (303). Although different pharmaceuticals behaved differently, the powders did not lose their medicinal properties after grinding by this method. Improved measurement and digital control techniques resulted in in-line blending schemes that offer significant time and money savings (304). Three industrial blending situations were described which demonstrated the advantages of in-line blending. Because direct measurement of individual granule strength by crushing techniques is tedious and invariably gives a wide scatter of results for irregular granules, Hunter (305) described a method based on a friability test which correlated well with the direct crushing method. The effects of intragranule porosity and granule strength on some tablet properties were investigated (306). It appeared that compaction pressures eliminated any of these effects except at low pressures. The influences of five spheronization process variables—water content, extruder speed, extruder screen size, spheronizer speed, and residence time in the spheronizer—were evaluated on several granulation parameters (307). By using a complete factorial design, it was possible to define statistically significant effects of these process variables as well as any linear interactions. A mixture of starch and sulfanilamide, processed in a rotary granulator, was compared with one processed in an oscillating granulator with respect to porosity, specific surface, grain fluidity, and dissolution time (308). The effect of differences in density and compactness on the tablet was discussed.

In a study of the influence on pharmaceutical granulations of the type and capacity of mixers, it was determined that the initial densification of the wet mass was directly related to the capacity, but the rate of densification and binder distribution were similar for the three mixers studied (309). The influences of batch size, droplet distribution, adhesive strength and concentration, and drying times were factors that determined the size distribution of granules formed during granulation in a fluidized bed (310). Various methods for drying pharmaceuticals were discussed and evaluated with respect to the time required to achieve satisfactory dryness (311). In the study, the fluidized-bed dryer–granulator approach was found to be the best. The effect of temperature on the drying process was analyzed (312). The kinetics of constant rate and decreasing rate were described. The mathematical equations fitting the drying process using a fluidized bed were deter-

Table IX—Additional References on Comminution, Mixing, Granulation, and Drying

Reference	Topic
316	Influence of addition of organic and inorganic powders on degradation of polyvinylpyrrolidone by ball-milling in air
317	High frequency drying of pharmaceutical tablets and their physical properties
318	Review of vacuum drying in chemical and pharmaceutical industries
319	Optimization of processing of pharmaceuticals including fluidization
320	Discussion of granulation theories and mechanism of granule formation and growth
321	Mathematical evaluation of granule growth rate
322	Theories of granulation and different types of granulators
323	Production of granules by compaction
324	Effect of humidity on disintegration rates and hardness of compressed tablets

mined (313). From the corresponding nomograms, the rates of the drying time in relation to a given initial moisture content could be determined. Pitkin and Carstensen (314) determined that granules dry by a diffusional process and that, therefore, moisture content is a function of particle size. Where granules are not case hardened, the moisture levels equilibrate and the granulation is uniform when it reaches the tablet press. The following new techniques for tablet processing were discussed: drying by microwave, granulation and drying in one operation, and dry granulation without subsequent drying (315).

Additional references on comminution, mixing, granulation, and drying are listed in Table IX.

Powder Characteristics—Fell (325) investigated the influence of fines on the flow and compaction properties of conventionally processed and spray-dried lactose. He concluded that the fines of spray-dried lactose may well be formed in a different manner from the bulk of the material and, thus, behave differently under load. Flow or fracture may occur more readily, providing greater areas of bonding, leading to stronger tablets. The effect of crystal habit and particle shape upon the physical properties of tablets produced from cubic and dendritic crystals was reported (326). Tablets formed from the dendritic crystals, which had the larger shape index, were stronger than those formed from the cubic crystals. The effects of the particle shape and the ratio of interparticle cohesion–particle weight on the initial fractional voidage before tapping, the rate of tapping–compaction, and the final fractional voidage attained by tapping were studied (327). The initial fractional voidage of rod-shaped particles was much greater than that of the irregular or spherical ones and was explained in terms of the strong mechanical resistance caused by interlocking of particles due to the high elongation of the rod-like particles.

The specific volumes of three bulk solids at moisture contents up to 50% (w/w) under various consolidating stresses were shown to be dependent on the nature of the bulk solids (328). The influence of moisture on the packing properties and tensile strength of the three bulk solids was discussed in terms of the granulation process. An attempt to overcome the difficulties of the Jenike-type shear cell and to use a simpler procedure in a different shear cell, and thereby to reduce the quantity of powder required, was described (329). The yield loci obtained were very nearly linear. The process of sintering and its effect on the strength, pore structure, and rate of release of potassium chloride from a matrix tablet, prepared from a vinyl acetate–vinyl chloride copolymer, were investigated (330). Although the tensile strength of the tablets increased on sintering, the porosity and mean pore radius also increased, leading to a marked increase in release rate.

Additional articles relative to powder characteristics are listed in Table X.

Compression—It was shown that certain enzyme preparations lose activity when subjected to pressure (339). The concentration and distribution of stress by compression at several different pressures in convex-type tablets were studied (340), measuring specific enzyme activities of proteinase as a parameter. A new zone, which gave increased damage to the enzyme activity, was found that appeared about two-thirds from the center of the tablet in the longitudinal direction, and this zone was related to structural breaking during compression. Two strain gauges, diametrically opposed, were utilized on a tableting machine to study powder compression in tablet production (341). Granule size, crystal structure, humidity, and powder discharge were contributing factors to pressures required. A rotary tablet press was instrumented to permit production of tablets that would remain within preset weight tolerances (342). Tablets falling outside specifications were automatically rejected. The effect of compaction force on tablet dissolution using simple direct compression systems was investigated (343). For some systems, increase in pressure caused an increase in dissolution rate, while for other systems, increase in pressure caused a reduction in dissolution rate; the results were discussed in terms of the effects of the compaction process on interparticle bonding, fragmentation, and other tablet properties. A study was reported on the effect of the melting point of additives on the tensile strength of tablets measured by using a diametrical compression test (344). Tablets of equal density containing the same amount of additives showed a general decrease in strength as the melting point of the fatty acid additive increased, and this was attributed to different amounts of interparticle bonding resulting from melting of asperites on the particles at temperatures below their conventional melting points.

Compression runs on several powders of different particle size and hardness were made at a relatively low pressure range where fragmentation of particles did not take place (345). It was confirmed that the compaction parameters obtained were related to the pressure transmission ratio and the hardness of the material being compressed. For lactose tablets, it was shown that the effect of granule size on tablet hardness was less pronounced at high pressures (346). In another study, a linear relationship was found between compression pressure and disintegration time and hardness (347). This relationship oc-

Table X—Additional References on Powder Characteristics

Reference	Topic
331	Granulometric methods in testing pharmaceutical preparations
332	Manufacture and properties of highly dispersed calcium carbonate precipitate
333	Flow of granulation containing antibiotics and its effect on physicochemical behavior of tablets
334	Cohesion and flow of particulate solids
335	Studies on flowability of powder and interparticle cohesion
336	Pharmaceutical studies on physical properties of powders
337	Effect of sintering on pore structure and strength of plastic matrix tablets prepared from polyvinyl chloride
338	Moisture transfer effect in hard gelatin capsules of sodium cromoglycate (cromoglycic acid, sodium salt)

Table XI—Additional References on Compression

Reference	Topic
349	Compression cycles of crystalline substances for pharmaceutical use
350	Evaluation of creep curves from process of dynamic compression
351	Use of compressional force measurements in tableting
352	Use of compaction for obtaining tableting mixtures and limitations involved in this process
353	Elastic, plastic, and viscous properties, and characteristics of deformation processes in tablet masses
354	Effect of technological factors on release of active material
355	Review of dry compaction of pharmaceutical powders
356	Compression of medicinal preparations without pregranulation
357	Use of lubricants to avoid slip-stick during ejection of tablets
358	Production of tablets by direct compression

curred in all cases, regardless of the weight and granule size of the particles. The importance of punch length uniformity to the control of tablet weight variation was demonstrated on a rotary tablet press (348). Analysis of the relationship between punch length and compression force pointed to the uncertainty of the relationship between tablet weight and compression force when variations of upper and lower punch length are considered.

Other articles concerning compression are listed in Table XI.

Effects of Excipients—By using a scanning electron microscope, the location and structure of starch grains in experimental and commercial aspirin tablets and aspirin–phenacetin–caffeine tablets were studied (359). By observing tablet faces and cross sections before and after the addition of water, rupture of the surfaces was shown to occur where starch agglomerates were found; it was postulated that disintegration occurs by hydration of the hydroxy groups of the starch molecules, causing them to move apart. Disintegrant properties of sodium starch glycolate and a cation-exchange resin were examined in various tablet systems (360). Extreme efficiency, even at low concentrations, was demonstrated for both compounds. A study of the effects of six disintegrants on a water-soluble tablet showed that rice starch and bentonite caused a decrease in the disintegration time with little or no effect on the mechanical characteristics (361). An evaluation was made of the properties of five tablet disintegrants in two insoluble direct compression matrixes: dicalcium phosphate dihydrate and calcium–phosphato–carbonate complex (362). The effect of concentration of disintegrants on disintegration time was interpreted in terms of the difference in mechanisms of disintegrant action. Cross-linked polyvinylpyrrolidone was studied for its disintegration property in comparison with starch USP and alginic acid (363). Cross-linked polyvinylpyrrolidone demonstrated superiority over both these agents, and it was postulated that capillary activity of the cross-linked polyvinylpyrrolidone is responsible for its disintegration property. The dissolution and disintegration of a number of experimental formulations of chloramphenicol capsules were dependent on capsule size, diluents, lubricants, and filling methods (364). Measurements of the rate of liquid penetration through powder beds of similar compounds to those used in capsules did not adequately reflect the dissolution profiles of the various formulations.

Sodium alginate was evaluated as a tablet binder for lactose tablets in comparison with acacia and gelatin (365). Sodium alginate compared favorably with regard to mechanical properties of the tablet produced, but the disintegration time of tablets was not increased as sodium alginate concentration increased above 1%. In a study of binder dilution effects on granulation, it was concluded that this factor had insignificant effects on the average granule size and granule density of granulations manufactured in a fluid-bed spray granulator (366). However, considerable influence was observed on granule friability, bulk density, interparticulate porosity, and, thus, flow rate. In three of the four formulations tested, the surfactant magnesium lauryl sulfate was equivalent to the hydrophobic magnesium stearate as a lubricant (367). Magnesium lauryl sulfate was superior to sodium lauryl sulfate; thus the goal of finding a compound with excellent lubricating properties but without waterproofing liability was achieved. A limiting concentration of 1.5% was determined for sodi-

Table XII—Additional References on Effects of Excipients

Reference	Topic
373	Tableting properties of sulfameter (sulfamethoxydiazine) formulations
374	Factors affecting capsule shell dissolution rate
375	Pharmaceutical studies on cyclandelate fine granules
376	Direct compression of pure excipients and excipients in presence of phenobarbital on reciprocating machine
377	Comparative evaluation of excipients for direct compression
378	Pharmaceutical-technological problems in preparation of tablets with colored active ingredients
379	Effect of certain tablet formulation factors on antimicrobial activity of tetracycline hydrochloride and chloramphenicol
380	Release of easily soluble drug from hydrophobic tablet matrix
381	Mechanism of action of flow-regulating agents
382	Effect of stearic acid and calcium stearate on quality of tablets
383	Effect of moisture on crushing strength of sucrose tablets
384	Dependence of pill disintegration and active ingredient release on pill mass composition and other factors
385	Dragées with tocopherol acetate
386	Effect of dibasic calcium phosphate and polysorbate 80 on disintegration and rate of release of active substance from tablets
387	Use of carboxymethyl starch as binding and disintegration rate-improving additive in tablet production
388	Binding activity of some adjuvants and their influence on physical characteristics of granules and tablets
389	Influence of starch and lactose on release rate of drugs from hard gelatin capsules
390	Influence of excipient type and drug particle size upon small-scale mixing process
391	Use of adsorbents to prevent mottling in colored tablets

um and magnesium stearates as lubricants for assisting the flow of granules into tablet dyes (368). Aluminum stearate was unsuitable during compression due to its inadequate coating of the granules or to its intense adsorption to granules, making it unavailable for lubrication.

The shear strength of fatty acids decreased with increasing carbon chain length to an optimum of 18 carbon atoms, followed by an increase (369). Lubricating efficiency, however, first increased and then decreased under the same conditions. In an attempt to avoid intertablet dose variation in nitroglycerin sublingual tablets, a formulation containing polyethylene glycol was prepared (370). With concentrations of polyethylene glycol equivalent to 85% of the nitroglycerin, the tablets maintained their content uniformity for long periods even at 37 and 45°, thus assuring a more uniform and predictable dose to the patient. The effect of finely divided silica on the antifoaming properties of polydimethylsiloxane, when formulated in a typical antiflatulent tablet, was examined (371). A dynamic froth test was used to show that removable or extractable dimethicone by ether extraction of the tablet powder markedly reduces the antifoaming properties of the powder despite retention of a small percentage of the polydimethylsiloxane dispersed on the surface of the silica. A rather novel method to study the relation of porosity to other physical properties of tablets was reported (372). The method consisted of granulating tablet mixtures with varying amounts of ammonium carbonate as an additive and allowing the tablets to sit for certain periods as the ammonium carbonate decomposed, leaving pores in the tablets.

Additional references on effects of excipients are listed in Table XII.

Tablet Coating—Heyd (392) evaluated the operational characteristics of an automatic, airless, spray tablet-coating system, with particular emphasis on volume of fluid delivery and spray pattern characteristics. He determined that a linear relationship existed between the pressure employed and the volume of fluid delivered and that viscosity had very little effect on the volume of fluid delivered. The influence of the solvents, ethanol and isopropyl alcohol, on the tablet bed temperature during spray coating was investigated (393). The temperature at equilibrium of the rotating tablet bed depended on tablet composition, solvent, solvent temperature, and temperature and velocity of the forced drying air. The effect of surface coating on the dissolution rate of potassium chloride solid disks was reported (394). It appeared that the major factor controlling the effect of a hydrophobic substance on the dissolution rate of a solid was the attachment of the substance to the surface of the solid.

The effects of additives on a solvent-free formulation suitable for use as a film coating were described (395). Coatings were applied by spraying molten mixtures onto tablets in a conventional coating pan; of the additives evaluated, only castor oil, cocoa butter, and isopropyl myristate improved the basic formulations. In a study describing the measurement of physical and chemical characteristics of film coating, it was determined that cellulose films had higher tensile strength and elastic deformation than methacrylic acid polymers and that the addition of plasticizers increased, whereas pigments decreased, viscosity, tensile strength, and tear resistance (396). Dissolution rate–pH profiles of several films for enteric coatings were also determined. The various standard methods for tablet coating were compared economically as well as in light of modern pollution requirements (397). A review compared the traditional sugar coating and coloring methods to the modern film coating and pigment-suspension coloring methods (398).

Suspensions—A comprehensive review of suspensions, including formulation, reduction of particle size, augmentation of the viscosity of the liquid phase, influence of concentration, and addition of surfactants, was presented (399). The degree of flocculation of sulfamerazine suspensions, as represented by relative sedimentation volume, was determined as a function of both surfactant and electrolyte concentrations (400). The results emphasized the importance of knowing the location, as well as the concentration, of the surfactant and were consistent with the Derjaquin, Landau, Verwey, and Overbeek theory. The particle-size distribution of commercial samples of hydrocortisone and norgestrel suspensions was determined by use of the Coulter counter, model B, and the raw experimental data so obtained were digitalized by use of the Weiball equation (401). It was shown that the concept of controlled aggregation may be usefully applied to the formulation of these suspensions. The sedimentation volume of procaine penicillin G suspensions varied with the concentration and molecular weight of polyvinylpyrrolidone (402).

Kayes (403) studied the effect of surface-active agents on the ζ-potential of particles in a model suspension system containing polyoxyethylene monohexadecyl ethers and sodium lauryl sulfate. The results suggested some type of multilayer adsorption with sodium lauryl sulfate adsorbed in reverse orientation, possibly attached to the ethylene oxide chains after they had covered the particle surface. A review was presented on the measurement of the ζ-potentials in nonaqueous systems (404). A flow-through diffusion chamber was developed to determine the release rate of the active ingredient from salicylamide suspensions as a function of its concentration and the concentration of dispersing and stabilizing additives (405). Release rates decreased with increasing concentrations of additives, with sodium carboxymethylcellulose having a higher release rate-retarding effect than tragacanth gum. Although sulfathiazole (norsulfazole) suspensions could not be prepared using sodium bentonite alone, easily prepared suspensions were made possible by the addition of methylcellulose or sodium carboxymethylcellulose (406).

Emulsions—Criteria were discussed for the selection of emulsion stabilizers (407). Some surface-active agents used as stabilizers were listed and their characteristics were given. In evaluating the method of preparation on the critical hydrophilic-lipophilic

Table XIII—Additional References on Emulsions

Reference	Topic
417	Stability of emulsions of oxyethylated alcohols
418	Glycerides of pyroglutamic and malic acids as emulsifiers
419	Pharmacotechnical study of fatty esters of polyethylene glycol in emulsion systems
420	Testing of emulsion stability and emulsion uniformity
421	Review of water-in-oil emulsions
422	Review of methods for choosing emulsifying agents
423	Review of nonaqueous emulsion systems
424	Review of various concepts of emulsion stability
425	Review of emulsification and emulsion stability
426	Review of determination of potency of emulsifying agents

balance (HLB) of a liquid petrolatum emulsion, it was discovered that the method of manufacturing changed the critical HLB (408). In this particular study, emulsions made at lower temperatures required higher HLB values for satisfactory products. The rate of separation of oil from mineral oil–water emulsions stabilized with sodium lauryl sulfate and several other stabilizing agents was determined at 5–30° in an ultracentrifuge (409). The emulsions were all found to be less stable at higher temperatures, but the change in stability with temperature was not caused primarily by changes in viscosity. In studying the relationship between globular size and ζ-potential, an exponential relationship between the apparent ζ-potential and mean globule size was found (410). The emulsions showed apparent instability behavior when the ζ-potential was reduced to approximately 25.0 mv. The emulsifying properties of linseed mucilage were evaluated, and it demonstrated considerable advantages over those of polysorbate 80, gum arabic, and gum tragacanth (411). While stable emulsions of liquid paraffin or cod liver oil with 4% aqueous methylcellulose solution showed rather high stability, those made with gelatin were less stable and their stability was dependent upon the purity of gelatin and the amount of acid added (412). No stable emulsion could be prepared with carboxymethylcellulose.

Liquid petrolatum emulsions with hydrophilic and hydrophobic surfactants were used to compare two methods for determining the stability of emulsions (413). Both the HLB method and a method using phase diagrams were evaluated, with the latter being the more accurate. Studies of phase diagrams confirmed that the Schulman microemulsion was not an emulsion but a solubilized solution (414). The conditions necessary to produce microemulsions with 5–10% solubilizer were elucidated. Reichmann and Petersen (415) prepared emulsions of glycerin and mineral oil using anionic, cationic, and nonionic surfactants. The effects of temperature and aging on droplet size and viscosity were evaluated, and the decrease in viscosity correlated well with droplet size growth. *Physical* methods for determining types of emulsion were recapitulated briefly, and the theory of emulsion stability was considered (416). Tests employed in the laboratory were summarized, and the physical and chemical methods available for process control were discussed with illustrative measurement curves.

Other references relative to emulsions are listed in Table XIII.

Ointments and Creams—The use of aqueous borax in formulating cold creams with beeswax dissolved in mineral oil provided whiteness, stability, and ease of formulation (427). The best samples were obtained with half-neutralization of the beeswax acid, and the borax behaved as if supplying 1 molecule sodium hydroxide/molecule of borax under these conditions. The water-release capacity of creams was determined by the diffusion of salicylate added to the creams (428). The consistency of emulsions strongly affected water diffusion, with the water-release capacity being much greater from liquid emulsions than from thick creams. A lubricant gel of optimal consistency containing a local anesthetic was formulated which could be sterilized by γ-irradiation (429). The formulation consisted of 1% carbomer gel, neutralized by 2% lidocaine (lignocaine) base, and the biological availability of the local anesthetic was assessed using an *in vitro* method. The degree of dispersion in various types of ointment bases except petrolatum was in direct relation to the release of salicylic acid from the base (430). Increased hydrophilicity of the ointment base improved the release rate. Emulsions containing 7.5% *o*-phenylphenol and the emulsifiers polysorbates, sorbitan esters, and a polyoxyethylene derivative of ricinoleic acid (Cremophor) had only a slight residual disinfectant activity (431). On the other hand, emulsions with natural emulsifiers such as gum arabic retained their activity for 53 days. The penetration of 1% neomycin sulfate through the skin and into the blood of rabbits was enhanced fivefold from a water–oil ointment base containing 30% dimethyl sulfoxide (432).

Bone oil (and the fatty ointment bases prepared from it) had the chief disadvantage of low water absorbability, aggravated by the addition of water-soluble drugs and remedied by the addition of emulsifiers (433). Emulsion ointment bases with the highest water content and the lowest concentration of emulsifying agent were obtained with HLB values of 4.5–5.5. A continuous manufacturing method, including the necessary equipment (434), was discussed for cosmetic creams. Consistencies of petrolatums of different melting points and of liquid–solid paraffin mixtures were determined (435). Suitable consistencies could be obtained by replacement of a part of the petrolatum with mixtures of solid and liquid paraffin to the extent of 12.5–15%. In hydrocarbon ointments, the strength of plastic gels was proportional to the log of the molecular weight of the solid gel phase (436). No such regular relationship could be found for polyethylene glycol gels. The rheological conditions operative during spreading of topical preparations on the skin were determined for a series of aqueous gels and oil-in-water emulsions (437). Where relevant, all results were compared with previously reported work on lipophilic formulations.

Table XIV—Additional References on Ointments and Creams

Reference	Topic
439	Gel stabilization and emulsifying properties of cholesterol under conditions of heat sterilization
440	Evaluation of quality of petrolatum in relation to its composition
441	Emulsion ointment bases using oxyethylated aliphatic alcohols
442	Pharmaceutical ointments utilizing a 5% solution of methylcellulose as a base
443	Formulations for waterproof film-forming preparations
444	Use of bone fats as ingredient in ointment bases and stabilization of them with antioxidants
445	Interactions of anthralin, salicylic acid, and zinc oxide in pastes
446	Analysis of local anesthetic preparations of different basic materials
447	Comparison of different pharmacopeial prescriptions using wool alcohol ointments
448	Optimization experiments for the formulation of wool alcohol ointments
449	Comparative analysis of different polyethylene-type ointment bases
450	Choice of suitable base for ammoniated mercury ointment
451	Granulometric composition of boric acid suspension ointments
452	Preparation of suspension ointments with sodium sulfacetamide
453	Cooling effect of currently used, topical dermatological preparations
454	Physical, chemical, and microbiological methods for evaluating liberation of medicinal substances from ointments
455	Shea butter as base for ointments and creams
456	Mowrah butter as ointment base ingredient

Hersey and Cook (438) stressed the importance of dose, or sample size, and particle size for assuring the homogeneity of suspension-type pharmaceutical ointments.

Other references pertaining to ointments and creams are listed in Table XIV.

Suppositories—The course of melting and resolidification of suppository bases was followed by consequent variations in transparency (457). Extreme and intermediate values of light transmission provided the data for plotting a melting-point transparency curve, by means of which it was possible to control the composition and homogeneity of these and similar pharmaceutical bases. The effects on the uniformity of drug distribution in suppositories and of the addition of lanolin, higher alcohols and their esters, emulsifying wax, polysorbate 80, and polysorbate 60 to various suppository bases were studied (458). The addition of surface-active compound improved uniformity only when it was appropriately matched with the suppository base. The changes, under storage conditions, in breaking strength, disintegration time, and consistency of various suppository bases were studied (459). Quality grades for the characterization of consistency were suggested.

The release of halidor fumarate from suspension-type suppositories of different composition was investigated by *in vitro*, chemical, and biological methods (460). The release rate was increased in all cases by increasing the surfactant added to the base. Salicylate suppositories were prepared using polyethylene glycol 1540 and polyethylene glycol 6000 in various proportions (461). Salicylate release differed markedly for bases composed solely of polyethylene glycol 1540 or 6000; but when suppositories contained a mixture of the two polyethylene glycols, the rate of release approximated that observed for a base composed solely of polyethylene glycol 6000. By applying mathematical methods to the optimization of the processing of medicinals, sedimentation of sodium chloride in suppositories prepared by molding was studied (462). By using mathematical calculations, optimum conditions of preparation could readily be determined. A review of *in vitro* and *in vivo* testing methods for the release of drugs from suppositories was presented (463). Physicochemical properties of various suppository bases, such as wetting characteristics, viscosity, melting time, and melting range, were discussed.

Table XV—Additional References on Suppositories

Reference	Topic
464	Experimental justification of rectal route for administration of doxapram
465	New formulations for suppository bases for tropical use
466	Release and adsorption of amobarbital (barbamyl) from polyethylene glycol base rectal suppositories
467	Hydrogenated peanut oil as fatty base for suppositories
468	Student experiment in preparation and evaluation of suppository formulations

Additional references on suppositories can be found in Table XV.

Aerosols—Reviews in this field included the technology of production and sterilization of aerosols (469), propellants used for aerosols (470), different methods for studying particle size and concentration in aerosols (471), the growth of the aerosol market (472), and a general review of medicinal aerosols (473). In a study to determine the optimum methods for formulation of aerosol emulsion concentrates, the most suitable were obtained by adding aqueous triethanolamine at room temperature to a myristic acid–mineral oil solution at 54.4° (474). A theory to account for the efficiency of this procedure was proposed, which involved the formation of a triethanolamine myristate–myristic acid complex during the initial addition of the aqueous phase. Aerosol foam stability was determined by visual observation of time-dependent changes in foams of different propellant composition (475). Compositions containing both a liquid crystal phase and a liquid phase gave rise to foams with pronounced stability compared with those where only a liquid phase was present.

A multistage liquid impinger was used to determine the particle-size distribution of aerosols generated by several pressurized inhalers containing isoproterenol (isoprenaline) in solution and as a suspension (476). Although suspension-type inhalers delivered aerosols containing much less coarse materials than solution-type inhalers, the use of finely ground powders was not judged sufficient in itself to ensure the absence of coarse material. For evaluation of oral in-

halation aerosols, Karig (477) designed a model lung chamber which was a compartmentalized unit based on certain parameters of the human respiratory tract. A vacuum system was used to regulate the flow rate through the chamber, and it was found to be a suitable device for evaluating medicinal and pharmaceutical aerosol units.

Timed Release—A simple method for the production of drug-impregnated silicone rubber implants for sustained-release drug administration was described (478). The method involved incorporating the drug in unpolymerized silicone rubber, adding a catalyst, and casting the drug–silicone rubber mixture in a hemicylindrical shape in a methacrylate mold. Silicone membranes containing various concentrations of testosterone were prepared by mechanical mixing (479). The amount of testosterone ranged from 5 to 20% by weight, and a definite increase in permeability was observed with an increasing amount of the drug. Low density polyethylene, homogeneously loaded with 2% progesterone and 12% barium sulfate, was tested as a matrix from which to fabricate biochemically active intrauterine devices (480). Progesterone release rates were initially high but reached a constant value of 14 μg/day/cm^2 after the 6th day; the release patterns *in utero* were closely simulated by those in a continuous-flow system and in the rat peritoneal cavity.

The release of pyrimethamine from epoxy resin and silicone disks was compared (481). After 2 months, 32.5% of the totally incorporated drug was released from the silicone disk while the epoxy disk released 16.7%. An investigation of the diffusion rate of chloroquine diphosphate from silicone rubber disks was reported (482). All samples showed high release rates during the first few days, followed by much slower and more or less constant drug release over a period of months. Long-term release studies of antimalarials from polymers and copolymers of lactic and glycolic acids were carried out to evaluate their potential as sustained-release implants (483). In general, the release rate of the drugs was shown to be more strongly dependent on chemical loading of the polymer–chemical matrix than on the type of polymer used in these tests.

A solid dosage form with constant release was developed based on the concept of a constant driving force, a constant diffusion path, and a constant surface for mass transport during drug release (484). Constant release tablets were manufactured by compressing an insoluble, nondisintegrating, and noneroding porous coat onto a soluble substance like potassium chloride, sodium salicylate, or sodium pentobarbital. Boylan and Banker (485) described a physicochemical approach to the preparation of drug-containing matrix systems in which a soluble anionic drug was entrapped, on a molecular scale, in coagulated polymer emulsion systems. The resulting dry product was designed to provide controlled, prolonged release. An investigation was described for the development of a process utilizing suspension polymerization for the production of prolonged-release medicated dosage forms (486). The effect of production variables upon dissolution of acetaminophen from these dosage forms was reported. The relationship between the release rate of cyclazocine from composites of polylactic acid and the molecular weight of the polymer and the form of the composite, as a film sealed in an envelope or as discrete small particles, was investigated (487). Phenobarbital microcapsules and floccules showed that sustained release of the drug, as exhibited by different dissolution rates, ranged from 1.5 to 24 times that of the powder (488). The most pronounced sustained release was demonstrated by floccules where cellulose triacetate was the coating material.

Formulations and procedures were described for the coating of tablets with polymethacrylate films to achieve a time-controlled release of active substances in selected areas of the digestive tract (489). L-Asparaginase was immobilized in semipermeable microcapsules which retained the enzyme and allowed asparagine to diffuse in (490). After intraperitoneal injection in mice, the encapsulated enzyme lowered plasma asparagine levels to zero and maintained that level for 7 days. Due to its biodegradable and noninflammatory nature, collagen was suggested as the ideal material for prolonging drug activity in the eye (491). Estradiol, progesterone, and methyltestosterone were incorporated into 8–10-mm blocks of 10% polyacrylamide (cyanogum-41) gel and implanted in rats (492). The effect of introduced hormones was

Table XVI—Additional References on Timed Release

Reference	Topic
493	Development of sustained-release antispasmodic tablet
494	Development of slow release in potassium chloride tablets
495	Acrylic coatings in controlled-release tablet manufacture
496	Review of biopharmaceutical aspects of sustained-release drugs
497	Methods for producing prolonged effects of drugs
498	Review of oral sustained-release dosage forms
499	Higher fatty acids and their glycerol esters in orally administered medicines with prolonged action
500	Bioavailability of potassium from slow-release tablet
501	Production of long-acting tablets using sugarcane wax
502	Lithium absorption from ordinary and sustained-released tablets
503	Prolonged-release hydrocortisone therapy
504	Polymer coatings for retardation of drug release
505	Effects of formaldehyde vapor and solution on drug release from hardened medicated pellets
506	Sustained-release formulations of tolbutamide
507	Use of ethylcellulose as excipient in slow-release drug preparations
508	Comparison of bioavailability of aminophylline in conventional base and continuous-release base
509	*In vitro* and *in vivo* diffusion of antitumor agent from silicone rubber capsules
510	Coating of pharmaceuticals by phase separation of cellulose derivatives
511	Microencapsulation and flocculation techniques in pharmaceutical formulations
512	Effect of palmitic and lauric acids and their glycerol esters on delayed drug release

noted 3 days after implantation and lasted for at least 33 days.

Additional references pertaining to timed release may be found in Table XVI.

Cosmetics—Microbiological contamination of cosmetic products and its control continue to be subjects of interest to the cosmetic industry. To facilitate a literature search relevant to this critical problem, the subject has been divided into the following subclassifications: microbiological contamination of cosmetics and aspects of formulation and technology of cosmetics.

Microbiological Contamination of Cosmetics—The primary sources of contamination present in cosmetic preparations were found to be makeup water and raw materials (513). Microbial organisms from a city water supply can multiply rapidly in a deionizing column and seed an entire distribution system. Techniques for reducing microbial levels in deionized water systems such as formalin decontamination, recirculation, and point-of-use filtration and the principles of clean system design were discussed. In addition to good manufacturing practices, adequate preservation is necessary together with tests to ensure the adequacies of the preservative used (514). Testing required for quality control must be accurate, simple to perform, and rapid. Goldman (515) described how the aerobic plate count technique fulfills these criteria. The major variables associated with control of microbial growth and antimicrobial action in cosmetics were considered (516). The advantages and disadvantages of approximately a dozen preservatives generally accepted for use in cosmetic preparations were reviewed. Physicochemical techniques allowing quantitative assessment of interactions between preservatives and other formulation ingredients were described (517). A survey of microbiological methods for indicating the practical significance of such interactions was included.

The microbiological quality of a variety of used and unused cosmetics and cosmetic applicators was investigated (518). The incidence of contamination was significantly higher for used cosmetics than for unused cosmetics. Likewise, 100% of the used cosmetic applicators were heavily contaminated, whereas only 27.5% of the unused applicators contained bacteria. A preservative evaluation procedure was described which involved a 13-week incubation using staphylococci and Gram-negative bacteria, fungi, and several microorganisms specific to the manufacturing area (519). Systems difficult to preserve were water-in-oil emulsions containing pigments and high concentrations of nutrient oils and proteins. Stable emulsions containing polysorbates and sorbitan esters increased the effectiveness of water-insoluble antibacterial materials, including essential oils such as thyme (520). Six commercially available ointment products were studied for sterility before and after use in a hospital patient care area (521). Of the partially used tubes, 93% were contaminated whereas 11% of the tubes were contaminated prior to use. A list of preservatives was presented which included quaternary and phenolic compounds, salicylanilides, acids, esters, salts, alcohols, and several miscellaneous compounds; suggested analytical methods were also discussed (522).

Table XVII—Additional References on Microbiological Contamination of Cosmetics

Reference	Topic
523	Microbial content of cosmetics and nonsterile drugs
524	Microbial contamination of cosmetics and toiletries
525	Antimicrobial properties of bay oil and other phenolic essential oils
526	Microbial profile of used eye cosmetics by examination of both applicator and product
527	Microbiological profile of eye cosmetics by examination of product only
528	Triclosan (Irgasan DP 300) activity as preservative in cosmetics
529	Microbiological and physical factors relative to preservatives
530	Discussion of preservation of cosmetic products
531	Antimicrobial contact sensitization in humans

Table XVII lists additional references on microbiological contamination of cosmetics.

Aspects of Formulation and Technology of Cosmetics—The objective evaluation of cosmetic properties on skin can be difficult because of the sensitivity of skin to many variables (532). New techniques were devised to measure the physical components of smoothness and, by using these, a psychophysical equation for skin smoothness was established. Fatty products applied as lipstick base components showed different rheological properties depending on their gel structure (533). Addition of metallic salts increased the viscosity value and thixotropic index. A description of techniques, developed to show that protein treatment of hair fibers results both in deposition on outer surfaces and penetration of the cuticle, was presented (534). While water is recognized as an effective plasticizer of dry skin, cosmetic moisturizers help retain inherent moisture in the skin (535). Thus, the oil bath was shown to be an effective lubrication method for generalized skin dryness.

Toxicological evaluation of cosmetic preparations was discussed in terms of toxicity, irritancy, allergic sensitivity, photosensitivity, and carcinogenicity (536). In each case, techniques and methods of evaluation were presented. The effectiveness of suntan lotions and related skin protective cosmetics was tested by the Jadasson patch test (537). Since many of these lotions are used in athletics and it is possible that some lotion moves with the sweat into the eye, the effect of the lotion on the conjunctival sac had to be investigated. Hematoxylin–eosin-stained paraffin sections of the upper eyelids of rabbits were examined by light microscopy for residual pigmentation and cellular reaction in rabbits killed 1, 7, and 21 days following injection of cosmetic colors into the eyelids (538). Although none of the materials tested was an irritant, it was concluded that a more sensitive test is needed to identify the potential of a color to cause conjunctival pigmentation.

Surfactants present in cosmetic formulations can interact with preservatives, and these interactions

Table XVIII—Additional References on Aspects of Formulation and Technology of Cosmetics

Reference	Topic
548	Evaluation of chemical binders and their effect on pressed powders
549	Use of natural products in cosmetic and toiletry preparations
550	Effect of cosmetic oils in aerosol antiperspirant formulations
551	After-bath powders
552	Bath salts
553	Evaluation of foaming power of bubble bath preparations
554	Review of after-bath emollients
555	Types of bath oils
556	Liquid bubble bath preparations
557	Dry bubble bath formulations
558	Perfuming of bubble bath preparations
559	Monomolecular film bath oils
560	Preparation and stabilization of bath satins
561	Review of bath and body lotions
562	General principles of deodorant soaps
563	Properties of polyacrylamides in cosmetic preparations
564	Chemical aspects of jojoba oil and its application to cosmetic preparations
565	Use of egg oil in cosmetic products
566	Uses of sucrose esters in cosmetic formulations
567	Physical properties of hydrophilic cosmetic oils
568	Deodorant and antiperspirant cosmetic preparations
569	Skin irritancy testing for perfuming agents in cosmetics
570	Use of collagen and gelatin in cosmetic preparations
571	Cosmetic application of vitamins
572	Physical and chemical properties of cosmetics with isostearics
573	Review of cosmetic chemistry advances during 1972
574	Review of fatty materials in cosmetic formulations
575	New allantoin derivatives for cosmetic and dermatological applications
576	Review of gums in drugs, cosmetics, and foods (Part I)
577	Review of gums in drugs, cosmetics, and foods (Part II)
578	Review of composition of hypoallergenic cosmetics
579	Application of extract of *Lithospermi radix* in cosmetics
580	Review of cosmetic oils and fats and their derivatives
581	Galenical and cosmetic aspects of lipstick
582	Physical and chemical characteristics of synthetic triglycerides for pharmaceutical and cosmetic industries
583	Preparation and characteristics of biologically active principles for cosmetic use
584	Use of specialty starch products in treating oily hair
585	Industrial production of cosmetic emulsions in Germany
586	Defatting and fat regeneration of scalp and hair after shampooing with various surfactants
587	Review of hair-coloring agents
588	Review of basic requirements for shampoo preparations
589	Possibilities for improving quality of hair sprays
590	Preparation of cream shampoos from domestic raw materials
591	Review of effects of surfactants on hair (Part I)
592	Review of effects of surfactants on hair (Part II)
593	Review of commonly used perfuming agents for shampoos
594	Survey of raw materials and formulations of shampoos
595	Review of hair-setting lotions and hair sprays
596	New types of hair-setting sprays having semipermanent properties
597	Effects of shampoo on hair, skin, and hair follicles
598	Influence of hormones on hair growth

can reduce or, in some cases, enhance the preservative efficiency. Coates (539) presented guidelines to aid the formulator in choosing preservative and surfactant materials. In the same vein, interactions between preservatives and thickening agents must be considered, and a listing of known reactions was surveyed (540). Crystallization of cetyl alcohol from cosmetic emulsions removed it from the phase interface and caused the emulsion to break (541). This crystallization could be reduced by controlling the concentration of the emulsifier in the formulation. Current theories of autoxidation and antioxidants were reviewed, with special reference to cosmetics and raw materials used in the manufacture of cosmetics (542). The relationship between dispersion of inorganic pigments in water in the presence of surface-active agents and protection of the dispersed pigments from gel formation was discussed (543). A new color-control scale, giving good results in the routine control of high quality cosmetics, was discussed (544).

A major breakthrough in the formulation and processing of soap, which led to a new type of bar soap, was reported (545). Comparisons of its properties with those of opaque and transparent soaps were presented. The active ingredients of hair-setting formulations were discussed and their curl-retention properties were compared (546). The importance of spreading action in hair sprays was discussed from the points of view of the wettability of hair fibers by hair spray solutions and the rate of spreading of such solutions in bundles of hair fibers (547). The rate of spreading was shown to depend mainly on the viscosity of the solution, the rate of evaporation of the solvent, and the rate of increase in viscosity due to evaporation.

Other papers related to aspects of formulation and technology of cosmetics are listed in Table XVIII.

Packaging—A brief review of the historical, chemical, and practical aspects of pharmaceutically useful plastic materials was presented (599). Stability parameters such as temperature and vapor transmission, as related to drug packaging, were discussed (600). The predominant types of sorption found in reactions between dissolved medicinals and plastics were adsorption and absorption (601). General relationships and effects of such factors as plastic material, solvent base, active substance, and various external parameters were detailed. Sorption of leucinocaine, butacaine, tetracaine, oxybucaine, and tetracaine hydrochloride (Farmocaine) in aqueous solutions by polypropylene, polystyrene, polyvinyl chloride, and polycarbonate did not affect stability (602). On the other hand, polyamides and polyethylene

Table XIX—Additional References on Packaging

Reference	Topic
610	Stability of injection solutions in polyethylene containers
611	Normalization of plastics with regard to sorption of drugs from aqueous solutions
612	Protection of pharmaceuticals in solutions against light-induced decomposition by use of amber glass
613	Light transmission of pharmaceutical containers
614	Design of child-resistant closure for glass bottles
615	Review of available child-safe closures
616	Use of blister and strip packaging in child-safety packaging
617	Ethylene oxide gas sterilization of packaging materials
618	Review of progress in industrial pharmaceutical packaging technology
619	Review of modern trends in pharmaceutical packaging
620	Description of new bicompartmental pack
621	Description of legal standards and measuring technique directions for the pharmaceutical industry
622	Packaging and delivery of nitroglycerin tablets with regard to loss of strength

caused a decrease in concentration due to sorption. The influence of two preservatives, benzalkonium chloride and thimerosal, on the adsorption of phenylephrine hydrochloride by polyethylene was investigated (603). The data indicated apparent binding of phenylephrine hydrochloride to low density polyethylene by means of a preservative agent, and their interaction was most significant at room temperature, with elevated temperature disrupting the apparent weak binding. It was reported that solutions of sorbic acid stored in polypropylene, polyvinyl chloride, polyethylene, and glass containers showed significant loss except when refrigerated or when an antioxidant was present (604). A readily consultable table of preservative losses in widely used plastic containers was presented (605).

The effect of temperature, pressure, and velocity of heat sealing on the mechanical strength of a polyethylene seam was studied (606). The strength depended on pressure and was independent of temperature and velocity of sealing. A rationale used to predict which esters can safely be included in anhydrous cosmetic formulations placed in polystyrene containers was illustrated (607). Under consideration were anhydrous products existing as pastes, creams, and molded units at ambient temperatures. The advantages of the unit dose system suggested its application to the packaging of biological products (608). Selection of the particular unit dose system was dependent on the stability and compatibility of the biological with the packaging component. It was reported that roll-feed systems are reaching higher and higher speeds and can offer pharmaceutical manufacturers a high level of product security by instrumental means (609).

Other papers in the area of packaging can be found in Table XIX.

Equipment—Descriptions of the evaluation of various types of automatic ampul and vial inspection devices were presented. Included were the evaluation of the Autoskan equipment (623), the Rota machine (624), and the Strunck machine (625). Washing of ampuls was facilitated and improved by preliminary exposure of the ampuls to ultrasonic waves (626). A modified ampul-washing machine which incorporated an ultrasound generator was described. The determination of particle size in dispersed systems with the Coulter counter, using data processing, was described (627). The quantitative determination of large particles could also be calculated. A review of the theory, techniques, and equipment employed in the laboratory and in the industrial plant for lyophilization of pharmaceuticals was presented (628). Methods of freezing and sublimation, including ideal temperatures for this process, were discussed. A new apparatus, used on an industrial scale for freezing vials to be lyophilized, resulting in a dried mass in the shape of an internal hollow paraboloid with very thin layers, was described (629). Water purification by filtration, distillation, and ion exchange was compared with reverse osmosis (630). The ability of reverse osmosis to produce sterile, pyrogen-free dialysate, in addition to rejecting 95% of all salts and organic compounds with a molecular weight of 200 or more, presented advantages to manufacturers and hospitals.

A model lung chamber was designed for the evaluation of oral inhalation aerosols (631). The chamber was a compartmentalized unit based on certain parameters of the human respiratory tract and a vacuum system was used to regulate the flow rate through the chamber. Solutions of varying strengths of isoproterenol hydrochloride and phenylephrine hydrochloride, aerosolized using several common aerosol devices, demonstrated the model lung chamber to be a suitable device for evaluating medicinal and

Table XX—Additional References on Equipment

Reference	Topic
635	Description of equipment for eliminating introduction of air during mixing operations
636	Description of weighing control procedures in automatic cosmetic manufacturing systems
637	Description of in-line continuous mixing and processing operation for cosmetic products
638	Use of foam heat-exchange apparatus in ampul production
639	Evaluation of Marzocchi ampul-filling machine
640	Description of improved machine design for stopper washing
641	Use of compulsion gauges in automatic selection of tablets
642	Review of available methods for automatic control of tablet weight
643	Instrumentation for evaluation of dustiness of tableting materials
644	Review of various capsule-filling machines
645	Pilot size equipment available for pharmaceutical plants
646	Use of rotor-pulsation apparatus for preparing disperse drugs
647	Description of apparatus based on pulsating air currents for drying granulates of pharmaceutical preparations
648	Description of new powder proportioner for pharmacy use
649	Particle-size measurements using πMC computer for particle counting and measurement

pharmaceutical aerosol units. A Zanasi LZ/64 capsule-filling machine was instrumented with strain gauges and fitted to a modified dosator piston which had been calibrated with a loaded beam (632). Three main regions could be distinguished on the oscillograph: a force representing compression of powder into the dosator, a retention force carryover of the plug to the capsule body, and an ejection force as the plug is ejected into the capsule. Goodhart *et al.* (633) presented a study to determine the relative merits of various tablet hardness testers now being used. From the results obtained, it was apparent that there are distinct advantages to using a hardness tester with a mechanical drive rather than a pneumatic type because more uniform force application rates may be achieved and there is less maintenance work and less need for calibration checks. A study was conducted to design and build a laboratory extruder and to evaluate various factors relating to its use for the preparation of both wet and hot fusion granulations (634). Data were reported on torque, powder throughput, liquid required, and attainment of uniform consistency.

Additional references on equipment can be found in Table XX.

PHYSICAL PHARMACY

Two crystalline modifications of meprobamate were prepared (650) and each crystalline modification was identified by melting point, X-ray diffraction pattern, and IR spectra. In contact with water, the metastable phase underwent reversion to the stable phase. Different thermodynamic properties, *e.g.*, heats of fusion, heats of solution, enthalpy, entropy, and free energy difference and transition temperature, were also determined. Two polymorphic forms of tolbutamide were identified by IR spectroscopy, X-ray diffraction, and differential thermal analysis. Both crystalline modifications had similar dissolution rates in distilled water and simulated intestinal fluid; when given to fasting beagles, there was no difference in their absorption rates (651).

Of seven different sulfonamides, sulfamethoxypyridazine, sulfacetamide, sulfathiazole, and sulfaguanidine were identified as existing in different polymorphic forms (652). In work with labile triazinoindoles, two aqueous topical suspensions in fine particles were prepared (653). Upon aging, both suspensions produced crystal growth, even when protective colloid methylcellulose was added. These crystals were found to be monohydrates of the respective triazinoindoles and they readily lost water of hydration under mild heat. Both hydrates could be air milled with no water loss. One hydrate was formulated in the suspension form and found to be free of crystal growth for 2 years.

The dehydration kinetics of theophylline monohydrate transformation directly to a crystalline anhydrous form, with apparent zero-order kinetics, were studied as well as the dehydration kinetics of ampicillin trihydrate transformation to an amorphous state (654). Micronized ampicillin trihydrate, which is commercially available, contained small amounts of excipients and, as a result, exhibited a different kinetic order and a faster rate of transformation. The thermal dehydration of cortisone acetate was studied using IR spectroscopy (655); the unstable monohydrate phase changed to anhydrous Forms B, C, and D. The kinetics of interconversion of sulfameter (sulfamethoxydiazine) crystalline phases and the effect of various additives on the rate of transformation of the more energetic sulfameter phase to the water-stable phase in the aqueous suspensions were studied using representative structurally related compounds, viscosity-imparting agents, surfactants, and coloring agents to inhibit this transformation (656, 657). Significant transformation-retarding effects were observed in most cases. The effects varied from slight retardation to almost complete inhibition of the transformation for more than 1 year (*e.g.*, using 1% polyvinylpyrrolidone).

The anomalous behavior of oxyclozanide polymorphs was studied, and three polymorphs were identified using X-ray powder diffraction (658). The different polymorphic phases exhibited variable behavior both toward aqueous solubility and stability in suspension in terms of phase transformation and crystal growth. The polymorphism of aspirin was studied (659), and the two polymorphic phases previously recommended were prepared. X-ray diffraction analysis showed both forms to be monoclinic and could not identify any polymorphic differences. The dissolution rates of Forms I and II were within tolerance and depended upon the different crystal surface. This effect was also responsible for the different heats of solution. The electronic scan microscope clearly showed the different surfaces of Forms I and II. The saturation solubility and the dissolution rate of sulfathiourea were determined (660). Only two of the varieties on the market were suitable for solubility investigations. The two crystalline phases were enantiotropic and possessed identical solubilities at 24°, but the variety with the lower melting point was 14% more soluble at 50° than the variety with the higher melting point.

By using differential scanning colorimetry, the properties of two metastable phases of chloramphenicol palmitate, the δ-form and the sub-α-form, and the occurrence of the sub-$\dot{\alpha}$-form during the manufacture of chloramphenicol palmitate oral suspension were clarified (661). The pharmaceutical application of inclusion compounds was reviewed (662) in which the actions of urea, thiourea, deoxycholic acid, cyclodextrin, and perhydrotriphenylene were covered. In a study of the formation of a mesomorphic (liquid crystalline) system by highly concentrated solutions of dioctyl sodium sulfosuccinate in an homologous series of five even-numbered chain length *n*-aliphatic hydrocarbon solvents, dioctyl sodium sulfosuccinate concentration, solvent chain length, and temperature significantly affected the formation of the mesomorphic phase (663). At constant temperature, the concentration of dioctyl sodium sulfosuccinate required to produce a mesomorphic phase increased as the solvent chain length increased from octane to dodecane and decreased to hexadecane.

The mutual diffusion coefficient, D_v, for the binary

solution of sucrose in water at 23 points over the concentration range of 9–300 kg/m^3 at 298°K was measured (664). Experiments with the concentrated solutions showed that for a given concentration the areas of the fringe deviation graphs varied with the initial concentration difference, $\Delta\rho$; but since D_v did not vary with $(\Delta\rho)^2$, the diffusion coefficient was not "concentration dependent." The capillary method was used to determine the diffusive transport properties of radioactive salicylate ion in the presence of a commonly used polyelectrolyte, sodium carboxymethylcellulose (665). In a solution of this polymer, the self-diffusion coefficient of salicylate decreased only moderately, even though the bulk macroscopic viscosity increased to about 2–3 orders of magnitude. These data were evaluated with two theories from the literature. The tracer drug release rate out of the polymer solutions was also studied and was more rapid than if the polymer were not present. Increases of up to 40% were observed. The equilibrium dialysis of salicylic acid from solutions of polysorbate 20 and 80 was studied, simulating the system using an analog computer (666). Rate constants for the partition of salicylic acid out of polysorbate micelles into water were obtained by fitting computer-generated curves to experimentally determined data. The release of salicylic acid from polysorbate micelles was independent of surfactant concentration but dependent on the micelle–aqueous partition ratio of salicylic acid and its concentration in the donor and recipient cells.

In a series of experiments, the diffusion rate of the encapsulated drug was a function of microcapsule size (667). The influence of the coating upon diffusion and the determination of the thickness of the different coatings were also included. An equation was developed and was verified by microscopic measurements of microspheres previously sliced with a microtome. Four microencapsulation and three flocculation techniques were investigated using phenobarbital as the model drug; gelatin, sodium alginate, and sodium carboxymethylcellulose as water-soluble coating materials; and ethylcellulose and cellulose triacetate as water-insoluble coating materials (668). The amount of phenobarbital bound to the product was determined quantitatively, and the coating–core ratio of each product was calculated. Microcapsules of phenacetin were prepared by coacervation of aqueous cellulose acetate phthalate solutions (669). Appropriate solutions were made by dissolving cellulose acetate phthalate in an equivalent concentration of disodium hydrogen phosphate. A triangular phase diagram of a coacervation system was elaborated by using sodium sulfate as the coacervating agent, and the coacervation and encapsulation conditions were optimized. The amount of drug encapsulated had no significant effect on particle-size distribution of the capsules; however, it did influence the release rates of the drug, indicating that the drug diffusion through the shells was the controlling step.

By modifying gelatin, which is a proven packaging material because its protection to small particles permits controlled release, it was possible to relate the type of capsule wall material to the chemistry of the phase to be encapsulated (670). The consumption of glutaraldehyde by various acid- and alkali-precursor gelatin–gum arabic coacervate gels over a range of conditions was studied (671), and glutaraldehyde consumption by several gelatin gels was determined. All gels consumed 0.3–1.6 mmoles glutaraldehyde/g gelatin. Acid and alkali gelatin–gum arabic gels had similar glutaraldehyde uptakes at 4°. Glutaraldehyde consumption by acid-precursor gelatin–gum arabic gels increased significantly with increasing gelation temperature (4–28°) due to the temperature-dependent changes in the gel structure. Microencapsulation of various specific pharmaceuticals was reviewed by several authors, with special emphasis on coacervation (672–674).

In the microbiological determination of drug partitioning, the functional dependence of the partition coefficient on the drug concentration and also partition coefficient profiles of several antimicrobial drugs were developed (675, 676). The usefulness of this method was demonstrated by comparing the partition coefficients of the same antimicrobial drugs obtained with traditional chemical analysis. By using literature data, the contribution of hydroxyl and carboxyl groups to solute activity and partition coefficients was investigated (677). Both polar functions

Table XXI—Additional References on Physical Pharmacy

Reference	Topic
678	Physical constants and purity profiles of 115 drug substances
679	Physicochemical properties of prostaglandin $F_{2\alpha}$
680	Physicochemical properties of chloral hydrate
681	Physicochemical properties of clidinium bromide
682	Physicochemical properties of dexamethasone
683	Physicochemical properties of dioctyl sodium sulfosuccinate
684	Physicochemical properties of 5-fluorouracil
685	Physicochemical properties of isopropamide
686	Physicochemical properties of levallorphan tartrate
687	Physicochemical properties of sulfamethoxazole
688	Diffuse reflectance, its quantitative application to acetaminophen (*N*-acetyl-*p*-aminophenol) excipient-induced degradation
689	Current aspects of pharmaceutics
690	Review of lipophilic character and biological activity of drugs (the parabolic case)
691	Review of water-soluble cellulose derivatives
692	Surface diffusion in monomolecular films
693	Kinetics of degradation of crystalline networks of aspirin and aminopyrine (aminophenazone) associated in a solid phase
694	Differential thermal analysis and X-ray diffraction studies of griseofulvin–succinic acid solid dispersions
695	Physical properties of cholesterol and cholesteryl esters
696	Coacervate formation by sodium salicylate with benzalkonium chloride
697	Effect of hydroxy group on coacervate formation by sodium hydroxybenzoates with benzalkonium chloride
698	Distribution and selectivity coefficients at optimum pH values of buffers
699	Misconceptions and thermodynamic untenability of deviations from pH–partition hypothesis

gave rise to reduced activity coefficients for aromatic solutes in water, and differences existed between ring and α-substitution. Partition coefficients were similarly affected, but the magnitude of the group contribution to the free energy of transfer was dependent on the nature of the solute and the organic partition solvent.

Additional references relating to physical pharmacy are listed in Table XXI.

Dissolution—The dissolution kinetics of gallstones based on four different models were developed (700). One model was based upon simple diffusion-controlled dissolution and another upon a leaching process. The remaining two models related to interfacial coat-type barriers. Calculations were carried out employing models with reasonable input parameters. The theoretical dissolution rate based on a simple dissolution model would predict that a 2.5-mm stone should dissolve in several days into an undersaturated bile solution. Both clinical and *in vitro* experiments showed that much longer times were needed. Experiments were designed for investigating and comparing the *in vitro* dissolution kinetics of human cholesterol gallstones and cholesterol monohydrate compressed pellets (701), and the rates of gallstone dissolution compared well with the dissolution rate obtained with the cholesterol monohydrate pellets in the solvents investigated. The dissolution rates for both stones and pellets in organic aqueous solvents were extremely rapid and were diffusion-controlled processes. In a sodium cholate solution, the dissolution rates were two to three times slower than rates predicted by diffusion theory; the data generated suggested a modest interfacial resistance to dissolution. The rates obtained in 2% bile acid–1% lecithin solutions were about 17 times slower than diffusion-controlled processes. These results point to an interfacial barrier to dissolution which may be very important clinically.

By using dextrose, galactose, and sucrose, glass dispersions were developed with corticosteroids, and by using mannitol, partial solid solutions were prepared (702). The results, using the NF XIII dissolution method, revealed a marked increase in the rate of dissolution of the corticosteroids contained in a solid dispersion when compared to the dissolution rate of the plain corticosteroid powder. The increase in the dissolution rates was attributed to: *(a)* the presence of the corticosteroid in a very fine state of subdivision, *(b)* the increased wettability of the corticosteroid powder, and *(c)* the molecular dispersion of the drug in the partial solid solution. In work on the dissolution behavior of solid drugs, a method was developed for determining the transition temperature between two polymorphs and between the hydrate and anhydrous phases of drugs by measuring the initial dissolution rates (703, 704). An equation was derived describing the dissolution of monodisperse particles beyond the point where concentrations are small compared to solubility. If it was assumed that a stagnant layer model applied, the thickness of these layers was of the same order of magnitude as calculated *via* the Hixson–Crowell treatment but dissolution rate constants were 1.5–2 times as large. The application of the equation to the dissolution of hydrocortisone, levodopa, and *p*-hydroxybenzoic acid was shown (705). The equilibrium solubility and dissolution rate of sulfamethazine were remarkably inhibited in the presence of benzoic acid (706). The effect was dependent on the concentration of both benzoic acid and sulfamethazine in the system. The inhibition of sulfamethazine dissolution was synchronous with the adsorption of the benzoic acid on the sulfonamide particles. As low as 5 mg % polyvinylpyrrolidone prevented the adsorption of the benzoic acid on sulfamethazine and, consequently, the suppressive effect of benzoic acid on sulfamethazine dissolution was no longer shown.

A eutectic mixture of phenobarbital and urea was prepared and its dissolution and absorption were compared with those of pure phenobarbital (707). The drug in eutectic form had faster dissolution and absorption rates than in pure material. The factors involved in the growth and dissolution of crystals were reviewed, with special emphasis on the pharmaceutical and biological implications of these phenomena (708).

Correlation of the dissolution rate of digoxin tablets and their bioavailability was discussed by several investigators who found that there were wide dissolution rate differences between lots from different companies and between different lots from the same company (709–712). It was recommended that a minimal acceptable level of dissolution rate be established for commercial digoxin tablets. Fresh samples of 11 brands of prednisone tablets were tested for dissolution time, hardness, and disintegration time (713). Four samples failed to comply with the USP XVIII monograph requirement for prednisone tablets and a fifth sample was very doubtful. There was no correlation between tablet hardness, dissolution rate, and disintegration. The dissolution method gave consistent results with deaerated water only. Rank-order correlations were demonstrated among dissolution, disintegration, and several measures of bioavailability for tablets of aminosalicylic acid and its salts (714). The correlation between the disintegration time and the percent of the dose excreted in the urine was examined quantitatively using both linear and quadratic models. The results supported the use of either the disintegration or the dissolution test to control the availability of this drug and suggested control limits for these tests.

With the USP dissolution apparatus, the times required for 60% release of the active ingredient in two clinically different brands of chlorpromazine hydrochloride tablets were 5.7 and 35.4 min (715). The data obtained for these two products indicated that, if the apparatus was carefully standardized, the USP method yielded reproducible results. However, mesh size of basket, depth of the basket-stirrer assembly in the dissolution container, and stirrer speed alter the dissolution profiles. The effect of 5 years of storage on dissolution of two different sodium salicylate tablets was investigated (716). The first tablet was manufactured with gelatin and the second one with polyethylene glycol 4000 as binders. The effect of storage was most noticeable in the dissolution of tab-

Table XXII—Additional References on Dissolution

Reference	Topic	Reference	Topic
729	Classification of dissolution tests on basis of their hydrodynamics	742	Evaluation of effective surface areas of micronized powders from dissolution rate measurements
730	Disintegration and dissolution tests for dextran sulfate sodium tablets	743	Practical significance of dissolution rate determinations
731	Dissolution–dialysis method of assessing *in vitro* drug availability of prednisolone tablets	744	Effects of various hydrodynamic conditions on dissolution rate determinations
732	Dissolution and solubility of triamcinolone acetonide	745	Experimental verification of solid–liquid interfacial concentration developed during interfacially controlled dissolution of a solid
733	Dissolution rates of cholesterol monohydrate crystals and human cholesterol gallstones in bile acid–lecithin solutions, and the enhancing effect of added alkyl quaternary ammonium salts	746	Review of dissolution rates of slightly water-soluble drugs
		747	Review of physical and chemical factors affecting dissolution rate of drugs
734	Effect of formulation on dissolution of sodium warfarin tablets	748	Dissolution properties of poly(alkyl vinyl ether–maleic anhydrides) and partial ester derivatives
735	Dissolution studies on sulfameter (sulfamethoxydiazine) formulations	749	Influence of micelle–drug solubilization on dissolution rates
736	*In vitro* determination of dissolution rates of oxytetracycline tablets and interlaboratory comparison of USP XVIII method, beaker method with propeller, and beaker method with magnetic stirring	750	Dissolution rate as parameter in structure–activity studies
		751	Dissolution tests and interpretation of anomalies observed in dissolution process of sulfoquinoxaline based on salt formation
737	*In vitro* determination of dissolution rates of tablets, and interlaboratory comparison of USP XVIII method with two other methods using 15 batches of tablets of eight different brands	752	*In vitro* dissolution of solid pharmaceuticals for oral administration
		753	Dissolution profile of log-normal powders, exact expression
738	Compendial dissolution characteristics of commercial formulations	754	Importance of considering variables when using magnetic basket dissolution apparatus
739	Effect of solvent flow on dissolution rate of nondisintegrating potassium chloride disk	755	Prediction of dissolution rates of slightly water-soluble drugs questioned
740	Effect of dissolution medium and moisture content of powder on dissolution of chloramphenicol capsules	756	Comparative analysis of solution rate of active ingredients from tablets, using USP and Becherglas methods
741	Improvement and simplification of dissolution rate measurement and its application to solubility determinations	757	Preservative release from creams and emulsions, dissolution method

lets containing gelatin. This result may be due to changes in tablet structure during storage because the content of sodium salicylate in the tablet was not changed. The storage had the least effect on tablets containing polyethylene glycol 4000.

The *in vitro* release rates of potassium ions from slow-release potassium chloride tablets from 12 sources were investigated (717). Dissolution rates were determined using a modified nonsink method and a modified sink method. Medicament release in both methods was continuously monitored using a potassium-ion specific electrode. The release rate constants were derived and the applicability of the Noyes–Whitney equation, the Hixson–Crowell cube root law, and Higuchi's equation was studied. The most satisfactory products appeared to be those prepared from a fat-wax potassium chloride matrix, an insoluble wax coat on a nondisintegrating wax core, and a combination of potassium chloride, cellulose acetate phthalate, ethylcellulose, and polyethylene glycol.

Haringer *et al.* (718) compared the dissolution of tablets using the official USP–NF rotating basket, the bent basket, and the newly designed L-shaped Teflon holder–stirrer. In these studies, the latter two devices were superior to the official device. A rotating filter–stationary basket *in vitro* dissolution test apparatus was designed and evaluated (719). The major advantages of this apparatus were suggested to be: *(a)* precision-controlled variable intensity of mild laminar liquid agitation; *(b)* continuous or intermittent filtration of representative dissolution fluid samples through a nonclogging filter; *(c)* convenient means for introducing solid samples in a stationary basket and positioning at a set level in the fluid medium; *(d)* minimal mechanical impacts, abrasion, and wear of the solid samples; and *(e)* simultaneous determinations of the disintegration–dissolution rates of tablets and capsules. Dissolution rates of five different lots of an antidiabetic tablet were evaluated by the new apparatus and correlated with *in vivo* activity.

In experiments comparing the accuracy of four dissolution models, using aspirin and prednisone tablets, the modified Levy beaker method was the most accurate at relatively low agitation frequencies as encountered *in vivo* after oral administration (720). Several different formulations of pentobarbituric acid tablets were manufactured and were used to illustrate the ability of the magnetic basket dissolution apparatus to differentiate between the dissolution of tablets with differences in particle size of active ingredients, in formulation, and in hardness (721). An *in vitro* technique for testing the disintegration and dissolution of tablets and capsules was developed (722). The apparatus consisted of a beaker with a cylindrical well in the bottom into which is placed a platform containing the dosage form. Comparison between the official and the new method indicated that the official test does not differentiate

between capsule formulations containing hydrophobic lubricants. The effects of capsule formulation factors such as type and level of lubricant and disintegrant, as well as the presence of surfactants, were also determined. The disintegration and dissolution of tablets containing starch, alginic acid, sodium starch glycolate, and two types of calcium sodium alginate were studied (723). The dissolution times were determined with both the beaker and the basket methods. The results indicated that when tablets contain adhesive substances, such as the alginates, an adhesive gel is formed which tends to block the basket pores. It was recommended that great care should be taken when estimating the dissolution of tablets containing such substances; for these products, there are probably advantages in the use of the beaker-type apparatus.

The rate of solution of potassium chloride and sodium chloride from compressed disks was determined under controlled conditions in water at 25° in solutions of varying concentrations of polyvinylpyrrolidone, polyethylene glycol 6000, and cetomacrogol 1000 (724). As expected, dissolution rate constants decreased with increasing bulk solution viscosity, but no one equation relating the rate constant and bulk viscosity fitted the results for the systems studied. In studies on dissolution rates, the effect of flow rates using a continuous-flow, column-type apparatus was determined (725, 726). The flow method of agitation was compared to three other types used with the static beaker procedure. The advantages of the column-type apparatus in obtaining low intensity of agitation without sacrificing accuracy and homogeneity were discussed. The solvent flow patterns in the column-type apparatus also were determined by using a flow visualization technique. A supporting bed of glass spheres in the dissolution chamber ensured laminar flow, and this method was preferred over the complex, poorly defined flow found with static beaker methods.

The data available on the influence of fluid motion in dissolution rate determinations and the knowledge regarding GI motion were reviewed (727). The use of a continuous flowing-stream apparatus to follow tablet dissolution was studied (728). A dissolution chamber with a commercially available filter unit was designed to follow tablet dissolution through use of either a sodium-ion electrode or a spectrophotometric analytical module. The effect of variation of flow rate on the dissolution profile and the ability of the apparatus to differentiate between the common tablet parameters of hardness and drug potency were also shown.

Table XXII lists additional references on dissolution.

Solubility-Solubilization Phenomena—The solubility of chloramphenicol palmitate in propylene glycol-water systems was determined (758). The solubility was 0.004 mg/ml in pure water and 4.95 mg/ml in pure propylene glycol. Additions of propylene glycol to water did not significantly alter the water solubility of the drug until about 60% (w/w) was added. Then the solubility increased logarithmically in a manner approximately proportional to the propylene glycol concentration of the system. By using available data on the dielectric constants of these solvents, the solubility parameter for chloramphenicol palmitate was calculated to be 11.8. The aqueous solubility of cholesterol, testosterone, progesterone, and diethylstilbestrol at 30° was reported using a radioactive assay procedure (759). The solubility of platyphylline, seneciphylline, and their hydrogen tartrates was determined for 19 solvents at 20° and at the solvent boiling temperatures (760). Mayer and Kata (761) developed a method for determining the solubility of substances in ointment and suppository bases; the drug is added to the base and stirred for 1 hr at 37°, the undissolved portion is separated with a membrane filter, and solubility is then determined.

The solubilization of several pairs of preservatives by the nonionic surfactant cetomacrogol was reported (762). In all cases the addition of a second preservative altered the equilibrium of the first to an extent that depended on a particular cosolute and the concentration added. The tetramethyl-substituted amides of pimelamide, suberamide, and sebacamide markedly enhanced the solubility of glutethimide in a solution (763). Partition studies, surface tension measurements, and light-scattering measurements strongly suggested that the amides are associated at infinitely dilute concentrations and that further aggregation of these associated molecules occurred with the possible formation of micelles at concentrations slightly higher than those observed for surfactants. Solubility of glutethimide was increased significantly above the CMC and, from the nature of the solubility curve, a micellar type of solubilization appeared to be dominant.

Solubilization of khellin by caffeine was reported, where the solubilizing effect was attributed to complex formation (764). The degree of solubilization of heptane, toluene, and heptanol by nonionic-ionic surfactant mixtures (sodium oleate and alfapol) depended on the degree of ethoxylation and the hydrophilic properties of the alkylphenol (765). Investigations of the solubilization behavior of mixed micelles of the nonionic surfactant polyethylene glycol, monododecyl ether, and anionic surfactants, *e.g.*, phenylalkanesulfonates, or alkylbenzenesulfonates toward a water-insoluble dye showed that the position of the benzene ring in the hydrocarbon chain of the anionic surfactant significantly affected the dye solubility (766).

Table XXIII—Additional References on Solubility-Solubilization Phenomena

Reference	Topic
767	HLB and molecular size as factors in increasing mutual solubility of oil and water by solubilizers
768	Solubilization efficiency of surfactants
769	Solubilization properties of nonionic surfactants
770	Content of free surfactant in aqueous phase of the aqueous emulsifying ointment DAB 7 and its solubilizing effect on pharmaceuticals

Other papers in the area of solubility–solubilization phenomena are listed in Table XXIII.

Membrane Permeation and Release—A transport cell was designed for examining *in vitro* solute transfer across biological membranes (771). When using the intestine as a model membrane, a primary advantage of the method was that there was no need to evert the intestine. This eliminated the influence of eversion on the structural and functional integrity of the intestine and thus its possible influence on solute transfer. Preliminary studies using salicylamide were performed to quantitate various parameters of the apparatus. A structure–activity model based on diffusional theories was developed, where the ability of each member of the biologically active homologous series to reach the receptor site was equated with the relative ability to permeate the biological barriers (772). The equations are generally applicable for transport across membranes and can be of use in describing a variety of passive absorption or permeation phenomena.

In the 1–5 pH range, a linear relationship was found between the rate constant for salicylic acid transfer across a cellophane membrane and the fraction of ionized drug present at different pH's (773). The rate constant for ionized molecules was about 60% of that for unionized molecules. The presence of polysorbates 20 and 80 in a drug solution markedly decreased the apparent transfer rate constant of salicylic acid at low pH. The effect of various substances on amobarbital permeation through polydimethylsiloxane membranes was studied (774). The rate of drug transfer across the membrane depended on the pH because only the unionized species were eligible for transfer.

The simultaneous dissolution and permeation of a drug from solid oral dosage forms were analyzed by a treatment based on Fick's second law of diffusion (775). The dissolution rate constants were obtained from the permeation lag time, while the coefficients of permeability were estimated from the rate of drug transfer across the membrane under steady-state conditions. Drug–excipient interactions, if any, would be expected to affect the rate of transfer across the membrane. Therefore, from a single experiment, the dissolution rate and the extent of drug and excipient interaction could be obtained. The permeability of cellophane membranes to the nonionic surfactant cetomacrogol 1000 was investigated using equilibrium dialysis, dynamic dialysis, and an ultrafiltration technique; cellophane and silicone rubber membranes also were compared in an equilibrium dialysis study of the interaction of chlorocresol with cetomacrogol (776). The permeability and interaction studies showed that the cellophane membranes were permeable to the surfactant.

The transport of solute into and through a heterogeneous system involving interfacial barriers was theoretically investigated (777). The system consisted of a "donor" bulk aqueous phase, the aqueous diffusion layer, and a matrix in which oil droplets of uniform size were dispersed. The theoretical method employed accounted quantitatively for the barriers existing at the oil droplet–water interface, and the technique had general applicability to all situations involving a heterogeneous medium in which the local interface equilibrium was achieved slowly.

The effect of six commercial nonionic surfactants on thioridazine absorption in goldfish was compared to the effect of polysorbate 80 (778). The index of absorption rate used was the reciprocal death time when the fish were immersed in the solution under study. Three of the surfactants tested had no effect below their CMC; the remaining three surfactants increased the reciprocal death time with a biphasic response. The factor determining whether the surfactant increases the absorption rate appeared to be the configuration of the surfactant molecule rather than the HLB or surface activity.

The transport of 3-*O*-methyl-D-glucose in liposome dispersions prepared from lecithin–dicetyl phosphate (10:1) and lecithin–dicetyl phosphate–cholesterol (10:1:1) was studied (779). The transport results with 3-*O*-methyl-D-glucose yielded a permeability coefficient 50 times larger than that for D-glucose. The dispersions prepared from lecithin–dicetyl phosphate containing 10% cholesterol yielded a permeability coefficient that was 2.4 times smaller than the dispersions prepared without cholesterol. The analysis of the results indicated that for relatively large permeability coefficients, as obtained in these studies, the dilution–release experiments showed greater sensitivity in the determination of this parameter compared to the direct release experiments. The transport of taurocholic acid-[cholic-^{3}H(G)] was studied in liposome dispersions prepared from lecithin–dicetyl phosphate in buffered glucose solutions at different pH's (780). The pH dependence of the permeability coefficient from the study indicated that the unionized form of taurocholic acid was preferentially transported at low pH and that the taurocholate ion was the main species involved at high pH.

The release of sulfathiazole from different ointment bases was studied (781, 782), and the effect of polysorbate 80 and sorbitan monostearate on the release of sulfathiazole from bases containing either lard or petrolatum was determined. The gelatin plate, chromatography, and dialysis test were adopted and used under identical conditions for evaluations of release of drugs from ointment bases. The release rate of drugs was found to be dependent on: *(a)* the composition of the ointment base, *(b)* the concentration of the drug, and *(c)* the composition of the diffusion medium (783). The influence of five types of ointment bases on the release of tetracycline hydrochloride, chlortetracycline (biomycin) hydrochloride, chlornitromycin, and erythromycin base was studied (784). There was a difference in the degree of the *in vitro* release of the active substances from the various ointment bases studied. Under the same experimental conditions, various concentrations of hyaluronidase did not particularly influence the degree of release of the various antibiotics.

The effect of surfactant concentration on drug release from ointment bases was studied, and the concentration of nonionic surfactants between 0.05 and 0.10% gave the optimum release (785). The suitabili-

Table XXIV—Additional References on Membrane Permeation and Release

Reference	Topic
788	Systems approach to study of drug transport across membranes using suspension cultures of mammalian cells
789	Effects of membrane materials and viscosity of aqueous phase on permeability of polyamide microcapsules toward electrolytes
790	Permeation behavior of surfactant solutions through cellulose acetate membranes
791	Prediction of permeation rates and potential usefulness of polyethylene as *in vitro* membrane for drug availability prediction
792	Release of water-soluble and water-insoluble active drugs from anhydrous lipid ointment bases
793	Review of drug release from ointments and drug penetration through skin
794	Review of release and absorption of medicinal substances from ointment bases, and factors affecting therapeutic effectiveness of ointment
795	Dynamics of drug release from ointment bases, and influence of dimethyl sulfoxide on release of salicylic acid
796	*In vitro* release of an amine salified by a water-soluble polyelectrolyte, and factors influencing the release rate
797	*In vitro* release of an amine salified by a hydrosoluble polyelectrolyte, and comparison with other types of gels and consideration of the mechanism of release
798	Release of nystatin from ointment bases

ty of several water-soluble and oleaginous ointment bases for use with sodium sulfacetamide and sulfanilamide was studied (786). A formulation containing 5% sodium sulfacetamide in a base comprised of 60% polyethylene glycol 400 and 40% polyethylene glycol 4000 gave the best release of the drug and the highest antibacterial effect. The addition of polysorbate 80 had no significant effect. The water-soluble sulfonamide was released more efficiently than the water-insoluble sulfonamide. Oleaginous bases were less satisfactory.

New polymers in drug delivery were studied (787). Pilocarpine in 0.3, 1.0, and 3.0% solutions was absorbed by disks of a hydrophilic plastic of the sort used in soft contact lenses. The *in vitro* release of the active drug was compared with *in vivo* contact lenses which were fitted to rabbits whose pupil dilation responses were measured as a response to the amount of drug released. As control experiments, rabbits were given drugs topically in the usual manner. The results showed that pilocarpine can be administered in a hydrophilic plastic which takes it up and that the prolongation of release gives a mode of treatment that is as effective as a series of topical installations.

Additional references on membrane permeation and release are listed in Table XXIV.

Complexation—Studies related to complexation phenomena are categorized into: *(a)* interactions of drugs with biological substances, and *(b)* interactions of drugs with nonbiological substances.

Interactions of Drugs with Biological Substances—The binding of antibiotics to bovine plasma protein was studied by an ultrafiltration technique at 4° (799). The binding rate decreased in the order: tetracyclines > macrolides > chloramphenicols > penicillins > glycosides. Gentamicin did not bind to bovine plasma proteins. Tetracycline had the highest recovery rate, whereas aminodeoxykanamycin had the highest binding activity rate. The optimum pH for binding was 5–8. The binding of demeclocycline and oxytetracycline to bovine serum albumin was studied using fluorescent methods (800) and was shown to be hydrophobic. Two strong binding sites, at or near the tryptophan residues of bovine serum albumin, were found for both tetracyclines. The equilibrium constants for tetracyclines increased with increasing protein concentration, and the number of binding sites on the protein decreased with increasing protein concentration. This finding suggested the possibility of the sharing of one tetracycline molecule by more than one protein molecule at relatively high protein concentrations. The same investigators also calculated the equilibrium constants and the number of binding sites for the binding of 1-anilinonaphthalene-8-sulfonate to human and bovine serum albumins, using the fluorescent method and an equation derived from the Scatchard multiple-equilibrium treatment (801). They compared the results and the equations with other equations used in protein binding studies. Treatment of data by this modified method showed a clear determination of the number of binding sites.

By using *in vitro* experiments with eye fluids and tissues as well as *in vivo* studies in rabbits, the concept of competitive inhibition as a means of significantly improving drug bioavailability was supported (802). Pilocarpine nitrate, a miotic drug with low binding affinity for albumin, had a 10-fold increase in biological activity in the presence of the competitive inhibitor cetylpyridinium chloride. An ultrafiltration method was devised for determining binding constants for some common antibiotics to plasma proteins (803). For penicillin derivatives, the binding decreased in the order: dicloxacillin > cloxacillin > oxacillin > penicillin G > carbenicillin > meticillin > ampicillin. The degree of binding of 37 antibiotics to bovine and ovine serums, after treatment with therapeutic doses, was determined by equilibrium dialysis and ultrafiltration (804). The extent of binding varied from 3% for cephalosporin and kanamycin to greater than 95% for novobiocin and fusidic acid. The capacity of bovine and ovine serums to bind antibiotics was similar to the reported capacity of human serum.

The interaction of L-(1-^{3}H)-methadone with solution of purified human γ-globulin and human plasma was studied by equilibrium dialysis (805). The percent of methadone bound to γ-globulin was dependent on drug and protein concentrations. Serum protein binding determinations for erythromycin, lincomycin, and clindamycin utilizing ultrafiltration of serum containing antibiotic in a concentration of 5 μg/ml and tube dilution techniques revealed a high degree of binding: erythromycin base, 73%; erythromycin propionate, 93%; lincomycin, 72%; and clindamycin, 94% (806). In studies on complex formation between macromolecules and drugs, sodium sac-

charin was bound much more than *N*-methylsaccharin to human serum albumin, demonstrating that the type of binding was ionic (807). Hydroflumethiazide and bendroflumethiazide were more bound when ionized. The bonding of acetaminophen (paracetamol) to human and porcine plasma at both toxic and therapeutic concentrations was investigated by ultrafiltration and equilibrium dialysis over the range of 50–300 μg/ml (808). Plasma protein binding occurred at acetaminophen concentrations greater than 60 μg/ml. The extent of protein binding at the plasma concentration of 280 μg/ml of the drug was between 15 and 21% for both pigs and humans.

Following the intravenous injection of sulfamethylphenazole, sulfamerazine (sulfamethyldiazine), sulfadimethoxine, sulfamethazine, and sulfaphenazole to horses, their biological half-lives were calculated to be 8–12 hr (809). Plasma protein binding was greatest with sulfamethylphenazole and least with sulfamerazine. Based on the plasma protein binding of the sulfonamides, large amounts of sulfamethylphenazole and small amounts of sulfamerazine have to be administered to be therapeutically effective. When binding of amphetamine and related compounds to plasma proteins was investigated, 3,4-methylenedioxyamphetamine was bound to plasma protein to a greater extent than amphetamine, which may explain the differences in the concentration of drug transported into the central nervous system (CNS) (810). The protein binding of three tritiated muscle relaxants was studied and, after electrophoretic separation, ^{3}H-dimethyltubocurarine was bound most by γ-globulin whereas ^{3}H-gallamine and ^{3}H-decamethonium were bound mainly to the β-globulin fraction (811).

Table XXV—Additional References on Interactions of Drugs with Biological Substances

Reference	Topic
814	Competitive binding of 2-(4′-hydroxybenzeneazo)benzoic acid and α-(4-chlorophenoxy)-α-methylpropionic acid to serum albumins
815	Binding of propranolol to human plasma
816	Influence of protein binding on pharmacokinetics of sulfanilamides in rats
817	Excretion, plasma protein binding, and dosage of sulfonamides in cattle
818	Excretion, plasma protein binding, and dosage of sulfonamides in swine
819	Binding of fenoprofen to human plasma albumin
820	Competitive binding of two drugs for single binding site on albumin
821	Effect of protein binding on degradation of hexobendine in plasma
822	Interaction of penicillins with phospholipids
823	Binding of calcium 2,5-dihydroxybenzosulfonate-^{35}S to human serum
824	Binding of drugs to plasma proteins of swine during perinatal period
825	Interaction of mechlorethamine and isophosphamide with bovine serum albumin
826	Review of physical methods for studying drug-protein binding
827	Review of effects of binding to plasma proteins on distribution, activity, and elimination of drugs
828	Review of factors affecting drug binding to plasma proteins

Trichloroacetic acid precipitation caused the binding of phenylthiourea to the erythrocytes of a number of vertebrates (812). In rats, mice, and dogs, Scatchard plots of the binding data indicated that two sets of receptors may be involved in the binding. The total binding capabilities of the sets of receptors were of the same order of magnitude, but one set was of much greater affinity than the other. The induced binding of phenylthiourea to erythrocytes was probably related to acidity, because a neutral precipitating agent did not cause binding. Judis (813), utilizing equilibrium dialysis for the estimation of protein binding, studied several coumarin derivatives for their abilities to displace sulfonylureas from human serum albumin. All coumarin derivatives caused reduction in the binding of the sulfonylureas, although there was no clearcut pattern with a variation in the pH.

Additional references pertaining to interactions of drugs with biological substances are given in Table XXV.

Interactions of Drugs with Nonbiological Substances—The interactions between dextroamphetamine sulfate and dextrates in buffered solutions at three different temperatures and dextroamphetamine sulfate concentrations were studied (829). On heating, solutions containing dextroamphetamine sulfate and dextrates became progressively darker than solutions containing dextroamphetamine sulfate or dextrates alone. The rate of browning in these solutions increased with increasing temperature and pH and decreased with increasing dextroamphetamine sulfate concentration. From the relationship shown in the plots of absorbance against time, the browning reaction was assumed to follow an apparent zero-order rate law. In work on the influence of auxiliary material on pharmaceuticals, the interactions between surface-active poly(oxyethylene)ethers and esters of nicotinic acid (niacin) took place in the hydrophobic interior and in the hydrophilic exterior of the micelles (830). The degree of binding of the esters to the micelles depended particularly on the physicochemical properties of the esters. A strict relationship for the surface-active poly(oxyethylene)ethers in their ability to bind and to stabilize esters of nicotinic acid was also observed (831). The higher the ability to bind, the better was the stabilizing effect. A crystalline oxytetracycline–magnesium nicotinate (1:1) complex was prepared which was more soluble and stable than plain oxytetracycline base (832). The decomposition of the oxytetracycline–magnesium nicotinate complex was first order.

The heat of bonding of sodium lauryl sulfate with polyvinylpyrrolidone and the amount of sodium lauryl sulfate bound to polyvinylpyrrolidone in an aqueous medium were measured at 25° by a twin-type conduction calorimeter and by an equilibrium dialysis method, respectively; both the heat and the amount of bonding increased with an increasing concentration of sodium lauryl sulfate up to the CMC and then reached a plateau (833). The heat of bonding increased linearly with the increase in the amount of bonding below the CMC and became con-

Table XXVI—Additional References on Interactions of Drugs with Nonbiological Substances

Reference	Topic
835	Interaction between chlorpromazine and polysorbate 80
836	Caffeine-gentisic acid complexes with low water solubility and their potential use
837	Review of interactions between alcohol and drugs
838	Effect of titanium dioxide surface reactions with sodium lauryl sulfate on efficacy of medicinal preparations
839	Influence of temperature and nature of hydrophobic groups on thermodynamic parameters of hydrophobic bonding in model polymeric system and their implications in drug–biopolymer interactions
840	Complexing capacity of barbituric acids and its relation to solubility
841	Review of drug interactions with particular reference to their metabolism
842	Interaction of tetracyclines with metal ions
843	Interaction between chlorpromazine base and sorbitan monooleate

stant, indicating that the heat of micelle formation was almost the same as the heat of bonding. Hem *et al.* (834) studied the formation of 1:1 molar complexes between sucrose and the following penicillins: potassium penicillin G USP, potassium phenoxymethyl penicillin USP, sodium dicloxacillin monohydrate, and anhydrous ampicillin. The degree of complexation was greatest with sodium dicloxacillin and least with ampicillin. The rate of degradation of complexed penicillin was five to six times the rate for the uncomplexed penicillin.

Additional references related to interactions of drugs with nonbiological substances are listed in Table XXVI.

Surface Phenomena—The publications dealing with surface phenomena are divided into four major categories: *(a)* interface studies, *(b)* adsorption studies, *(c)* general properties of surfactants, and *(d)* micelle studies. However, because of the obvious overlap among these categories, the reader with special interest in this field should consider the entire section.

Interface Studies—Bond *et al.* (844) devised and improved an apparatus for measuring both the interfacial tension by the DuNouy ring method and the film elongation, which uses a stepmotor to raise or lower the interface past the ring. An apparatus for studying monomolecular films, by which the subphase can be changed without disturbing the film, was developed and the effectiveness of the apparatus was studied (845). Almost 100% of the subphase could be replaced when 1500 ml of the subphase was exchanged over 20 min. The effect of subphase exchange on human serum albumin films of different concentrations was studied. The films became condensed when a water subphase was exchanged with water, apparently because of loss of some protein from the surface. The effect was more pronounced when films were spread using larger amounts of human serum albumin.

Three recent methods for investigating the physical state existing in boundary layers formed between contacting solid surfaces, with and without a lubricant, were reviewed (846). The error in the calculation of surface tension was discussed (847). The calculation of surface tension from air-bubble data led to erroneous results when the dimension of the vessel in which the surface tension was determined was disregarded. An equation was developed taking into account the size effect of the experimental vessel.

Table XXVII—Additional References on Interface Studies

Reference	Topic
852	Orientation of high molecular weight surfactants at interface and in stable emulsions
853	Membrane potentials of sodium lauryl sulfate solutions at 25°
854	Cohesive force of 2-methyl-5-vinylpyridinium sulfate–2-vinylpyridinium sulfate at oil–water interface
855	Modified Flachsbart–Anliker model for study of interfaces

A study was conducted on the oil–water partitioning and interfacial adsorption of ^{3}H-2-pyrrolidylmethyl *N*-methylcyclopentylphenylglycolate (848). Among the physical parameters examined were partition coefficient, permeation constant, stability constant, and rate constant of the parent drug in a two-phase system of water and a lipid, didodecyl phosphate. Didodecyl phosphate greatly accelerated the rate of oil–water partitioning of the parent compound and exhibited interfacial adsorption with it. The presence of polyanions, such as hyaluronic acid, in the aqueous phase promoted the transfer of drug from the oil to water phase. The interaction of sorbitan esters in liquid paraffin with sodium lauryl sulfate in water to form spontaneous interfacial emulsions was studied by photographing the interfacial phenomenon at different stages (849). Sorbitan trioleate did not demonstrate spontaneous emulsification as readily as the monolaurate or monooleate compounds. A film balance approach using continuous compression was used to study the interaction of the carcinogen 1,2:5,6-dibenzanthracene and the noncarcinogen 1,2:3,4-dibenzanthracene with insoluble monolayers of cholesterol (850). Surface pressure and surface potential of mixed dibenzanthracene–cholesterol films spread on water and saline were studied. The results showed an association of 1,2:5,6-dibenzanthracene and no association of 1,2:3,4-dibenzanthracene with cholesterol. Surface potential data supported the concept of carcinogen–cholesterol association. Microemulsions, which were spontaneously produced upon mixing hexadecane, hexanol, potassium oleate, and water in specific proportions were studied (851). The drop-volume measurements of the hexadecane–water interface in the presence of hexanol or potassium oleate revealed that these surfactants decreased the interfacial tension of the hexadecane–water interface.

Additional references on interface studies are listed in Table XXVII.

Adsorption Studies—The uptake of benzoic acid on sulfamethazine (sulfadimidine) particles was studied (856). Depending on the concentration of sulfamethazine in the system, benzoic acid was adsorbed to the extent of 94%. Data from the adsorp-

Table XXVIII—Additional References on Adsorption Studies

Reference	Topic
862	Use of thermal gravimetric analysis, GLC, and mass spectrometry in sorption studies, and evaluation of clustering functions of ethanol–water–polyurethane system
863	Adsorption and structure formation of polyvinyl alcohols on interfaces in emulsions
864	Selection of sorption conditions for purified diphtheria toxoid prepared on different culture media
865	Thermodynamic consistency test for adsorption of liquids and vapors on solids

tion experiments were shown to fit a Langmuir plot for systems containing up to 0.2 g/100 ml of sulfamethazine. The suppressive effect of three hydrophilic polymers on the benzoic acid adsorption was also studied; the results followed the sequence polyvinylpyrrolidone > methylcellulose > sodium carboxymethylcellulose. The effect of pH on sorption of sulfonamides on nylon 6 was reported (857). The bonding of the sulfonamides resulted in an uncharged condition through H bridges to acid amide groups (cross-links) and hydrophobic reactions, with the sorption maximum lying at the isoelectric point.

In vitro adsorption of oxyphenonium bromide, oxyphencyclimine hydrochloride, clidinium bromide, chlordiazepoxide hydrochloride, and hydroxyzine hydrochloride was determined (858). The adsorbents used were aqueous suspensions of magnesium oxide, magnesium trisilicate, calcium carbonate, aluminum hydroxide, kaolin, and bismuth subcarbonate. In most cases, magnesium oxide and magnesium trisilicate showed the highest adsorptive capacity, calcium carbonate and aluminum hydroxide were intermediate, and kaolin and bismuth subcarbonate showed the least adsorptive capacity. The adsorption of benzoic acid and crystal violet on kaolin was investigated to elucidate the influence of the system dielectric constant and the electrolyte content on this drug–adjuvant interaction (859). The differing results obtained with the two adsorbates reflected the dissimilar adsorption sites on the kaolin and the different mechanisms involved in the uptake of acids and bases on clays. The experimental data were satisfactorily explained by a consideration of the effect of both the dielectric constant and the electrolyte concentration and valency on adsorbent and adsorbate characteristics.

The interaction between colloidal titanium dioxide and tetradecylpyridinium chloride, in aqueous suspensions containing various inorganic chloride salts at pH 8, was evaluated using a two-phase titration to determine the cation content and conductometric measurements to determine chloride ion (860). Surfactant adsorption was dependent on the inorganic salt content and varied with type of anion and cation. Surfactant adsorption appeared to affect the exchange equilibrium at the titanium dioxide interface and the aggregation properties of the amphiphilic cations. The relationship between adsorption from liquids and adsorption from unsaturated vapors was derived (861). The surface excess for adsorption from liquids could be calculated from equilibrium data on adsorption of unsaturated gases. The equations for the surface excess were derived from simple type I and type II models of gas adsorption.

Table XXIX—Additional References on General Properties of Surfactants

Reference	Topic
872	Review of balanced amphoteric surfactants
873	Review of determination and uses of HLB of surfactants
874	Review of determination of HLB of surfactants
875	Review of physicochemical studies of surfactants in nonaqueous medium
876	Review of solubilization properties of oil-soluble surfactants
877	Review of applications of surfactants
878	Review of action of surfactants in nonaqueous media
879	Review of chemical structure, classification, and properties of surfactants
880	Effect of molecular weight on surfactant properties of sulfonmethane (sulfonol) chloride
881	Review of properties and uses of surfactants

Additional references on adsorption studies are listed in Table XXVIII.

General Properties of Surfactants—The determination of the HLB of surfactants using GLC was investigated (866, 867). The use of partial molal volume to correlate with the HLB of nonionic surfactants was recommended (868). Measurements showing the wetting power of solutions prepared with nonionic nonylphenol polyglycol ether surfactants containing different numbers of ethylene oxide units increased with surfactant concentration up to the CMC (869). Above the CMC, the surfactants with HLB values of 10.9–17.6 gave poorer wetting with an increase of the HLB value. The oil concentration of stable emulsions was characteristic of the emulsion stability and was explained in terms of lowering of the interfacial tension by the emulsifier. The cloud point of aqueous solutions of nonionic surfactants prepared by ethoxylation of *o*-cresol, isooctylphenol, C_9–C_{18} alcohols, and coconut fatty acid monoethanolamide on addition of sodium chloride, potassium chloride, ammonium chloride, calcium chloride, magnesium chloride, and barium chloride was independent of the hydrophobic part of the surfactant, decreased linearly with electrolyte concentration, and was dependent on the lyotropic number of the cation, increasing in the order given above (870). The method of reversed GC was used to determine the polarity index on nonionic surface-active agents (871). The correlation of the real HLB value with the polarity index did not indicate any linear character.

Additional studies on the general properties of surfactants are listed in Table XXIX.

Micelle Studies—Solutions of optically active amphetamine isomers, in various concentrations, were used for the preparation of nonionic surfactant solutions, and the CMC was determined using interference refractometry (882). No significant effect of the amine antipodes on the CMC of the surfactant was observed. Parrott and Braun (883), using micellar diffusion coefficients calculated by means of dissolution rate and solubility measurements, employed the

Table XXX—Additional References on Micelle Studies

Reference	Topic
889	Model describing kinetics of micellization at concentrations exceeding the second CMC
890	Review of recent advances in chemistry of micelles
891	Critical concentrations of micelle formation of polyethylene glycol alkyl ethers
892	Review of kinetics of micelle formation by various relaxation methods
893	Determination of CMC of surfactants in organic solvents
894	Review of methods used for determination of critical concentration for micelle formation of surface-active agents in solution
895	Review of micelle formation in surfactant solutions
896	Review of current theories and recent results on thermodynamics of micelle formation and structure of micelles of nonionic surfactants in water
897	Electrostatic and electrokinetic potentials of surfactant micelles in aqueous solutions
898	Comparative study of properties of solutions of surfactants using surface tension measurements
899	Methods for determining second CMC of aqueous solution of sodium lauryl sulfate using fluorescence depolarization
900	Formation of micelles from ionic surfactants, and interpretation of surface tension curve minimum
901	Micellar behavior in solutions of the three-component system of bile acid salt–*n*-decanol–water
902	Calculation of thermodynamic parameters controlling micellization, micellar binding, and solubilization
903	Spectrophotometric determination of CMC of nonionic surfactants
904	Methods for determining second CMC of aqueous solution of sodium lauryl sulfate using light scattering

Stokes-Einstein equation to estimate the relative micelle size and micellar weight of benzoic acid–micelle species in solutions of polysorbate 80. The necessity of considering the relative viscosity of the micellar solutions and the variance of diffusion coefficients with concentration was demonstrated. Under the experimental conditions described, it did not seem justifiable to use the Stokes–Einstein equation in the determination of micellar weight and/or size. The CMC's were determined in mixed aqueous solutions of two homologous nonionic–anionic or nonionic–ionic surface-active agents from surface tension–concentration curves (884). The results were compared with the previous equation for CMC as a function of the mixing ratio, indicating that the mixed micelles behaved thermodynamically like ideal mixtures. The CMC values measured in homologous systems agreed with the equation. In nonionic–ionic systems, the CMC values of the mixed solutions were smaller than calculated by the equation.

The CMC of different polysorbates was determined by measuring the density of their aqueous solutions at 24.88° with a new instrument which can measure accurately the change in natural frequency of a hollow oscillator of constant volume when filled with a solution of an unknown density (885). The frequency change is transformed into density by calibrating the instrument with liquids of known densities. By applying the intercept method, partial specific volumes of water and the surfactant were obtained from the density of each surfactant solution. These partial quantities indicated that the formation of micelles was associated with an increase in the partial specific volume of the surfactant and a concomitant decrease in that of water.

The CMC of three nonionic surfactants was studied by interferometric measurements of refractive index, UV spectroscopy, surface tension, and dye solubilization determination (886). Good agreement was shown to exist between the results obtained by the various methods. The effects of various concentrations of testosterone and both *l*- and *d*-amphetamine isomers on the CMC values of the three surfactants were also determined, and the changes in the free energies of micellization were calculated. It was shown that the effect of the solubilized species on the thermodynamic parameters controlling the micellization process could be complex. Temperature dependence of the rate of micellization of sodium octyl sulfate was determined at 288–333°K, where the experimentally determined CMC passed through a minimum (887). The Beer's law curve for aqueous solutions of typical surface-active azo dyes and two typical colorless surfactants (hexadecyltrimethylammonium bromide and hexadecylpyridinium bromide), when plotted to relatively high concentrations, reveals a normal type of deviation toward the concentration axis over the initial concentration range, followed by a linear branch with positive slope (888). The intersection of the two branches occurred at a concentration corresponding to the CMC determined by other physical means.

Additional references on micelle studies are given in Table XXX.

Dispersion Stabilization—Hallworth and Carless (905) investigated the effect of a long-chain alcohol on the stability of paraffin-in-water emulsions containing alkyl sulfates. *n*-Octadecanol increased the stability of emulsions of light petroleum with sodium lauryl sulfate and caused a greater increase in light petroleum emulsions with sodium cetyl sulfate. The most likely cause of increased stabilization brought about by octadecanol was thought to be increased coherence of the interfacial film, which has considerably greater viscoelasticity than films without the alcohol and is thus able to stabilize the oil droplets against coalescence.

Two aqueous triethanolamine myristate–halogenated hydrocarbon (Freon) propellant emulsions with different degrees of stability were studied in conjunction with their corresponding foams to determine if any relationship existed between the properties of the emulsions and those of the foams (906). Microscopic and visual observations showed that the surfactant system producing emulsified propellant droplets with the smaller diameters also produced foams with an initially smaller bubble size and a slower increase in bubble size after discharge. The systems with the small emulsified droplets were the most stable and produced the most stable foams. An experimental model was developed in which the stability of water-in-oil emulsions, used in effecting prolonged or enhanced responses to vaccines, could be

Table XXXI—Additional References on Dispersion Stabilization

Reference	Topic
912	Dispersion state of protein-stabilized emulsions, and dependence of globule size and size distribution upon pH in concentrated oil-in-water systems
913	Comparison of theoretical equations for potential energy of electrostatic repulsion of colloidal particles at constant surface charge
914	Relationship of stability of emulsions with energy of adsorption, average volume of a single drop, and concentration of surface-active stabilizers
915	Polymer-induced flocculation of pharmaceutical suspensions
916	Sedimentation in dilute emulsion
917	Photometric investigations regarding agglomeration and dispersion in suspensions
918	High viscosity and high stability emulsions for cutaneous use
919	Measurement of forces between particles in disperse systems
920	Review of colloidal state including classification of colloidal systems, factors affecting stability of colloidal state, and flocculation
921	Conditions for formation and stability of emulsions forming near critical mixing temperature of tricosane-8-hydroxyquinoline system
922	Efficiency of control methods in evaluation of emulsion quality
923	Adsorption of nonionic surfactants on sulfathiazole and naphthalene, and flocculation-deflocculation behavior of these suspensions
924	Role of molecular diffusion in bulk stability of oil-in-water hydrocarbon emulsions
925	Charge of emulsified oil particles, and case of anionic emulsifying agent
926	Industrial application of ζ-potential studies, and effect of electrolytes on dilute suspensions
927	Effect of surfactants on electrochemical activity of oil-in-water-type emulsions stabilized by solid emulsifiers
928	Electron microscopic study of mechanism of flocculation
929	Stability of emulsions stabilized by nonionic surfactants

studied in simple environments of known constitutions (907). A decrease in emulsion stability was noted with a decrease in pH and constant ionic strength, with an increase in ionic strength and constant pH, or with an increase in temperature at a constant pH and ionic strength. Protein concentration did not affect the stability.

A survey of 68 oil-in-water emulsions, containing 20–40% liquid paraffin oil and 5–10% emulsifier, showed that 40 were stable for less than 3 months; the best emulsions contained secondary and tertiary esters of phosphoric acid with lauryl tetraglycol ether (908). Most of the apparently stable emulsions were finely dispersed and homogeneous. Changes were found in the particle size of either salicylic acid or ethionamide suspended in petrolatum base, particularly when nonionic surfactants were present during storage (909). Depending on their concentration, surfactants reduced the degree of dispersion to a substantially great extent, whereby the larger particles grew at the expense of the smaller ones. Tsukiyama and Takamura (910) studied the effects of emulsifying agents on water-in-oil-type emulsions; in the systems studied, they found that sorbitan trioleate was the best emulsifying agent. Tagats surfactants, comparable to polysorbates and polyoxyethylene derivatives of fatty alcohols (Myrjs and Brijs), had the same stabilizing effect on a suspension of phenoxymethyl penicillin and an emulsion of castor oil (911). The optimal hydrophilic–lipophilic equilibrium value for a suspension of 10% phenoxymethyl penicillin was two, while the value for castor oil emulsion was 12.

Additional references on dispersion stabilization are given in Table XXXI.

Rheology—Liquid paraffin-in-water emulsions, stabilized by mixed emulsifiers of a surfactant (cetrimide or cetomacrogol) and a long-chain alcohol, were used as a model system to represent pharmaceutical semisolids (930). They were examined in their linear viscoelastic regions using creep and oscillatory techniques. The agreement between transformed functions and those obtained directly from oscillatory measurements was generally good. In work on oscillatory testing of oil-in-water emulsions containing mixed emulsifiers of the surfactant–long-chain alcohol type, the self-bodying action and the influence of surfactant chain length were studied (931, 932). The rheology of a new topical vehicle, fatty alcohol–propylene glycol (FAPG) cream base, was investigated over 25–37° (933). Continuous shear rheograms obtained with the Ferranti-Shirley cone and plate viscometer were hysteresis loops with a spur point; loop areas, yield values, and apparent viscosities decreased with an increase in temperature. In creep, the base was viscoelastic with a low limit of linearity with respect to strain. Patient acceptance of skin spreadability of the base was assessed by using a master curve concept; the spreading properties were close to the preferred values for maximum patient acceptance.

The influence of alcohol chain length and homolog composition on the rheological stability of cetrimide emulsions was also studied (934). Upon aging, the consistency of emulsions prepared with cetostearyl alcohol increased while that of emulsions prepared with cetyl and stearyl alcohols decreased. Measure-

Table XXXII—Additional References on Rheology

Reference	Topic
936	Rheological characteristics of a base containing petrolatum (Vaseline), white wax, cholesterol, and stearyl alcohol
937	Relationships among structure, properties, and stability of salves containing surface-active substances, and interaction between emulsifiers and liquid phase of gels
938	Rheology of oily suspension suppositories of mefenamic acid
939	Rheological characteristics of cold cream
940	Review of uses of rheology in pharmaceutical field
941	Viscosity and rheological changes in bentonite gel following addition of various salts
942	Effect of aging on rheological properties of gelatin gels
943	Rheological properties of some cellulose solutions
944	Structural and mechanical properties of bases containing methylcellulose solutions
945	Rheological study of fatty acid–soap systems
946	Rheological properties of lipophilic bases applied to cosmetics
947	Rheological study of salve bases

ment of viscosity of carbomer dispersions showed a reduced viscosity which increased very rapidly with an increasing concentration of carbomer (935). The increase in viscosity was further decreased by addition of sodium chloride. Measurements of ionic strength of these dispersions by a viscometric method gave results that were 10–20% of the theoretical strength as calculated from the normality of the ionized carboxylic acid group. These results were then discussed in relation to interactions between macromolecules.

Additional references on rheology are provided in Table XXXII.

PHARMACEUTICAL ASPECTS

Antibiotics—The influence of binding, disintegration, and lubricating filling substances on the flow of granules containing oxacillin or ampicillin, as well as on the hardness and disintegration of the prepared tablets, was discussed (948). Oxacillin was electrostatically charged, but no electrostatic charges were established in ampicillin. Therefore, ultraamylopectin, which was also electrostatically charged, was unsuitable as an additive for tablets containing oxacillin but was successfully used in ampicillin tablets. A silicone lubricant (Aerosil) neutralized the electric charges in the two antibiotics, improved the flow of the granules, and increased the hardness and disintegration of the tablets. Gelatin glue and 5% ethylcellulose were the most suitable binding agents.

The stabilization of aqueous solutions of sodium penicillin G was investigated using a mixture of 0.5% methenamine and 1% disodium edetate and compared to using methenamine sodium citrate (949). The rate of decomposition was less with disodium edetate. With this combination, the penicillin remained stable for 3 days at 30°. The influence of trichloroacetate anion on the *n*-octanol–aqueous phosphate buffer apparent partition coefficient of various tetracyclines was determined (950). At acidic pH values, the presence of trichloroacetate significantly increased the apparent partition coefficients of most tetracycline analogs studied, presumably through intermolecular ion-pairing in the positively charged tetracycline moiety and the trichloroacetate anion. From intermediate to mildly alkaline pH values, trichloroacetate had essentially no effect on partitioning. The alteration of the apparent partition coefficients of the tetracycline antibiotics by intermolecular ion-pair formation was discussed in terms of its relationship to the absorption of these compounds.

The compatibility of five antibiotics with seven polyethylene glycol gels was studied immediately after preparation as well as after 1, 3, 7, 12, and 36 weeks (951). Chloramphenicol and neomycin sulfate were stable in all of the gels studied. Erythromycin lactobionate was stable for 7 weeks. An antifungal preparation containing nystatin (stamycin) was stable in an emulsifier-free gel. Polyethylene glycol gels were not appropriate for tetracycline hydrochloride. An examination was made of the suspension characteristics of antibiotic granules or fine powders with various concentrations of sodium carboxymethylcellulose and distilled water (952). Antibiotic suspensions with sodium carboxymethylcellulose solution of 0.125% concentration and distilled water showed the same sedimentation profile, resulting in a hard cake formation of dispersed antibiotics. Due to its high viscosity, sodium carboxymethylcellulose solution in a concentration of 0.5% showed low resuspendability for the dispersed phase. Sodium carboxymethylcellulose at 0.25% was suitable as a suspending medium for syrupy antibiotic suspensions.

Table XXXIII—Additional References on Antibiotics

Reference	Topic
953	Penicillin G and ampicillin interactions with phospholipids
954	Measurement of wettability of antibiotic powders
955	Effect of processing on stability of troleandomycin and erythromycin propionate suspensions
956	Review of pharmaceutical aspects of parenteral penicillins
957	Review of interactions of antibiotics with other pharmaceuticals
958	Effect of oleandomycin and its combinations with tetracycline, chloramphenicol, erythromycin, lincomycin, and 1′-demethyl-4′-depropyl-4′-(*R* and *S*)-*n*-pentylclindamycin on microbial generation of *E. coli*
959	Formation of polyvinylpyrrolidinone complexes of amphotericin B during coprecipitation by an aprotic solvent
960	Production of thermostable chloramphenicol (synthomycin) and sulfamidochrysoidine (streptocid) emulsions using the new nonionic emulsifier oxysterone

Additional references on antibiotics are found in Table XXXIII.

Radiopharmaceuticals—The use of radionuclides for diagnostic purposes, with descriptions of the preparation of a ^{99m}Tc–iron–ascorbic acid complex and a ^{99m}Tc–sulfur colloid, using a Mo-Tc generator, was reviewed (961). Radiopharmaceuticals used for diagnosis of blood, liver, pancreas, and heart diseases were reviewed (962), as was the design of the synthesis of radioisotope-labeled drugs with their stability and storage (963). The development and production of various radioactive drugs were reviewed (964), and other radiopharmaceutical reviews were presented (965, 966).

BIOPHARMACEUTICS

The various publications dealing with biopharmaceutics were subdivided according to the area of special interest. However, because of the obvious overlap in subject matter, the reader seeking a thorough review should consider the entire section.

A model was proposed for determining the bioavailability of drugs whose elimination from a one-compartment body model occurs by one or more apparent first-order processes in parallel with one capacity-limited elimination process (967). Another model was based on estimates of renal clearance, plasma clearance, and urinary excretion of unchanged drug. The method was totally compatible with pharmacokinetic models and lent itself to a more flexible sampling schedule which made it independent (968). The average amount of drug in the body at steady state upon repetitive dosing in a two-compartment

open system was related to the average steady-state plasma level by the apparent volume of distribution (V_β) at steady state rather than by the apparent volume of distribution at pseudodistribution equilibrium, despite the fact that the average steady-state plasma level is directly proportional to $1/V_\beta$ (969).

A series of review articles dealt with: bioavailability, clinical effectiveness, and the public interest (970); design of *in vivo* studies of bioavailability, biometrical considerations (971); use of physical and animal models to assess bioavailability (972); overview of the analysis and interpretation of bioavailability studies in humans (973); and physiological and pharmacokinetic complexities in bioavailability testing (974).

As a single entity, the bioavailability of digoxin tablets attracted the most attention in the field of biopharmaceutics. The absorption of a commercial digoxin tablet preparation of low as well as high therapeutic potency and of digoxin dissolved in alcohol was studied in digitalized patients and compared with the dissolution rates of the tablets (975). The bioavailability of the low potency tablet was markedly inferior to that of the high potency tablet, which did not differ significantly from that of digoxin in alcoholic solution. A significant correlation between bioavailability and the dissolution rate was also found. The investigators suggested that measurement of the dissolution rate might be used as a guide to the bioavailability of various digoxin tablet preparations. The commercial digoxin radioimmunoassay procedure was modified so that the sensitivity was increased 20-fold (976). By using this assay, significant differences in plasma levels in different brands of digoxin tablets were found as determined by the analysis of variance at 0.5, 1, 72, and 240 hr, and the peak plasma levels differed significantly. Beveridge *et al.* (977) recommended following urinary excretion in addition to plasma levels to estimate the bioavailability of different digoxin formulations. In an evaluation of the bioavailability of digoxin preparations available to a Naval hospital, variations in the early absorption of four digoxin oral preparations were found; however, serum levels at 5 hr were essentially the same and the urinary recovery was similar (978).

The bioavailability of dicumarol from three different commercial tablets was determined by measuring plasma levels in dogs and by an *in vitro* dissolution rate test (979). The products showed significant difference in plasma levels, area under plasma level curves, peak prothrombin time responses, and rates of dissolution, even though they contained the labeled amount of dicumarol. A comparative study was done with methyltestosterone sublingual and oral tablets to find if there were any differences in their bioavailability (980). The sublingual methyltestosterone was absorbed faster. Its extent of bioavailability approached twice that resulting from an equal dose of orally administered drug. This may explain the clinical experience that milligram for milligram, methyltestosterone sublingual tablets have greater potency than orally administered tablets.

Various dosage forms of butaperazine were administered to patients, and the levels of butaperazine in the blood were determined at regular intervals (981). The oral concentrate formulation produced the highest blood level, the intramuscular form produced the lowest, and the tablet form was intermediate. When the blood and urine levels of tetracycline hydrochloride were monitored in normal subjects throughout a 96-hr treatment period, the bioavailability of film-coated tetracycline hydrochloride tablets was inferior to that of capsules (982). In general, the dissolution time of capsule preparations was shorter than that of tablet preparations. The bioavailability of some steroids administered orally was followed when they were put into oily and aqueous vehicles (983). The highest amount of GI absorption occurred from oily solutions.

Clindamycin availability in humans from clindamycin 2-palmitate and clindamycin 2-hexadecylcarbonate compared to clindamycin hydrochloride was determined (984); the palmitate ester was the superior ester and was bioequivalent to clindamycin hydrochloride in humans. The initial urinary excretion rate of chloramphenicol was decreased in humans when the drug was administered orally with milk instead of water (985). This difference was suggested to be due to the drug–milk protein binding. The bioavailability of potassium from orally administered 10% potassium chloride solution was compared to a slow-release potassium chloride tablet (986). The urinary potassium excretion increased sooner and reached greater peak levels after the solution was administered. In both cases, greater amounts of potassium appeared in the urine when it had been administered in the fasting state rather than in the postprandial state. Hydrochlorothiazide tablets from 10 of 39 Canadian companies failed to meet the USP XVIII dissolution requirements (987). However, the bioavailability in drug absorption parameters did not give correlations of predictive value with the formulation dissolution times. It was also noted that the dissolution time of some commercial hydrochlorothiazide tablets was decreased after storage.

The factors affecting the therapeutic activity of rectal preparations, such as chemical modifications of the drug, presence of adjuvants in vehicle, various dosage forms, and pharmaceutical processes used in formulation, were reviewed (988). The absorption rate of sulfanilamide and sulfisoxazole in rabbits decreased in the order: oral > subcutaneous > rectal administration (989). When comparing water-soluble, emulsified, or oleaginous substances such as suppository bases, it was found that the emulsified base suppositories gave similar values to oral and subcutaneous administration, while the drugs prepared with oleaginous bases had smaller absorption rate constants.

The *in vivo* bioavailability and the *in vitro* dissolution rates of several commercial tolbutamide tablets were compared (990), and no detectable statistically significant differences among the dosage forms in terms of percent drug recovered, maximum excretion rate, or time of maximal excretion rate could be found. However, there were marked differences in the *in vitro* dissolution rates among the formulations

Table XXXIV—Additional References on Biopharmaceutics

Reference	Topic
1005	Review of biological availability of drugs
1006	Review of statistical methods in evaluation of *in vivo* performance of dosage forms
1007	Review of factors influencing drug absorption, administration, and elimination
1008	Review of factors influencing drug availability at receptor site
1009	Review of bioavailability of peroral dosage forms and factors influencing it
1010	Review of materials for injection with immediate effect
1011	Review of problems encountered when using animals for bioavailability testing
1012	Review of basis of biopharmaceutical testing of drug bioavailability
1013	Review of sites of drug transport and disposition, with special emphasis on permeability of blood–brain barrier to drugs
1014	Review of chemical, biological, and clinical evaluation of drug equivalency
1015	Review of routes of drug administration, with special emphasis on diffusion and active transport of drugs through cell membranes
1016	Review of factors that modify drug activity and patient response
1017	Chemical equivalence or therapeutic equivalence
1018	Chemical equivalence and therapeutic nonequivalence of various drugs in pharmaceutical forms
1019	Bioavailability of aspirin tablets registered in Finland
1020	Urinary excretion of ampicillin administered in four dosage forms in humans
1021	Clindamycin dose–bioavailability relationships
1022	Bioavailability of codeine preparations in rats
1023	Comparison of oral and percutaneous routes in humans for systemic administration of ephedrines
1024	Review of bioavailability of griseofulvin, tetracycline, tolbutamide, chloramphenicol, nitrofurantoin, and sulfadiazine
1025	Bioavailability of nitrates in the dog
1026	Biological equivalence of oxytetracycline hydrochloride capsules from Colombian markets
1027	*In vitro* availability of phenobarbital from solubilized systems
1028	Comparative availability of Czechoslovakian and foreign phenoxymethyl penicillin-type preparations in blood serum of volunteers
1029	Bioavailability of salicylamide from tablets
1030	Review of bioavailability of sodium warfarin
1031	Vehicle and route of administration as parameters affecting operant behavioral effects of Δ^9-tetrahydrocannabinol
1032	Biopharmaceutical studies on macrolide antibiotic SF-837
1033	Absorption and topographic distribution of 4-bromophenylisothiocyanate-^{35}S on normal guinea pig skin in various bases
1034	Percutaneous absorption of heparin-^{35}S from specially prepared oil-in-water emulsion
1035	Modification of cutaneous permeability after application of dermal preparations, and action of hydrocortisone ointment
1036	Absorption of hydrocortisone acetate from hydrophilic ointments
1037	Absorption, excretion, and metabolism of subcutaneously and topically applied mafenide acetate
1038	Percutaneous absorption and distribution of 2-naphthol in humans
1039	Effect of excipients on percutaneous absorption of nicotinic acid esters
1040	Optimization of dermatological formulations of retinoic acid
1041	Bioavailability of different ointments containing sodium sulfacetamide (sodium sulfacyl) and potassium iodide
1042	Comparative bioavailability of proprietary hydrophilic topical steroid preparations
1043	Biopharmaceutical studies on percutaneous absorption of vitamin A from ointments
1044	Review of release and cutaneous absorption of drugs from dermatological preparations
1045	Barrier and reservoir function of human stratum corneum for topically applied drugs
1046	Percutaneous absorption of drugs, and time course of cutaneous reservoir of drugs
1047	Quantitative effect of topically applied anti-inflammatory agents on external ocular inflammation in rats

examined in pH 6.45 buffer. A crossover absorption study of seven oral oxytetracycline and two tetracycline formulations was made (991). *In vitro* analysis of disintegration and dissolution was also carried out on these preparations. When the rate of dissolution was correlated with absorption, it was found that with one preparation the dissolution rate was slow and incomplete and the absorption was inferior, whereas with another preparation the dissolution was quite rapid and the absorption was quite good. An *in vitro* method for studying the release of active ingredients from suppositories was devised (992). The suppository was surrounded by a pH 7.8 buffer solution in a dialysis chamber which was continuously perfused with artificial plasma; the latter was pumped through a flow cell for direct, continuous spectrophotometric reading. These results were compared with data obtained by *in vivo* urinary excretion of proxyphylline after it was administered as a suppository to human subjects. A good correlation between the percent absorbed *in vivo* by the rectal route and the percent released *in vitro* was observed when the amount of proxyphylline released *in vitro* was between 15 and 85%.

In work on the mechanism of percutaneous absorption, the permeation rates of a homologous series of primary alcohols (C_1–C_{10}) through skin were studied (993). The alcohols were applied from aqueous solutions and as pure liquids. The permeation behavior in the two cases was compared in terms of: *(a)* transport rates of the alcohols, *(b)* distribution equilibrium between the tissue and vehicle, and *(c)* damage to the tissue produced by the vehicle. Fick's law was found to hold as an approximation for both the aqueous and the liquid alcohol systems. An electrometric study was done to find the effects of ionic surfactants on the permeability of human epidermis (994). Three ionic surfactants of a homologous series were studied (R—COONa, R—OSO_3Na, and R—NH_3Cl). A similar pattern of relative surfactant activity was shown for each series of surfactants. The C_8 compounds showed no effect, the C_{10} compounds showed slow but distinct increases in conductance, and maximal effects occurred at C_{12} and C_{14} but less at C_{16}.

Percutaneous absorption through the damaged skin lacking stratum corneum greatly increased as compared with that of intact skin (995). The initial

absorption pattern, which was distinctly recognized in the intact skin, almost disappeared in the damaged skin; the absorption of the drugs occurred by simple diffusion of a first-order rate from the start of the experiment. The absorption of the drugs in the intact skin was almost negligible when the drugs were in an ionized state; however, in damaged skin, there was a distinct absorption of ionized drugs. Comparison of the rate of absorption through mouse skin of several water-soluble substances from emulsion-type ointments decreased with an increase in the molecular size of the compound studied (996). Using different water–glycerin ratios, different solutions of methyl nicotinate with identical thermodynamic activity were prepared and their percutaneous absorption was followed (997). The results showed that the time of onset of erythema was the same for all solutions of equal thermodynamic activity. Thus, the rate of penetration was mainly dependent on the thermodynamic activity of the penetrant.

Application of dimethyl sulfoxide to the human skin increased skin permeability for electrolytes, with the maximum effect after 20 min and a lessening effect afterward (998). Similarly, application of sodium lauryl sulfate to human skin increased electrolyte permeability, thus facilitating the entrance of potentially harmful detergent ingredients such as metals (999). The *in vitro* penetration of four different radiolabeled hydrocortisone creams was measured in human skin (1000) and the highest activity was found in the horny layer of the skin. When using a water-in-oil emulsion, a longer penetration period was observed with a large reservoir in the horny layer. The oil-in-water emulsions gave no distinct reservoir. The amount of hydrocortisone found in the epidermis and the cutis was low when petrolatum and water-in-oil emulsions were used. Absorption of salicylic acid and *p*-aminosalicylic acid in 5% ethanol through intact rat skin decreased as pH increased and followed the pH–partition hypothesis (1001).

The properties of the cutaneous barrier, methods for measuring the efficiency of the cutaneous barrier and *in vivo* and *in vitro* percutaneous absorption, and the importance of physicochemical factors were reviewed (1002). With the extrathermodynamic approach, for many series of drugs the percutaneous absorption through intact skin is highly dependent upon the lipophilic character, measured by the log partition coefficient from octanol–water, ether–water, and other suitable solvent systems (1003). A review of the absorption of drugs through the skin was presented (1004).

Additional references on biopharmaceutics are listed in Table XXXIV.

Effects of Physicochemical Properties—Different physicochemical factors affecting the absorption of sulfonamides from rat small intestine were studied (1048) including partition coefficient, adsorption to rat blood, adsorption to activated charcoal, molecular weight, and dissociation constants. The intestinal absorption of sulfonamides was satisfactorily predicted with regression analysis. Absorption of isomeric and N^1-heterocyclic sulfonamides from rat small intestine also was studied, and the physicochemical properties were correlated with absorption of unionized sulfonamides (1049). The rate of absorption of the undissociated form of the compounds could be correlated to partitioning to *n*-octanol and molecular weight.

Plasma half-lives, plasma metabolites, and anticoagulant efficacies of the enantiomers of warfarin were studied in humans (1050). *S*-(−)-Warfarin was a more potent anticoagulant than *R*-(+)-warfarin in humans. However, *S*-warfarin was cleared more rapidly from the plasma compared to *R*-warfarin. The different mean plasma half-lives for *R*- and *S*-warfarin were 45.4 and 33 hr, respectively. The influence of raw materials used in drugs on the bioavailability of the active components was studied (1051). The various effects of polymorphism, granulation, valence, pK, partition coefficient, and ester formation were considered. Beckett and Shenoy (1052) studied the effect of *N*-alkyl chain length and stereochemistry on the absorption, metabolism, and urinary excretion of *N*-alkylamphetamines in humans. The total metabolism of (+)-methyl-, ethyl-, and *n*-propylamphetamine was greater than that of the corresponding (−)-isomers, but there was no difference in the total metabolism of (+)- and (−)-*n*-butylamphetamine. Molecular weight and chemical structure as factors in the biliary excretion of sulfonamides in the rats were studied (1053). In the N^4-position, when substituted with various carboxyacyl groups, and the N^2-position, with acetyl or 2-thiazolyl, there appeared to be a threshold value for the molecular weight above which biliary excretion became appreciable.

The bioavailability of digoxin was also studied as affected by the particle size of the different formulations studied (1054). Tablets and capsules made of crude material of digoxin, which passed the British Pharmacopoeia requirements, and after it had been crushed to a finer particle size were given to seven volunteers. The serum digoxin levels were followed, and the results showed that formulations made with the finer particles gave higher area under concentration curves than did formulations made with coarse material. Human plasma levels of digoxin tablets prepared with 3.7-, 12-, and 22-μm particles were compared, and it was found that the smaller the particle size the higher the plasma levels (1055). Absorption of sulfanilamide and sulfisoxazole from the rabbit rectum and intestine was influenced by the particle size of these drugs, with the absorption rate constant being proportional to the log of the reciprocal of the particle size while the dissolution rate constant was proportional to the reciprocal of the particle size (1056).

A homologous series of straight-chain lincomycin 2-monoesters, comprised of both acyl and carbonate esters, was synthesized (1057). Good antibacterial activity was observed with esters of chain lengths from C_4 to C_{16}. Esters with chain lengths from C_{12} to C_{16} were tasteless and highly active *in vivo*. The long-chain lincomycin 2-esters gave the desired properties required for formulation as a tasteless pediatric preparation. Clindamycin was chemically modified to provide *in vivo* reversible derivatives that

Table XXXV—Additional References on Effects of Physicochemical Properties

Reference	Topic
1060	Statistical approach to evaluating effect of physical and chemical factors on fecal excretion of chlorophenothane
1061	Review of effect of chemical modification of drugs on biological availability
1062	Effect of stereochemistry of warfarin on its metabolism
1063	Review of newer physicochemical methods useful in bioavailability studies
1064	Chance correlations in structure-activity studies using multiple-regression analysis
1065	Structure-activity correlations of 1,3-benzodioxole synergists
1066	Structure-activity correlation of mitomycin derivatives
1067	Structure-activity correlation for substrates of phenylethanolamine *N*-methyltransferase
1068	Structure-activity correlation of antineoplastic drugs
1069	Structure-activity correlations of kinins
1070	Effectiveness of pharmaceuticals related to their physical form
1071	Effect of chain length in homologous series of anionic surfactants on irritant action and toxicity
1072	Substituent-effect analyses of rates of metabolism and excretion of sulfonamide drugs
1073	Utilization of operational schemes for analog synthesis in drug design
1074	Physicochemical studies on elucidating the distribution behavior of aminopyrine
1075	Correlations between physical and physicochemical properties (pH value, binding agents, coating, *etc.*) of medicinals and various forms of administration
1076	Review of effect of particle size of different dosage forms on pharmacological action
1077	Effect of particle size on bioavailability of trimethoprim-sulfamethoxazole preparations

might be utilized in special dosage forms (1058). A series of 2- and 3-monoesters improved the taste properties. Highly water-soluble salts were also prepared to provide intramuscular injectable preparations. A review of different ways of changing the pharmacokinetics of drugs by modifying the properties of the multicompartment system or by changing the physicochemical properties of the active drug was presented (1059).

Additional studies on the effects of physicochemical properties are listed in Table XXXV.

Effects of Formulation—The general applicability of the polyvinylpyrrolidone coprecipitation technique as a method for enhancing GI absorption of orally administered hydrophobic drugs was explored with digitoxin (1078). The relative absorption characteristics of digitoxin alone and as a 1:9 physical mixture and coprecipitate with polyvinylpyrrolidone were determined indirectly by measuring the oral LD_{50} values in rats. The *in vivo* data obtained provided evidence that digitoxin was absorbed from the coprecipitate at a significantly faster rate and was present in the body at a much higher level than when equivalent doses of either the drug alone or a physical mixture with polyvinylpyrrolidone was orally administered. A correlation was found between the *in vitro* dissolution rates of these systems at 37° and their *in vivo* toxicities. *In vitro* dissolution and *in vivo* absorption characteristics of various nitrofurantoin and nitrofurantoin–deoxycholic acid preparations were studied (1079). *In vitro* particulate dissolution studies showed that the dissolution rate of a 1:5 molar ratio nitrofurantoin–deoxycholic acid coprecipitate was approximately six times greater than the dissolution rate of the 1:5 physical mixtures. Similar results were also obtained with *in vivo* absorption where the 1:5 coprecipitate showed significant increases in both the initial urinary excretion and the total cumulative amount of unchanged nitrofurantoin. The GI absorption characteristics of micronized griseofulvin from an oil-in-water emulsion dosage form, an oil suspension, and an aqueous suspension were assessed in rats (1080). The emulsion form produced a mean peak plasma antibiotic level 1.5 and 2.3 times higher than the oil and aqueous suspensions, respectively, after a slight delay.

Bioavailability studies of acetaminophen rectal dosage forms with various polyethylene glycol bases and water in humans showed statistically significant differences both in the rate and the extent of absorption (1081). The dissolution rate studies showed that one factor controlling the initial rate of absorption was the speed with which polyethylene glycol bases released the drug into the rectal fluids. Another factor was the apparent partition coefficient which controlled the transfer of drugs across a lipoidal barrier. The appearance of radioactivity in the blood plasma of dogs was more delayed and of longer duration after administration of coated sustained-release tablets containing 300 mg of ^{14}C-*O*-(β-hydroxyethyl)rutoside than after administration of rapid-release capsules that contained the same amount of drug (1082).

Dissolution rate and absorption for one film-coated and four sugar-coated oxytetracycline tablet preparations were determined (1083). The dissolution in 0.1 *M* hydrochloric acid and in simulated intestinal fluid of film-coated tablets was faster than with sugar-coated tablets, although absorption studies in humans did not show these differences. The urinary excretion of a conventional and a slow-release tablet of 300 mg heptaminol was followed (1084). The average peak excretion occurred in the first 2 hr after ingestion and after 4–6 hr for the conventional tablet and the delayed-action tablet, respectively. Starting with the 6–8-hr period, excretion levels became higher for the slow-release tablets as compared with the conventional ones. In simple suspensions, particle size of sulfisoxazole influenced both the rates of absorption and dissolution (1085). However, when formulated in a vehicle containing a surface-active flocculating agent and methylcellulose, the particle-size differences were not as pronounced. Berlin *et al.* (1086) determined the bioavailability of diazepam in various formulations from their steady-state plasma concentration data. The suspension form showed lower values during steady state as a result of incomplete absorption.

Absorption Control and Alteration—Absorption of phenolsulfonphthalein by healthy adults was decreased significantly during the 1st hr when the drug

was administered in very viscous sodium alginate solution or when the subject had been premedicated with propantheline (1087). Sodium alginate had no effect on the total amount of phenolsulfonphthalein absorbed; pretreatment with an anticholinergic agent increased the total amount of phenolsulfonphthalein recovered in the urine from an average of 16 to 24% of the dose. The effect was attributed to a decrease of the GI transit rate. The influence of dosage form on the antipyretic activity of acetaminophen administered intraperitoneally in the rat was studied; the solution form produced an antipyretic response twice that of the same dose administered as a suspension (1088). This experiment indicated that ED_{50}, LD_{50}, and relative potency calculations may be inaccurately determined if dosage form influences on bioavailability of an insoluble drug are not considered in the design and evaluation of animal drug testing procedures.

Alterations in the absorption of dicumarol by various excipient materials were studied (1089). The drug was combined with the excipient by an equilibration process and was administered orally. Significant differences were noticed in the plasma levels of dicumarol with six of the 10 excipients studied. Both magnesium oxide and magnesium hydroxide significantly increased the plasma levels of dicumarol while talc, colloidal magnesium aluminum silicate, aluminum hydroxide, or starch resulted in significantly lower plasma levels of the drug. The investigators suggested that these types of interactions may be an explanation for differences in the bioavailability of dicumarol from different dosage formulations. The effect of adding polyethylene glycol 400 or polysorbate 80 on the absorption of virginiamycin was studied (1090, 1091). Blood concentrations of virginiamycin were 2.5 times higher when the antibiotic was administered to rats orally in conjunction with 5% polyethylene glycol 400. This result was attributed to the increase of solubility of the antibiotic. Above 5% concentration, the blood levels progressively decreased due to the partition coefficient, which favored the aqueous over the oily phase, causing a decrease in the amount of antibiotic available for absorption. When polysorbate 80 was administered with virginiamycin, it increased the solubility and the absorption of virginiamycin. Similarly, polysorbate 80 increased the availability of aspirin in humans as compared to dosing with aspirin alone (1092). The possible effect of complex formation between drugs and adjuvants on the dissolution rates of drugs from tablets was determined (1093). Generally, the higher the adjuvant–drug ratio and the greater the drug interaction tendency between drug and adjuvant, the more pronounced was the influence of excipient on the dissolution rate of drugs.

Liquid chlorpromazine, with or without gel antacids, was given orally to humans (1094). Plasma chlorpromazine levels were significantly lower with gel antacid–chlorpromazine combinations than with chlorpromazine alone. The effect of nonsteroidal anti-inflammatory drugs on the absorption and excretion of sulfadimethoxine in rabbits was studied (1095); the simultaneous administration of indomethacin or benzydamine altered the absorption of sulfadimethoxine by delaying gastric emptying and thus increasing the time for sulfadimethoxine to reach its primary absorption site.

A set of *in vivo* and *in vitro* experiments was designed to show the drug–protein interaction in tissues and fluids of the eye and the effect that this interaction had on drug bioavailability (1096). Equilibrium dialysis experiments, using pilocarpine nitrate, demonstrated that extensive binding to proteins in tears, cornea, and aqueous humor does occur. This was confirmed by using pilocarpine nitrate and following its effect on the pupillary diameter. Theophylline alone gave better *in vitro* dissolution and *in vivo* availability than a theophylline–phenobarbital complex, indicating that bioavailability may be influenced by complexation or interaction of the two drugs in the tablet formulation (1097).

Patients on digoxin therapy, when using propantheline, had an increase of serum digoxin levels; when using metoclopramide, they had reduced digoxin serum concentrations (1098). These results showed that any change in GI motility produced by the two drugs was responsible for the altered bioavailability of digoxin. By using premicellar concentrations of sodium taurocholate, sodium tauroglycholate, and sodium deoxycholate, the dissolution rate of aspirin and salicylamide was enhanced (1099). Similarly, an increase in the intestinal absorption of both drugs was observed in rats. This increased absorption may be due to alterations in permeability characteristics of intestinal mucosa cells. In a study designed to determine the rate of gastric emptying of phenol red in the rabbit, aminopyrine considerably delayed the gastric emptying of phenol red (1100). However, caffeine, which has an increasing effect on human gastric secretion, did not affect the rate of emptying of phenol red.

The effect of sodium glycocholate upon the partitioning behavior and GI absorption of isopropamide iodide was studied (1101). Sodium glycocholate progressively increased the partitioning of isopropamide from a physiological aqueous buffer into *n*-octanol below the CMC of the bile salt, but increased partitioning was inhibited above this value. The formation of a lipid-soluble ion-pair between the bile salt anion and the quaternary cation was suggested as the mechanism of enhanced partitioning. Absorption from the rat ileum *in situ* in the presence of sodium glycocholate below and above its CMC did not follow a similar pattern. It was suggested that the GI absorption of the isopropamide cation cannot be increased in the presence of bile salt molecules through ion-pair formation or mixed micelle formation. A study was conducted to evaluate the influence of dietary calcium carbonate and sodium sulfate in chick rations containing oxytetracycline (1102); the sodium sulfate improved the absorption of oxytetracycline, while calcium carbonate at concentrations greater than 1% inhibited the absorption of oxytetracycline.

Ramachander *et al.* (1103) studied the effect of concurrent administration of choline salicylate and acetaminophen on their mutual biotransformation in

Table XXXVI—Additional References on Absorption Control and Alteration

Reference	Topic
1111	Effect of surfactants on drug absorption, and changes in drug stability in both biosurfactant and synthetic surfactant solutions estimated by thiol-disulfide exchange reaction *in vitro*
1112	Effect of surfactants on drug absorption, and mechanism of action of sodium glycocholate on absorption of benzoylthiamine disulfide in presence of sodium lauryl sulfate and polysorbate 80
1113	Effect of sodium taurodeoxycholate on biological membranes, and release of phosphorus, phospholipid, and protein from everted rat small intestine
1114	Mechanisms of drug absorption and drug solution
1115	Review of relationships among drug plasma concentrations, elimination pathways, extent of renal impairment, and dosage regimen modifications in patients with renal impairment
1116	Review of drug-induced malabsorption
1117	Release of active substance after oral administration of a β-cyclodextrin inclusion compound to humans
1118	Distribution of phenothiazines between aqueous and organic phases and buccal absorption
1119	Quantitative approach to *in vitro* availability of drugs from nonionic surfactant solutions
1120	Review of drugs affecting gastric emptying rate and drug absorption
1121	Modifications of absorption and excretion of trimethoprim and sulfamethoxazole predicted from buccal mucosa
1122	Calculation of rate constants in forward drug transfer reactions
1123	Influence of polysorbate 20 and sodium cholate on uptake of *p*-hydroxybenzoates by frogs, *Rana pipiens*
1124	Programmed release of active drugs from preparations for oral use
1125	Excretion of *trans*-Δ^9-tetrahydrocannabinol and its metabolites in intact and bile duct-cannulated rats
1126	Influence of sodium taurocholate, cholestyramine, and simethicone-containing formulation (Mylanta) on intestinal absorption of glucocorticoids in the rat

the rat. Concurrent administration of the two drugs did not alter the plasma salicylic acid levels but resulted in a slight increase of the plasma acetaminophen values at 5 and 10 min. Differing degrees of glucuronidation of the two drugs may explain this interaction which, however, appeared too low to be of clinical significance. The absorption of a quaternary ammonium compound, *N,N*-bis(phenylcarbamoylmethyl)dimethylammonium chloride, was studied *in situ* in the small intestine of the rat in the presence of salicylate and trichloroacetate (1104), and both significantly enhanced the disappearance of the drug from the intestinal lumen. Both ionic agents exerted their greatest influence on the initial absorption rate of the drug and the effect tended to decline with time thereafter. The effect of fenfluramine on the intestinal absorption of triglycerides was studied; *dl*-fenfluramine hydrochloride decreased plasma triglycerides in fed rats but had no effect in fasted rats (1105). It was postulated that the lowering of the plasma triglycerides by *dl*-fenfluramine hydrochloride was partially due to inhibition of intestinal absorption of triglycerides.

Jaffe and coworkers (1106, 1107) studied the effect of altered urinary pH on tetracycline and doxycycline excretion in humans. Alkalinization of the urine significantly enhanced the cumulative renal excretion of both drugs as compared with acidic urine treatments. Altered tubular reabsorption was considered to have caused this effect, since tetracyclines have been shown to be more lipid soluble at their isoelectric pH (approximately the pH of the acidic urine treatment) than at more alkaline pH's. The effect of food on the GI absorption of amobarbital was studied in the rat (1108). The presence of food in the GI tract decreased significantly the serum and brain levels of amobarbital and also reduced the sleeping time induced by the drug. Since amobarbital is mostly absorbed from the small intestine, it was assumed that the decreased pharmacological activity of amobarbital was due to delayed gastric emptying. The urinary excretion of fenfluramine and ethylamphetamine and their main metabolites norfenfluramine and amphetamine was studied in humans with different urinary pH's as a result of their different diets (1109). More (+)-fenfluramine hydrochloride and (+)-ethylamphetamine hydrochloride were excreted when the urine was acidic. Milk and soluble milk proteins decreased the rate of dialysis of caffeine through semipermeable membranes, indicating complex formation (1110). This was also verified by determining the half-lives of absorption of black coffee and black coffee with milk, which were 15 and 30 min, respectively.

Additional references on absorption control and alteration are listed in Table XXXVI.

Absorption Mechanisms—Levodopa was found to be actively transported in rat intestine (1127). As a result of this active transport, it was suggested that there would be a greater difference in the bioavailability of this drug compared to drugs that are absorbed by passive diffusion alone. The transport and binding of methotrexate in rats were studied following intravenous doses of 0.05, 0.25, 2.5, and 25 mg/kg (1128). The transport was saturable and influenced by a strong intracellular binding. Following intragastric administration of thiazolidinecarboxylic acid (hepalidine) to rats, the drug passed rapidly from the stomach to the intestine, where it was rapidly absorbed in the blood (1129). Thiazolidinecarboxylic acid appeared to be absorbed intact by an active transport mechanism. Sodium warfarin was absorbed in the dissociated form by the human stomach and small intestine by a first-order reaction (1130). Curves obtained after intraduodenal and intravenous administrations gave a good simultaneous fit with a two-compartment model, which included an additional compartment accounting for the delay of sodium warfarin in the gastric mucosa. Sulfobromophthalein was excreted in bile of rats 85 and 81% after intravenous and retrograde biliary administrations, respectively (1131). After administration of sulfobromophthalein by either means, metabolites of the drug were observed in bile. No transformation of

the drug in the bile *in vitro* was detected. The data provided evidence that sulfobromophthalein was absorbed from the biliary system into hepatocytes. The transfer behavior of cephalexin across the everted rat intestine was studied using physiological phosphate buffers (1132), and it appeared that a passive transfer process was involved. The rate of transfer of cephalexin across the everted rat intestine increased as the mucosal solution was made more alkaline.

PHARMACOKINETICS

Not only has the number of papers dealing with pharmacokinetics increased yearly, but for the first time a journal dealing specifically with pharmacokinetics is available, *i.e.*, the *Journal of Pharmacokinetics and Biopharmaceutics*. According to the introductory statement by the editors, this journal will be devoted to illustrating the importance of pharmacokinetics and biopharmaceutics in understanding the mechanisms of drug action, design, therapy, and evaluation.

Pharmacokinetics is the study of the kinetics of absorption, distribution, metabolism, and excretion of drugs and their corresponding pharmacology and therapeutic and toxic responses in animals and humans. As a result of this definition, the section called drug absorption which was reviewed separately in previous years will be combined as one section with pharmacokinetics.

Wagner and Sedman (1133) derived equations that quantitatively describe the rate of GI and buccal absorption of acidic and basic drugs as a function of the pH of aqueous lumenal contents and time. They also derived an equation that describes the renal clearance of acidic or basic drugs as a function of urinary pH. In essence, these equations quantitate the pH–partition hypothesis and explain most related observed data in the literature. The results suggested that the aqueous diffusion layer may not rate-limit absorption of monomeric drug molecules but that absorption was rate limited by transfer of drug out of the membrane *in vivo*. Another model was presented for relating turnover time in goldfish to the concentration of drug in the bathing solution (1134). The model was based on passive transport and the existence of a critical concentration of drug within the fish which was necessary for turnover. The developed model was applied to the dose–response data of eight homologous esters of *p*-aminobenzoic acid.

The most commonly used methods for studying intestinal drug absorption, the *in vitro* everted rat gut and the *in situ* rat intestinal loop, were compared with GI absorption using various penicillins, cephalosporins, and tetracyclines (1135). Based on these observations, the *in situ* intestinal loop of the rat appeared to be the most suitable animal model for predicting human drug absorption.

The principle of area analysis was used in the development of a metabolic and pharmacokinetic model for an extensively biotransformed drug (1136). N_4-Ethoxyacetylsulfamethoxazole and its three biotransformation products were administered intravenously to a monkey on separate occasions. Excellent agreement was obtained between the simulated and the actual blood levels of the intact drug and its three biotransformation products. Pharmacokinetic studies were carried out to determine the possible effects of product inhibition on drug elimination (1137). Theoretical considerations and digital computer simulations showed that an apparent increase in the biological half-life of a drug with increasing dose may result from product inhibition if the dissociation constant for the drug metabolite–enzyme complex is appreciably lower than the Michaelis constant for drug–enzyme complexes, if drug metabolite levels remain relatively constant for some time due to slow elimination of the metabolite, and if the level of drug in the body does not appreciably exceed the apparent *in vivo* Michaelis constant.

Wagner (1138) reviewed some old equations and derived some new equations that indicate certain properties of the Michaelis–Menton equation and its integrated forms. He derived an equation that accurately estimates the slope of the linear decline of concentrations from the values of C_0, k_m, and V_m. It was also pointed out that if a metabolite is formed by Michaelis–Menton kinetics, then: *(a)* one would not expect linear plots of cumulative amount of metabolite excreted in the urine *versus* time, and *(b)* the plasma clearance of the drug would change with dose and would be expected to be different following administration of the same dose in a rapidly available and a slowly available dosage form. The kinetics of a drug eliminated by first-order processes in a perfusion-limited isolated perfused organ system were examined and compared with a compartmental model (1139). In the perfusion model, the mean clearance determined by dividing the dose by the area under the blood concentration profile and the steady-state clearance were shown to be equal. A computer program called COMPT was developed for optimizing the solution of integral compartmental models of drug distribution by nonlinear regression analysis (1140). This version of COMPT was designed to solve the two-compartment open model of intravenous drug administration.

A mathematical analysis was made of the type of results to be expected by the classic pharmacokinetic treatment of plasma level data when, in addition to absorption, the drug was simultaneously lost to an extravascular compartment *via* either a parallel first- or zero-order process (1141). A method was presented to develop individualized dosage regimens for cardiac antiarrhythmic drugs by applying steady-state kinetics to pharmacokinetic parameters obtained from single-dose studies (1142, 1143). Dosage regimen calculations were given for intravenous infusion of lidocaine and for oral administration of procainamide and propranolol. An iterative least-squares method for finding the best fit multiexponential equation to observed data was presented (1144). This computer program, written in ALGOL, permitted the routine fitting of most pharmacokinetic data. Theoretical pharmacokinetics, which included the simple one-

compartment model, the one-compartment model with parallel first-order elimination, the two-compartment model, the multiple-compartment model, and the nonlinear nonhomogeneous multiple-compartment model, were reviewed (1145). A method for calculating oral drug absorption constants with two-compartment disposition, based mainly on the maximum point of the concentration–time curve, was developed further and shown to give stable values when random noise was applied to concentration values (1146). Perrier and Gibaldi (1147) warned that calculation of absorption rate constants from plasma drug concentration–time data by commonly employed methods cannot be performed with any degree of confidence unless the drug is known to be completely absorbed as such.

A mathematical technique for estimating the kinetic parameters that control patient response to oral anticoagulant administration was presented (1148). The technique utilized routinely obtained and recorded data such as anticoagulant dose regimen and prothrombin times. Computer-simulated single and multicompartment analyses on the kinetics of placental drug metabolism indicated the need to characterize fully drug metabolism in the mother (1149). Only a measure of relative exposure provided a meaningful basis for determining the potential effects on the fetus of drugs given to the mother during gestation. A mathematical model incorporating features of current theories of pharmacokinetics was advanced using control system theory and was tested on the pharmacokinetics of digitalis glycosides (1150). An attempt was made to simplify two-compartment models into one-compartment models and to see if they could adequately approximate the two-compartment models and be useful for clinical purposes (1151). A review of the effect of temperature on pharmacokinetics including drug absorption, distribution, metabolism, and excretion was presented (1152), as was a review of pharmacokinetics and molecular modification and their implications in drug design and evaluation (1153).

Last year produced the first report of the American Pharmaceutical Association bioavailability pilot project, which outlined the various pharmacokinetic tests and parameters recommended by the task force (1154). The GI absorption of chlormadinone acetate and norethindrone was studied in a rat *in situ* preparation (1155). Both steroids were absorbed to a greater extent in the intestine. The effects of bile duct cannulation, ethanol, and exogenous bile salts were also investigated. Results of studies with flurazepam hydrochloride using rats demonstrated a rapid and complete absorption of the compound, which was followed by a rapid excretion with no apparent accumulation in any tissue (1156). The blood level profile of flurazepam was also studied in humans (1157). The major metabolite was found to be *N*-desalkylflurazepam, which reached steady-state levels after 7 days.

The absorption, distribution, and metabolic fate of seclazone was studied in the rat, dog, and rhesus monkey (1158). Seclazone was readily absorbed by all species. The half-life of blood radioactivity following oral administration of radioactive drug was 10, 8.5, and 6 hr in the rat, beagle hound, and rhesus monkey, respectively. Following oral administration of fenfluramine hydrochloride in human volunteers, fenfluramine was rapidly absorbed by the intestine, accumulating in the tissues (1159). Two hours after administration, norfenfluramine was detected in the plasma. Both fenfluramine and its metabolite were excreted slowly.

Several studies were done on the absorption, metabolism, and excretion of various drugs, including droperidol in humans (1160); macrolide antibiotic SF-837 in rats, dogs, and humans (1161); ^{14}C-niflumic acid [2-(3-trifluoromethylanilino)nicotinic acid] in dogs and humans (1162); propylthiouracil in albino rats (1163); methimazole in albino rats (1164); oxandrolone in humans (1165); and ^{35}S-2-mercaptopropionylglycine in rats (1166).

Clindamycin hydrochloride was administered both orally and parenterally to rats and dogs (1167). Based upon the identical areas under the plasma *versus* time curves, plus the fact that the distribution of the drug excreted in urine and feces was independent of the route of administration, it was concluded that, after oral administration, the absorption of this drug into the bloodstream was almost complete and little appeared to pass through the GI tract for direct elimination. Based on the metabolic patterns found in the urine of both the rat and the dog dosed with clindamycin hydrochloride, sulfoxidation and *N*-demethylation were the predominant metabolic routes in the rat, while conjugation of glucuronic acid and sulfoxidation were the major pathways in the dog (1168). The *in vivo* absorption patterns of four sulfonamides after administration to rabbits as suppositories, with or without buffer reagents, were compared by estimating the blood concentration of sulfonamide as a function of time (1169). These studies showed that both the rate and extent of absorption of sulfonamides were considerably enhanced by the rectal administration of the buffered suppository.

Doluisio *et al.* (1170) studied the pharmacokinetics of intramuscularly administered kanamycin in normal healthy adults and found them to be independent of dose. Plasma levels were described by a one-compartment body model. Kanamycin serum levels during repetitive dosing were accurately predicted from single-dose studies. The pharmacokinetics of oral and intravenous doses of ampicillin were studied when ampicillin was given directly and as its inactive precursor, hetacillin (1171). The major effect of intravenous hetacillin was that early plasma, urine, and peripheral compartment levels of ampicillin resemble those from a rapid absorption process. In oral use in fasting subjects, ampicillin capsules were absorbed to only 32% while hetacillin capsules were absorbed 38%.

The pharmacokinetics of iodochlorhydroxyquin was studied in humans (1172). A clearcut dose–plasma concentration relationship was obtained, and no evidence of accumulation was found. Clindamycin phosphate, when given intramuscularly or intravenously to humans, was rapidly hydrolyzed in the

serum to active clindamycin (1173). The active drug was then distributed rapidly to other fluids and tissues and was handled similarly after intravenous and intramuscular administrations. In a study of the pharmacokinetics of tetracycline hydrochloride, the absorption of the solid dosage form proceeded by a two-step mechanism: *(a)* dissolution in the stomach, which was a function of the dose, formulation variables of the drug, and the pH of the gastric fluid contents; and *(b)* gastric emptying into the intestine where the lumen fluids are favorable for absorption of drug in solution but contribute very little to the dissolution of the emptied particles unless well formulated (1174). In the presence of sulfaethidole, the serum levels of dicloxacillin and penicillin G were significantly increased while the serum levels of oxacillin, methicillin, and ampicillin were relatively unchanged (1175). The extent of protein binding influenced the renal clearance of the penicillins. As the percent of bound penicillin increased, the renal clearance decreased. The total clearance of penicillins from the body did not exhibit any relationship with the extent of protein binding.

The concentrations of diphenylhydantoin in the blood of male rats after intravenous injection were determined over a sufficiently wide range to permit comparison of rates of decline at the same absolute and relative concentrations (1176). This comparison led to the conclusion that the elimination of diphenylhydantoin in the rat cannot be described by first-order or simple Michaelis–Menten kinetics but was qualitatively consistent with product inhibition of diphenylhydantoin metabolism. A pharmacokinetic analysis of digoxin in humans was applied to digoxin dosage adjustment in severe renal failure (1177). The analysis revealed that digoxin distribution and elimination in humans could be described adequately by a two-compartment open kinetic model. Because of the finding of a pronounced decrease in the apparent volume of distribution of digoxin in severe renal failures, it was suggested that the loading dose be decreased in these patients.

The pharmacokinetics of sotalol in dogs was studied, and unchanged sotalol was excreted up to 90% in the urine (1178). There was no protein binding, and the partition coefficient between plasma and the red blood cells was unity. Pharmacokinetics of diazepam in humans following single intravenous and oral administration and chronic oral administration were studied (1179). The intravenous blood level data were fitted with a three-compartment open-model system containing both a "shallow" and a "deep" compartment. Orally administered diazepam was rapidly and completely absorbed. Following chronic administration, the minimum and the maximum steady-state levels of diazepam were successfully predicted utilizing pharmacokinetic parameters obtained following intravenous administration. The oral bioavailability and pharmacokinetics of soluble and resin-bound forms of amphetamine and phentermine were studied in humans (1180). The one-compartment open model with first-order drug absorption was fitted to the data from each subject by nonlinear regression methods which provided an excellent fit. In both cases, the rate constant for absorption was significantly lower and less variable for the resinated compound.

The pharmacokinetics of ^{3}H-methotrexate were studied in 22 patients with malignancies (1181). Following the intravenous administration, the plasma disappearance was triphasic. It was observed that methotrexate had a long terminal half-life, which may explain the high incidence of toxicity in patients receiving chronic low-dose methotrexate therapy.

Pharmacokinetics of pentobarbital were determined after intravenous administration (1182). Pentobarbital was distributed in at least two kinetically distinct body compartments: *(a)* a central or "serum" compartment, and *(b)* a peripheral or "tissue" compartment. In oral administration, it was found that the presence of food significantly reduced the apparent absorption rate but not the total amount absorbed. In addition, several other papers appeared on the pharmacokinetics of specific drugs: propylthiouracil in humans (1183), warfarin in humans (1184), intravenous theophylline in humans (1185), isosorbide in humans (1186), minocycline in humans (1187), adriamycin in humans (1188), tobramycin and gentamicin in humans (1189), tolbutamide in rabbits (1190), digoxin in humans (1191), (+)-, (−)-, and (±)-hexobarbital in humans (1192), and phentermine and chlorphentermine in rats (1193).

Additional references on pharmacokinetics are listed in Table XXXVII.

Table XXXVII—Additional References on Pharmacokinetics

Reference	Topic	Reference	Topic
1194	Routes of drug administration, and absorption of drugs from GI tract	1200	Review of kinetics of drug absorption, elimination, placental transfer, and biliary excretion
1195	Routes of drug administration, and buccal absorption of drugs	1201	Review of absorption and distribution of drugs in the organism
1196	Routes of drug administration, and subcutaneous and intramuscular injection of drugs	1202	Review of individual pharmacokinetic differences in humans
1197	Routes of drug administration, and absorption, distribution, and excretion of gaseous anesthetics	1203	Review of pharmacokinetics and cell population growth models in cancer chemotherapy
1198	Routes of drug administration, and aerosols	1204	Review and general discussion of pharmacokinetics
1199	Review of absorption, distribution, and excretion of drugs	1205	Biotransformation of iomeglamic acid

(continued)

Table XXXVII—*Continued*

Reference	Topic
1206	Review of absorption, distribution, and metabolism of various classes of drugs in animals and humans
1207	Review of compartmental modeling of pharmacokinetic action
1208	Review of theoretical aspect of pharmacokinetics
1209	Review of role of pharmacokinetics in pharmaceutical research
1210	Review of pharmacokinetics of intravenous injection
1211	Sartorius absorption model for investigating absorption of passively transported drugs *in vitro* with artificial lipid barriers
1212	Effect of route of administration on drug metabolism
1213	Solvent drag influence on intestinal absorption of aminopyrine and antipyrine
1214	Methods of obtaining preliminary estimates to fit two-term exponential model to blood concentration data
1215	Review of implication of biotransformation of a medicament on therapeutic potentiality and dangers of its use
1216	Significance of linear decrease in plasma drug levels for pharmacokinetics
1217	Review of theory and applications concerning intermittent dosing, continuous applications, nonaccumulative dose schedules, and calculation of initial doses
1218	Review of role of pharmacokinetics in biopharmaceutical research
1219	Graphical determination of rate constants of first-order reactions
1220	Definition and determination of important pharmacokinetic parameters for dosage regimen in one-compartment model
1221	Pharmacodynamic model for cell-cycle-specific chemotherapeutic agents
1222	Drug transfer across intact rat intestinal mucosa following surgical removal of serosa and muscularis externa
1223	Absorption, excretion, and urinary metabolic pattern of ^{3}H-albuterol aerosol in humans
1224	Synergistic effect of ampicillin and dicloxacillin, and absorption and excretion
1225	Distribution of aspirin in rumen and corpus tissues of rat stomach during first 4 min after administration
1226	Metabolism of benzydamine hydrochloride, and species differences and identification of unconjugated metabolites in rabbit urine
1227	GI absorption and anti-inflammatory effect of bromelain
1228	Factors influencing intestinal absorption of calcium
1229	Absorption of organic arsenical compounds from rat small intestine
1230	Absorption kinetics of different brands of chloramphenicol
1231	Metabolism of cloxazolam, and distribution, excretion, and biotransformation in rats and mice
1232	Cyclophosphamide metabolism in the rabbit
1233	Intestinal absorption of ^{3}H-digitalis glycosides in experimental animals and humans
1234	Absorption of orally given digoxin preparations
1235	Double peak in the plasma–drug curve after oral digoxin and lanatoside C
1236	GI absorption of iopanoic acid
1237	Physiological disposition of a new diuretic, ^{14}C-metolazone, in dogs
1238	Absorption and distribution of naloxone in rats after oral and intravenous administrations
1239	Absorption of nicotine 1′-*N*-oxide and its reduction in GI tract in humans
1240	Metabolic fate of nitrofuran derivatives, and degradation by small intestinal mucosa and absorption from GI tract
1241	Metabolism of oxaflumazine
1242	Kinetics of absorption of pralidoxime chloride in dogs
1243	Prazepam metabolism in rats
1244	Accumulation and steady-state concentrations during chronic oral administration of propranolol in humans
1245	Excretion and metabolism of reserpine in renal failure
1246	Plasma concentrations and urinary excretions of sulfamethoxazole and trimethoprim in humans
1247	Absorption of drugs from rat lung
1248	Dissolution and absorption of sulfathiazole
1249	Absorption and distribution of ^{14}C-sulfobenzylpenicillin
1250	Absorption of tetracyclines in sheep intestines
1251	Pharmacokinetics of antibacterial activity of a new semisynthetic penicillin, 6-(1-aminocyclohexylcarboxamido)penicillanic acid
1252	Elimination kinetics of amobarbital in mothers and their newborn infants
1253	Comparative study of pharmacokinetics of amphetamine
1254	Effects of diethyl dithiocarbamate and ethanol on *in vivo* metabolism and pharmacokinetics of amphetamine in the rat
1255	Ampicillin pharmacokinetics in mice and humans
1256	Kinetics of three structurally related bicyclic antidepressant compounds in the dog
1257	Routes and kinetics of excretion of arsenic in rats administered organoarsenical drugs
1258	Biopharmaceutical and pharmacokinetic aspects of aspirin intoxication in humans
1259	Pharmacokinetics of apazone-^{14}C (azapropazone-^{14}C) in rats
1260	Pharmacokinetic studies on apazone-^{14}C dihydrate in humans
1261	Absorption, distribution, biotransformation, and excretion of azidocillin in mice, rats, and dogs
1262	Intestinal absorption, intestinal distribution, and excretion of ^{14}C-butylscopolamine in rats
1263	Pharmacokinetics of carbenicillin in neonates of normal and low birth weight
1264	Pharmacokinetic studies of carbenicillin in newborns and prematures
1265	Serum and blood concentration of sodium cephalexin in humans given single intramuscular and intravenous injections
1266	Pharmacokinetics of a new cephalosporin, cephacetrile sodium (CIBA BA 36278A)
1267	Comparative billiary excretion of different cephalosporins
1268	Cephradine absorption and excretion in fasting and nonfasting volunteers
1269	Pharmacokinetics of (2-chlorophenyl)diphenyl-1-imidazolylmethane
1270	Biopharmaceutical evaluation of catechin (cyanidanol) tablets using pharmacokinetic techniques
1271	Metabolism and pharmacokinetics of a new nonsteroid, anti-inflammatory agent, clonixin, in rats, dogs, and monkeys
1272	Pharmacokinetics of creatinol *O*-phosphate
1273	Absorption, organ distribution, and metabolism of diethylaminoethanol after oral administration to rats
1274	Metabolism and excretion of diethylpropion in humans under acidic urine conditions
1275	Pharmacokinetics of digoxin and its 4‴-acetyl and methyl derivatives in rats
1276	Pharmacokinetics of cardiac glycosides, digoxin and digitoxin, in dogs
1277	Metabolism of antihypertensive agent, 1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylic acid diethyl ester
1278	Pharmacokinetics of diphenyl(2-chlorophenyl)-1-imidazolylmethane-^{14}C after topical applications

Table XXXVII—*Continued*

Reference	Topic
1279	Pharmacokinetics and distribution of diphenylhydantoin in kittens
1280	Pharmacokinetic study of patient with diphenylhydantoin toxicity
1281	Pharmacokinetics of dipropylacetamide in rats after oral administration
1282	Absorption, distribution, and excretion of doxapram hydrochloride in rats
1283	Behavior of doxycycline administered orally or intravenously
1284	Effect of route of administration on distribution of ellipticine in mice
1285	Kinetics of entry and distribution of fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate
1286	Pharmacokinetic studies on flupenthixol and flupenthixol decanoate in humans
1287	Pharmacokinetics of ^{14}C-fominoben in rats and gravid mice
1288	Pharmacokinetics of gentamicin after repeated administration
1289	Pharmacokinetics and metabolism of glyburide (glibenclamide) in presence of phenylbutazone
1290	Pharmacokinetics of glibornuride
1291	Pharmacokinetics of guanazole in humans
1292	Pharmacokinetics of heparin and heparinoids
1293	Pharmacokinetics of ^{3}H-hexoprenaline in rats
1294	Pharmacokinetics, toleration, and safety of indanylcarbenicillin in humans
1295	Pharmacokinetics of indomethacin in pregnant women and in parturient women and their newborns
1296	Pharmacokinetics of iron absorption with a new iron preparation
1297	Pharmacokinetics of isoniazid in humans
1298	Comparative pharmacokinetics of a semisynthetic aminoglycoside derived from kanamycin (BB-K8) and kanamycin in dogs and humans
1299	Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans
1300	Half-life, metabolism, and excretion of tritiated luteinizing hormone-releasing hormone in humans
1301	Metronidazole pharmacokinetics in nonpregnant women
1302	Pharmacokinetics of metronidazole and tinidazole in humans
1303	Plasma levels and derived pharmacokinetic characteristics of unchanged nitrazepam in humans
1304	Pharmacokinetics of nortriptyline in humans after single and multiple oral doses, and predictability of steady-state plasma concentrations from single-dose plasma level data
1305	Genetic and pathological basis for individual differences in pharmacokinetics of nortriptyline and diphenylhydantoin in humans
1306	Review on interindividual differences in pharmacokinetics of nortriptyline and diphenylhydantoin
1307	Pharmacokinetics of ^{14}C-labeled penicillamine
1308	Determination and pharmacokinetics of oxacillin and ampicillin on simultaneous administration
1309	Comparative pharmacokinetics of oxazepam and nortriptyline after single oral doses in humans
1310	Pharmacokinetics of pirazocillin in dogs and rats
1311	Pharmacokinetics of polymyxin methanesulfonic acid in rats
1312	Pharmacokinetic studies of practolol in humans
1313	Pharmacokinetics of dextro-, levo-, and racemic propranolol in humans
1314	Pharmacokinetics of rifampin in patients with impaired renal function, before and during hemodialysis
1315	Sodium salicylate pharmacokinetics in dogs
1316	Biotransformation and pharmacokinetics of salicylate in newborn animals
1317	Renal contribution to overall metabolism of drugs, and biotransformation of salicylic acid to salicyluric acid in humans
1318	Pharmacokinetics of capobenate sodium [sodium 6-(3,4,5-trimethoxybenzamido)hexanoate; C-3] in humans
1319	Pharmacokinetics of succinic acid dinitrile in animals and humans
1320	Pharmacokinetics of sulfaclomide in early pregnancy
1321	Pharmacokinetics of sulfaguanole, and multiple-dose kinetics in humans
1322	Absorption, distribution, excretion, and metabolism of sulfamethoxazole in rats
1323	Pharmacokinetics of trimethoprim and its combination with sulfamethoxazole in humans after single and chronic oral administration
1324	Bacteriological and pharmacokinetic studies of sulfamethoxazole–trimethoprim
1325	Pharmacodynamics and pharmacokinetics of sulfamethoxazole and trimethoprim
1326	Pharmacokinetic data of combination of sulfamethoxazole plus trimethoprim in patients with renal impairment
1327	Pharmacokinetics of tetraethylammonium in cats
1328	Uptake and distribution of thiopental after oral, rectal, and intramuscular administration, and effect of hepatic metabolism and injection site blood flow
1329	Pharmacokinetic studies of tobramycin and gentamicin in humans
1330	Pharmacokinetics of trichloroethanol and metabolites, and interconversions among variously referenced pharmacokinetic parameters
1331	Pharmacokinetics of the antibiotic virginiamycin in rats
1332	Pharmacokinetic aspects of drug absorption, distribution, and elimination

REFERENCES

(1) W. J. McKeehan, *J. Pharm. Sci.*, **52**, 613(1963).
(2) W. J. McKeehan and L. C. Lappas, *ibid.*, **53**, 695(1964).
(3) L. C. Lappas and R. E. Dempski, *ibid.*, **54**, 931(1965).
(4) R. E. Dempski and G. P. Polli, *ibid.*, **55**, 645(1966).
(5) G. P. Polli and L. J. Ravin, *ibid.*, **56**, 781(1967).
(6) L. J. Ravin and P. D. Bernardo, *ibid.*, **57**, 1075(1968).
(7) P. D. Bernardo and E. J. Russo, *ibid.*, **58**, 777(1969).
(8) E. J. Russo and T. L. Benney, *ibid.*, **59**, 883(1970).
(9) T. L. Benney and W. E. Hamlin, *ibid.*, **60**, 959(1971).
(10) W. E. Hamlin and A. C. Shah, *ibid.*, **61**, 989(1972).
(11) A. C. Shah and A. K. Herd, *ibid.*, **62**, 1033(1973).
(12) *Ibid.*, **62**, 1217(1973).
(13) J. S. Cox, *Proc. Symp. Disodium Cromoglycate Alleg. Airways Dis.*, **1970**, 13; through *Chem. Abstr.*, **78**, 37764p(1973).
(14) E. Seferowicz, *Przegl. Dermatol.*, **59**, 559(1972); through *Chem. Abstr.*, **78**, 163966u(1973).
(15) G. Jecsai, *Termeszet Vilaga*, **103**, 443(1972); through *Chem. Abstr.*, **78**, 75795g(1973).
(16) W. L. Lund, R. J. McBride, J. B. Murray, and G. Smith, *Pharm. J.*, **211**, 331(1973).
(17) R. M. E. Richards and R. J. McBride, *J. Pharm. Sci.*, **62**, 585(1973).
(18) H. Schott and C. Y. Young, *ibid.*, **62**, 1797(1973).
(19) I. R. Schmolka, *J. Soc. Cosmet. Chem.*, **24**, 577(1973).
(20) M. S. Parker, *Soap Perfum. Cosmet.*, **46**, 223(1973); through *Chem. Abstr.*, **79**, 45643j(1973).
(21) T. J. McCarthy, *Pharm. Weekbl.*, **108**, 449(1973); through *Chem. Abstr.*, **79**, 45735r(1973).
(22) A. Sina, M. K. Youssef, A. A. Kassem, and M. A. Attia, *Indian J. Pharm.*, **35**, 47(1973); through *Chem. Abstr.*, **79**,

70162j(1973).

(23) R. T. Yousef, M. A. El-Nakeeb, and S. Salama, *Pharm. Ind.*, **35**, 154(1973); through *Chem. Abstr.*, **79**, 45758a(1973).

(24) R. T. Yousef, M. A. El-Nakeeb, and S. Salama, *Can. J. Pharm. Sci.*, **8**, 54(1973).

(25) Z. Csath-Stincel and G. Horvath, *Rev. Med. (Tirgu-Mures)*, **18**, 337(1972); through *Chem. Abstr.*, **78**, 88589t(1973).

(26) T. S. Kondrat'eva, L. A. Ivanova, and S. A. Iktisamov, *Zdravookhr. Kaz.*, **7**, 48(1972); through *Chem. Abstr.*, **78**, 75836w(1973).

(27) F. Modrzejewski and B. Gogolewski-Mikucka, *Ann. Acad. Med. Lodz*, **12**, 359(1971); through *Chem. Abstr.*, **79**, 23557g(1973).

(28) R. M. E. Richards and R. J. McBride, *Pharm. J.*, **210**, 118(1973).

(29) A. Fiebig, J. Felczak, B. Pankowska, and B. Woyczikowski, *Farm. Pol.*, **28**, 1145(1972); through *Chem. Abstr.*, **79**, 9847v(1973).

(30) E. Apostolo, D. Gerosa, and P. Zaia, *Boll. Chim. Farm.*, **111**, 637(1972); through *Chem. Abstr.*, **78**, 88583m(1973).

(31) J. I. Yablonski, *Cosmet. Perfum.*, **88**(8), 39(1973).

(32) C. Plachy and V. Hanus, *Prum. Potravin*, **23**, 244(1972); through *Chem. Abstr.*, **78**, 33773t(1973).

(33) K. N. Gaind and K. R. Jain, *Indian J. Pharm.*, **34**, 119(1972); through *Chem. Abstr.*, **78**, 62140q(1973).

(34) W. Schweisheimer, *Fette, Seifen, Anstrichm.*, **75**, 330(1973); through *Chem. Abstr.*, **79**, 57561u(1973).

(35) H. Fuehrer, *Seifen, Oele, Fette, Wachse*, **98**, 677(1972); through *Chem. Abstr.*, **78**, 20096z(1973).

(36) W. Mullen, W. Shepherd, and J. Labovitz, *Surv. Ophthalmol.*, **17**, 469(1973); through *Chem. Abstr.*, **79**, 45679a(1973).

(37) F. S. Skinner, *Informationsdienst, Arbeitsgemeinsch. Pharm. Verfahrenstech.*, **18**, 256(1972); through *Chem. Abstr.*, **79**, 108020b(1973).

(38) F. Jaminet, *Labo-Pharma-Probl. Tech.*, **21**, 43(1973); through *Chem. Abstr.*, **79**, 108014c(1973).

(39) A. A. Sinkula and C. Lewis, *J. Pharm. Sci.*, **62**, 1757(1973).

(40) A. Verain and M. Bienvenu, *Labo-Pharma-Probl. Tech.*, **20**, 53(1972); through *Chem. Abstr.*, **78**, 47681y(1973).

(41) A. Verain and G. Bienvenu, *Bull. Tech., Gattefosse SFPA*, **66**, 29(1971); through *Chem. Abstr.*, **78**, 7774z(1973).

(42) M. Rothe, *Nahrung*, **16**, 473(1973); through *Chem. Abstr.*, **78**, 115105r(1973).

(43) P. L. Bedoukian, *Cosmet. Perfum.*, **88**(4), 3(1973).

(44) H. C. Saunders, *ibid.*, **88**(11), 31(1973).

(45) R. E. M. Randebrock, *Parfums, Cosmet., Savons Fr.*, **3**, 382(1973); through *Chem. Abstr.*, **79**, 129070h(1973).

(46) H. Fuehrer, *Seifen, Oele, Fette, Wachse*, **99**, 173(1973); through *Chem. Abstr.*, **79**, 9763q(1973).

(47) G. Riezos, *Mfg. Chem. Aerosol News*, **44**, 37(1973).

(48) H. Fuehrer, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi Saponi, Cosmet., Aerosol*, **54**, 911(1972); through *Chem. Abstr.*, **78**, 151540n(1973).

(49) V. Lodi, *ibid.*, **54**, 903(1972); through *Chem. Abstr.*, **78**, 140350z(1973).

(50) J. D. Guillaume, *Seifen, Oele, Fette, Wachse*, **98**, 673(1972); through *Chem. Abstr.*, **78**, 20091u(1973).

(51) D. P. Anonis, *Cosmet. Perfum.*, **88**(5), 5(1973).

(52) J. W. Cooper, H. C. Ansel, and D. E. Cadwallader, *J. Pharm. Sci.*, **62**, 1156(1973).

(53) E. C. Gehret, *Tluszcze, Srodki Piorace, Kosmet.*, **17**, 204(1973); through *Chem. Abstr.*, **79**, 129067n(1973).

(54) C. Jouffrey, *Sci. Tech. Pharm.*, **2**, 117(1973); through *Chem. Abstr.*, **79**, 149302p(1973).

(55) S. S. Chang, *Food Technol.*, **27**, 27(1973).

(56) F. S. Tanasienko, *Mezhdunar, Kongr. Efirnym Maslam*, **1**, 327(1971); through *Chem. Abstr.*, **78**, 140339c(1973).

(57) J. Tusakov, *ibid.*, **1**, 371(1971); through *Chem. Abstr.*, **78**, 140335y(1973).

(58) S. Manheimer, *Cosmet. Perfum.*, **88**(6), 3(1973).

(59) S. Sabetay, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **54**, 898(1972); through *Chem. Abstr.*, **78**, 151541p(1973).

(60) A. F. Polyakov, V. V. Osipov, and N. A. Turysheva, *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki*, **49**, 109(1972); through *Chem. Abstr.*, **78**, 20122e(1973).

(61) A. Van der Gen, *Parfums, Cosmet., Savons Fr.*, **2**, 356(1972); through *Chem. Abstr.*, **78**, 7735n(1973).

(62) K. W. Schoenfeld, *Aerosol Rep.*, **12**, 45(1973); through *Chem. Abstr.*, **78**, 163920z(1973).

(63) P. Dupaigne, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **54**, 559(1973); through *Chem. Abstr.*, **78**, 101857a(1973).

(64) O. P. Belozerova, A. G. Daragan, V. M. Avakumov, M. L. Lobanova, A. P. Grishina, Z. V. Statkevich, and M. S. Belyakova, *Khim.-Farm. Zh.*, **7**, 40(1973); through *Chem. Abstr.*, **79**, 23553c(1973).

(65) E. H. Polak, *Cosmet. Perfum.*, **88**(6), 3(1973).

(66) H. Mack and M. Koepsel, *Parfuem. Kosmet.*, **54**, 223(1973); through *Chem. Abstr.*, **79**, 139611z(1973).

(67) R. D. Morris and T. F. Craft, *Int. J. Appl. Radiat. Isotop.*, **24**, 245(1973).

(68) M. I. Blake, K. A. Makris, and J. Tio, *Amer. J. Hosp. Pharm.*, **30**, 441(1973).

(69) C. W. Whitworth, H. W. Jun, and L. A. Luzzi, *J. Pharm. Sci.*, **62**, 1721(1973).

(70) C. W. Whitworth, L. A. Luzzi, B. B. Thompson, and H. W. Jun, *ibid.*, **62**, 1372(1973).

(71) E. Z. Kagan, G. P. Gryadunova, N. S. Smirnova, and N. A. Vakulenko, *Farmatsiya (Moscow)*, **22**, 11(1973); through *Chem. Abstr.*, **79**, 83450b(1973).

(72) E. I. Voropanov, O. I. Belova, and A. P. Arzamastsev, *ibid.*, **22**, 25(1973); through *Chem. Abstr.*, **79**, 9838t(1973).

(73) H. Broda and A. Kurasz, *Farm. Pol.*, **28**, 979(1972); through *Chem. Abstr.*, **78**, 47727t(1973).

(74) G. N. Aristov and V. K. Yashchenko, *Farmatsiya (Moscow)*, **21**, 41(1972); through *Chem. Abstr.*, **78**, 115155g(1973).

(75) J. B. Portnoff, M. W. Henley, and G. P. Polli, *Bull. Parenteral Drug Ass.*, **27**, 84(1973).

(76) G. H. Kronberg and B. H. Takman, *J. Pharm. Sci.*, **62**, 823(1973).

(77) L. Roller, *Aust. J. Pharm. Sci.*, **2**, 20(1973); through *Chem. Abstr.*, **79**, 70155j(1973).

(78) N. D. Weiner, W. C. Bruning, and A. Felmeister, *J. Pharm. Sci.*, **62**, 1202(1973).

(79) S. A. Salakawy and Y. Hammouda, *Pharmazie*, **27**, 595(1972); through *Chem. Abstr.*, **78**, 7785d(1973).

(80) S. A. Fusari, *J. Pharm. Sci.*, **62**, 122(1973).

(81) S. Aldous, R. Nation, and R. Thomas, *Aust. J. Pharm. Sci.*, **1**, 61(1972); through *Chem. Abstr.*, **78**, 163999g(1973).

(82) J. Tingstad and J. Dudzinski, *J. Pharm. Sci.*, **62**, 1856(1973).

(83) A. Stamm and C. Mathis, *J. Pharm. Belg.*, **28**, 328(1973); through *Chem. Abstr.*, **79**, 70178u(1973).

(84) J. Tingstad, J. Dudzinski, L. Lachman, and E. Shami, *J. Pharm. Sci.*, **62**, 1361(1973).

(85) N. Tuchel, *Farmacia (Bucharest)*, **21**, 209(1973); through *Chem. Abstr.*, **79**, 83435a(1973).

(86) L. M. Kleinman, J. A. Tangrea, J. F. Gallelli, J. H. Brown, and E. Gross, *Amer. J. Hosp. Pharm.*, **30**, 1054(1973).

(87) M. Struhar, M. Heliova, V. Springer, M. Chalabala, and J. Majer, *Acta Fac. Pharm., Univ. Comeniana*, **24**, 111(1973); through *Chem. Abstr.*, **79**, 118276d(1973).

(88) W. Horsch, H. Kuehn, and S. Rosenberger, *Pharmazie*, **27**, 613(1972); through *Chem. Abstr.*, **78**, 62096e(1973).

(89) J. Cotte, *Parfums, Cosmet., Savons Fr.*, **3**, 321(1973); through *Chem. Abstr.*, **79**, 57564x(1973).

(90) S. Adamski and E. Pawlak, *Acta Pol. Pharm.*, **29**, 409(1972); through *Chem. Abstr.*, **78**, 47713k(1973).

(91) J. Dolby, B. Gunnarsson, L. Kronberg, and H. Wikner, *Pharm. Acta Helv.*, **47**, 615(1972); through *Chem. Abstr.*, **78**, 47711h(1973).

(92) N. S. Volkova, J. Franco-Betancourt, U. Vasquez, I. Pedroso, and M. Reboso, *Sov.-Kubinsk. Rybokhoz. Issled.*, **3**, 175(1971); through *Chem. Abstr.*, **78**, 47698j(1973).

(93) W. Horsch and H. Kuehn, *Pharmazie*, **28**, 135(1973); through *Chem. Abstr.*, **78**, 128383e(1973).

(94) E. I. Zatula and N. A. Bugrim, *Farmatsiya (Moscow)*, **21**, 72(1972); through *Chem. Abstr.*, **78**, 115157j(1973).

(95) A. Rogers and G. Smith, *Pharm. J.*, **211**, 353(1973).

(96) I. Popa and M. Rosetti, *Farmacia (Bucharest)*, **20**, 585(1972); through *Chem. Abstr.*, **78**, 164022v(1973).

(97) A. Przybilka and B. Linke, *Krankenhaus-Apoth.*, **22**, 28(1972); through *Chem. Abstr.*, **79**, 83440y(1973).

(98) S. Naito and S. Shimizu, *J. Pharm. Sci.*, **62,** 82(1973).
(99) A. Fiebig, J. Felczak, and K. Starostka, *Farm. Pol.*, **29,** 169(1973); through *Chem. Abstr.*, **79,** 35077p(1973).
(100) W. Weglowska and E. Szyszko, *ibid.*, **29,** 309(1973); through *Chem. Abstr.*, **79,** 108025g(1973).
(101) W. E. Gold, *J. Hosp. Pharm.*, **31,** 12(1973); through *Chem. Abstr.*, **78,** 128380b(1973).
(102) S. S. Larsen, *Arch. Pharm. Chemi, Sci. Ed.*, **1,** 541(1973); through *Chem. Abstr.*, **79,** 83444c(1973).
(103) *Ibid.*, **1,** 41(1973); through *Chem. Abstr.*, **79,** 83445d(1973).
(104) E. Azaz, M. Donbrow, and R. Hamburger, *Pharm. J.*, **211,** 15(1973).
(105) N. I. Laricheva, B. A. Marulin, Z. P. Fedorova, N. I. Andrievskii, L. F. Klimenko, and Z. M. Boltanova, *Gematol. Pereliv. Krovi*, **7,** 107(1972); through *Chem. Abstr.*, **78,** 7788g(1973).
(106) V. F. Goren'kov and L. A. Musatova, *Farmatsiya (Moscow)*, **22,** 71(1973); through *Chem. Abstr.*, **79,** 70156k(1973).
(107) G. Milhaud and L. Pinault, *Recl. Med. Vet.*, **149,** 219(1973); through *Chem. Abstr.*, **79,** 9787a(1973).
(108) H. Seydel and R. Voigt, *Pharmazie*, **27,** 660(1972); through *Chem. Abstr.*, **78,** 33869d(1973).
(109) V. D. Pupynina, G. I. Kazakova, and A. K. Abdrashitov, *Sovrem. Probl. Gematol. Pereliv. Krovi*, **41,** 50(1970); through *Chem. Abstr.*, **79,** 70180p(1973).
(110) Y. Datt, *Pharmacos*, **17,** 41(1972); through *Chem. Abstr.*, **79,** 35051a(1973).
(111) S. Vianello, N. Chemello, and O. Cucconi, *Farmaco, Ed. Prat.*, **28,** 65(1973); through *Chem. Abstr.*, **78,** 101940x(1973).
(112) H. Robert, *Prod. Probl. Pharm.*, **27,** 1108(1972); through *Chem. Abstr.*, **78,** 115140y(1973).
(113) W. Grimm, *Pharm. Ind.*, **35,** 79(1973); through *Chem. Abstr.*, **79,** 9825m(1973).
(114) M. Traisnel and H. Robert, *Labo-Pharma-Probl. Tech.*, **21,** 63(1973); through *Chem. Abstr.*, **79,** 70116x(1973).
(115) H. Zacek, *Pharm. Ind.*, **34,** 667(1972); through *Chem. Abstr.*, **78,** 62077z(1973).
(116) D. C. Monkhouse, L. V. Campen, and A. J. Aguiar, *J. Pharm. Sci.*, **62,** 576(1973).
(117) L. W. Brown and A. A. Forist, *ibid.*, **62,** 145(1973).
(118) *Ibid.*, **62,** 1365(1973).
(119) A. A. Forist and D. J. Weber, *J. Pharm. Sci.*, **62,** 318(1973).
(120) M. I. Amin and J. T. Bryan, *ibid.*, **62,** 1768(1973).
(121) R. H. Manzo and M. M. de Bertorello, *ibid.*, **62,** 154(1973).
(122) S. Asakura, *Yakuzaigaku*, **32,** 131(1972); through *Chem. Abstr.*, **79,** 149306t(1973).
(123) B. J. Millard, D. J. Priaulx, and E. Shotton, *J. Pharm. Pharmacol.*, **25,** 24P(1973).
(124) K. Kigasawa, N. Ikari, K. Ohkubo, and S. Haga, *Yakugaku Zasshi*, **93,** 272(1973).
(125) J. P. Hou and J. W. Poole, *J. Pharm. Sci.*, **62,** 783(1973).
(126) J. Philip and D. H. Szulczewski, *ibid.*, **62,** 1479(1973).
(127) T. R. Bates, C. H. Nightingale, and E. Dixon, *J. Pharm. Pharmacol.*, **25,** 470(1973).
(128) N. N. Dement'eva and M. I. Kuleshova, *Farmatsiya (Moscow)*, **22,** 40(1973); through *Chem. Abstr.*, **79,** 70157m(1973).
(129) E. Pawelczyk, M. Opielewicz, and M. Zajac, *Diss. Pharm. Pharmacol.*, **24,** 499(1972); through *Chem. Abstr.*, **78,** 47744w(1973).
(130) D. Brooke, R. E. Davis, and R. J. Bequette, *Amer. J. Hosp. Pharm.*, **30,** 618(1973).
(131) J. C. Etter, *Bull. Tech. Gattefosse SFPA*, **66,** 39(1971); through *Chem. Abstr.*, **78,** 7793e(1973).
(132) C. W. Whitworth, H. W. Jun, and L. A. Luzzi, *J. Pharm. Sci.*, **62,** 1184(1973).
(133) E. Pawelczyk and M. Zajac, *Diss. Pharm. Pharmacol.*, **24,** 491(1972); through *Chem. Abstr.*, **78,** 47743v(1973).
(134) J. Slingsby and D. A. Zuck, *Can. J. Pharm. Sci.*, **7,** 115(1972); through *Chem. Abstr.*, **78,** 62126q(1973).
(135) D. P. Vaughan and A. H. Beckett, *J. Pharm. Pharmacol.*, **25,** 993(1973).
(136) I. Grabowska, R. Kaliszan, and P. Zoga, *Acta Pol. Pharm.*, **30,** 173(1973); through *Chem. Abstr.*, **79,** 108049t(1973).
(137) I. Racz, P. Spiegl, and K. Jentzsch, *Acta Pharm. Hung.*, **43,** 18(1973); through *Chem. Abstr.*, **78,** 164024w(1973).
(138) K. Howorka, B. Howorka, and R. Meyer, *Pharmazie*, **28,** 136(1973); through *Chem. Abstr.*, **78,** 128395k(1973).
(139) L. Faith, D. Georch, and V. Springer, *Cesk. Farm.*, **21,** 353(1972); through *Chem. Abstr.*, **78,** 128391f(1973).
(140) G. I. Loseva and N. I. Shukailo, *Antibiotiki (Moscow)*, **17,** 895(1972); through *Chem. Abstr.*, **78,** 7786e(1973).
(141) K. D. Schlecht and C. W. Frank, *J. Pharm. Sci.*, **62,** 258(1973).
(142) R. C. Lanman, T. M. Ludden, and L. S. Schanker, *ibid.*, **62,** 1461(1973).
(143) B. Lynn, *Pharm. J.*, **210,** 19(1973).
(144) A. A. Kassem and E. H. Girgis, *Bull. Fac. Pharm., Cairo Univ.*, **10,** 275(1973); through *Chem. Abstr.*, **79,** 9817k(1973).
(145) M. S. De Buochberg, J. Allegrini, M. Zuccarelli, and C. Bessiere, *Trav. Soc. Pharm. Montpellier*, **32,** 191(1972); through *Chem. Abstr.*, **78,** 33864y(1973).
(146) A. E. Elkouly, N. A. Elsayed, and A. M. Motawi, *Mfg. Chem. Aerosol News*, **44**(8), 37(1973).
(147) S. Shadomy, D. L. Brummer, and A. V. Ingroff, *Amer. Rev. Resp. Dis.*, **107,** 303(1973); through *Chem. Abstr.*, **78,** 115177r(1973).
(148) J. M. T. Hamilton-Miller, *J. Pharm. Pharmacol.*, **25,** 401(1973); through *Chem. Abstr.*, **79,** 35087s(1973).
(149) J. Konecny, E. Felber, and G. Bruner, *J. Antibiot.*, **26,** 135(1973).
(150) D. Mitev, *Farmatsiya (Sofia)*, **22,** 24(1972); through *Chem. Abstr.*, **79,** 9829r(1973).
(151) V. D. Kartseva, B. P. Bruns, N. G. Kruzhkova, and N. A. Bannova, *Khim.-Farm. Zh.*, **6,** 54(1972); through *Chem. Abstr.*, **78,** 33881b(1973).
(152) H. Koch and M. Koch, *Deut. Gesundheitsw.*, **28,** 245(1973); through *Chem. Abstr.*, **79,** 9824k(1973).
(153) M. Dakie and M. Peric, *Tehnol. Mesa*, **13,** 314(1972); through *Chem. Abstr.*, **78,** 164028b(1973).
(154) A. A. Kassem and E. H. Girgis, *Bull. Fac. Pharm., Cairo Univ.*, **10,** 239(1973); through *Chem. Abstr.*, **79,** 9867b(1973).
(155) L. I. Loginova and I. A. Orlov, *Khim.-Farm. Zh.*, **7,** 36(1973); through *Chem. Abstr.*, **79,** 118267b(1973).
(156) P. Antolik, P. Veber, J. Lesko, and L. Hana, *Cesk. Fysiol.*, **21,** 353(1972); through *Chem. Abstr.*, **79,** 70163k(1973).
(157) J. R. Wattimena, C. Siregar, S. Kosasih, and A. Emielizar, *Acta Pharm.*, **3,** 116(1972); through *Chem. Abstr.*, **79,** 70175r(1973).
(158) L. Hosia and H. A. M. El-Shibini, *Farm. Aikak.*, **81,** 167(1972); through *Chem. Abstr.*, **78,** 128381c(1973).
(159) *Ibid.*, **81,** 133(1972); through *Chem. Abstr.*, **78,** 128384f(1973).
(160) L. B. Sokolov, K. M. Nichugovskaya, and Y. F. Sveshnikov, *Antibiotiki (Moscow)*, **17,** 793(1972); through *Chem. Abstr.*, **78,** 24066n(1973).
(161) A. I. Cohen, P. T. Funke, and M. S. Puar, *J. Pharm. Sci.*, **62,** 1559(1973).
(162) Z. M. Akopyan, *Biol. Zh. Arm.*, **26,** 84(1973); through *Chem. Abstr.*, **79,** 118266a(1973).
(163) E. Otero Aenlle and J. R. Chantres Antoranz, *An. Real Acad. Farm.*, **38,** 253(1972); through *Chem. Abstr.*, **78,** 75827u(1973).
(164) E. I. Kozlov, R. A. Ivanova, L. S. Savosina, and V. V. Klyuchkin, *Khim.-Farm. Zh.*, **7,** 40(1973); through *Chem. Abstr.*, **79,** 96907f(1973).
(165) T. Anmo, M. Washitake, Y. Takashima, M. Isohata, M. Furuya, and K. Koike, *Vitamins*, **46,** 193(1972); through *Chem. Abstr.*, **78,** 7791c(1973).
(166) A. Popovici, *Farmacia (Bucharest)*, **21,** 109(1973); through *Chem. Abstr.*, **79,** 70159p(1973).
(167) L. A. Lyubavina, V. M. Melekhova, O. A. Sevryugina, and A. S. Girich, *Vop. Pitan.*, **31,** 72(1972); through *Chem. Abstr.*, **78,** 33863x(1973).
(168) R. D. McAlpine, M. Cocivera, and H. Chen, *Can. J. Chem.*, **51,** 1682(1973).
(169) T. Yamaha, S. Nambaru, and T. Adachi, *Eisei Shikenjo Hokoku*, **90,** 53(1972); through *Chem. Abstr.*, **78,** 164010q(1973).
(170) Z. Olszewski, H. Krutul, and U. Tarantowicz, *Farm. Pol.*, **29,** 157(1973); through *Chem. Abstr.*, **79,** 70174q(1973).
(171) R. Valerio and R. Bottoni, *Farmaco, Ed. Prat.*, **28,**

276(1973); through *Chem. Abstr.*, **79,** 35089u(1973).

(172) R. E. Phares and J. Hramchenko, *Drug Cosmet. Ind.*, **112**(4), 62(1973).

(173) H. M. Scott, *J. Soc. Cosmet. Chem.*, **24,** 65(1973).

(174) G. A. Harrewijn, D. A. A. Mossel, and J. De Groote, *Ned. Melk-Zuiveltijdschr.*, **26,** 141(1972); through *Chem. Abstr.*, **78,** 115150b(1973).

(175) M. Picault, *Fr. Pharm.*, **26,** 67(1973); through *Chem. Abstr.*, **79,** 9795b(1973).

(176) P. Contreras, M. Lladser, and A. Arancibia, *Farmaco, Ed. Prat.*, **27,** 552(1972); through *Chem. Abstr.*, **78,** 7803h(1973).

(177) I. Gorina, A. Slutskova, G. Ryzhkova, and Y. Eremin, *Tr. Kalinin. Politekh. Inst.*, **13,** 133(1972); through *Chem. Abstr.*, **78,** 75839z(1973).

(178) J. A. Kitchener, *J. Soc. Cosmet. Chem.*, **24,** 709(1973).

(179) T. Okada, K. Itoh, and S. Kitani, *J. Colloid Interface Sci.*, **42,** 88(1973).

(180) J. B. Schwartz, J. R. Flamholz, and R. H. Press, *J. Pharm. Sci.*, **62,** 1165(1973).

(181) M. Chalabala, M. Heliova, I. Lichnerova, J. Rak, J. Maly, J. Slany, and J. Starha, *Cesk. Farm.*, **21,** 411(1972); through *Chem. Abstr.*, **78,** 115147f(1973).

(182) V. P. Safonov, P. V. Lipatin, and T. P. Litvinova, *Farmatsiya (Moscow)*, **22,** 16(1973); through *Chem. Abstr.*, **78,** 128397n(1973).

(183) I. A. Murav'ev and V. G. Nazarova, *ibid.*, **22,** 20(1973); through *Chem. Abstr.*, **79,** 9837s(1973).

(184) G. Katsui, *Yukagaku*, **21,** 719(1972); through *Chem. Abstr.*, **78,** 47676a(1973).

(185) T. Sato, H. Terada, and F. Ozawa, *Asahi Garasu Kogyo Gijutsu Shoreikai Kenkyu Hokoku*, **21,** 233(1972); through *Chem. Abstr.*, **79,** 58031h(1973).

(186) I. Mladenov, M. Nedev, S. Srebrova-Nedeva, and D. Abadzhiev, *Farmatsiya (Sofia)*, **22,** 16(1972); through *Chem. Abstr.*, **79,** 9834p(1973).

(187) H. Broda, *Ann. Pharm. (Poznan)*, **10,** 93(1973); through *Chem. Abstr.*, **79,** 35105w(1973).

(188) G. Brigand, *Parfums, Cosmet., Savons Fr.*, **2,** 414(1972); through *Chem. Abstr.*, **78,** 33774u(1973).

(189) O. N. Yalcindag, *Turk Hij. Tecr. Biyol. Derg.*, **32,** 164(1972); through *Chem. Abstr.*, **78,** 163964s(1973).

(190) R. L. Baticle, *Labo-Pharma-Probl. Tech.*, **21,** 33(1973); through *Chem. Abstr.*, **78,** 163971s(1973).

(191) G. A. Stayukha, V. E. Goryushko, and V. S. Mikhailov, *Khim. Teknol. (Kiev)*, **1,** 45(1973); through *Chem. Abstr.*, **78,** 164017x(1973).

(192) B. Idson, *Drug Cosmet. Ind.*, **112**(2), 38(1973).

(193) M. J. Groves, *Pharm. J.*, **210,** 185(1973).

(194) *Ibid.*, **211,** 163(1973).

(195) *Ibid.*, **211,** 166(1973).

(196) A. Williams and M. I. Barnett, *Pharm. J.*, **211,** 190(1973).

(197) J. Masuda and J. Beckerman, *Amer. J. Hosp. Pharm.*, **30,** 72(1973).

(198) R. C. Hohmann, N. Conca, and K. P. Munnelly, *Bull. Parenteral Drug Ass.*, **27,** 96(1973).

(199) T. G. Somerville and M. Gibson, *Pharm. J.*, **211,** 128(1973).

(200) S. J. Turco and N. M. Davis, *Amer. J. Hosp. Pharm.*, **30,** 611(1973).

(201) Y. S. Lim, S. Turco, and N. M. Davis, *ibid.*, **30,** 518(1973).

(202) P. B. Ryan, R. P. Rapp, P. P. DeLuca, W. O. Griffin, Jr., J. D. Clark, and D. Cloys, *Bull. Parenteral Drug Ass.*, **27,** 1(1973).

(203) S. J. Turco and N. M. Davis, *ibid.*, **27,** 207(1973).

(204) R. M. Gesler, P. J. Garvin, B. Klamer, R. U. Robinson, C. R. Thompson, W. R. Gibson, F. C. Wheeler, and R. G. Carlson, *ibid.*, **27,** 101(1973).

(205) R. L. Nedich, *ibid.*, **27,** 228(1973).

(206) A. K. Singla, *Pharmacos*, **17,** 47(1972); through *Chem. Abstr.*, **79,** 35055e(1973).

(207) M. B. Pinckney, Jr., L. A. Luzzi, and J. C. Price, *J. Pharm. Sci.*, **62,** 1863(1973).

(208) M. B. Pinckney, Jr., L. A. Luzzi, and T. E. Needham, Jr., *ibid.*, **62,** 80(1973).

(209) L. Ernerot, S. Thoren, and E. Sandell, *Acta Pharm. Suecica*, **10,** 141(1973); through *Chem. Abstr.*, **79,** 45698f(1973).

(210) M. Bornstein, J. C. Boylan, and D. K. Koenig, *Amer. J. Hosp. Pharm.*, **30,** 793(1973).

(211) I. G. Brizell and J. Shatwell, *Pharm. J.*, **211,** 73(1973).

(212) G. E. Greene, *Bull. Parenteral Drug Ass.*, **27,** 195(1973).

(213) J. A. Bashir and K. E. Avis, *ibid.*, **27,** 68(1973).

(214) A. T. Florence, A. W. Jenkins, and A. H. Loveless, *J. Pharm. Pharmacol.*, **25,** 120P(1973).

(215) U. Hiort, *Deut. Apoth.-Ztg.*, **113,** 749(1973); through *Chem. Abstr.*, **79,** 57632(1973).

(216) B. K. Apte, *East. Pharm.*, **15,** 27(1972); through *Chem. Abstr.*, **78,** 128366b(1973).

(217) M. Todorova and I. Georgieva-Borisova, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, **8,** 463(1972); through *Chem. Abstr.*, **78,** 164037d(1973).

(218) *Ibid.*, **8,** 469(1972); through *Chem. Abstr.*, **78,** 164036c(1973).

(219) J. Polderman, *Labo-Pharma-Probl. Tech.*, **20,** 65(1972); through *Chem. Abstr.*, **78,** 47682z(1973).

(220) H. Jacobson and I. Gibbs, *J. Pharm. Sci.*, **62,** 1543(1973).

(221) A. Benitez Diaz, *Medicamenta, Ed. Farm.*, **40,** 259(1972); through *Chem. Abstr.*, **79,** 96900y(1973).

(222) E. Hvidberg, T. Bols, and N. Jacobsen, *Ugeskr. Laeger*, **135,** 1221(1973); through *Chem. Abstr.*, **79,** 108015d(1973).

(223) D. Ziedler, *Farm. Pol.*, **29,** 499(1973); through *Chem. Abstr.*, **79,** 108013b(1973).

(224) B. Lynn and A. Jones, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1,** 701(1972); through *Chem. Abstr.*, **79,** 23547d(1973).

(225) W. R. Wilkinson, L. L. Flores, and J. N. Pagones, *Drug Intel. Clin. Pharm.*, **7,** 226(1973).

(226) E. Selles-Flores and M. P. Lopez-Ayllon, *Galenica Acta*, **24,** 95(1971); through *Chem. Abstr.*, **78,** 101905q(1973).

(227) K. Kottke and F. Friedrich, *Pharmazie*, **28,** 43(1973); through *Chem. Abstr.*, **78,** 115202v(1973).

(228) M. K. Gluzman and N. M. Nikolaeva, *Farm. Zh. (Kiev)*, **27,** 57(1972); through *Chem. Abstr.*, **78,** 101949g(1973).

(229) E. Trandafilova, *Farmatsiya (Sofia)*, **23,** 53(1973); through *Chem. Abstr.*, **79,** 45671s(1973).

(230) O. I. Belova, V. V. Karchevskaya, and N. J. Bessonova, *Farmatsiya (Moscow)*, **21,** 22(1972); through *Chem. Abstr.*, **78,** 33888j(1973).

(231) A. Genova and P. Papazova, *Farmatsiya (Sofia)*, **22,** 25(1972); through *Chem. Abstr.*, **78,** 164014u(1973).

(232) A. Genova, S. Banikova, M. Todorova, and M. Bakalova, *Tr. Nauchnoizsled Khim.-Farm. Inst.*, **7,** 367(1972); through *Chem. Abstr.*, **78,** 164035b(1973).

(233) M. Todorova and A. Genova, *ibid.*, **8,** 441(1972); through *Chem. Abstr.*, **78,** 164038e(1973).

(234) M. Todorova, *ibid.*, **8,** 435(1972); through *Chem. Abstr.*, **78,** 164054g(1973).

(235) R. Greppin and B. T. Nguyen, *Oesterr. Apoth. Ztg.*, **27,** 125(1973); through *Chem. Abstr.*, **78,** 164066n(1973).

(236) H. Bour, *Prod. Probl. Pharm.*, **27,** 1085(1972); through *Chem. Abstr.*, **78,** 115141z(1973).

(237) G. Takacsi Nagy, *Gyogyszereszet*, **16,** 361(1972); through *Chem. Abstr.*, **78,** 47685c(1973).

(238) R. Huettenrauch, J. Jacob, and I. Benesch, *Pharmazie*, **27,** 797(1972); through *Chem. Abstr.*, **78,** 75851x(1973).

(239) A. Uhlir, *Pharm. Ind.*, **35,** 356(1973); through *Chem. Abstr.*, **79,** 108029m(1973).

(240) D. F. Spooner, *Bull. Parenteral Drug Ass.*, **27,** 257(1973).

(241) P. A. Kiritsy and R. Engvale, *ibid.*, **27,** 279 (1973).

(242) S. S. Chrai, T. F. Patton, A. Mehta, and J. R. Robinson, *J. Pharm. Sci.*, **62,** 1112(1973).

(243) W. Mullen, W. Shepard, and J. Labovitz, *Surv. Ophthalmol.*, **17,** 469(1973).

(244) I. Rucker, R. Kettrey, F. Bach, and L. Zeleznick, *Ann. Ophthalmol.*, **4,** 1000(1972); through *Chem. Abstr.*, **78,** 33890d (1973).

(245) D. W. Newton, C. H. Becker, and G. Torosian, *J. Pharm. Sci.*, **62,** 1538(1973).

(246) J. L. O'Neill, G. P. Polli, and D. T. K. Fong, *Bull. Parenteral Drug Ass.*, **27,** 201(1973).

(247) A. Brunzell and G. Nilsson, *Acta Pharm. Suecica*, **10,** 247(1973); through *Chem. Abstr.*, **79,** 57635w(1973).

(248) R. Prans, I. Bretteschneider, L. Krejci, and D. Kalvodova, *Ophthalmologica*, **165,** 62(1972); through *Chem. Abstr.*, **79,**

9827p(1973).
(249) H. M. Scott, *Pharma Int., Engl. Ed.*, **4**, 20(1972); through *Chem. Abstr.*, **78**, 101899r(1973).
(250) M. C. Allwood and R. Hambleton, *J. Pharm. Pharmacol.*, **25**, 559(1973).
(251) M. C. Allwood, *Lab. Pract.*, **22**, 532(1973); through *Chem. Abstr.*, **79**, 70165n(1973).
(252) C. W. Bruch, *Aust. J. Pharm. Sci.*, **2**, 1(1973); through *Chem. Abstr.*, **79**, 70124y(1973).
(253) G. Y. Kivman, E. A. Aslamazova, S. N. Milovanova, V. A. Slashcheva, G. A. Sapozhnikova, V. S. Pozdnyakova, and N. I. Kalamova, *Khim.-Farm. Zh.*, **7**, 46(1973); through *Chem. Abstr.*, **78**, 115196w(1973).
(254) S. R. Andersen, *Bull. Parenteral Drug Ass.*, **27**, 49(1973).
(255) J. D. White and T. J. Bradley, *J. Pharm. Sci.*, **62**, 1634(1973).
(256) T. O. McDonald, K. Kasten, R. Hervey, S. Gregg, A. R. Borgmann, and T. Murchison, *Bull. Parenteral Drug Ass.*, **27**, 153(1973).
(257) R. F. Schmitt, J. J. Brennan, and R. Berube, *ibid.*, **27**, 15(1973).
(258) S. G. Schulman, *J. Pharm. Sci.*, **62**, 1745(1973).
(259) K. G. Gupta, K. K. Vyas, and N. S. Sekhon, *ibid.*, **62**, 841(1973).
(260) E. S. Saleh and D. J. Hook, *J. Hosp. Pharm.*, **30**, 276(1972); through *Chem. Abstr.*, **78**, 47776h(1973).
(261) S. A. Grachev, B. A. Chakchir, and L. D. Ryabykh, *Khim.-Farm. Zh.*, **7**, 47(1973); through *Chem. Abstr.*, **79**, 70192u(1973).
(262) F. Takuma and J. Sato, *Ikakikaigaku Zasshi*, **42**, 352(1972); through *Chem. Abstr.*, **79**, 70195x(1973).
(263) E. A. Scheuermann, *Pharma Int., Engl. Ed.*, **3**, 5(1972); through *Chem. Abstr.*, **78**, 62080v(1973).
(264) W. Suess and J. E. Jena, *Pharmazie*, **27**, 615(1972); through *Chem. Abstr.*, **78**, 33906p(1973).
(265) W. Kuezel and E. Zillgith, *ibid.*, **28**, 205(1973); through *Chem. Abstr.*, **79**, 9791x(1973).
(266) J. C. Dearden and G. R. Weeks, *J. Pharm. Sci.*, **62**, 843(1973).
(267) J. C. Guichard, *Ann. Anesthesiol. Fr.*, **13**, 344(1972); through *Chem. Abst*, **79**, 9798e(1973).
(268) J. Borneff, *Gesundheitsw. Desinfek.*, **65**, 65(1973); through *Chem. Abstr.*, **79**, 70194w(1973).
(269) H. P. Hortig, *Bull. Parenteral Drug Ass.*, **27**, 38(1973).
(270) W. A. Hennig, H. S. Stern, R. J. Lanza, and Y. S. Murthy, *ibid.*, **27**, 30(1973).
(271) G. W. Riedel and E. C. D. Todd, *Can. J. Pharm. Sci.*, **8**, 23(1973).
(272) H. D. Hochstein, R. J. Elfin, J. F. Cooper, E. B. Seligmann, Jr., and S. M. Wolff, *Bull. Parenteral Drug Ass.*, **27**, 139(1973).
(273) E. Aspostolo, E. Lanzarotti, and P. Zaia, *Farmaco, Ed. Prat.*, **28**, 115(1973); through *Chem. Abstr.*, **78**, 115197x(1973).
(274) M. Olariu and Z. Csath, *Rev. Med. (Tirgu-Mures)*, **18**, 468(1972); through *Chem. Abstr.*, **78**, 164033z(1973).
(275) H. Radermacher, *Krankenhaus-Apoth.*, **22**, 36(1972); through *Chem. Abstr.*, **78**, 101974m(1973).
(276) K. Kereluk and R. A. Gammon, *Develop. Ind. Microbiol.*, **13**, 399(1972); through *Chem. Abstr.*, **78**, 115200t(1973).
(277) B. Roquefeuil, M. Gaucher, and J. Du Cailar, *Ann. Anesthesiol. Fr.*, **13**, 357(1972); through *Chem. Abstr.*, **79**, 9868c(1973).
(278) F. Roujas, *ibid.*, **13**, 367(1972); through *Chem. Abstr.*, **79**, 9871y(1973).
(279) F. Cambrosio, *Informationsdienst, Arbeitsgemeinsch. Pharm. Verfahrenstech.*, **18**, 213(1972); through *Chem. Abstr.*, **79**, 108021c(1973).
(280) K. E. Schulte and G. Henke, *Arch. Pharm. (Weinheim)*, **306**, 182(1973); through *Chem. Abstr.*, **78**, 164002p(1973).
(281) G. Hangay, T. Bartha, I. Janovszky, P. Gere, and L. Kuti, *Izotoptechnika*, **15**, 526(1972); through *Chem. Abstr.*, **78**, 164067p(1973).
(282) T. Oba, T. Horibe, H. Kikuchi, and J. Mori, *Eisei Shikenjo Hokoku*, **90**, 15(1972); through *Chem. Abstr.*, **78**, 164068q(1973).
(283) J. Blazek, *Pharmazie*, **28**, 339(1973); through *Chem. Abstr.*, **79**, 57653a(1973).
(284) R. T. Chkhaidze, T. K. Bakhtadze, U. D. Bregvadze, T. I. Darchiashvili, R. B. Chelishvili, and A. I. Tavberidze, *Tr. Gruz. Nauch.-Issled. Inst. Pishch. Prom.*, **4**, 296(1971); through *Chem. Abstr.*, **78**, 33789c(1973).
(285) H. Ploesch, *Apothekerprakt. Pharm.-Tech. Assistent*, **19**, 17(1973); through *Chem. Abstr.*, **79**, 9792y(1973).
(286) K. Ruig, *Pharm. J.*, **211**, 301(1973).
(287) A. Lavie, *Soc. Tech. Pharm. Lyons, Fr.*, **1**, 79(1972); through *Chem. Abstr.*, **79**, 45666u(1973).
(288) M. Galinski, S. Ivanoff, and J. Laurenty, *Ann. Anesthesiol. Fr.*, **13**, 421(1972); through *Chem. Abstr.*, **78**, 128402k(1973).
(289) K. Nankov, T. Kutsarova, and R. Ovcharov, *Farmatsiya (Sofia)*, **22**, 31(1972); through *Chem. Abstr.*, **78**, 164013t(1973).
(290) H. G. Patzwaldt, D. Winkler, F. Oberdoerster, V. Lukaszewicz, J. Fabig, G. Janetzky, E. Stahl, and I. Gabriel, *Pharmazie*, **27**, 603(1972); through *Chem. Abstr.*, **78**, 62086b(1973).
(291) F. Cirotteau, *Ann. Anesthesiol. Fr.*, **13**, 353(1972); through *Chem. Abstr.*, **79**, 9797d(1973).
(292) I. Christenson and B. Jansson, *Sv. Farm. Tidskr.*, **77**, 120(1973); through *Chem. Abstr.*, **78**, 151583d(1973).
(293) C. Sonntag, *Z. Militaermed.*, **13**, 330A(1972); through *Chem. Abstr.*, **78**, 115198y(1973).
(294) J. C. Ghnassia, *Ann. Anethesiol. Fr.*, **13**, 337(1972); through *Chem. Abstr.*, **79**, 9799f(1973).
(295) J. B. Schwartz, J. R. Flamholz, and R. H. Press, *J. Pharm. Sci.*, **62**, 1518(1973).
(296) R. F. Waterman, E. D. Sumner, J. N. Baldwin, and F. W. Warren, *ibid.*, **62**, 1317(1973).
(297) H. Masayoshi, *Nippon Yakuzaishikai Zasshi*, **24**, 14(1972); through *Chem. Abstr.*, **78**, 47687e(1973).
(298) M. Sugihara, *ibid.*, **24**, 21(1972); through *Chem. Abstr.*, **78**, 62075x(1973).
(299) J. Jacob, *Zentralbl. Pharm., Pharmakother. Laboratoriumsdiagn.*, **111**, 1235(1972); through *Chem. Abstr.*, **78**, 128367c(1973).
(300) Y. Takahama and T. Hitoshi, *Kyushu Yakugakkai Kaiho*, **25**, 37(1972); through *Chem. Abstr.*, **78**, 101958j(1973).
(301) A. La Manna, *Sci. Tech. Pharm.*, **1**, 581(1972); through *Chem. Abstr.*, **79**, 45689d(1973).
(302) A. La Manna, *Pharm. Ind.*, **34**, 840(1972); through *Chem. Abstr.*, **78**, 101904p(1973).
(303) M. L. Ezerskii, L. A. Travina, and S. I. Eidel'shtein, *Khim.-Farm. Zh.*, **6**, 52(1972); through *Chem. Abstr.*, **78**, 33893g(1973).
(304) J. D. Pomfret, *J. Soc. Cosmet. Chem.*, **24**, 593(1973).
(305) B. M. Hunter, *J. Pharm. Pharmacol.*, **25**, 111p(1973).
(306) J. N. C. Healey, J. F. Humphreys-Jones, and V. Walters, *ibid.*, **25**, 109p(1973).
(307) H. J. Malinowski, *Diss. Abstr., Int.*, **34**, 2748B(1973).
(308) J. L. Terrier, D. Duchene, J. Clerc, and F. Puisieux, *Ann. Pharm. Fr.*, **30**, 827(1972); through *Chem. Abstr.*, **78**, 151607q(1973).
(309) B. M. Hunter and D. Ganderton, *J. Pharm. Pharmacol.*, **25**, 71P(1973).
(310) A. R. Gupte, *Pharm. Ind.*, **35**, 17(1973); through *Chem. Abstr.*, **78**, 164052e(1973).
(311) B. Terrier de la Chaise and F. Le Perdriel, *ibid.*, **34**, 823(1972); through *Chem. Abstr.*, **78**, 101955f(1973).
(312) V. I. Gorodnichev, G. N. Borisov, and V. I. Egorova, *Khim.-Farm. Zh.*, **6**, 58(1972); through *Chem. Abstr.*, **78**, 88579q(1973).
(313) S. M. Reprintseva, N. V. Fedorovich, N. M. Syroid, and K. G. Chizhik, *Teplo-Massoperenos, Dokl. Vses. Soveshch., 4th*, **6**, 270(1972); through *Chem. Abstr.*, **78**, 115170h(1973).
(314) C. Pitkin and J. T. Carstensen, *J. Pharm. Sci.*, **62**, 1215(1973).
(315) B. Terrier de La Chaise and F. Le Perdriel, *Sci. Tech. Pharm.*, **1**, 545(1972); through *Chem. Abstr.*, **79**, 45695c(1973).
(316) N. Kaneniwa and A. Ikekawa, *Chem. Pharm. Bull.*, **21**, 1539(1973).
(317) G. Schepky, *Pharm. Ind.*, **34**, 752(1972); through *Chem. Abstr.*, **78**, 115154f(1973).
(318) S. S. Srivastava, *Indian Chem. Mfg.*, **11**, 33(1973); through *Chem. Abstr.*, **79**, 83413s(1973).
(319) G. Takacs, P. Fekete, and L. Szilagyi, *Magy. Kem. Lapja*, **26**, 465(1971); through *Chem. Abstr.*, **79**, 108022d(1973).
(320) O. Woerts, *Pharma Int., Engl. Ed.*, **6**, 12(1972); through *Chem. Abstr.*, **78**, 151586g(1973).

(321) O. Woerts, *Pharm. Ind.*, **34**, 820(1972); through *Chem. Abstr.*, **78**, 101951b(1973).

(322) O. Woerts, *Sci. Tech. Pharm.*, **1**, 539(1972); through *Chem. Abstr.*, **79**, 45696d(1973).

(323) M. Poulet and P. Guiot, *ibid.*, **1**, 557(1972); through *Chem. Abstr.*, **79**, 45690x(1973).

(324) K. Ahmed and G. M. A. S. Khan, *Bangladesh Pharm. J.*, **2**, 23(1973); through *Chem. Abstr.*, **79**, 83447f(1973).

(325) J. T. Fell, *J. Pharm. Pharmacol.*, **25**, 109P(1973).

(326) E. Shotton and B. A. Obiorah, *ibid.*, **25**, 37P(1973).

(327) K. Kurihara and I. Ichikawa, *Chem. Pharm. Bull.*, **21**, 2278(1973).

(328) T. Eaves and T. M. Jones, *J. Pharm. Pharmacol.*, **25**, 729(1973).

(329) E. N. Hiestand, S. C. Valvani, C. B. Peot, E. P. Strzelinski, and J. F. Glasscock, Jr., *J. Pharm. Sci.*, **62**, 1513(1973).

(330) R. C. Rowe, P. H. Elworthy, and D. Ganderton, *J. Pharm. Pharmacol.*, **25**, 12P(1973).

(331) K. Nikolics, *Gyogyszereszet*, **17**, 48(1973); through *Chem. Abstr.*, **78**, 115138d(1973).

(332) M. Nedev, I. Mladenov, S. Srebrova-Nedeva, and D. Abadzhiev, *Farmatsiya (Sofia)*, **22**, 9(1972); through *Chem. Abstr.*, **78**, 164046f(1973).

(333) L. Tomasini, M. Goshkaryans, V. Tomova, and V. Andonova, *ibid.*, **23**, 30(1973); through *Chem. Abstr.*, **79**, 83436b(1973).

(334) S. S. Jayasinghe, *Process Technol. Int.*, **17**, 872(1972); through *Chem. Abstr.*, **78**, 88838y(1973).

(335) K. Kurihara and I. Ichikawa, *Chem. Pharm. Bull.*, **21**, 394(1973).

(336) K. Kigasawa, M. Saito, H. Iimura, and K. Watabe, *Yakugaku Zasshi*, **93**, 629(1973).

(337) R. C. Rowe, P. H. Elworthy, and D. Ganderton, *J. Pharm. Pharmacol.*, **25**, 112P(1973).

(338) J. H. Bell, N. A. Stevenson, and J. E. Taylor, *ibid.*, **25**, 96P(1973).

(339) I. Horikoshi, *Farumashia*, **8**, 296(1972); through *Chem. Abstr.*, **79**, 23556f(1973).

(340) I. Horikoshi, N. Takeguchi, M. Morri, and A. Sano, *Chem. Pharm. Bull.*, **21**, 2136(1973).

(341) Y. Pourcelot-Roubeau, C. Jeannin, and A. Verain, *J. Pharm. Belg.*, **27**, 600(1972); through *Chem. Abstr.*, **78**, 33892f(1973).

(342) M. C. B. Van Oudtshoorn, E. Blignaut, J. G. Van der Watt, and L. Wuyts, *Pharm. Weekbl.*, **108**, 135(1973); through *Chem. Abstr.*, **78**, 115199z(1973).

(343) K. A. Khan and C. T. Rhodes, *Pharm. Acta Helv.*, **47**, 594(1972); through *Chem. Abstr.*, **78**, 47728u(1973).

(344) P. York and N. Pilpel, *J. Pharm. Pharmacol.*, **25**, 1P(1973).

(345) A. Otsuka, K. Danjo, and H. Sunada, *Chem. Pharm. Bull.*, **21**, 428(1973).

(346) A. M. Sakr, H. M. El-Sabbagh, and M. S. Mesiha, *Mfg. Chem. Aerosol News*, **44**, 29(1973).

(347) A. M. Sakr and A. A. Kassem, *ibid.*, **43**, 37(1972); through *Chem. Abstr.*, **78**, 33883d(1973).

(348) W. C. Ling, *J. Pharm. Sci.*, **62**, 2007(1973).

(349) A. Djiane, F. Altglas, J. Clerc, J. Paris, D. Duchene, and F. Pruisieuz, *Ann. Pharm. Fr.*, **30**, 617(1972); through *Chem. Abstr.*, **78**, 33891e(1973).

(350) M. Morii, N. Takeguchi, and I. Horikoshi, *Chem. Pharm. Bull.*, **21**, 589(1973).

(351) M. Juslin, *Farm. Aikak.*, **82**, 25(1973); through *Chem. Abstr.*, **79**, 45672t(1973).

(352) M. Poulet and P. Guiot, *Pharm. Ind.*, **34**, 828(1972); through *Chem. Abstr.*, **78**, 101959k(1973).

(353) E. E. Borzunov, *Fiz.-Khim. Mekh. Liofol'nost Dispersn. Sist.*, **3**, 204(1971); through *Chem. Abstr.*, **78**, 33889k(1973).

(354) S. Klaudianos, *Pharm. Ind.*, **34**, 976(1972); through *Chem. Abstr.*, **78**, 164042b(1973).

(355) J. Chalumet, C. Jeannin, A. Mirouze, M. Poulet, Y. Pourcelot, and G. Fabre, *Sci. Tech. Pharm.*, **1**, 349(1972); through *Chem. Abstr.*, **79**, 70103r(1973).

(356) I. D. Osipova, M. V. Shteingart, V. G. Gandel, and S. A. Nosovitskaya, *Farmatsiya (Moscow)*, **22**, 22(1973); through *Chem. Abstr.*, **79**, 139635k(1973).

(357) J. A. Hersey, E. T. Cole, and J. E. Rees, *Aust. J. Pharm. Sci.*, **2**, 21(1973); through *Chem. Abstr.*, **79**, 70183s(1973).

(358) K. A. Khan and C. T. Rhodes, *Can. J. Pharm. Sci.*, **8**, 1(1973).

(359) W. Lowenthal and J. H. Wood, *J. Pharm. Sci.*, **62**, 287(1973).

(360) K. A. Khan and C. T. Rhodes, *Mfg. Chem. Aerosol News*, **44**, 48(1973).

(361) A. M. Sakr, A. A. Kassem, and N. A. Farrag, *ibid.*, **44**(1), 37(1973).

(362) K. A. Khan and C. T. Rhodes, *Can. J. Pharm. Sci.*, **8**, 77(1973).

(363) S. S. Kornblum and S. B. Stoopak, *J. Pharm. Sci.*, **62**, 43(1973).

(364) S. A. Khalil and L. M. M. Ali, *Acta Pharm. Suecica*, **9**, 563(1972); through *Chem. Abstr.*, **78**, 115179t(1973).

(365) A. M. Sakr, A. A. Kassem, S. A. A. Aziz, and A. H. Shalaby, *Can. J. Pharm. Sci.*, **8**, 6(1973).

(366) W. L. Davies and W. T. Gloor, Jr., *J. Pharm. Sci.*, **62**, 170(1973).

(367) H. C. Caldwell and W. J. Westlake, *Can. J. Pharm. Sci.*, **8**, 50(1973).

(368) P. P. Georgakopoulos, *Pharm. Delt., Epistem. Ekdosis.* **2**, 21(1972); through *Chem. Abstr.*, **78**, 164040z(1973).

(369) M. J. Juslin and E. S. Erkkila, *Farm. Aikak.*, **81**, 189(1972); through *Chem. Abstr.*, **78**, 88588s(1973).

(370) S. A. Fusari, *J. Pharm. Sci.*, **62**, 2012(1973).

(371) J. E. Carless, J. B. Stenlake, and W. D. Williams, *J. Pharm. Pharmacol.*, **25**, 849(1973).

(372) M. Garamvolgyi-Horvath and G. Kedvessy, *Pharm. Ind.*, **34**, 682(1972); through *Chem. Abstr.*, **78**, 62091z(1973).

(373) U. Conte, C. Caramella, P. Colombo, and A. La Manna, *Farmaco, Ed. Prat.*, **28**, 161(1973); through *Chem. Abstr.*, **78**, 140380j(1973).

(374) F. S. Hom, S. A. Veresh, and J. J. Miskel, *J. Pharm. Sci.*, **62**, 1001(1973).

(375) T. Sato, T. Kobayashi, and A. Okada, *Meiji Seika Kenkyu Nempo*, **12**, 112(1972); through *Chem. Abstr.*, **78**, 47760y(1973).

(376) J. M. Esnard, J. Clerc, H. Tebbi, D. Duchene, J. Levy, and F. Puisieux, *Ann. Pharm. Fr.*, **31**, 103(1973); through *Chem. Abstr.*, **79**, 45746v(1973).

(377) G. K. Bolhuis and C. F. Lerk, *Pharm. Weekbl.*, **108**, 469(1973); through *Chem. Abstr.*, **79**, 45761w(1973).

(378) G. Stampf, B. Kovacs, and L. Gyarmati, *Gyogyszereszet*, **16**, 372(1972); through *Chem. Abstr.*, **78**, 33886g(1973).

(379) A. Asker, M. El-Nakeeb, M. Motawi, and N. El-Gindy, *Pharmazie*, **27**, 600(1972); through *Chem. Abstr.*, **78**, 7804j(1973).

(380) R. Shekerdzhiiski and T. Trandafilov, *ibid.*, **27**, 586(1972); through *Chem. Abstr.*, **78**, 7787f(1973).

(381) P. H. List and B. W. Mueller, *Pharm. Ind.*, **34**, 963(1972); through *Chem. Abstr.*, **78**, 164026z(1973).

(382) M. V. Kuznetsova, *Sb. Nauch. Tr., Tsent. Aptech. Nauch.-Issled. Inst.*, **12**, 78(1971); through *Chem. Abstr.*, **78**, 62138v(1973).

(383) G. K. Bolhuis, C. F. Lerk, and J. W. Soer, *Pharm. Weekbl.*, **108**, 337(1973); through *Chem. Abstr.*, **79**, 57611k(1973).

(384) U. Bogs and A. Daerr, *Pharmazie*, **28**, 112(1973); through *Chem. Abstr.*, **78**, 164049j(1973).

(385) W. Czarnecki, *Farm. Pol.*, **29**, 63(1973); through *Chem. Abstr.*, **78**, 164044d(1973).

(386) B. N. Amirov and O. P. Belozerova, *Farmatsiya (Moscow)*, **22**, 18(1973); through *Chem. Abstr.*, **78**, 139631f(1973).

(387) G. Stampf, *Gyogyszereszet*, **17**, 125(1973); through *Chem. Abstr.*, **79**, 35104v(1973).

(388) H. Delonca, J. Joachim, J. Munerot, and A. Freida, *Farmaco, Ed. Prat.*, **28**, 3(1973); through *Chem. Abstr.*, **78**, 88586q(1973).

(389) J. E. Davies and J. T. Fell, *J. Pharm. Pharmacol.*, **25**, 431(1973).

(390) M. C. R. Johnson, *ibid.*, **25**, 162P(1973).

(391) N. A. Armstrong, G. A. March, C. J. De Blaey, and J. Polderman, *ibid.*, **25**, 163P(1973).

(392) A. Heyd, *J. Pharm. Sci.*, **62**, 818(1973).

(393) N. O. Lindberg and E. Jonsson, *Acta Pharm. Suecica*, **9**, 581(1972); through *Chem. Abstr.*, **78**, 140378q(1973).

(394) J. V. Fee, D. J. W. Grant, and J. M. Newton, *J. Pharm. Pharmacol.*, **25**, 149P(1973).

(395) P. A. Tuerck and D. E. McVean, *J. Pharm. Sci.*, **62**, 1534(1973).

(396) K. Bayer, M. Soliva, and P. Speiser, *Pharm. Ind.*, **34**, 677(1972); through *Chem. Abstr.*, **78**, 75815p(1973).

(397) J. F. Pickard and J. E. Rees, *ibid.*, **34**, 833(1972); through *Chem. Abstr.*, **78**, 101893j(1973).

(398) G. Hortobagyi, *Gyogyszereszet*, **17**, 121(1973); through *Chem. Abstr.*, **79**, 35047d(1973).

(399) F. Soenen, *Sci. Tech. Pharm.*, **2**, 63(1973); through *Chem. Abstr.*, **79**, 45673u(1973).

(400) J. V. Bondi, R. L. Schnaare, P. J. Niebergall, and E. T. Sugita, *J. Pharm. Sci.*, **62**, 1731(1973).

(401) M. P. Short and C. T. Rhodes, *Can. J. Pharm. Sci.*, **8**, 46(1973).

(402) M. Nakagaki and H. Ninomiya, *Yakugaku Zasshi*, **93**, 177(1973).

(403) J. B. Kayes, *J. Pharm. Pharmacol.*, **25**, 164P(1973).

(404) I. Tari, *Shikizai Kyokaishi*, **45**, 657(1972); through *Chem. Abstr.*, **78**, 88837x(1973).

(405) A. Muranyi, *Gyogyszereszet*, **17**, 161(1973); through *Chem. Abstr.*, **79**, 57623r(1973).

(406) V. A. Davydova, *Farmatsiya (Moscow)*, **22**, 13(1973); through *Chem. Abstr.*, **78**, 128399q(1973).

(407) A. A. Abramzon, I. I. Vol'fenzon, and V. M. Kiseleva, *Zh. Prikl. Khim. (Leningrad)*, **45**, 2700(1972); through *Chem. Abstr.*, **78**, 128716r(1973).

(408) M. Seiller, T. Legras, I. Lo, J. P. Treguier, and F. Puisieux, *Pharm. Acta Helv.*, **47**, 516(1972); through *Chem. Abstr.*, **78**, 20149u(1973).

(409) R. D. Vold and K. L. Mittal, *J. Colloid Interface Sci.*, **42**, 436(1973).

(410) A. K. Dorle and R. Devraj, *Indian J. Pharm.*, **34**, 105(1972); through *Chem. Abstr.*, **78**, 88851x(1973).

(411) E. Minkov, S. Bogdanova, and T. Penovska, *Farmatsiya (Sofia)*, **23**, 13(1973); through *Chem. Abstr.*, **79**, 45747w(1973).

(412) J. Kanpczyk, L. Krowczynski, and B. Kreps, *Farm. Pol.*, **29**, 237(1973); through *Chem. Abstr.*, **79**, 57615q(1973).

(413) F. Puisieux, M. Seiller, and J. P. Treguier, *Prod. Probl. Pharm.*, **27**, 1092(1972); through *Chem. Abstr.*, **79**, 9833n(1973).

(414) K. Shinoda and H. Kunieda, *J. Colloid Interface Sci.*, **42**, 381(1973).

(415) K. W. Reichmann and R. V. Petersen, *J. Pharm. Sci.*, **62**, 1850(1973).

(416) E. L. Roehl, *Soap Perfum. Cosmet.*, **45**, 343(1972); through *Chem. Abstr.*, **78**, 20095y(1973).

(417) O. G. Gryazina, E. M. Gluzman, and L. A. Andreeva, *Farm. Zh. (Kiev)*, **28**, 64(1973); through *Chem. Abstr.*, **78**, 151555w(1973).

(418) G. Proserpio, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol.*, **54**, 354(1972); through *Chem. Abstr.*, **78**, 5698d(1973).

(419) A. Parera and J. M. Sune, *Ars Pharm.*, **12**, 445(1971); through *Chem. Abstr.*, **79**, 35096u(1973).

(420) E. L. Roehl, *Seifen, Oele, Fette, Wachse*, **98**, 568(1972); through *Chem. Abstr.*, **78**, 7736p(1973).

(421) E. S. Lower, *Relata Tech. Chim. Biol. Appl.*, **4**, 269(1972); through *Chem. Abstr.*, **79**, 35334v(1973).

(422) J. P. Treguier, I. Lo, M. Seiller, and F. Puisieux, *Sci. Tech. Pharm.*, **1**, 371(1972); through *Chem. Abstr.*, **79**, 70114v (1973).

(423) T. Matsumoto and T. Tange, *Nippon Secchaku Kyokai Shi*, **9**, 183(1973); through *Chem. Abstr.*, **79**, 97206p(1973).

(424) J. P. Taylor and L. Marszall, *Farm. Pol.*, **28**, 1101(1972); through *Chem. Abstr.*, **78**, 101889n(1973).

(425) A. Kitahara, *Shikizai Kyokaishi*, **45**, 571(1972); through *Chem. Abstr.*, **78**, 18026h(1973).

(426) J. M. Sune and J. A. Castera, *Galenica Acta*, **24**, 3(1971); through *Chem. Abstr.*, **78**, 20135m(1973).

(427) J. Pickthall, *Soap Perfum. Cosmet.*, **46**, 337(1973); through *Chem. Abstr.*, **79**, 118260u(1973).

(428) L. Gyarmati, E. Farkas, and A. Csontos, *Olaj. Szappan, Kozmet.*, **21**, 55(1972); through *Chem. Abstr.*, **78**, 7745r(1973).

(429) I. Adams and S. S. Davis, *J. Pharm. Pharmacol.*, **25**, 640(1973).

(430) B. Fecak, J. Kucera, and V. Veber, *Acta Fac. Pharm., Univ. Comeniana*, **21**, 219(1972); through *Chem. Abstr.*, **78**, 64047g(1973).

(431) V. Monev, E. Minkov, and T. Boneva, *Farmatsiya (Sofia)*, **22**, 19(1972); through *Chem. Abstr.*, **79**, 9845t(1973).

(432) B. Bazhdekov, A. Durmishev, I. Lakovska, and N. Tsankov, *Dermatol. Venerol. (Sofia)*, **11**, 185(1972); through *Chem. Abstr.*, **78**, 128396m(1973).

(433) L. Draganova, S. Yakimov, and K. Khristov, *Pharmazie*, **28**, 388(1973); through *Chem. Abstr.*, **79**, 70181q(1973).

(434) N. P. Redmond and P. W. Haltenberger, *J. Soc. Cosmet. Chem.*, **23**, 637(1972); through *Chem. Abstr.*, **78**, 20116f (1973).

(435) A. Cerezo Galan, *Galenica Acta*, **24**, 171(1971); through *Chem. Abstr.*, **78**, 101931v(1973).

(436) R. Huettenrauch and U. Schmeiss, *Pharmazie*, **28**, 272(1973); through *Chem. Abstr.*, **79**, 35119d(1973).

(437) B. W. Barry and M. C. Meyer, *J. Pharm. Sci.*, **62**, 1349(1973).

(438) J. A. Hersey and P. Cook, *J. Pharm. Pharmacol.*, **25**, 121P(1973).

(439) W. Horsch, R. Seifferth and M. Ullrich, *Pharmazie*, **27**, 800(1972); through *Chem. Abstr.*, **78**, 75835v(1973).

(440) M. K. Gluzman, R. G. Zaslavskaya, Y. N. Kiryukhin, and N. G. Kozlova, *Farmatsiya (Moscow)*, **22**, 17(1973); through *Chem. Abstr.*, **79**, 83449h(1973).

(441) A. G. Gryazina, E. M. Gluzman, and L. A. Andreeva, *Farm. Zh. (Kiev)*, **28**, 47(1973); through *Chem. Abstr.*, **79**, 96921f(1973).

(442) O. I. Ryaposova and B. V. Nazarov, *Farmatsiya (Moscow)*, **22**, 14(1973); through *Chem. Abstr.*, **79**, 96916h(1973).

(443) G. Proserpio, *Prod. Probl. Pharm.*, **27**, 815(1972); through *Chem. Abstr.*, **78**, 7744q(1973).

(444) L. Draganova, *Farmatsiya (Sofia)*, **22**, 19(1972); through *Chem. Abstr.*, **78**, 164015v(1973).

(445) H. J. Hulsebosch and M. Ponec-Waelsch, *Dermatologica*, **144**, 287(1972); through *Chem. Abstr.*, **78**, 75809q(1973).

(446) A. Frohlich and A. Antal, *Acta Pharm. Hung.*, **42**, 197(1972); through *Chem. Abstr.*, **79**, 9840n(1973).

(447) H. Sucker, *Pharm. Ind.*, **34**, 748(1972); through *Chem. Abstr.*, **78**, 128394j(1973).

(448) *Ibid.*, **35**, 85(1973); through *Chem. Abstr.*, **79**, 9843r (1973).

(449) P. Keseru and K. Katona, *Acta Pharm. Hung.*, **43**, 73(1973); through *Chem. Abstr.*, **79**, 9849x(1973).

(450) A. A. Kassem, S. A. Zaki, and O. El Taib, *Bull. Fac. Pharm., Cairo Univ.*, **10**, 295(1971); through *Chem. Abstr.*, **79**, 9853u(1973).

(451) I. Jalsenjak and V. Petricic, *Acta Pharm. Jugoslav.*, **23**, 119(1973); through *Chem. Abstr.*, **79**, 57616r(1973).

(452) V. Petricic, M. Kupinic, and M. Becirevic, *ibid.*, **23**, 127(1973); through *Chem. Abstr.*, **79**, 57617s(1973).

(453) D. Werchan and R. Ludwig, *Pharmazie*, **27**, 670(1972); through *Chem. Abstr.*, **78**, 62101c(1973).

(454) I. M. Pertsev, G. S. Bashura, D. P. Salo, I. A. Muravev, and O. A. Pimenov, *Farm. Zh. (Kiev)*, **27**, 6(1972); through *Chem. Abstr.*, **78**, 33820f(1973).

(455) H. C. Mital and F. D. Dove, *Drug Cosmet. Ind.*, **113**(4), 46(1973).

(456) S. Purwar and G. P. Srivastava, *Indian J. Pharm.*, **35**, 54(1973).

(457) M. Ferratini and S. Rigamonti, *Boll. Chim. Farm.*, **112**, 116(1973); through *Chem. Abstr.*, **79**, 96920e(1973).

(458) N. S. Nikolaenko, B. I. Dashevskaya, and M. K. Gluzman, *Khim.-Farm. Zh.*, **7**, 43(1973); through *Chem. Abstr.*, **79**, 96908g(1973).

(459) G. Regdon, G. Mezey, and E. Regdon-Kiss, *Acta Pharm. Hung.*, **43**, 57(1973); through *Chem. Abstr.*, **79**, 9848w(1973).

(460) L. Gyarmati, I. Racz, A. Csontos, and E. Satory, *ibid.*, **42**, 278(1972); through *Chem. Abstr.*, **78**, 47710g(1973).

(461) H. W. Puffer and W. J. Crowell, *J. Pharm. Sci.*, **62**, 242(1973).

(462) B. Bochev, S. Yakimov, T. Trandafilov, and A. Veleva, *Pharmazie*, **28**, 337(1973); through *Chem. Abstr.*, **79**, 45726p(1973).

(463) K. B. M. Bevernage and J. Polderman, *Pharm. Weekbl.*, **108**, 429(1973); through *Chem. Abstr.*, **79**, 35050z(1973).

(464) J. Macabies, J. M. Bourgeois, and X. Baillat, *Therapie*, **27**, 693(1972); through *Chem. Abstr.*, **78**, 92527p(1973).

(465) N. N. Salib, M. Abdel-Khalek, and M. A. Shams-Eldin, *UAR J. Pharm. Sci.*, **12**, 209(1971); through *Chem. Abstr.*, **78**, 88504m(1973).

(466) Y. I. Khadzhai, A. V. Nikolaeva, B. I. Dashevskaya, Z.

I. Nikolaeva, and M. K. Gluzman, *Farmatsiya (Moscow)*, **21**, 16(1972); through *Chem. Abstr.*, **78**, 66969q(1973).

(467) A. I. Tentsova and V. V. Sergeev, *Sb. Nauch. Tr., Tsent. Aptech. Nauch.-Issled. Inst.*, **11**, 52(1971); through *Chem. Abstr.*, **78**, 75840t(1973).

(468) E. L. Parrott, *Amer. J. Pharm. Educ.*, **37**, 39(1973).

(469) L. Stanoeva and M. Kirkova, *Farmatsiya (Sofia)*, **23**, 46(1973); through *Chem. Abstr.*, **79**, 83411q(1973).

(470) M. Kirkova and L. Stanoeva, *ibid.*, **23**, 42(1973); through *Chem. Abstr.*, **79**, 96870p(1973).

(471) I. Williams and A. B. Hedley, *Rep. Progr. Appl. Chem.*, **57**, 635(1972); through *Chem. Abstr.*, **79**, 139946n(1973).

(472) R. K. Gamadia and M. R. Nearn, *ibid.*, **56**, 753(1971); through *Chem. Abstr.*, **78**, 34230a(1973).

(473) J. M. Aiache, *Farmaco, Ed. Prat.*, **28**, 243(1973); through *Chem. Abstr.*, **79**, 45691y(1973).

(474) P. A. Sanders, *J. Soc. Cosmet. Chem.*, **24**, 623(1973).

(475) G. Jederstrom, L. Rydhag, and S. Friberg, *J. Pharm. Sci.*, **62**, 1979(1973).

(476) J. H. Bell, K. Brown, and J. Glasby, *J. Pharm. Pharmacol.*, **25**, 32P(1973).

(477) A. W. Karig, *Diss. Abstr. Int.*, **34**, 2120B(1973).

(478) H. S. Ormsbee, III, and C. F. Ryan, *J. Pharm. Sci.*, **62**, 255(1973).

(479) R. L. Shippy, S. T. Hwang, and R. G. Bunge, *J. Biomed. Mater. Res.*, **7**, 95(1973); through *Chem. Abstr.*, **78**, 101961e(1973).

(480) D. R. Kalkwarf, M. R. Sikov, L. Smith, and R. Gordon, *Contraception*, **6**, 423(1972); through *Chem. Abstr.*, **78**, 33900g(1973).

(481) J. C. Fu, A. Kale, and D. L. Moyer, *J. Biomed. Mater. Res.*, **7**, 193(1973); through *Chem. Abstr.*, **79**, 35076n(1973).

(482) *Ibid.*, **7**, 71(1973); through *Chem. Abstr.*, **78**, 101962f(1973).

(483) D. L. Wise, *Govt. Rep. Announce. (U.S.)*, **73**, 58(1973); through *Chem. Abstr.*, **79**, 57627v(1973).

(484) C. F. Lerk, W. J. Bolink, and K. Zuurman, *J. Pharm. Pharmacol.*, **25**, 151P(1973).

(485) J. C. Boylan and G. S. Banker, *J. Pharm. Sci.*, **62**, 1177(1973).

(486) R. W. Croswell, *Diss. Abstr. Int.*, **34**, 2747B(1973).

(487) J. H. R. Woodland, S. Yolles, D. A. Blake, M. Helrich, and F. J. Meyer, *J. Med. Chem.*, **16**, 897(1973).

(488) N. N. Salib, *Pharm. Ind.*, **35**, 150(1973); through *Chem. Abstr.*, **79**, 45720g(1973).

(489) K. Lehmann, *Rev. Quim. Ind. (Rio de Janeiro)*, **41**, 208(1972); through *Chem. Abstr.*, **78**, 101952c(1973).

(490) T. M. S. Chang, *Enzyme*, **14**, 95(1973); through *Chem. Abstr.*, **79**, 57633u(1973).

(491) A. L. Rubin, K. H. Stenzel, T. Miyata, M. J. White, and M. Dunn, *J. Clin. Pharmacol.*, **13**, 312(1973).

(492) T. Bednarik, J. Cervenka, A. Kotasek, and M. Brestak, *Cesk. Farm.*, **21**, 329(1972); through *Chem. Abstr.*, **78**, 33882c(1973).

(493) A. A. Kassem, A. M. Sakr, and H. Abdou, *Mfg. Chem. Aerosol News*, **44**, 43(1973).

(494) A. A. Kassem, A. M. Sakr, A. A. Kassem, Jr., and H. Abdou, *ibid.*, **44**, 23(1973).

(495) K. Lehmann, *ibid.*, **44**, 39(1973).

(496) P. Speiser, *Labo-Pharma-Probl. Tech.*, **20**, 32(1972); through *Chem. Abstr.*, **78**, 79499m(1973).

(497) J. R. Boissier and J. P. Tillement, *Therapie*, **28**, 427(1973); through *Chem. Abstr.*, **79**, 96918k(1973).

(498) Y. Boer, *Pharm. Weekbl.*, **108**, 109(1973); through *Chem. Abstr.*, **78**, 101890f(1973).

(499) L. Starha and M. Chalabala, *Acta Fac. Pharm., Univ. Comeniana*, **21**, 171(1972); through *Chem. Abstr.*, **78**, 164048h(1973).

(500) D. Ben-Ishay and K. Engelman, *Clin. Pharmacol. Ther.*, **14**, 250(1973); through *Chem. Abstr.*, **78**, 164050c(1973).

(501) E. Orban and I. Lopez Valiente, *Acta Pharm. Hung.*, **43**, 9(1973); through *Chem. Abstr.*, **78**, 164053f(1973).

(502) U. Otto, L. Paalzow, and G. Suren, *Acta Pharm. Suecica*, **9**, 595(1972); through *Chem. Abstr.*, **78**, 115178s(1973).

(503) S. Lerman, P. Davis, and W. B. Jackson, *Can. J. Ophthalmol.*, **8**, 114(1973); through *Chem. Abstr.*, **79**, 9850r(1973).

(504) B. Chodkowska-Granicka, Z. Pawlak, E. Pawlak, and J. Surowiecki, *Acta Pol. Pharm.*, **29**, 625(1972); through *Chem. Abstr.*, **79**, 9852t(1973).

(505) D. R. Rao and V. S. Rao, *Indian J. Pharm.*, **35**, 89(1973); through *Chem. Abstr.*, **79**, 57638z(1973).

(506) G. S. Bhoyar, D. M. Brahmankar, and A. K. Dorle, *ibid.*, **34**, 151(1972); through *Chem. Abstr.*, **78**, 62135s(1973).

(507) A. Gumma, M. A. Dermanci, and F. Bel, *Pharm. Acta Helv.*, **47**, 577(1972); through *Chem. Abstr.*, **78**, 62142s(1973).

(508) C. Boroda, R. B. Miller, S. T. Leslie, E. G. Nicol, and J. Thompson, *J. Clin. Pharmacol.*, **13**, 386(1973).

(509) M. L. Rosenblum, D. L. Bowie, and M. D. Walker, *Cancer Res.*, **33**, 906(1973); through *Chem. Abstr.*, **79**, 73415e(1973).

(510) S. A. H. Khalil and S. S. El-Gamal, *Pharmazie*, **28**, 385(1973); through *Chem. Abstr.*, **79**, 70166p(1973).

(511) N. N. Salib, *Pharm. Ind.*, **35**, 217(1973); through *Chem. Abstr.*, **79**, 45728r(1973).

(512) L. Starha and M. Chalabala, *Cesk. Farm.*, **21**, 311(1972); through *Chem. Abstr.*, **78**, 33867b(1973).

(513) F. W. Dawson, *J. Soc. Cosmet. Chem.*, **24**, 655(1973).

(514) K. W. Wallhaeusser, *Parfuem. Kosmet.*, **53**, 305(1972); through *Chem. Abstr.*, **78**, 47653r(1973).

(515) C. L. Goldman, *Cosmet. Perfum.*, **88**(2), 3(1973).

(516) W. E. Rosen and P. A. Berke, *J. Soc. Cosmet. Chem.*, **24**, 663(1973).

(517) D. Coates and R. Woodford, *Cosmet. Perfum.*, **88**(4), 5(1973).

(518) G. E. Myers and F. M. Pasutto, *Can. J. Pharm. Sci.*, **8**, 19(1973).

(519) M. Lanzet, *CTFA Cosmet. J.*, **4**, 4(1972); through *Chem. Abstr.*, **78**, 33793z(1973).

(520) J. Allegrini, S. De Buochberg, and A. Boillot, *Prod. Probl. Pharm.*, **29**, 819(1972); through *Chem. Abstr.*, **78**, 75830q(1973).

(521) E. J. Wargo, *Amer. J. Hosp. Pharm.*, **30**, 332(1973).

(522) C. H. Wilson, *CTFA Cosmet. J.*, **4**, 8(1972); through *Chem. Abstr.*, **78**, 33792y(1973).

(523) S. Tenenbaum, *Cosmet. Perfum.*, **88**(2), 5(1973).

(524) G. E. Myers and F. M. Pasutto, *ibid.*, **88**(7), 5(1973).

(525) N. G. Martinez Nadal, A. E. Montalvo, and M. Seda, *ibid.*, **88**(10), 37(1973).

(526) J. F. McConville and C. B. Anger, *ibid.*, **88**(8), 29(1973).

(527) D. W. Anderson, Jr., J. F. McConville, and C. B. Anger, *ibid.*, **88**(8), 25(1973).

(528) M. Fontana and G. Proserpio, *Riv. Ital. Essenze Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **55**, 265(1973); through *Chem. Abstr.*, **79**, 118261v(1973).

(529) D. Coates, *Mfg. Chem. Aerosol News*, **44**, 35(1973).

(530) A. Maruszerski, *CTFA Cosmet. J.*, **4**, 2(1972); through *Chem. Abstr.*, **78**, 33794a(1973).

(531) F. N. Marzulli and H. I. Maibach, *J. Soc. Cosmet. Chem.*, **24**, 399(1973).

(532) J. K. Prall, *ibid.*, **24**, 693(1973).

(533) A. Rutkowski and Z. Elsner, *Cosmet. Perfum.*, **88**(7), 3(1973).

(534) E. S. Cooperman and V. L. Johnsen, *ibid.*, **88**(7), 3(1973).

(535) B. Idson, *ibid.*, **88**(3), 3(1973).

(536) G. Rialdi, *Relata Tech. Chim. Biol. Appl.*, **4**, 401(1972); through *Chem. Abstr.*, **79**, 57563w(1973).

(537) W. Wittels, *Parfuem. Kosmet.*, **54**, 74(1973); through *Chem. Abstr.*, **79**, 9760m(1973).

(538) F. N. Marzulli, K. J. Davis and P. D. Yoder, *CTFA Cosmet. J.*, **3**, 42(1971); through *Chem. Abstr.*, **78**, 47652q(1973).

(539) D. Coates, *Mfg. Chem. Aerosol News*, **44**(8), 41(1973).

(540) *Ibid.*, **44**, 34(1973).

(541) G. E. Mapstone, *Aust. Chem. Process. Eng.*, **25**, 18(1972); through *Chem. Abstr.*, **78**, 163936j(1973).

(542) S. Marcinkiewicz, *Tluszcze, Srodki Piorace, Kosmet.*, **16**, 3(1972); through *Chem. Abstr.*, **78**, 47634k(1973).

(543) M. Nara, Y. Akiyama, and Y. Murui, *Shikizai Kyokaishi*, **45**, 593(1972); through *Chem. Abstr.*, **78**, 33770q(1973).

(544) M. Fujiwara, S. Kato, S. Yuasa, K. Morita, and A. Fiyita, *Cosmet. Perfum.*, **88**(9), 49(1973).

(545) J. W. Barnhart, Jr., *ibid.*, **88**(3), 11(1973).

(546) R. Heilingoetter, *Amer. Cosmet. Perfum.*, **87**(11), 31(1972); through *Chem. Abstr.*, **78**, 62056s(1973).

(547) R. W. Rance, *J. Soc. Cosmet. Chem.*, **24**, 501(1973).

(548) M. L. Schlossman and A. J. Feldman, *ibid.*, **24**, 357(1973).

(549) P. Alexander, *Cosmet. Perfum.*, **88**(9), 35(1973).
(550) H. M. Lee and M. Coopersmith, *ibid.*, **88**(5), 5(1973).
(551) M. L. Schlossman, *ibid.*, **88**(3), 11(1973).
(552) W. R. Markland, *ibid.*, **88**(3), 11(1973).
(553) D. Stephan, *ibid.*, **88**(3), 9(1973).
(554) J. J. Slack, *ibid.*, **88**(3), 7(1973).
(555) F. Siegel, M. Slade, and R. Silkaitis, *ibid.*, **88**(3), 7(1973).
(556) R. P. Brandan and E. Kroll, *ibid.*, **88**(3), 7(1973).
(557) A. Shultz, *ibid.*, **88**(3), 5(1973).
(558) J. P. Paventini, *ibid.*, **88**(3), 5(1973).
(559) D. L. Courtney, *ibid.*, **88**(3), 5(1973).
(560) L. S. David, *ibid.*, **88**(3), 3(1973).
(561) R. R. Egan, *ibid.*, **88**(3), 3(1973).
(562) W. R. Schubert, *ibid.*, **88**(3), 7(1973).
(563) H. Isacoff, *ibid.*, **88**(2), 3(1973).
(564) T. K. Miwa, *ibid.*, **88**(1), 3(1973).
(565) D. Melnick, *ibid.*, **88**(1), 3(1973).
(566) J. F. L. Chester, *Mfg. Chem. Aerosol News*, **44**(7), 31(1973).
(567) K. G. Ludwig, P. Hameyer, and V. Cianchini, *Seifen, Oele, Fette, Wachse*, **98**, 889(1972); through *Chem. Abstr.*, **78**, 88509s(1973).
(568) E. L. Roehl, *ibid.*, **99**, 155(1973); through *Chem. Abstr.*, **79**, 9761n(1973).
(569) V. Lodi, *Soap Perfum. Cosmet.*, **46**, 87(1973); through *Chem. Abstr.*, **79**, 9762p(1973).
(570) A. Bria, *Ind. Usoara*, **20**, 332(1973); through *Chem. Abstr.*, **79**, 139607c(1973).
(571) K. Hennies, *Riechst., Aromen, Koerperpflegem.*, **23**, 241(1973); through *Chem. Abstr.*, **79**, 129068p(1973).
(572) G. Proserpio, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **54**, 744(1972); through *Chem. Abstr.*, **78**, 115114t(1973).
(573) P. G. I. Lauffer, *CTFA Cosmet. J.*, **4**, 24(1972); through *Chem. Abstr.*, **79**, 57552s(1973).
(574) R. Cornon, *Rev. Fr. Corps Gras*, **20**, 271(1973); through *Chem. Abstr.*, **79**, 57553t(1973).
(575) S. B. Mecca, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **54**, 445(1972); through *Chem. Abstr.*, **78**, 33771r(1973).
(576) B. Idson, *Drug Cosmet. Ind.*, **113**(5), 42(1973).
(577) *Ibid.*, **113**(6), 48(1973).
(578) R. Wallish, *Cosmet. Perfum.*, **88**(6), 7(1973).
(579) H. Futagoishi and T. Abe, *ibid.*, **88**(1), 5(1973).
(580) H. Hirota, *Yukagaku*, **21**, 725(1972); through *Chem. Abstr.*, **78**, 62043k(1973).
(581) G. Lerch, *Parfuem. Kosmet.*, **54**, 9(1973); through *Chem. Abstr.*, **78**, 75759y(1973).
(582) R. Molini, *Relata Tech. Chim. Biol. Appl.*, **4**, 141(1972); through *Chem. Abstr.*, **78**, 75779e(1973).
(583) F. Fussi, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **54**, 513(1972); through *Chem. Abstr.*, **78**, 75778d(1973).
(584) F. Nowak, *Cosmet. Perfum.*, **88**(2), 3(1973).
(585) G. Lerch, *Riv. Ital. Essenze, Profumi, Piante Offic., Aromi, Saponi, Cosmet., Aerosol*, **54**, 505(1972); through *Chem. Abstr.*, **78**, 75784c(1973).
(586) M. Gloor, J. Rietkoetter, and H. C. Friederich, *Fette, Seifen, Anstrichm.*, **75**, 200(1973); through *Chem. Abstr.*, **79**, 9757r(1973).
(587) J. F. Corbett, *Rev. Progr. Color. Relat. Top.*, **4**, 3(1973); through *Chem. Abstr.*, **79**, 57551r(1973).
(588) C. Bertinetto, *Relata Tech. Chim. Biol. Appl.*, **4**, 471(1972); through *Chem. Abstr.*, **79**, 57562v(1973).
(589) S. Takada, *Parfums, Cosmet., Savons Fr.*, **2**, 490(1972); through *Chem. Abstr.*, **78**, 62055r(1973).
(590) R. Y. Leites, A. Y. Rabinovich, E. Y. Bukhman, and N. T. Kuznetsova, *Maslo-Zhir. Prom.*, **8**, 28(1972); through *Chem. Abstr.*, **78**, 62057r(1973).
(591) R. R. Riso, *Drug Cosmet. Ind.*, **113**(4), 39(1973).
(592) *Ibid.*, **113**(5), 46(1973).
(593) D. P. Anonis, *Drug Cosmet. Ind.*, **112**(4), 42(1973).
(594) P. Alexander, *Tluszcze, Srodki Piorace, Kosmet.*, **16**, 3(1972); through *Chem. Abstr.*, **78**, 62041h(1973).
(595) E. L. Roehl, *Aerosol Rep.*, **11**, 474(1972); through *Chem. Abstr.*, **78**, 75760s(1973).
(596) F. Sardo, *Amer. Cosmet. Perfum.*, **87**, 43(1972); through *Chem. Abstr.*, **78**, 75775a(1973).
(597) Y. Watanabe, *Yukagaku*, **21**, 909(1972); through *Chem. Abstr.*, **78**, 75777c(1973).
(598) F. J. Ebling, *Cosmet. Perfum.*, **88**(10), 41(1973).
(599) J. H. De Wilde, *Pharm. Weekbl.*, **107**, 724(1972); through *Chem. Abstr.*, **78**, 33818m(1973).
(600) E. Spingler, *ibid.*, **107**, 813(1972); through *Chem. Abstr.*, **78**, 101901k(1973).
(601) B. Skaletzki and W. Wollman, *Pharmazie*, **28**, 1(1973); through *Chem. Abstr.*, **78**, 140385q(1973).
(602) G. Bauer and E. Ullmann, *Pharm. Ind.*, **34**, 674(1972); through *Chem. Abstr.*, **78**, 62157a(1973).
(603) A. Karig, G. E. Peck, and G. J. Sperandio, *J. Pharm. Sci.*, **62**, 396(1973).
(604) T. J. McCarthy, C. R. Clark, and J. A. Myburgh, *Cosmet. Perfum.*, **88**(5), 5(1973).
(605) T. J. McCarthy, *ibid.*, **88**(11), 41(1973).
(606) P. P. Percherskii, *Farm. Zh. (Kiev)*, **27**(6), 75(1972); through *Chem. Abstr.*, **78**, 7853z(1973).
(607) M. Havass and A. Schuster, *Cosmet. Perfum.*, **88**(5), 3(1973).
(608) C. C. Mascoli and E. D. Mascoli, *Bull. Parenteral Drug Ass.*, **27**, 234(1973).
(609) R. Wood, *Mfg. Chem. Aerosol News*, **44**(8), 28(1973).
(610) H. Kempa, G. Brockelt, and R. Pohloudek-Fabini, *Pharmazie*, **27**, 653(1972); through *Chem. Abstr.*, **78**, 62102d(1973).
(611) E. Ullmann and F. Sommer, *Pharm. Ind.*, **34**, 351(1972); through *Chem. Abstr.*, **78**, 164069r(1973).
(612) J. Surowiecki and L. Krowcznyski, *Acta Pol. Pharm.*, **29**, 399(1972); through *Chem. Abstr.*, **78**, 47714m(1973).
(613) M. Wayer, *Gyogyszereszet*, **17**, 210(1973); through *Chem. Abstr.*, **79**, 108045p(1973).
(614) K. R. Elmer, *Mfg. Chem. Aerosol News*, **44**(7), 28(1973).
(615) R. Wood, *ibid.*, **44**(7), 22(1973).
(616) R. E. Palmisano and S. Sackarow, *Drug Cosmet. Ind.*, **112**(2), 42(1973).
(617) D. E. Alguire, *Food Technol.*, **27**, 64(1973).
(618) K. Hieke, *Zentralbl. Pharm., Pharmakother. Laboratoriumsdiagn.*, **111**, 1123(1972); through *Chem. Abstr.*, **78**, 101894k(1973).
(619) J. F. Pickard and J. E. Rees, *Sci. Tech. Pharm.*, **1**, 567(1972); through *Chem. Abstr.*, **79**, 45697e(1973).
(620) R. Wood, *Mfg. Chem. Aerosol News*, **44**(7), 49(1973).
(621) J. Verch and W. Preuss, *Pharm. Ind.*, **34**, 336(1972); through *Chem. Abstr.*, **78**, 163992z(1973).
(622) H. L. M. Cox, *Pharm. Weekbl.*, **108**, 605(1973); through *Chem. Abstr.*, **79**, 108032g(1973).
(623) P. R. Rasanen and R. C. Louer, *Bull. Parenteral Drug Ass.*, **27**, 243(1973).
(624) A. B. McGinn, *ibid.*, **27**, 247(1973).
(625) R. J. Walsh and J. A. Monahan, *ibid.*, **27**, 250(1973).
(626) R. M. Kuznetsova, M. A. Seletskii, and B. I. Sotskov, *Khim.-Farm. Zh.*, **7**, 33(1973); through *Chem. Abstr.*, **79**, 9869d(1973).
(627) B. V. Klot-Heydenfeldt and P. Rohdewald, *Pharm. Ztg.*, **117**, 1518(1972); through *Chem. Abstr.*, **78**, 62121j(1973).
(628) M. S. Martinis Marchi Jellicich, *Farmaco, Ed. Prat.*, **27**, 599(1972); through *Chem. Abstr.*, **78**, 33817k(1973).
(629) A. Rigoli, *J. Pharm. Sci.*, **62**, 465(1973).
(630) A. L. Kunz, *Bull. Parenteral Drug Ass.*, **27**, 266(1973).
(631) A. W. Karig, G. E. Peck, and G. J. Sperandio, *J. Pharm. Sci.*, **62**, 811(1973).
(632) G. C. Cole and G. May, *J. Pharm. Pharmacol.*, **24**, 122P (1972); through *Chem. Abstr.*, **78**, 62155y(1973).
(633) F. W. Goodhart, J. R. Draper, D. Dancz, and F. C. Ninger, *J. Pharm. Sci.*, **62**, 297(1973).
(634) F. W. Goodhart, J. R. Draper, and F. C. Ninger, *ibid.*, **62**, 133(1973).
(635) P. R. Isler, *Drug Cosmet. Ind.*, **112**(5), 46(1973).
(636) A. Castillo, *ibid.*, **112**(2), 56(1973).
(637) S. J. Cher, *J. Soc. Cosmet. Chem.*, **24**, 639(1973).
(638) V. A. Zhukov and L. B. Sarapkin, *Khim.-Farm. Zh.*, **7**, 30(1973); through *Chem. Abstr.*, **79**, 9870x(1973).
(639) M. R. Nazareth, *Bull. Parenteral Drug Ass.*, **27**, 24(1973).
(640) G. H. Hopkins, *ibid.*, **27**, 114(1973).
(641) J. C. Guyot, M. Traisnel, P. Bonnet, A. Delacourte-Thi-

baut, B. Devise, and P. Leterme, *Prod. Probl. Pharm.*, **28**, 276(1973); through *Chem. Abstr.*, **79**, 79197z(1973).

(642) K. Ridgway and J. J. Deer, *Pharm. J.*, **210**, 255(1973).

(643) G. Gold, R. N. Duvall, B. T. Palermo, and R. L. Hurtle, *J. Pharm. Sci.*, **62**, 1530(1973).

(644) K. Ridgway and J. A. Callow, *Pharm. J.*, **211**, 281(1973).

(645) D. P. McDonald, *Mfg. Chem. Aerosol News*, **44**(8), 23(1973).

(646) M. A. Balabudkin and G. N. Borisov, *Khim.-Farm. Zh.*, **7**, 29(1973); through *Chem. Abstr.*, **79**, 108023e(1973).

(647) V. I. Yuditskii, *ibid.*, **6**, 25(1972); through *Chem. Abstr.*, **78**, 33907q(1973).

(648) G. E. Meerkop and V. V. Zhurko, *Farmatsiya (Moscow)*, **22**, 70(1973); through *Chem. Abstr.*, **78**, 128403m(1973).

(649) P. Bontemps, *Bull. Soc. Fr. Ceram.*, **95**, 77(1972); through *Chem. Abstr.*, **78**, 34318k(1973).

(650) J. A. Clements and S. D. Popli, *Can. J. Pharm. Sci.*, **8**, 88(1973).

(651) D. L. Simmons, R. J. Ranz, N. D. Gyanchandani, and P. Picotte, *ibid.*, **7**, 121(1972); through *Chem. Abstr.*, **78**, 62119q(1973).

(652) O. Karacsonyi, K. Nikolics, and G. Bidlo, *Acta Pharm. Hung.*, **42**, 203(1972); through *Chem. Abstr.*, **78**, 33861v(1973).

(653) H. C. Caldwell, *J. Pharm. Sci.*, **62**, 334(1973).

(654) E. Shefter, H. L. Fung, and O. Mok, *ibid.*, **62**, 791(1973).

(655) J. E. Carless, M. A. Moustafa, and H. D. C. Rapson, *J. Pharm. Pharmacol., Suppl.*, **24**, 130P(1972); through *Chem. Abstr.*, **78**, 62120h(1973).

(656) M. A. Moustafa, S. A. Khalil, A. R. Ebian, and M. M. Motawi, *ibid.*, **24**, 921(1972); through *Chem. Abstr.*, **78**, 33872z(1973).

(657) A. R. Ebian, M. A. Moustafa, S. A. Khalil, and M. M. Motawi, *J. Pharm. Pharmacol.*, **25**, 13(1973).

(658) J. T. Pearson and G. Varney, *J. Pharm. Pharmacol., Suppl.*, **25**, 62P(1973).

(659) K. Bauer and H. Voege, *Pharm. Ind.*, **34**, 960(1972); through *Chem. Abstr.*, **78**, 164025y(1973).

(660) M. Kuhnert-Brandstaetter and A. Burger, *ibid.*, **34**, 353(1972); through *Chem. Abstr.*, **78**, 164027a(1973).

(661) M. A. Miyamoto, T. Kiyotaki, N. A. Kisoh, T. Mitsunaga, and T. Maeda, *Chem. Pharm. Bull.*, **21**, 1857(1973).

(662) K. H. Froemming, *Pharm. Unserer Zeit*, **2**, 109(1973); through *Chem. Abstr.*, **79**, 96860k(1973).

(663) R. E. Rosenfeld and S. G. Frank, *J. Pharm. Sci.*, **62**, 1194(1973).

(664) A. A. Deshmukh and R. Fleming, *J. Pharm. Pharmacol., Suppl.*, **25**, 17P(1973).

(665) K. F. Farng and K. G. Nelson, *J. Pharm. Sci.*, **62**, 1435(1973).

(666) J. H. Collett, R. Withington, and P. H. Price, *J. Pharm. Pharmacol.*, **25**, 974(1973).

(667) L. Si-Nang, P. F. Carlier, P. Delort, J. Gazzola, and D. Lafont, *J. Pharm. Sci.*, **62**, 452(1973).

(668) N. N. Salib, *Pharm. Ind.*, **34**, 671(1972); through *Chem. Abstr.*, **78**, 75831r(1973).

(669) H. P. Merkle and P. Speiser, *J. Pharm. Sci.*, **62**, 1444(1973).

(670) A. Courts, *Chem. Ind.*, **19**, 943(1973).

(671) C. Thies, *J. Colloid Interface Sci.*, **44**, 133(1973); through *Chem. Abstr.*, **79**, 58038r(1973).

(672) O. N. Yalcindag, *Kim. Sanayi*, **20**, 143(1972); through *Chem. Abstr.*, **78**, 115137c(1973).

(673) B. S. Nath, *Indian J. Pharm.*, **35**, 26(1973); through *Chem. Abstr.*, **78**, 115183q(1973).

(674) A. T. M. Serajuddin, *Bangladesh Pharm. J.*, **1**, 6(1972); through *Chem. Abstr.*, **79**, 70105t(1973).

(675) S. Javidan and R. G. Mrtek, *J. Pharm. Sci.*, **62**, 420(1973).

(676) *Ibid.*, **62**, 424(1973).

(677) S. S. Davis, *J. Pharm. Pharmacol.*, **25**, 982(1973).

(678) L. T. Grady, S. E. Hays, R. H. King, H. R. Klein, W. J. Mader, D. K. Wyatt, and R. O. Zimmerer, Jr., *J. Pharm. Sci.*, **62**, 456(1973).

(679) T. J. Roseman and S. H. Yalkowsky, *ibid.*, **62**, 1680(1973).

(680) J. E. Fairbrother, *Anal. Profiles Drug Subst.*, **2**, 85(1973); through *Chem. Abstr.*, **79**, 23530t(1973).

(681) B. C. Rudy and B. Z. Senkowski, *ibid.*, **2**, 145(1973); through *Chem. Abstr.*, **79**, 23528y(1973).

(682) E. M. Cohen, *ibid.*, **2**, 163(1973); through *Chem. Abstr.*, **79**, 23525v(1973).

(683) S. Ahuja and J. Cohen, *ibid.*, **2**, 199(1973); through *Chem. Abstr.*, **79**, 23529z(1973).

(684) B. C. Rudy and B. Z. Senkowski, *ibid.*, **2**, 221(1973); through *Chem. Abstr.*, **79**, 23527x(1973).

(685) R. S. Santoro, R. J. Warren, G. D. Roberts, E. V. White, and P. P. Begosh, *ibid.*, **2**, 315(1973); through *Chem. Abstr.*, **79**, 23532v(1973).

(686) B. C. Rudy and B. Z. Senkowski, *ibid.*, **2**, 339(1973); through *Chem. Abstr.*, **79**, 23531u(1973).

(687) *Ibid.*, **2**, 467(1973); through *Chem. Abstr.*, **79**, 23526w(1973).

(688) D. G. Pope, *Diss. Abstr. Int.*, **34**, 2749B(1973).

(689) W. Lund, J. B. Murray, R. M. E. Richards, and G. Smith, *Pharm. J.*, **211**, 11(1973).

(690) C. Hansch and J. M. Clayton, *J. Pharm. Sci.*, **62**, 1(1973).

(691) M. J. Veter, *Parfums, Cosmet., Savons Fr.*, **2**, 549(1972); through *Chem. Abstr.*, **78**, 62038n(1973).

(692) S. T. Chung and J. C. Berg, *Hwahak Konghak*, **10**, 231(1972); through *Chem. Abstr.*, **79**, 97210k(1973).

(693) S. Moisescu, *Farmacia (Bucharest)*, **21**, 169(1973); through *Chem. Abstr.*, **79**, 108026h(1973).

(694) W. L. Chiou and S. Niazi, *J. Pharm. Sci.*, **62**, 498(1973).

(695) J. L. Sheumaker, *Diss. Abstr. Int.*, **33**, 3171B(1973).

(696) D. Shah, B. Ecanow, M. Sadove, and F. Shieh, *J. Pharm. Sci.*, **62**, 1210(1973).

(697) D. Shah, B. Ecanow, and R. Balagot, *ibid.*, **62**, 1902(1973).

(698) L. I. Brutko, D. Z. Yaskina, and L. P. Sapegina, *Sb. Nauch. Tr., Tsent. Aptech. Nauch.-Issled. Inst.*, **12**, 150(1971); through *Chem. Abstr.*, **78**, 62100b(1973).

(699) V. F. Smolen, *J. Pharm. Sci.*, **62**, 77(1973).

(700) W. I. Higuchi, F. Sjuib, D. Mufson, A. P. Simonelli, and A. F. Hofmann, *ibid.*, **62**, 942(1973).

(701) W. I. Higuchi, S. Prakongpan, and F. Young, *ibid.*, **62**, 945(1973).

(702) L. V. Allen, Jr., *Diss. Abstr. Int.*, **34**, 742B(1973).

(703) M. Kanke and K. Sekiguchi, *Chem. Pharm. Bull.*, **21**, 878(1973).

(704) K. Sekiguchi, M. Kanke, Y. Tsuda, K. Ishida, and Y. Tsuda, *ibid.*, **21**, 1592(1973).

(705) P. Pothisiri and J. T. Carstensen, *J. Pharm. Sci.*, **62**, 1468(1973).

(706) R. N. Nasipuri and S. A. H. Khalil, *ibid.*, **62**, 473(1973).

(707) A. M. Agrawal, R. L. Nikore, and A. K. Dorle, *Indian J. Pharm.*, **35**, 41(1973); through *Chem. Abstr.*, **78**, 115176q(1973).

(708) R. Tawashi and J. Piccolo, *Soc. Argent. Farm. Bioquim. Ind.*, **12**, 671(1972); through *Chem. Abstr.*, **79**, 45670r(1973).

(709) J. Lindenbaum, V. P. Butler, Jr., J. E. Murphy, and R. M. Cresswell, *Lancet* **1**, 1215(1973).

(710) B. F. Johnson, H. Greer, J. McCrerie, C. Bye, and A. Fowle, *ibid.*, **1**, 1473(1973).

(711) A. H. Beckett and D. A. Cowan, *Pharm. J.*, **211**, 111 (1973).

(712) E. J. Fraser, R. H. Leach, J. W. Poston, A. M. Bold, L. S. Culank, and A. B. Lipede, *J. Pharm. Pharmacol.*, **25**, 968(1973).

(713) S. R. Dorey and D. Marsden, *J. Hosp. Pharm.*, **30**, 207(1972); through *Chem. Abstr.*, **78**, 7802g(1973).

(714) R. E. Schirmer, J. W. Kleber, and H. R. Black, *J. Pharm. Sci.*, **62**, 1270(1973).

(715) B. Desta and M. Pernarowski, *Drug. Intel. Clin. Pharm.*, **7**, 408(1973).

(716) E. Kristoffersson and K. Keto, *Farm. Aikak.*, **82**, 45(1973); through *Chem. Abstr.*, **79**, 45725n(1973).

(717) W. H. Thomas, *J. Pharm. Pharmacol.*, **25**, 27(1973).

(718) G. Haringer, B. J. Poulsen, and R. N. Havemeyer, *J. Pharm. Sci.*, **62**, 130(1973).

(719) A. C. Shah, C. B. Peot, and J. F. Ochs, *ibid.*, **62**, 671(1973).

(720) G. K. Bolhuis, C. F. Lerk, and K. Zuurman, *Pharm. Weekbl.*, **108**, 49(1973); through *Chem. Abstr.*, **78**, 75826t(1973).

(721) T. E. Needham, R. E. Shepherd, and L. A. Luzzi, *J. Pharm. Sci.*, **62**, 470(1973).

(722) F. W. Goodhart, R. H. McCoy, and F. C. Ninger, *ibid.*, **62,** 304(1973).

(723) K. A. Khan and C. T. Rhodes, *Can. J. Pharm. Sci.*, **8,** 29(1973).

(724) A T. Florence, P. H. Elworthy, and A. Rahman, *J. Pharm. Pharmacol.*, **25,** 779(1973).

(725) J. Tingstad, E. Gropper, L. Lachman, and E. Shami, *J. Pharm. Sci.*, **62,** 293(1973).

(726) J. Tingstad, J. Dudzinski, L. Lachman, and E. Shami, *ibid.*, **62,** 1527(1973).

(727) R. Tawashi and S. Bisaillon, *Pharm. Acta Helv.*, **48,** 245(1973).

(728) T. E. Needham, Jr., L. A. Luzzi, and W. D. Mason, *J. Pharm. Sci.*, **62,** 1860(1973).

(729) V. Kumari, *Pharmacos*, **17,** 60(1972); through *Chem. Abstr.*, **79,** 35088t(1973).

(730) K. Matsushima, S. Sugayama, and H. Ueki, *Iryo*, **26,** 611(1972); through *Chem. Abstr.*, **78,** 151593g(1973).

(731) R. E. Northern, J. L. Lach, and J. H. Fincher, *Amer. J. Hosp. Pharm.*, **30,** 622(1973).

(732) L. H. Block and R. N. Patel, *J. Pharm. Sci.*, **62,** 617(1973).

(733) W. I. Higuchi, S. Prakongpan, and F. Young, *ibid.*, **62,** 1207(1973).

(734) A. Amann, *ibid.*, **62,** 1573(1973).

(735) G. P. Bettinetti, F. Giordano, and A. LaManna, *Farmaco, Ed. Prat.*, **28,** 330(1973); through *Chem. Abstr.*, **79,** 70154h(1973).

(736) A. K. Kristensen, L. Duchleiter, C. F. Wiese, and O. Wulff, *Dan. Tidsskr. Farm.*, **46,** 185(1972); through *Chem. Abstr.*, **78,** 128379h(1973).

(737) A. K. Kristensen, L. Duchleiter, M. Benthin, B. Myhre, P. Finholt, A. Smit, A. O. Pedersen, C. F. Wiese, and O. Wulff, *Arch. Pharm. Chemi, Sci. Ed.*, **1,** 31(1973); through *Chem. Abstr.*, **79,** 45718n(1973).

(738) R. D. Hossie, I. J. McGilveray, G. L. Mattok, and C. A. Mainville, *Can. J. Pharm. Sci.*, **8,** 37(1973).

(739) J. V. Fee, D. J. W. Grant, and J. M. Newton, *J. Pharm. Pharmacol., Suppl.*, **25,** 148P(1973).

(740) S. A. H. Khalil and L. M. M. Ali, *Indian J. Pharm.*, **35,** 59(1973); through *Chem. Abstr.*, **79,** 23551a(1973).

(741) M. Kanke and K. Sekiguchi, *Chem. Pharm. Bull.*, **21,** 871(1973).

(742) A. Hoelgaard and N. Hoeller, *Arch. Pharm. Chemi, Sci. Ed.*, **1,** 1(1973); through *Chem. Abstr.*, **79,** 35078q(1973).

(743) S. Potter, *J. Hosp. Pharm.*, **30,** 294(1972); through *Chem. Abstr.*, **78,** 101934y(1973).

(744) F. L. Underwood, *Diss. Abstr. Int.*, **33,** 3172B(1973).

(745) C. D. Shively, *ibid.*, **34,** 2123B(1973).

(746) F. Bertolotti, S. DeLeo, F. Fontani, and G. Sekules, *Boll. Chim. Farm.*, **112,** 163(1973); through *Chem. Abstr.*, **79,** 83410p(1973).

(747) L. Simioni and R. Bottoni, *ibid.*, **112,** 191(1973); through *Chem. Abstr.*, **79,** 83409v(1973).

(748) C. W. Woodruff, *Diss. Abstr. Int.*, **34,** 2123B(1973).

(749) J. A. Rees and J. H. Collett, *J. Pharm. Pharmacol., Suppl.*, **25,** 147P(1973).

(750) J. H. Collett, J. C. Dearden, and E. Tomlinson, *ibid.*, **25,** 136P(1973).

(751) T. Paal and P. Regos, *Gyogyszereszet*, **17,** 59(1973); through *Chem. Abstr.*, **78,** 128377f(1973).

(752) G. C. Ceschel, *Cron. Farm.*, **15,** 335(1972); through *Chem. Abstr.*, **79,** 9796c(1973).

(753) D. Brooke, *J. Pharm. Sci.*, **62,** 795(1973).

(754) L. Luzzi and T. Needham, *ibid.*, **62,** 1907(1973).

(755) J. A. Hersey, *ibid.*, **62,** 514(1973).

(756) B. Selemczi, A. Smit, and P. Finholt, *Acta Pharm. Hung.*, **42,** 254(1972); through *Chem. Abstr.*, **78,** 47726s(1973).

(757) T. J. McCarthy, *Cosmet. Perfum.*, **88,** 61(1973).

(758) J. A. Rogers and J. G. Nairn, *Can. J. Pharm. Sci.*, **8,** 75(1973).

(759) D. K. Madan and D. E. Cadwallader, *J. Pharm. Sci.*, **62,** 1567(1973).

(760) N. G. Larionov, G. G. Zapesochnaya, N. A. Fedyunina, S. V. Rusakova, and A. I. Ban'kovskii, *Farmatsiya (Moscow)*, **21,** 43(1972); through *Chem. Abstr.*, **78,** 7799m(1973).

(761) A. Mayer and M. Kata, *Pharmazie*, **28,** 214(1973); through *Chem. Abstr.*, **78,** 164011r(1973).

(762) M. J. Crooks and K. F. Brown, *J. Pharm. Pharmacol.*, **25,** 281(1973).

(763) P. P. DeLuca, L. Lachman, and H. G. Schroeder, *J. Pharm. Sci.*, **62,** 1320(1973).

(764) H. A. M. El-Shibini, S. Abd-Elfattah, and M. M. Motawi, *Pharmazie*, **27,** 570(1972); through *Chem. Abstr.*, **78,** 20160r(1973).

(765) V. N. Verezhnikov and L. S. Kotlyar, *Kolloid. Zh.*, **35,** 534(1973); through *Chem. Abstr.*, **79,** 138018z(1973).

(766) F. Tokiwa and K. Tsujii, *Bull. Chem. Soc. Jap.*, **46,** 1338(1973); through *Chem. Abstr.*, **79,** 80644g(1973).

(767) H. Kunieda and K. Shinoda, *Nippon Kagaku Kaishi*, **11,** 2001(1972); through *Chem. Abstr.*, **78,** 60029m(1973).

(768) V. Matejekova and L. Novak, *Petrochemia*, **12,** 64(1972); through *Chem. Abstr.*, **78,** 86304x(1973).

(769) M. J. Schwuger, *Kolloid-Z. Z. Polym.*, **250,** 703(1972); through *Chem. Abstr.*, **78,** 45399p(1973).

(770) W. Horsch, J. Koegel, C. Teich, and M. Wendrich, *Pharmazie*, **27,** 614(1972); through *Chem. Abstr.*, **78,** 47754z (1973).

(771) M. Mayersohn and K. Suryasaputra, *J. Pharm. Sci.*, **62,** 681(1973).

(772) S. H. Yalkowsky and G. L. Flynn, *ibid.*, **62,** 210(1973).

(773) R. Withington and J. H. Collett, *J. Pharm. Pharmacol.*, **25,** 273(1973).

(774) E. G. Lovering and D. B. Black, *J. Pharm. Sci.*, **62,** 602(1973).

(775) E. G. Lovering and K. B. McRae, *ibid.*, **62,** 971(1973).

(776) S. J. A. Kazmi and A. G. Mitchell, *ibid.*, **62,** 1299(1973).

(777) T. Yotsuyanagi, W. I. Higuchi, and A. H. Ghanem, *ibid.*, **62,** 40(1973).

(778) J. M. N. Gillan and A. T. Florence, *J. Pharm. Pharmacol., Suppl.*, **25,** 136P(1973).

(779) Z. T. Chowhan, T. Yotsuyanagi, and W. I. Higuchi, *J. Pharm. Sci.*, **62,** 221(1973).

(780) Z. T. Chowhan and W. I. Higuchi, *ibid.*, **62,** 443(1973).

(781) Z. Olszewski and A. Kubis, *Acta Pol. Pharm.*, **29,** 615(1972); through *Chem. Abstr.*, **78,** 88572g(1973).

(782) A. Kubis, *ibid.*, **30,** 187(1973); through *Chem. Abstr.*, **79,** 108028k(1973).

(783) Z. Gruntova, M. Mandak, and K. Duckova, *Acta Fac. Pharm., Univ. Comeniana*, **21,** 195(1972); through *Chem. Abstr.*, **78,** 164012s(1973).

(784) L. Stanoeva and L. Tomasini, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, **8,** 451(1972); through *Chem. Abstr.*, **78,** 164019z(1973).

(785) L. B. R. Gandhiji and B. M. Mithal, *Indian J. Pharm.*, **35,** 66(1973); through *Chem. Abstr.*, **79,** 23550z(1973).

(786) A. A. Kassem, S. A. Zaki, and O. El Taib, *Bull. Fac. Pharm., Cairo Univ.*, **10,** 285(1973); through *Chem. Abstr.*, **79,** 9842q(1973).

(787) F. E. Leaders, G. Hecht, M. VanHoose, and M. Kellog, *Ann. Ophthalmol.*, **5,** 513(1973); through *Chem. Abstr.*, **79,** 35103u(1973).

(788) J. S. Turi, *Diss. Abstr. Int.*, **34,** 1443B(1973).

(789) K. Takamura, M. Koishi, and T. Kondo, *J. Pharm. Sci.*, **62,** 610(1973).

(790) C. Kamizawa and S. Ishizaka, *Bull. Chem. Soc. Jap.*, **45,** 2967(1972); through *Chem. Abstr.*, **78,** 86284r(1973).

(791) D. O. Jordan and A. E. Polack, *Aust. J. Pharm. Sci.*, **2,** 25(1973); through *Chem. Abstr.*, **79,** 70152f(1973).

(792) Z. Golucki, *Diss. Pharm. Pharmacol.*, **24,** 631(1972); through *Chem. Abstr.*, **78,** 88571f(1973).

(793) I. M. Pertsev, G. S. Bashura, D. P. Salo, I. A. Murav'ev, and O. A. Pimenov, *Farm. Zh. (Kiev)*, **27,** 7(1972); through *Chem. Abstr.*, **78,** 9v(1973).

(794) *Ibid.*, **27,** 15(1972); through *Chem. Abstr.*, **78,** 75804j(1973).

(795) I. Lakovska, B. Botev, and T. Trandafilov, *Pharmazie*, **28,** 252(1973); through *Chem. Abstr.*, **79,** 57610j(1973).

(796) E. Doelker and P. Buri, *Pharm. Acta Helv.*, **48,** 166(1973); through *Chem. Abstr.*, **79,** 23542y(1973).

(797) *Ibid.*, **48,** 287(1973); through *Chem. Abstr.*, **79,** 70161h(1973).

(798) A. Popovici, M. Rogosca, and M. Peter, *Rev. Med. (Tirgu-Mures)*, **18,** 461(1972); through *Chem. Abstr.*, **79,** 9855w(1973).

(799) T. Hashimoto, *Chemotherapy (Tokyo)*, **21,** 38(1973);

through *Chem. Abstr.*, **79**, 27456w(1973).

(800) J. K. H. Ma, H. W. Jun, and L. A. Luzzi, *J. Pharm. Sci.*, **62**, 1261(1973).

(801) *Ibid.*, **62**, 2038(1973).

(802) T. J. Mikkelson, S. S. Chrai, and J. R. Robinson, *J. Pharm. Sci.*, **62**, 1942(1973).

(803) P. VanSaanen, *Stud. Cercet. Med. Interna*, **14**, 167(1973); through *Chem. Abstr.*, **79**, 100360s(1973).

(804) G. Ziv and F. G. Sulman, *Antimicrob. Ag. Chemother.*, **2**, 206(1972); through *Chem. Abstr.*, **78**, 227q(1973).

(805) G. D. Olsen, *Clin. Pharmacol. Ther.*, **14**, 338(1973).

(806) R. C. Gordon, C. Regamey, and W. M. M. Kirby, *J. Pharm. Sci.*, **62**, 1074(1973).

(807) A. Agren and T. Back, *Acta Pharm. Suecica*, **10**, 223(1973); through *Chem. Abstr.*, **79**, 73519s(1973).

(808) B. G. Gazzard, A. W. Ford-Hutchinson, M. J. H. Smith, and R. Williams, *J. Pharm. Pharmacol.*, **25**, 964(1973).

(809) P. Tschudi, *Zentralbl. Veterinaermed., Reihe A*, **19**, 851(1972); through *Chem. Abstr.*, **78**, 23856h(1973).

(810) S. P. Baker and B. A. Hemsworth, *J. Pharm. Pharmacol., Suppl.*, **24**, 164P(1972); through *Chem. Abstr.*, **78**, 52590x(1973).

(811) M. A. Skivington, *Brit. J. Anaesthesiol.*, **44**, 1030(1972); through *Chem. Abstr.*, **78**, 66762s(1973).

(812) A. B. Combs and S. N. Giri, *J. Pharm. Sci.*, **62**, 631(1973).

(813) J. Judis, *ibid.*, **62**, 232(1973).

(814) Y. W. Chien, T. D. Sokoloski, C. L. Olson, D. T. Witiak, and R. Nazareth, *ibid.*, **62**, 440(1973).

(815) G. H. Evans and D. G. Shand, *Clin. Pharmacol. Ther.*, **14**, 494(1973).

(816) K. F. Funk, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother. 7th*, **1**, 161(1972); through *Chem. Abstr.*, **79**, 87397n(1973).

(817) P. Tschudi, *Zentralbl. Veterinaermed., Reihe A*, **20**, 145(1973); through *Chem. Abstr.*, **78**, 105896k(1973).

(818) *Ibid.*, **20**, 155(1973); through *Chem. Abstr.*, **78**, 105897m(1973).

(819) A. Rubin, P. Warrick, R. L. Wolen, S. M. Chernish, A. S. Ridolfo, and C. M. Gruber, Jr., *J. Pharmacol. Exp. Ther.*, **183**, 449(1972); through *Chem. Abstr.*, **78**, 79536w(1973).

(820) J. H. Perrin and D. A. Nelson, *J. Pharm. Pharmacol.*, **25**, 125(1973).

(821) N. Kolassa and K. Pfleger, *Arch. Int. Pharmacodyn. Ther.*, **199**, 394(1972); through *Chem. Abstr.*, **78**, 11413y(1973).

(822) J. M. Padfield and I. W. Kellaway, *J. Pharm. Pharmacol.*, **25**, 285(1973).

(823) C. Plessas, *Chem. Chron., Genike Ekdosis*, **37**, 62(1972); through *Chem. Abstr.*, **78**, 92464r(1973).

(824) C. R. Short and M. E. Tumbleson, *Toxicol. Appl. Pharmacol.*, **24**, 612(1973); through *Chem. Abstr.*, **79**, 73454s(1973).

(825) L. M. Allen and P. J. Creaven, *J. Pharm. Sci.*, **62**, 854(1973).

(826) C. F. Chignell, *Handb. Exp. Pharmakol.*, **28**(Part 1), 187(1971); through *Chem. Abstr.*, **78**, 23696f(1973).

(827) P. Keen, *ibid.*, **28**(Part 1), 213(1971); through *Chem. Abstr.*, **78**, 23697g(1973).

(828) P. Kourounakis and L. Kourounakis-Hadjipetrou, *Pharm. Delt., Epistem. Ekdosis*, **1**, 35(1971); through *Chem. Abstr.*, **78**, 23714k(1973).

(829) S. M. Blaug and W. Huang, *J. Pharm. Sci.*, **62**, 652(1973).

(830) E. Ullmann, K. Thoma, and B. C. Lippold, *Arch. Pharm. (Weinheim)*, **305**, 797(1972); through *Chem. Abstr.*, **78**, 47733s(1973).

(831) B. C. Lippold, K. Thoma, and E. Ullmann, *ibid.*, **305**, 803(1972); through *Chem. Abstr.*, **78**, 47732r(1973).

(832) A. Sina, M. K. Youssef, A. A. Kassem, and I. A. Attia, *Indian J. Pharm.*, **35**, 85(1973); through *Chem. Abstr.*, **79**, 57626u(1973).

(833) H. Kishimoto and K. Sumida, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **19**, 45(1971); through *Chem. Abstr.*, **78**, 31788c(1973).

(834) S. L. Hem, E. J. Russo, S. M. Bahal, and R. S. Levi, *J. Pharm. Sci.*, **62**, 267(1973).

(835) N. D. Phuong and J. Paiement, *Can. J. Pharm. Sci.*, **7**, 117(1972); through *Chem. Abstr.*, **78**, 62128s(1973).

(836) T. Higuchi and I. H. Pitman, *J. Pharm. Sci.*, **62**, 55(1973).

(837) I. J. Jofre, *Jornadas Argent. Toxicol. Anal., Actas, 1st*, **2**, 314(1972); through *Chem. Abstr.*, **79**, 87287b(1973).

(838) H. Rupprecht and M. Biedermann, *Pharm. Ind.*, **35**, 215(1973); through *Chem. Abstr.*, **79**, 57609r(1973).

(839) J. B. Nagwekar and N. Muangnoicharoen, *J. Pharm. Sci.*, **62**, 1439(1973).

(840) M. E. Cheboltasova, *Tr. Konf. Molodykh Uch.-Khim. Goroda Tomska, 1st*, 257(1970); through *Chem. Abstr.*, **78**, 47745x(1973).

(841) H. F. Morrelli and K. L. Melmon, *Clin. Pharmacol. Basic Princ. Ther.*, **1972**, 585; through *Chem. Abstr.*, **78**, 23713j(1973).

(842) T. V. Alykova and A. A. Terent'ev, *Tr. Konf. Molodykh Nauch. Sotrudnikov Astrakhan. Med. Inst., 2nd*, **1970**, 88; through *Chem. Abstr.*, **78**, 23809v(1973).

(843) J. Paiement, *Can. J. Pharm. Sci.*, **8**, 16(1973).

(844) W. D. Bond, K. Bischoff, and E. Sprunger, *Rev. Sci. Instrum.*, **44**, 779(1973); through *Chem. Abstr.*, **79**, 23751r(1973).

(845) A. W. Malick, A. Felmeister, and N. D. Weiner, *J. Pharm. Sci.*, **62**, 1871(1973).

(846) V. A. Semenova, N. T. Manolov, N. N. Borisov, and A. V. Prokopenko, *Poverkh. Sily Tonkikh Plenkakh Dispersnykh Sist., Sb. Dokl. Konf. Poverkh. Silam, 4th*, **1972**, 289; through *Chem. Abstr.*, **78**, 8138g(1973).

(847) V. A. Voronov and B. M. Nikitin, *Zavod. Lab.*, **39**, 721(1973); through *Chem. Abstr.*, **79**, 129488a(1973).

(848) H. Kimizuka and L. G. Abood, *J. Pharm. Sci.*, **62**, 740(1973).

(849) L. S. C. Wan and P. K. C. Poon, *Can. J. Pharm. Sci.*, **8**, 98(1973).

(850) A. A. Belmonte and J. Swarbrick, *J. Pharm. Sci.*, **62**, 481(1973).

(851) D. O. Shah, A. Tamjeedi, J. W. Falco, and R. D. Walker, Jr., *AIChE J.*, **18**, 1116(1972); through *Chem. Abstr.*, **78**, 34237h(1973).

(852) E. V. Gromov and A. A. Abramzon, *Poverkh. Yavleniya Polim.*, **1**, 28(1971); through *Chem. Abstr.*, **79**, 68081p(1973).

(853) K. Shirahama, *Kolloid-Z. Z. Polym.*, **250**, 620(1972); through *Chem. Abstr.*, **78**, 31791y(1973).

(854) B. C. Chatterjee and K. Ghosh, *J. Indian Chem. Soc.*, **49**, 751(1972); through *Chem. Abstr.*, **78**, 5700y(1973).

(855) F. Harahap, *Proc. Inst. Teknol. Bandung*, **6**, 1(1971); through *Chem. Abstr.*, **78**, 34234e(1973).

(856) S. A. H. Khalil and R. N. Nasipuri, *J. Pharm. Pharmacol.*, **25**, 138(1973).

(857) B. C. Lippold and B. H. Lippold, *Pharmazie*, **28**, 202(1973); through *Chem. Abstr.*, **79**, 45727q(1973).

(858) S. A. Khalil and M. A. Moustafa, *ibid.*, **28**, 116(1973); through *Chem. Abstr.*, **79**, 9826n(1973).

(859) N. A. Armstrong and C. D. Clarke, *J. Pharm. Sci.*, **62**, 379(1973).

(860) H. Rupprecht and M. Biedermann, *Pharm. Ind.*, **35**, 353(1973); through *Chem. Abstr.*, **79**, 118277e(1973).

(861) A. L. Myers and S. Sircar, *J. Phys. Chem.*, **76**, 3415(1972); through *Chem. Abstr.*, **78**, 8168s(1973).

(862) G. W. C. Hung, L. J. Nunez, and J. Autian, *J. Pharm. Sci.*, **62**, 1308(1973).

(863) A. A. Abramzon, E. V. Gromov, and N. N. Makagonova, *Kolloid. Zh.*, **35**, 122(1973); through *Chem. Abstr.*, **79**, 7151q(1973).

(864) V. I. Shanina-Vagina, E. A. Il'nitskaya, N. G. Chernikova, A. K. Vargina, T. G. Semykina, Z. I. Ershova, and A. N. Lobanova, *Vaktsiny Syvorotki*, **12**, 95(1970); through *Chem. Abstr.*, **78**, 47696g(1973).

(865) A. L. Myers and S. Sircar, *J. Phys. Chem.*, **76**, 3412(1972); through *Chem. Abstr.*, **78**, 8167r(1973).

(866) V. Krivich and M. K. Gluzman, *Kolloid. Zh.*, **35**, 364(1973); through *Chem. Abstr.*, **79**, 55234r(1973).

(867) G. D. Petrowski and J. R. Vanatta, *J. Amer. Oil Chem. Soc.*, **50**, 284(1973); through *Chem. Abstr.*, **79**, 93716g(1973).

(868) L. Marszall, *J. Pharm. Pharmacol.*, **25**, 254(1973).

(869) A. Lorine, M. Lelkes, and E. Wolfram, *Acta Chim. (Budapest)*, **77**, 155(1973); through *Chem. Abstr.*, **79**, 97387y(1973).

(870) F. Popescu and I. Ana, *Petrol Gaze*, **24**, 88(1973); through *Chem. Abstr.*, **79**, 80639j(1973).

(871) J. Broniarz, M. Wisniewski, and J. Szymanowski, *Tenside Deterg.*, **10**, 75(1973); through *Chem. Abstr.*, **78**,

149188k(1973).

(872) E. G. Lomax, *Soap, Cosmet., Chem. Spec.*, **48,** 29(1972); through *Chem. Abstr.*, **78,** 31801b(1973).

(873) J. Broniarz, J. Szymanowski, and M. Wisniewski, *Tluszcze, Srodki Piorace, Kosmet.*, **17,** 73(1973); through *Chem. Abstr.*, **79,** 20627u(1973).

(874) D. A. Rozhdestvenskii, *Maslo-Zhir. Prom.*, **4,** 19(1973); through *Chem. Abstr.*, **79,** 20626t(1973).

(875) A. Kitahara, *Yukagaku*, **22,** 397(1973); through *Chem. Abstr.*, **79,** 147610p(1973).

(876) A. Kitahara, *Kagaku Kogyo*, **24,** 1293(1973); through *Chem. Abstr.*, **79,** 147607t(1973).

(877) H. Arai, *Yukagaku*, **21,** 500(1972); through *Chem. Abstr.*, **78,** 5687z(1973).

(878) A. Kitahara, *Junkatsu*, **17,** 475(1972); through *Chem. Abstr.*, **78,** 5689b(1973).

(879) M. Kajl, *Pollena*, **16,** 3(1972); through *Chem. Abstr.*, **78,** 18028k(1973).

(880) M. A. Ashimov, M. A. Mursalova, M. A. Mamedova, V. S. Petrosyan, A. S. Gaisin, and V. D. Dzhafarov, *Azerb. Khim. Zh.*, **3,** 100(1972); through *Chem. Abstr.*, **79,** 80636f(1973).

(881) M. F. Saettone, *Relata Tech. Chim. Biol. Appl.*, **4,** 445(1972); through *Chem. Abstr.*, **79,** 45665t(1973).

(882) N. H. Choulis and L. H. Loh, *Can. J. Pharm. Sci.*, **8,** 64(1973).

(883) E. L. Parrott and R. J. Braun, *Chem. Pharm. Bull.*, **21,** 1042(1973).

(884) H. Lange and K. Beck, *Kolloid-Z. Z. Polym.*, **251,** 424(1973); through *Chem. Abstr.*, **79,** 138017y(1973).

(885) B. Farhadieh, *J. Pharm. Sci.*, **62,** 1685(1973).

(886) L. H. Loh, N. H. Choulis, and T. Rhodes, *Can. J. Pharm. Sci.*, **8,** 93(1973).

(887) J. Rassing, P. J. Sams, and E. Wyn-Jones, *J. Chem. Soc., Faraday Trans. 2*, **69,** 180(1973); through *Chem. Abstr.*, **78,** 76247s(1973).

(888) D. G. Duff and C. H. Giles, *J. Colloid Interface Sci.*, **41,** 407(1972); through *Chem. Abstr.*, **78,** 76143e(1973).

(889) J. E. Rassing and E. Wyn-Jones, *Chem. Phys. Lett.*, **21,** 93(1973); through *Chem. Abstr.*, **79,** 118605k(1973).

(890) N. Muller, *React. Kinet. Micelles, Proc. Amer. Chem. Soc. Symp., 1972* (1973); through *Chem. Abstr.*, **78,** 149187j(1973).

(891) V. I. Kofanov and Y. M. Glazman, *Poverkh. Yavleniya Zhidk. Zhidk. Rastvorakh*, **1,** 127(1972); through *Chem. Abstr.*, **79,** 35350x(1973).

(892) T. Nakagawa, *Yukagaku*, **22,** 181(1973); through *Chem. Abstr.*, **79,** 35337y(1973).

(893) S. Muto and K. Meguro, *Bull. Chem. Soc. Jap.*, **46,** 1316(1973); through *Chem. Abstr.*, **79,** 80643f(1973).

(894) J. Alba Mendoza, C. Gomez Herrera, and J. Pereda Marin, *Grasas Aceites (Seville)*, **24,** 236(1973); through *Chem. Abstr.*, **79,** 138016x(1973).

(895) A. Chwala, *Informationsdienst, Arbeitsgemeinsch. Pharm. Verfahrenstech.*, **16,** 199(1970); through *Chem. Abstr.*, **78,** 5686y(1973).

(896) H. G. Elias, *J. Macromol. Sci. Chem.*, **7,** 601(1973); through *Chem. Abstr.*, **78,** 99464z(1973).

(897) F. Tokiwa, *Advan. Colloid Interface Sci.*, **3,** 389(1972); through *Chem. Abstr.*, **78,** 86287u(1973).

(898) V. N. Zakharchenko and S. M. Larionov, *Strukt. Funkts. Biol. Membran*, **1971,** 167; through *Chem. Abstr.*, **78,** 86302v(1973).

(899) Y. Kubota, M. Kodama, and M. Miura, *Bull. Chem. Soc. Jap.*, **46,** 100(1973); through *Chem. Abstr.*, **78,** 113070b(1973).

(900) G. Brosowski, M. Rohr, and G. Lehmann, *Fette, Seifen, Anstrichm.*, **75,** 335(1973); through *Chem. Abstr.*, **79,** 68080n(1973).

(901) K. Fontell, *Kolloid-Z. Z. Polym.*, **250,** 825(1972); through *Chem. Abstr.*, **78,** 48284h(1973).

(902) P. Molyneux and C. T. Rhodes, *ibid.*, **250,** 886(1972); through *Chem. Abstr.*, **78,** 62556e(1973).

(903) R. C. Kapoor, P. Chand, and V. P. Aggarwala, *Anal. Chem.*, **44,** 2107(1972); through *Chem. Abstr.*, **78,** 60027j(1973).

(904) M. Kodama, Y. Kubota, and M. Miura, *Bull. Chem. Soc. Jap.*, **45,** 2953(1972); through *Chem. Abstr.*, **78,** 60028k(1973).

(905) G. W. Hallworth and J. E. Carless, *J. Pharm. Pharmacol., Suppl.*, **25,** 87P(1973).

(906) P. A. Sanders, *J. Soc. Cosmet. Chem.*, **24,** 87(1973).

(907) P. Steinberg and P. S. Norman, *J. Allergy Clin. Immunol.*, **51,** 238(1973); through *Chem. Abstr.*, **78,** 164039f(1973).

(908) F. Gstirner and C. Gaudich, *Deut. Apoth.-Ztg.*, **112,** 1583(1972); through *Chem. Abstr.*, **78,** 164055h(1973).

(909) R. Voigt, H. Florstedt, and M. Bornschein, *Pharmazie*, **28,** 378(1973); through *Chem. Abstr.*, **79,** 70169s(1973).

(910) S. Tsukiyama and A. Takamura, *Yakugaku Zasshi*, **93,** 875(1973); through *Chem. Abstr.*, **79,** 83759j(1973).

(911) I. Doncheva, E. Trandafilova, and T. Trandafilov, *J. Pharm. Belg.*, **28,** 209(1973); through *Chem. Abstr.*, **79,** 70153g(1973).

(912) T. Mita, K. Yamada, S. Matsumoto, and D. Yonezawa, *J. Texture Stud.*, **4,** 41(1973); through *Chem. Abstr.*, **78,** 151879e(1973).

(913) N. F. H. Ho, H. Toguchi, and W. I. Higuchi, *J. Pharm. Sci.*, **62,** 851(1973).

(914) A. A. Abramzon and Z. N. Slavina, *Kolloid. Zh.*, **35,** 118(1973); through *Chem. Abstr.*, **78,** 140683k(1973).

(915) A. Felmeister, G. M. Kuchtyak, S. Koziol, and C. J. Felmeister, *J. Pharm. Sci.*, **62,** 2026(1973).

(916) E. Wacholder, *Chem. Eng. Sci.*, **28,** 1447(1973); through *Chem. Abstr.*, **79,** 108340f(1973).

(917) B. Koglin, *Silicates Ind.*, **37,** 257(1972); through *Chem. Abstr.*, **78,** 34316h(1973).

(918) G. Rialdi, *Relata Tech. Chim. Biol. Appl.*, **4,** 25(1972); through *Chem. Abstr.*, **78,** 140379r(1973).

(919) L. Barclay, A. Harrington, and R. H. Ottewill, *Kolloid-Z. Z. Polym.*, **250,** 655(1972); through *Chem. Abstr.*, **78,** 34289b(1973).

(920) D. Eagland, *Contemp. Phys.*, **14,** 119(1973); through *Chem. Abstr.*, **78,** 164471r(1973).

(921) N. P. Fedoseeva, V. M. Kuchumova, L. A. Kochanova, E. D. Shchukin, and P. A. Rebinder, *Poverkh. Yavleniya Zhidk. Zhidk. Rastvorakh*, **1,** 157(1972); through *Chem. Abstr.*, **78,** 164495b(1973).

(922) Z. Csath-Stincel and M. Nagy, *Farmacia (Bucharest)*, **20,** 745(1972); through *Chem. Abstr.*, **79,** 9822h(1973).

(923) A. Otsuka, H. Sunada, and Y. Yonezawa, *J. Pharm. Sci.*, **62,** 751(1973).

(924) A. Smith and S. S. Davis, *J. Pharm. Pharmacol., Suppl.*, **25,** 117P(1973).

(925) L. Bardet, H. Delonca, and J. Lacoste, *Parfums, Cosmet., Savons Fr.*, **3,** 330(1973); through *Chem. Abstr.*, **79,** 57994n(1973).

(926) V. S. Gupta, S. K. Bhattacharjya, and B. K. Dutta, *Technology*, **9,** 322(1973); through *Chem. Abstr.*, **79,** 108438u(1973).

(927) Y. N. Grigorov, N. S. Sverdlova, and I. V. Okatova, *Elektropoverkhnostnye Yavleniya Dispersnykh Sist.*, **1972,** 64; through *Chem. Abstr.*, **79,** 108336j(1973).

(928) E. V. Kamenskaya, Y. A. Klyachko, and E. I. Evko, *Zh. Vses. Khim. Obshchest.*, **18,** 479(1973); through *Chem. Abstr.*, **79,** 118663c(1973).

(929) A. F. Koretskii and G. I. Plotnikova, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk.*, **4,** 28(1972); through *Chem. Abstr.*, **78,** 73933b(1973).

(930) G. M. Eccleston, B. W. Barry, and S. S. Davis, *J. Pharm. Sci.*, **62,** 1954(1973).

(931) B. W. Barry and G. M. Eccleston, *J. Pharm. Pharmacol.*, **25,** 244(1973).

(932) *Ibid.*, **25,** 394(1973).

(933) B. W. Barry, *J. Pharm. Pharmacol.*, **25,** 131(1973).

(934) G. M. Eccleston and B. W. Barry, *J. Pharm. Pharmacol., Suppl.*, **25,** 167P(1973).

(935) B. Testa and J. C. Etter, *Pharm. Acta Helv.*, **48,** 378(1973); through *Chem. Abstr.*, **79,** 96899e(1973).

(936) R. R. Morgado and A. A. Pinho, *An. Fac. Farm. Porto*, **31,** 43(1971); through *Chem. Abstr.*, **78,** 151567b(1973).

(937) E. Hunyadvari and I. Eros, *Sci. Pharm.*, **41,** 39(1973); through *Chem. Abstr.*, **78,** 164007u(1973).

(938) M. Saeki, *Sankyo Kenkyusho Nempo*, **24,** 91(1972); through *Chem. Abstr.*, **78,** 164001n(1973).

(939) R. R. Morgado and E. Azedo, *An. Fac. Farm Porto*, **31,** 51(1971); through *Chem. Abstr.*, **78,** 140349f(1973).

(940) S. Kaur, *Pharmacos*, **17,** 37(1972); through *Chem. Abstr.*, **79,** 35056f(1973).

(941) L. S. C. Wan and K. K. Tan, *Indian J. Pharm.*, **35,**

71(1973); through *Chem. Abstr.*, **79,** 35090n(1973).

(942) J. A. Robinson, I. W. Kellaway, and C. Marriott, *J. Pharm. Pharmacol., Suppl.*, **25,** 168P(1973).

(943) E. Kristoffersson, *Farm. Aikak.*, **81,** 146(1972); through *Chem. Abstr.*, **78,** 115165k(1973).

(944) O. I. Ryaposova, *Farmatsiya (Moscow)*, **21,** 36(1972); through *Chem. Abstr.*, **78,** 128385g(1973).

(945) K. Suzuki, K. Sakon, and T. Watanabe, *Zairyo*, **22,** 414(1973); through *Chem. Abstr.*, **79,** 55231n(1973).

(946) A. Rutkowski and Z. Elsner, *Cosmet. Perfum.*, **88**(7), 23(1973); through *Chem. Abstr.*, **79,** 70088q(1973).

(947) O. I. Ryaposova, *Tr. Perm. Gos. Med. Inst.*, **99,** 357(1970); through *Chem. Abstr.*, **78,** 33865z(1973).

(948) L. Tomasini, V. Andonova, M. Goshkaryan and V. Tomova, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, **8,** 427(1972); through *Chem. Abstr.*, **78,** 164018y(1973).

(949) A. A. Kassem and E. H. Girgis, *Bull. Fac. Pharm., Cairo Univ., 1971*, **10,** 187(1973); through *Chem. Abstr.*, **78,** 164030w(1973).

(950) P. R. Klink and J. L. Colaizzi, *J. Pharm. Sci.*, **62,** 97(1973).

(951) L. Adam, E. Szantho, E. Peteanu, and L. Domokos, *Rev. Med. (Tirgu-Mures)*, **18,** 453(1972); through *Chem. Abstr.*, **78,** 164051d(1973).

(952) M. Aoki, H. Fukuchi, N. Kasahara, S. Ishida, Y. Miura, and M. Kurano, *Yakuzaigaku*, **32,** 159(1972); through *Chem. Abstr.*, **79,** 149308v(1973).

(953) J. M. Padfield and I. W. Kellaway, *J. Pharm. Sci.*, **62,** 1621(1973).

(954) M. L. Ezerskii and G. M. Pis'mennaya, *Khim.-Farm. Zh.*, **6,** 50(1972); through *Chem. Abstr.*, **78,** 33862w(1973).

(955) V. Boyanova, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, **8,** 457(1972); through *Chem. Abstr.*, **78,** 164020t(1973).

(956) B. Lynn, *Isr. Pharm. J.*, **15,** 355(1972); through *Chem. Abstr.*, **78,** 143589v(1973).

(957) I. H. Stockley, *Pharm. J.*, **210,** 36(1973).

(958) C. M. Won and E. R. Garrett, *J. Pharm. Sci.*, **62,** 1087(1973).

(959) V. A. Vainshtein, *Tr. Leningrad. Nauch.-Issled. Inst. Antibiot.*, **9,** 17(1972); through *Chem. Abstr.*, **78,** 33870x(1973).

(960) B. I. Dashevskaya, R. G. Tartakovskaya, V. S. Krivich, and M. K. Gluzman, *Farmatsiya (Moscow)*, **22,** 23(1973); through *Chem. Abstr.*, **79,** 9836r(1973).

(961) B. Knie, *Roentgenpraxis (Stuttgart)*, **26,** 106(1973); through *Chem. Abstr.*, **79,** 57586f(1973).

(962) H. B. Hupf, *Hematopoietic Gastrointest. Invest. Radionuclides, Annu. Nucl. Med. Semin., 3rd, 1971*, **1972,** 109; through *Chem. Abstr.*, **78,** 131858u(1973).

(963) R. C. Thomas, *Annu. Rep. Med. Chem.*, **7,** 296(1972); through *Chem. Abstr.*, **78,** 33819n(1973).

(964) G. Kloss, K. H. Bremer, and K. Fruehauf, *Therapiewoche*, **23,** 1593(1973); through *Chem. Abstr.*, **79,** 23524u(1973).

(965) V. Grossman, *Cesk. Farm.*, **22,** 173(1973); through *Chem. Abstr.*, **79,** 83405r(1973).

(966) V. Blaha and Z. Krivsky, *ibid.*, **22,** 176(1973); through *Chem. Abstr.*, **79,** 83408u(1973).

(967) L. Martis and R. H. Levy, *J. Pharmacokin. Biopharm.*, **1,** 283(1973).

(968) K. C. Kwan and A. E. Till, *J. Pharm. Sci.*, **62,** 1494(1973).

(969) D. Perrier and M. Gibaldi, *J. Pharmacokin. Biopharm.*, **1,** 17(1973).

(970) G. Levy, *Pharmacology*, **8,** 33(1972); through *Chem. Abstr.*, **78,** 92353d(1973).

(971) J. E. Bearman and R. B. Loewenson, *ibid.*, **8,** 44(1972); through *Chem. Abstr.*, **78,** 92354e(1973).

(972) W. H. Barr, *ibid.*, **8,** 55(1972); through *Chem. Abstr.*, **78,** 105825m(1973).

(973) J. G. Wagner, *ibid.*, **8,** 102(1972); through *Chem. Abstr.*, **78,** 92355f(1973).

(974) S. Riegelman, *ibid.*, **8,** 118(1972); through *Chem. Abstr.*, **78,** 92356g(1973).

(975) E. Steiness, V. Christensen, and H. Johansen, *Clin. Pharmacol. Ther.*, **14,** 949(1973).

(976) R. G. Stoll, M. S. Christensen, E. Sakmar, D. Blair, and J. G. Wagner, *J. Pharm. Sci.*, **62,** 1615(1973).

(977) T. Beveridge, R. Schmidt, F. Kalberer, and E. Nüesch, *Lancet*, **2,** 499(1973).

(978) W. V. R. Vieweg and J. Sode, *Med. Ann. D.C.*, **42,** 136(1973); through *Chem. Abstr.*, **79,** 442b(1973).

(979) M. J. Akers, J. L. Lach, and L. J. Fischer, *J. Pharm. Sci.*, **62,** 1192(1973).

(980) D. Alkalay, L. Khemani, W. E. Wagner, Jr., and M. F. Bartlett, *J. Clin. Pharmacol.*, **13,** 142(1973).

(981) G. M. Simpson, R. Lament, T. B. Cooper, J. H. Lee, and R. B. Bruce, *ibid.*, **13,** 288(1973).

(982) C. M. Davis, J. V. Vandersarl, and E. W. Kraus, *Amer. J. Med. Sci.*, **265,** 69(1973); through *Chem. Abstr.*, **79,** 73811f(1973).

(983) G. Bruni and F. Galletti, *Boll. Chim. Farm.*, **112,** 110(1973); through *Chem. Abstr.*, **79,** 96866s(1973).

(984) A. A. Forist, R. M. DeHaan, and C. M. Metzler, *J. Pharmacokin. Biopharm.*, **1,** 89(1973).

(985) P. G. Shrotriya, I. K. Sachdev, R. K. Uppadhayay, and S. N. Sharma, *Indian J. Pharm. Educ.*, **7,** 22(1973); through *Chem. Abstr.*, **79,** 100749a(1973).

(986) D. Ben-Ishay and K. Engelman, *Clin. Pharmacol. Ther.*, **14,** 250(1973).

(987) I. J. McGilveray, R. D. Hossie, and G. L. Matlok, *Can. J. Pharm. Sci.*, **8,** 13(1973).

(988) F. Neuwald, *Pharma Int., Engl. Ed.*, **2,** 5(1972); through *Chem. Abstr.*, **78,** 88543y(1973).

(989) T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31,** 292(1971); through *Chem. Abstr.*, **79,** 142906e(1973).

(990) C. B. Tuttle, M. Mayersohn, and G. C. Walker, *Can. J. Pharm. Sci.*, **8,** 31(1973).

(991) T. Bergan, B. Oydvin, and I. Lunde, *Acta Pharmacol. Toxicol.*, **33,** 138(1973); through *Chem. Abstr.*, **79,** 96901z(1973).

(992) W. A. Ritschel and M. Banarer, *Bol. Soc. Quim. Peru*, **38,** 212(1972); through *Chem. Abstr.*, **79,** 87318n(1973).

(993) R. J. Scheuplein and I. H. Blank, *J. Invest. Dermatol.*, **60,** 286(1973).

(994) P. H. Dugard and R. J. Scheuplein, *ibid.*, **60,** 263(1973).

(995) M. Washitake, T. Yajima, T. Anmo, T. Arita, and R. Hori, *Chem. Pharm. Bull.*, **21,** 2444(1973).

(996) S. Hirose, K. Igarashi, K. Yawata, H. Fukuzawa, and A. Minato, *ibid.*, **21,** 1351(1973).

(997) J. Hadgraft, J. W. Hadgraft, and I. Sarkany, *J. Pharm. Pharmacol., Suppl.*, **25,** 122P(1973).

(998) G. Kiss and I. Horvath, *J. Soc. Cosmet. Chem.*, **23,** 807(1972); through *Chem. Abstr.*, **78,** 101868e(1973).

(999) *Ibid.*, **23,** 803(1972); through *Chem. Abstr.*, **78,** 101867d(1973).

(1000) A. Zesch and H. Schaefer, *Arch. Dermatol. Forsch.*, **246,** 335(1973); through *Chem. Abstr.*, **79,** 45760v(1973).

(1001) M. Siddiqi and W. A. Ritschel, *Sci. Pharm.*, **40,** 181(1972); through *Chem. Abstr.*, **78,** 66971j(1973).

(1002) P. Grasso and A. B. G. Lansdown, *J. Soc. Cosmet. Chem.*, **23,** 481(1972); through *Chem. Abstr.*, **78,** 11341y(1973).

(1003) E. J. Lien and G. L. Tong, *ibid.*, **24,** 371(1973).

(1004) M. Katz and B. J. Poulsen, *Handb. Exp. Pharmakol.*, **28**(Part 1), 103(1971); through *Chem. Abstr.*, **78,** 23694d(1973).

(1005) D. D. Breimer, *Pharm. Weekbl.*, **108,** 309(1973); through *Chem. Abstr.*, **79,** 66g(1973).

(1006) W. J. Westlake, *J. Pharm. Sci.*, **62,** 1579(1973).

(1007) M. Rowland, *Clin. Pharmacol., Basic Princ. Ther.*, **1972,** 21; through *Chem. Abstr.*, **78,** 37766r(1973).

(1008) A. Van der Kuy, *Pharm. Weekbl.*, **108,** 529(1973); through *Chem. Abstr.*, **79,** 57578e(1973).

(1009) W. A. Ritschel, *Boll. Chim. Farm.*, **112,** 137(1973); through *Chem. Abstr.*, **79,** 57584d(1973).

(1010) W. A. Ritschel, *Pharm. Ind.*, **35,** 273(1973); through *Chem. Abstr.*, **79,** 83414t(1973).

(1011) N. A. Diding, U. Otto, and L. Paalzow, *Sv. Farm. Tidskr.*, **77,** 582(1973); through *Chem. Abstr.*, **79,** 132757t(1973).

(1012) E. R. Garrett, *Klin. Pharmakol. Pharmakother., Zweite, Ueberarbeitete Erweiterte Auflage*, **1973,** 49; through *Chem. Abstr.*, **79,** 100339s(1973).

(1013) D. P. Rall, *Handb. Exp. Pharmakol.*, **28**(Part 1), 240(1971); through *Chem. Abstr.*, **78,** 23698h(1973).

(1014) Y. Asoh, *Farumashia*, **9,** 52(1973); through *Chem. Abstr.*, **78,** 143597w(1973).

(1015) C. Hogben and M. Adrian, *Handb. Exp. Pharmakol.*, **28**(Part 1), 1(1971); through *Chem. Abstr.*, **78,** 23688e(1973).

(1016) J. M. Rosenberg and K. Mann, *Drug Intel. Clin. Pharm.*, **7,** 346(1973).

(1017) P. P. Leblanc, *Vie Med. Can. Fr.*, **1**, 1015(1972); through *Chem. Abstr.*, **78**, 62078a(1973).
(1018) M. Borasi, *Boll. Chim. Farm.*, **112**, 1(1973); through *Chem. Abstr.*, **79**, 57583c(1973).
(1019) A. Perala-Suominen, *Farm. Aikak.*, **81**, 151(1972); through *Chem. Abstr.*, **78**, 115166m(1973).
(1020) J. L. Vila Jato, R. Cadorniga Carro, and J. C. Lopez Perz-Lanzac, *Farmaco, Ed. Prat.*, **28**, 49(1973); through *Chem. Abstr.*, **78**, 88570e(1973).
(1021) C. M. Metzler, R. DeHaan, D. Schellenberg, and W. D. VandenBosch, *J. Pharm. Sci.*, **62**, 591(1973).
(1022) M. S. Benedetti and D. A. Larue, *Arzneim.-Forsch.*, **23**, 826(1973); through *Chem. Abstr.*, **79**, 87303d(1973).
(1023) A. H. Beckett, J. W. Gorrod, and D. C. Taylor, *J. Pharm. Pharmacol., Suppl.*, **24**, 65P(1972); through *Chem. Abstr.*, **78**, 52927n(1973).
(1024) K. C. Mezey, *Aust. J. Pharm. Sci.*, **NS1**, 19(1972); through *Chem. Abstr.*, **78**, 79471w(1973).
(1025) S. G. Hastings, *Arch. Int. Pharmacodyn. Ther.*, **203**, 117(1973); through *Chem. Abstr.*, **79**, 100519a(1973).
(1026) E. Nunez O. and M. Arteaga C., *Rev. Colomb. Cienc. Quim.-Farm.*, **2**, 5(1972); through *Chem. Abstr.*, **79**, 70151e(1973).
(1027) V. F. Naggar, M. A. Moustafa, S. A. Khalil, and M. M. Motawi, *Can. J. Pharm. Sci.*, **7**, 112(1972); through *Chem. Abstr.*, **78**, 62133q(1973).
(1028) M. Hejzlar, E. Sasko, M. Paroubek, M. Safrankova, L. Hajkova, E. Krejcova, and M. Bohalova, *Farmakoter. Zpr.*, **17**, 371(1971); through *Chem. Abstr.*, **78**, 336z(1973).
(1029) B. A. Mulley, R. M. Rye, and P. Shaw, *J. Pharm. Pharmacol., Suppl.*, **25**, 150P(1973).
(1030) R. A. O'Reilly, *Pharmacology*, **8**, 181(1972); through *Chem. Abstr.*, **78**, 105826n(1973).
(1031) L. A. Borgen and W. M. Davis, *J. Pharm. Sci.*, **62**, 479(1973).
(1032) T. Mayama, T. Nakayoshi, M. Abe, and T. Miura, *Yakuszaigaku*, **32**, 7(1972); through *Chem. Abstr.*, **79**, 142905d(1973).
(1033) P. Hlavaty, J. Augustin, J. Matoska, and L. Drobnica, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th, 1971*, 1(Part 2), 923(1972); through *Chem. Abstr.*, **79**, 23555e(1973).
(1034) E. Schraven and D. Trottnow, *Arzneim.-Forsch.*, **23**, 274(1973); through *Chem. Abstr.*, **78**, 128398p(1973).
(1035) A. Popovici and D. Margineanu, *Farmacia (Bucharest)*, **20**, 567(1972); through *Chem. Abstr.*, **78**, 119151a(1973).
(1036) A. Popovici, V. Ciocanelea, and V. Ardeleanu, *ibid.*, **20**, 621(1972); through *Chem. Abstr.*, **78**, 164029c(1973).
(1037) K. Ishikawa, M. Akiyama, Y. Nohara, H. Tsuchiya, and S. Negi, *Nichidai Igaku Zasshi*, **32**, 499(1973); through *Chem. Abstr.*, **79**, 38432m(1973).
(1038) H. G. W. M. Hemels, *Brit. J. Dermatol.*, **87**, 614(1972); through *Chem. Abstr.*, **78**, 37849v(1973).
(1039) V. Henschel and F. Jaminet, *J. Pharm. Belg.*, **27**, 743(1972); through *Chem. Abstr.*, **78**, 119070y(1973).
(1040) D. A. Schlichting, W. M. Wooding, and M. Brown, *J. Pharm. Sci.*, **62**, 388(1973).
(1041) V. V. Vasilenko, V. M. Gretskii, and T. S. Samgina, *Farmatsiya (Moscow)*, **22**, 26(1973); through *Chem. Abstr.*, **79**, 132953d(1973).
(1042) R. Woodford and B. W. Barry, *J. Pharm. Pharmacol., Suppl.*, **25**, 123P(1973).
(1043) A. Popovici and V. Ardeleanu, *Farmacia (Bucharest)*, **21**, 155(1973); through *Chem. Abstr.*, **79**, 96903b(1973).
(1044) H. Schwarz, *Informationsdienst, Arbeitsgemeinsch. Pharm. Verfahrenstech.*, **18**, 111(1972); through *Chem. Abstr.*, **78**, 119018n(1973).
(1045) A. Zesch, H. Schaefer, and W. Hoffmann, *Arch. Dermatol. Forsch.*, **246**, 103(1973); through *Chem. Abstr.*, **78**, 131943t (1973).
(1046) M. Washitake, T. Yajima, T. Anmo, T. Arita, and R. Hori, *Chem. Pharm. Bull.*, **20**, 2429(1972); through *Chem. Abstr.*, **78**, 37863v(1973).
(1047) I. Maistrello, G. Rigamonti, C. Frova, and P. deRuggieri, *J. Pharm. Sci.*, **62**, 1455(1973).
(1048) T. Morishita, M. Yamazaki, N. Yata, and A. Kamada, *Chem. Pharm. Bull.*, **21**, 2309(1973).
(1049) K. Kitao, K. Kubo, T. Morishita, N. Yata, and A. Kamada, *ibid.*, **21**, 2417(1973).
(1050) D. S. Hewick and J. McEwen, *J. Pharm. Pharmacol.*, **25**, 458(1973).
(1051) P. Bagnaresi, D. Bulgarelli, A. Calvi, and G. Ferrarini, *Boll. Chim. Farm.*, **112**, 83(1973); through *Chem. Abstr.*, **79**, 96862n(1973).
(1052) A. H. Beckett and E. V. B. Shenoy, *J. Pharm. Pharmacol.*, **25**, 793(1973).
(1053) P. C. Hirom, P. Millburn, R. L. Smith, and R. T. Williams, *Xenobiotica*, **2**, 205(1972); through *Chem. Abstr.*, **78**, 11414z(1973).
(1054) A. J. Jounela and A. Sothmann, *Lancet*, **1**, 202(1973).
(1055) T. R. D. Shaw, J. E. Carless, M. R. Howard, and K. Raymond, *ibid.*, **2**, 209(1973).
(1056) T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 298(1971); through *Chem. Abstr.*, **79**, 142907f(1973).
(1057) W. Morozowich, A. A. Sinkula, F. A. MacKellar, and C. Lewis, *J. Pharm. Sci.*, **62**, 1102(1973).
(1058) A. A. Sinkula, W. Morozowich, and E. L. Rowe, *ibid.*, **62**, 1106(1973).
(1059) J. K. Seydel, *J. Pharmacol. Clin.*, **2**, 39(1972); through *Chem. Abstr.*, **78**, 151584e(1973).
(1060) R. H. Bishara, G. S. Born, V. L. Anderson, and J. E. Christian, *J. Pharm. Sci.*, **62**, 1420(1973).
(1061) D. D. Breimer, *Pharm. Weekbl.*, **108**, 661(1973); through *Chem. Abstr.*, **79**, 87269x(1973).
(1062) K. Chan, *Diss. Abstr. Int.*, **33**, 3569B(1973).
(1063) H. M. Fales, *Pharmacology*, **8**, 142(1972); through *Chem. Abstr.*, **78**, 92357h(1973).
(1064) J. G. Topliss and R. J. Costello, *J. Med. Chem.*, **15**, 1066(1972); through *Chem. Abstr.*, **78**, 11434f(1973).
(1065) B. Tinland, C. Decoret, and J. Badin, *Res. Commun. Chem. Pathol. Pharmacol.*, **4**, 131(1972); through *Chem. Abstr.*, **78**, 11425d(1973).
(1066) K. Uzu, K. Nakano, M. Shimizu, and S. Kinoshita, *Jap. J. Antibiot.*, **24**, 181(1971); through *Chem. Abstr.*, **78**, 11449q(1973).
(1067) R. W. Fuller and M. M. Marsh, *J. Med. Chem.*, **15**, 1068(1972); through *Chem. Abstr.*, **78**, 11435g(1973).
(1068) C. Hansch, N. Smith, R. Engle, and H. Wood, *Cancer Chemother. Rep., Part 1*, **56**, 443(1972); through *Chem. Abstr.*, **78**, 11426e(1973).
(1069) E. Schroeder, *Handb. Exp. Pharmakol.*, **25**, 324(1970); through *Chem. Abstr.*, **78**, 11424c(1973).
(1070) J. Polderman and A. B. Weekers-Andersen, *Pharm. Weekbl.*, **108**, 381(1973); through *Chem. Abstr.*, **79**, 9782v(1973).
(1071) H. Schott, *J. Pharm. Sci.*, **62**, 341(1973).
(1072) T. Fujita, *Advan. Chem. Ser.*, **114**, 80(1972); through *Chem. Abstr.*, **78**, 66734j(1973).
(1073) J. G. Topliss, *J. Med. Chem.*, **15**, 1006(1972); through *Chem. Abstr.*, **78**, 11428g(1973).
(1074) R. Nacheva and D. Mikhailova, *Farmatsiya (Sofia)*, **23**, 6(1973); through *Chem. Abstr.*, **79**, 87617j(1973).
(1075) L. Zathurecky, *Pharmazie*, **27**, 686(1972); through *Chem. Abstr.*, **78**, 33868c(1973).
(1076) B. Selmeczi, *Gyogyszereszet*, **17**, 81(1973); through *Chem. Abstr.*, **79**, 35054d(1973).
(1077) V. Bernareggi, G. Bugada, A. Cassola, G. Levi, and F. Moncalvo, *Boll. Chim. Farm.*, **112**, 177(1973); through *Chem. Abstr.*, **79**, 83439e(1973).
(1078) E. I. Stupak and T. R. Bates, *J. Pharm. Sci.*, **62**, 1806(1973).
(1079) R. G. Stoll, T. R. Bates, and J. Swarbrick, *ibid.*, **62**, 65(1973).
(1080) P. J. Carrigan and T. R. Bates, *ibid.*, **62**, 1476(1973).
(1081) S. N. Pagay, *Diss. Abstr. Int.*, **34**, 1169B(1973).
(1082) V. Mirkovitch, J. W. L. Robinson, F. Bel, and A. Gumma, *Arzneim.-Forsch.*, **23**, 967(1973); through *Chem. Abstr.*, **79**, 142883v(1973).
(1083) M. Johnsgard, A. O. Pedersen, and Y. Torud, *Norg. Apotekerforen. Tidskr.*, **81**, 112(1973); through *Chem. Abstr.*, **79**, 139632g(1973).
(1084) J. Rabiant, A. Soulairac, and N. Dorme, *Ann. Pharm. Fr.*, **30**, 601(1972); through *Chem. Abstr.*, **78**, 47755a(1973).
(1085) L. G. Miller, *Diss. Abstr. Int.*, **33**, 5370B(1973).
(1086) A. Berlin, B. Siwers, S. Agurell, A. Hiort, F. Sjoqvist, and S. Strom, *Clin. Pharmacol. Ther.*, **13**, 733(1972); through *Chem. Abstr.*, **78**, 7795g(1973).
(1087) J. J. Ashley and G. Levy, *J. Pharm. Sci.*, **62**, 688(1973).
(1088) M. H. Stolar, F. Siegel, and R. W. Morris, *ibid.*, **62**,

338(1973).
(1089) M. J. Akers, J. L. Lach, and L. J. Fischer, *ibid.*, **62,** 391(1973).
(1090) F. Fils, *J. Pharm. Belg.*, **27,** 689(1972); through *Chem. Abstr.*, **78,** 106107r(1973).
(1091) *Ibid.*, **27,** 543(1972); through *Chem. Abstr.*, **78,** 38062v(1973).
(1092) E. Cid and F. Jaminet, *Ann. Pharm. Fr.*, **31,** 73(1973); through *Chem. Abstr.*, **79,** 103s(1973).
(1093) G. J. Eide, *Acta Pharm. Suecica,* **10,** 229(1973); through *Chem. Abstr.*, **79,** 57618t(1973).
(1094) W. E. Fann, J. M. Davis, D. S. Janowsky, H. J. Sekerke, and D. M. Schmidt, *J. Clin. Pharmacol.*, **13,** 390(1973).
(1095) Y. Imamura and H. Ichibagase, *Chem. Pharm. Bull.*, **21,** 668(1973).
(1096) T. J. Mikkelson, S. S. Chrai, and J. R. Robinson, *J. Pharm. Sci.*, **62,** 1648(1973).
(1097) J. Bettis, J. Lach, and J. Hood, *Amer. J. Hosp. Pharm.*, **30,** 240(1973).
(1098) V. Manninen, J. Melin, A. Apajalahti, and M. Karesoja, *Lancet,* **1,** 398(1973).
(1099) S. Rajkondawar, R. L. Nikore, and A. K. Dorle, *Indian J. Pharm.*, **35,** 98(1973); through *Chem. Abstr.*, **79,** 87464g(1973).
(1100) S. Goto, T. Yamagata, O. Tsuzuki, and S. Iguchi, *Chem. Pharm. Bull.*, **21,** 2495(1973).
(1101) T. S. Gaginella, P. Bass, J. H. Perrin and J. J. Vallner, *J. Pharm. Sci.*, **62,** 1121(1973).
(1102) E. M. Omar, O. E. Mohamed, G. A. R. Kamar, and M. A. Soliman, *UAR J. Anim. Prod.*, **11,** 11(1971); through *Chem. Abstr.*, **78,** 23934g(1973).
(1103) G. Ramachander, F. D. Williams, and J. F. Emele, *J. Pharm. Sci.*, **62,** 1498(1973).
(1104) M. Gibaldi and B. Grundhofer, *ibid.*, **62,** 343(1973).
(1105) A. Bizzi, E. Veneroni, and S. Garattini, *Eur. J. Pharmacol.*, **23,** 131(1973); through *Chem. Abstr.*, **79,** 142968b(1973).
(1106) J. M. Jaffe, J. L. Colaizzi, R. I. Poust, and R. H. McDonald, Jr., *J. Pharmacokin. Biopharm.*, **1,** 267(1973).
(1107) J. M. Jaffe, *Diss. Abstr. Int.*, **33,** 5370B(1973).
(1108) S. Kojima, *Chem. Pharm. Bull.*, **21,** 2432(1973).
(1109) B. Wesley-Hadzija, *Can. J. Pharm. Sci.*, **8,** 101(1973).
(1110) F. Grab, *Diss. Abstr. Int.*, **33,** 4210B(1973).
(1111) I. Utsumi, K. Kohno, and Y. Takeuchi, *Chem. Pharm. Bull.*, **21,** 1727(1973).
(1112) *Ibid.*, **21,** 2161(1973).
(1113) S. Feldman, M. Reinhard, and C. Willson, *J. Pharm. Sci.*, **62,** 1961(1973).
(1114) D. J. Jollow and B. B. Brodie, *Pharmacology,* **8,** 21(1972); through *Chem. Abstr.*, **78,** 105824k(1973).
(1115) G. E. Schumacher, *Amer. J. Hosp. Pharm.*, **30,** 824(1973).
(1116) F. Rahman and G. D. Cain, *S. Med. J.*, **66,** 724(1973); through *Chem. Abstr.*, **79,** 87257s(1973).
(1117) K. H. Froemming and I. Weyermann, *Arzneim.-Forsch.*, **23,** 424(1973); through *Chem. Abstr.*, **78,** 164041a(1973).
(1118) D. Mikhailova, R. Nacheva, and R. Ovcharov, *Pharmazie,* **28,** 208(1973); through *Chem. Abstr.*, **79,** 9815h(1973).
(1119) J. H. Collett and R. Withington, *J. Pharm. Pharmacol.*, **25,** 723(1973).
(1120) R. Kato, A. Takanaka, K. Onoda, and Y. Omori, *Jap. J. Pharmacol.*, **22,** 434(1972); through *Chem. Abstr.*, **78,** 11555w (1973).
(1121) A. Bye, A. S. E. Fowle, and C. Pullin, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th,* **1,** 27(1972); through *Chem. Abstr.*, **79,** 142997k(1973).
(1122) W. O. Thompson and S. T. Christian, *J. Pharm. Sci.*, **62,** 328(1973).
(1123) C. W. Whitworth and H. W. Jun, *ibid.*, **62,** 1890(1973).
(1124) K. Lehmann, *Rev. Quim. Ind. (Rio de Janeiro),* **41,** 124(1972); through *Chem. Abstr.*, **78,** 47677b(1973).
(1125) R. F. Turk, W. L. Dewey, and L. S. Harris, *J. Pharm. Sci.*, **62,** 737(1973).
(1126) A. J. Ware and B. Combes, *Gastroenterology,* **64,** 1150(1973); through *Chem. Abstr.*, **79,** 73443n(1973).
(1127) D. Wade, P. Mearrick, and J. Morris, *Nature,* **242,** 463(1973).
(1128) R. L. Dedrick, D. S. Zaharko, and R. J. Lutz, *J. Pharm. Sci.*, **62,** 882(1973).
(1129) G. Peres and A. Rigal, *Gazz. Med. Ital.*, **131,** 272(1972); through *Chem. Abstr.*, **78,** 23849h(1973).
(1130) M. Siurala, O. Mustala, K. Pyorala, M. Kekki, M. Airaksinen, J. Jussial, H. Salmi, and R. Julkunen, *Acta Hepato-Gastroenterol.*, **19,** 190(1972); through *Chem. Abstr.*, **78,** 11729f(1973).
(1131) G. Czok and H. G. Dammann, *J. Pharm. Pharmacol.*, **24,** 820(1972); through *Chem. Abstr.*, **78,** 313q(1973).
(1132) E. D. Purich, *Diss. Abstr. Int.*, **34,** 2122B(1973).
(1133) J. G. Wagner and A. J. Sedman, *J. Pharmacokin. Biopharm.*, **1,** 23(1973).
(1134) S. H. Yalkowsky, O. S. Carpenter, G. L. Flynn, and T. G. Slunick, *J. Pharm. Sci.*, **62,** 1949(1973).
(1135) D. Perrier and M. Gibaldi, *ibid.*, **62,** 1486(1973).
(1136) S. A. Kaplan, M. L. Jack, S. Cotler, and K. Alexander, *J. Pharmacokin. Biopharm.*, **1,** 201(1973).
(1137) D. Perrier, J. J. Ashley, and G. Levy, *ibid.*, **1,** 231(1973).
(1138) J. G. Wagner, *ibid.*, **1,** 103(1973).
(1139) M. Rowland, L. Z. Benet, and G. G. Graham, *ibid.*, **1,** 123(1973).
(1140) M. Pfeffer, *ibid.*, **1,** 137(1973).
(1141) L. J. Leeson and H. Weintraub, *J. Pharm. Sci.*, **62,** 1936(1973).
(1142) R. H. Levy and G. H. Smith, *Amer. J. Hosp. Pharm.*, **30,** 398(1973).
(1143) *Ibid.*, **30,** 494(1973).
(1144) T. Koizumi, M. Ueda, and M. Kakemi, *Chem. Pharm. Bull.*, **21,** 2549(1973).
(1145) E. R. Garrett, *Klin. Pharmakol. Pharmakother., Zweite, Ueberarbeitete Eeweiterte Auflage,* **1973,** 29; through *Chem. Abstr.*, **79,** 118271y(1973).
(1146) L. Saunders and T. Natunen, *J. Pharm. Pharmacol., Suppl.*, **25,** 44P(1973).
(1147) D. Perrier and M. Gibaldi, *J. Pharm. Sci.*, **62,** 225(1973).
(1148) T. G. Theofanous and R. G. Barile, *ibid.*, **62,** 261(1973).
(1149) G. Levy and W. L. Hayton, *Fetal Pharmacol.*, **1973,** 29; through *Chem. Abstr.*, **78,** 105883d(1973).
(1150) E. Ranjbaran, J. N. Chung, A. W. Hahn, R. W. McLaren, and C. L. Partain, *Proc. Annu. Rocky Mt. Bioeng. Symp.*, **10,** 139(1973); through *Chem. Abstr.*, **79,** 96893y(1973).
(1151) T. Suzuki and Y. Saitoh, *Chem. Pharm. Bull.*, **21,** 1458(1973).
(1152) B. E. Ballard, *Pharmacol. Thermoregul., Proc. Satell. Symp.*, **1973,** 170; through *Chem. Abstr.*, **79,** 38374u(1973).
(1153) R. E. Notari, *J. Pharm. Sci.*, **62,** 865(1973).
(1154) L. W. Dittert and A. R. DiSanto, *J. Amer. Pharm. Ass.*, **NS13,** 421(1973).
(1155) K. S. Pelzmann, *J. Pharm. Sci.*, **62,** 1609(1973).
(1156) T. Nishikawa, K. Mineura, and H. Takahiza, *Yakugaku Zasshi,* **93,** 226(1973).
(1157) S. A. Kaplan, J. A. F. de Silva, M. L. Jack, K. Alexander, N. Strojny, R. E. Weinfeld, C. V. Puglisi, and L. Weissman, *J. Pharm. Sci.*, **62,** 1932(1973).
(1158) J. Edelson, J. F. Douglas, and B. J. Ludwig, *ibid.*, **62,** 229(1973).
(1159) D. B. Campbell, *Vie Med. Can. Fr.*, **2,** 34(1973); through *Chem. Abstr.*, **78,** 105895j(1973).
(1160) W. A. Cressman, J. Plostnieks, and P. C. Johnson, *Anesthesiology,* **38,** 363(1973); through *Chem. Abstr.*, **78,** 154685z(1973).
(1161) T. Shomura and K. Umemura, *Chem. Pharm. Bull.*, **21,** 1824(1973).
(1162) S. J. Lan, T. J. Chando, I. Weliky, and E. C. Schreiber, *J. Pharmacol. Exp. Ther.*, **186,** 323(1973); through *Chem. Abstr.*, **79,** 100386e(1973).
(1163) D. S. Sitar and D. P. Thornhill, *ibid.*, **183,** 440(1972); through *Chem. Abstr.*, **78,** 79535v(1973).
(1164) *Ibid.*, **184,** 432(1973); through *Chem. Abstr.*, **78,** 92380k(1973).
(1165) A. Karim, R. E. Ranney, J. Zagarella, and H. I. Maibach, *Clin. Pharmacol. Ther.*, **14,** 862(1973).
(1166) T. Chiba, H. Kitoo, and N. Toshioka, *Yakugaku Zasshi,* **93,** 112(1973).
(1167) F. F. Sun and R. S. P. Hsi, *J. Pharm. Sci.*, **62,** 1265(1973).
(1168) F. F. Sun, *ibid.*, **62,** 1657(1973).
(1169) T. Takubo, H. Matsumaru, S. Tsuchiya, and M. Hiura, *Chem. Pharm. Bull.*, **21,** 1440(1973).
(1170) J. T. Doluisio, L. W. Dittert, and J. C. LaPiana, *J. Pharmacokin. Biopharm.*, **1,** 253(1973).

(1171) W. J. Jusko and G. P. Lewis, *J. Pharm. Sci.*, **62,** 69(1973).
(1172) D. B. Jack and W. Riess, *ibid.*, **62,** 1929(1973).
(1173) R. M. Detlaan, C. M. Metzler, D. Schellenberg, and W. D. VandenBosch, *J. Clin. Pharmacol.*, **13,** 190(1973).
(1174) J. S. Adir, *Diss. Abstr. Int.*, **33,** 3746B(1973).
(1175) K. Desante, *ibid.*, **33,** 4364B(1973).
(1176) J. J. Ashley and G. Levy, *J. Pharmacokin. Biopharm.*, **1,** 99(1973).
(1177) R. H. Reuning, R. A. Sams, and R. E. Notari, *J. Clin. Pharmacol.*, **13,** 127(1973).
(1178) K. Schnelle and E. R. Garrett, *J. Pharm. Sci.*, **62,** 362(1973).
(1179) S. A. Kaplan, M. L. Jack, K. Alexander, and R. E. Weinfeld, *ibid.*, **62,** 1789(1973).
(1180) O. N. Hinsvark, A. P. Truant, D. J. Jenden, and J. A. Steinborn, *J. Pharmacokin. Biopharm.*, **1,** 319(1973).
(1181) D. H. Huffman, S. H. Wan, D. L. Azarnoff, and B. Hoogstraten, *Clin. Pharmacol. Ther.*, **14,** 572(1973).
(1182) R. B. Smith, L. W. Dittert, W. O. Griffen, Jr., and J. T. Doluisio, *J. Pharmacokin. Biopharm.*, **1,** 5(1973).
(1183) D. Schuppan, S. Riegelman, B. von Lehmann, A. Pilbrant, and C. Becker, *ibid.*, **1,** 307(1973).
(1184) A. Breckenridge and M. Orme, *Clin. Pharmacol. Ther.*, **14,** 955(1973).
(1185) P. A. Mitenko and R. I. Ogilvie, *ibid.*, **14,** 509(1973).
(1186) J. H. Nodine, K. N. Modi, M. Rhodes, V. Paz-Martinez, L. Ibarra, and R. J. Santos, *ibid.*, **14,** 196(1973).
(1187) H. Macdonald, R. G. Kelly, E. S. Allen, J. F. Noble, and L. A. Kanegis, *ibid.*, **14,** 852(1973).
(1188) R. S. Benjamin, C. E. Riggs, and N. R. Bachur, *ibid.*, **14,** 592(1973).
(1189) C. Regamey, R. C. Gordon, and W. M. M. Kirby, *ibid.*, **14,** 396(1973).
(1190) J. Shibasaki, R. Konishi, T. Morishita, and T. Ueki, *Chem. Pharm. Bull.*, **21,** 1754(1973).
(1191) J. E. Doherty, *Ann. Intern. Med.*, **79,** 229(1973); through *Chem. Abstr.*, **79,** 87270r(1973).
(1192) D. D. Breimer and J. M. van Rossum, *J. Pharm. Pharmacol.*, **25,** 762(1973).
(1193) H. Lullmann, E. Rossen, and K. U. Seiler, *ibid.*, **25,** 239(1973).
(1194) L. S. Schanker, *Handb. Exp. Pharmakol.*, **28,** 9(1971); through *Chem. Abstr.*, **78,** 23689f(1973).
(1195) A. H. Beckett and R. D. Hossie, *ibid.*, **28,** 25(1971); through *Chem. Abstr.*, **78,** 23690z(1973).
(1196) J. Schou, *ibid.*, **28,** 47(1971); through *Chem. Abstr.*, **78,** 23691a(1973).
(1197) H. Rackow, *ibid.*, **28,** 67(1971); through *Chem. Abstr.*, **78,** 23692b(1973).
(1198) L. T. Greene, *ibid.*, **28,** 88(1971); through *Chem. Abstr.*, **78,** 23693c(1973).
(1199) W. Oppelt, *Klin. Pharmakol. Pharmakother., Zweite, Ueberarbeitete Erwiterte Auflage,* **1973,** 66; through *Chem. Abstr.*, **79,** 100340k(1973).
(1200) P. G. Welling, *Foreign Compound Metab. Mammals,* **2,** 412(1972); through *Chem. Abstr.*, **78,** 154695c(1973).
(1201) D. B. Beleslin, *Med. Podmladak,* **24,** 103(1972); through *Chem. Abstr.*, **79,** 38343h(1973).
(1202) F. Sjoqvist, *Cah. Med.*, **14,** 292(1973); through *Chem. Abstr.*, **79,** 38360m(1973).
(1203) K. B. Bischoff, K. J. Himmelstein, R. L. Dedrick, and D. S. Zaharko, *Advan. Chem. Ser.*, **118,** 47(1973); through *Chem. Abstr.*, **79,** 132719g(1973).
(1204) J. G. Wagner, *Cron. Chim.*, **35,** 13(1972); through *Chem. Abstr.*, **78,** 11354e(1973).
(1205) S. Pfeifer, J. Schaeffner, and I. Bornschein, *Pharmazie,* **27,** 616(1972); through *Chem. Abstr.*, **78,** 66782y(1973).
(1206) L. Z. Benet, *Annu. Rep. Med. Chem.*, **7,** 259(1972); through *Chem. Abstr.*, **78,** 23755z(1973).
(1207) Fr. Gregoire, *J. Pharm. Belg.*, **27,** 631(1972); through *Chem. Abstr.*, **78,** 23748z(1973).
(1208) M. Nakagaki and T. Koizumi, *Farumashia,* **8,** 189(1972); through *Chem. Abstr.*, **78,** 143596v(1973).
(1209) A. Bieder and J. Gaillot, *Probl. Tech.*, **20,** 37(1972); through *Chem. Abstr.*, **78,** 92361e(1973).
(1210) J. M. Pla Delfina and A. Del Pozo Ojeda, *Medicamenta, Ed. Farm.*, **41,** 7(1973); through *Chem. Abstr.*, **79,** 96864q(1973).
(1211) H. Stricker, *Pharm. Ind.*, **35,** 13(1973); through *Chem. Abstr.*, **78,** 151595j(1973).
(1212) M. Gibaldi and S. Feldman, *Eur. J. Pharmacol.*, **19,** 323(1972); through *Chem. Abstr.*, **78,** 74n(1973).
(1213) H. Ochsenfahrt and D. Winne, *Life Sci.*, **11,** 1115(1972); through *Chem. Abstr.*, **78,** 37941u(1973).
(1214) B. K. Shah, *J. Pharm. Sci.*, **62,** 1208(1973).
(1215) R. Cahen, *J. Pharmacol. Clin.*, **3,** 67(1972); through *Chem. Abstr.*, **79,** 35060c(1973).
(1216) O. Smahel, O. Schmidt, J. Grafnetterova, and P. Truhlar, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th,* **1,** 5(1972); through *Chem. Abstr.*, **79,** 100729u(1973).
(1217) L. Dettli, *Klin. Pharmakol. Pharmakother., Zweite, Ueberarbeitete Erweiterte Auflage,* **1973,** 75; through *Chem. Abstr.*, **79,** 139628k(1973).
(1218) A. Bieder and J. Gaillot, *Farmaco, Ed. Prat.*, **27,** 471(1972); through *Chem. Abstr.*, **78,** 11348f(1973).
(1219) D. Mikhailova and I. Chobanova, *Arzneim.-Forsch.*, **22,** 2136(1972); through *Chem. Abstr.*, **78,** 119033p(1973).
(1220) J. K. Seydel, *J. Pharmacol. Clin.*, **2,** 53(1972); through *Chem. Abstr.*, **78,** 143617c(1973).
(1221) W. J. Jusko, *J. Pharmacokin. Biopharm.*, **1,** 175(1973).
(1222) D. L. Wolfe, S. C. Förland, and L. Z. Benet, *J. Pharm. Sci.*, **62,** 200(1973).
(1223) C. Lin, J. Magat, B. Calesnick, and S. Symchowicz, *Xenobiotica,* **2,** 507(1972); through *Chem. Abstr.*, **78,** 79545y-(1973).
(1224) H. Ishikawa, T. Suzuki, Y. Hoshino, T. Ando, and S. Goto, *Chemotherapy (Tokyo),* **21,** 1241(1973); through *Chem. Abstr.*, **79,** 142918k(1973).
(1225) C. H. Morris, J. E. Christian, R. R. Landolt, and W. G. Hansen, *J. Pharm. Sci.*, **62,** 1729(1973).
(1226) S. Kataoka, K. Taira, T. Ariyoshi, and E. Takabatake, *Chem. Pharm. Bull.*, **21,** 358(1973).
(1227) K. Izaka, M. Yamada, T. Kawano, and T. Suyama, *Jap. J. Pharmacol.*, **22,** 519(1972); through *Chem. Abstr.*, **78,** 38051r(1973).
(1228) M. R. Wills, *Lancet*, **1,** 820(1973).
(1229) S. W. Hwang and L. S. Schanker, *Xenobiotica,* **3,** 351(1973); through *Chem. Abstr.*, **79,** 142764g(1973).
(1230) M. Lakshamana, S. D. S. Seth, Shriniwas, and R. B. Arora, *Indian J. Med. Res.*, **61,** 138(1973); through *Chem. Abstr.*, **79,** 87q(1973).
(1231) H. Murata, K. Kougo, A. Yasumura, E. Nakajima, and H. Shindo, *Chem. Pharm. Bull.*, **21,** 404(1973).
(1232) G. F. Bories, M. P. Renerre, and J. C. Rougeot, *J. Anim. Sci.*, **36,** 931(1973); through *Chem. Abstr.*, **79,** 38426n(1973).
(1233) N. J. Greenberger and J. H. Caldwell, *Basic Clin. Pharmacol. Digitalis, Proc. Symp.*, **1972,** 15; through *Chem. Abstr.*, **78,** 154624d(1973).
(1234) D. H. Huffman and D. L. Azarnoff, *J. Amer. Med. Ass.*, **222,** 957(1972); through *Chem. Abstr.*, **78,** 37853s(1973).
(1235) R. Thomas and S. Aldous, *Lancet*, **2,** 1267(1973).
(1236) J. A. Nelson, A. A. Moss, H. I. Goldberg, L. Z. Benet, and J. Amberg, *Invest. Radiol.*, **8,** 1(1973); through *Chem. Abstr.*, **79,** 88r(1973).
(1237) A. I. Cohen, A. D. Hartman, O. N. Hinsvark, P. F. Kraus, and W. Zazulak, *J. Pharm. Sci.*, **62,** 931(1973).
(1238) S. H. Weinstein, M. Pfeffer, J. M. Schor, L. Franklin, M. Mintz, and E. R. Tutko, *ibid.*, **62,** 1416(1973).
(1239) P. Jenner, J. W. Gorrod, and A. H. Beckett, *Xenobiotica,* **3,** 341(1973); through *Chem. Abstr.*, **79,** 142763f(1973).
(1240) K. Tatsumi, T. Ou, T. Yamaguchi, and H. Yoshimura, *Chem. Pharm. Bull.*, **21,** 191(1973).
(1241) J. R. Boissier, A. Gerardin, and C. Dumont, *Ann. Pharm. Fr.*, **30,** 851(1972); through *Chem. Abstr.*, **79,** 27051k(1973).
(1242) E. F. Lemanowicz, *Diss. Abstr. Int.*, **33,** 1173B(1972); through *Chem. Abstr.*, **78,** 155q(1973).
(1243) J. P. Viau, J. E. Epps, and F. J. DiCarlo, *J. Pharm. Sci.*, **62,** 641(1973).
(1244) G. H. Evans and D. G. Shand, *Clin. Pharmcol. Ther.*, **14,** 487(1973).
(1245) T. T. Zsoter, G. E. Johnson, G. A. DeVeber, and H. Paul, *ibid.*, **14,** 325(1973).
(1246) K. Ohkubo, M. Ohta, S. Takeyama, Y. Ono, S. Awatag-

uchi, H. Hayasaka, Y. Ogawa, and T. Kitakaze, *Chemotherapy (Tokyo)*, **21**, 241(1973); through *Chem. Abstr.*, **79**, 73468z(1973).

(1247) J. S. Enna and L. S. Schanker, *Amer. J. Physiol.*, **223**, 1227(1972); through *Chem. Abstr.*, **78**, 24124e(1973).

(1248) J. W. Stover, *Diss. Abstr. Int.*, **34**, 1443B(1973).

(1249) S. Ishiyama, I. Nakayama, H. Iwamoto, and S. Iwai, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 1011(1972); through *Chem. Abstr.*, **79**, 38405e(1973).

(1250) A. A. Aliev and K. V. Shakhbazyan, *Veterinariya (Moscow)*, **9**, 86(1972); through *Chem. Abstr.*, **78**, 262x(1973).

(1251) E. Marmo, P. Petrone, A. Robertaccio, and M. Grassi, *G. Ital. Chemioter.*, **18**, 7(1971); through *Chem. Abstr.*, **78**, 143747v(1973).

(1252) B. Krauer, G. H. Draffan, F. M. Williams, R. A. Clare, C. T. Dollery, and D. F. Hawkins, *Clin. Pharmacol. Ther.*, **14**, 442(1973).

(1253) J. D. Baggot and L. E. Davis, *Res. Vet. Sci.*, **14**, 207(1973); through *Chem. Abstr.*, **79**, 73453r(1973).

(1254) J. Jonsson and T. Lewander, *J. Pharm. Pharmacol.*, **25**, 589(1973).

(1255) N. F. Kalabukhova, *Antibiotiki (Moscow)*, **18**, 416(1973); through *Chem. Abstr.*, **79**, 38428q(1973).

(1256) K. F. Overø, *J. Pharm. Pharmacol.*, **25**, 957(1973).

(1257) B. Cristau, M. Placidi, and P. Audibert, *Med. Trop. (Marseilles)*, **32**, 267(1972); through *Chem. Abstr.*, **78**, 11395u(1973).

(1258) T. Tsuchiya, *Diss. Abstr. Int.*, **33**, 801B(1972); through *Chem. Abstr.*, **78**, 11408a(1973).

(1259) L. Klatt and F. W. Koss, *Arzneim.-Forsch.*, **23**, 913(1973); through *Chem. Abstr.*, **79**, 142753c(1973).

(1260) *Ibid.*, **23**, 920(1973); through *Chem. Abstr.*, **79**, 142754d(1973).

(1261) C. H. Ramsay, N. O. Bodin, and E. Hansson, *Arzneim.-Forsch.*, **22**, 1962(1972); through *Chem. Abstr.*, **78**, 79533t(1973).

(1262) P. Pentikainen, A. Penttila, H. Vapaatalo, and R. Hackman, *J. Pharm. Pharmacol.*, **25**, 371(1973).

(1263) C. D. Morehead, S. Shelton, H. Kusmiesz, and J. D. Nelson, *Antimicrob. Ag. Chemother.*, **2**, 267(1972); through *Chem. Abstr.*, **78**, 79861y(1973).

(1264) L. Weingaertner, U. Sitka, R. Patsch, and D. Herrmann, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 99(1972); through *Chem. Abstr.*, **79**, 38664p(1973).

(1265) P. E. Gower, C. H. Dash, and C. H. O'Callaghan, *J. Pharm. Pharmacol.*, **25**, 376(1973).

(1266) K. Dvoracek, Z. Modr, O. Schmidt, and A. Necaskova, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 9(1972); through *Chem. Abstr.*, **79**, 38418m(1973).

(1267) J. M. Brogard, P. Haegele, M. Dorner, F. Kuntzmann, J. Lavillaureix, and J. Stahl, *ibid.*, **1**, 13(1972); through *Chem. Abstr.*, **79**, 38419n(1973).

(1268) C. Harvengt, P. DeSchepper, F. Lamy, and J. Hansen, *J. Clin. Pharmacol. New Drugs*, **13**, 36(1973); through *Chem. Abstr.*, **78**, 52500t(1973).

(1269) E. Marmo, P. Petrone, A. Robertaccio, and M. Grassi, *G. Ital. Chemioter.*, **18**, 11(1971); through *Chem. Abstr.*, **79**, 27202k(1973).

(1270) A. R. Giles and A. Gumma, *Arzneim.-Forsch.*, **23**, 98(1973); through *Chem. Abstr.*, **78**, 119054w(1973).

(1271) B. Katchen, S. Bauxbaum, J. Meyer, and J. Ning, *J. Pharmacol. Exp. Ther.*, **184**, 453(1973); through *Chem. Abstr.*, **78**, 79539z(1973).

(1272) A. Marzo, P. Ghirardi, and G. Croce, *Clin. Ter.*, **62**, 419(1972); through *Chem. Abstr.*, **78**, 80m(1973).

(1273) K. E. Schulte, E. Dreymann, and H. Moellmann, *Arzneim.-Forsch.*, **22**, 1381(1972); through *Chem. Abstr.*, **78**, 11405x(1973).

(1274) B. Testa and A. H. Beckett, *J. Pharm. Pharmacol.*, **25**, 119(1973).

(1275) N. Rietbrock, U. Abshagen, K. VonBergmann, and H. Kewitz, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **274**, 171(1972); through *Chem. Abstr.*, **78**, 11402u(1973).

(1276) E. M. Breznock, *Diss. Abstr. Int.*, **33**, 3832B(1973).

(1277) S. S. Walkenstein, A. P. Intoccia, T. L. Flanagan, B. Hwang, D. Flint, J. Weinstock, A. J. Villani, D. Blackburn, and H. Green, *J. Pharm. Sci.*, **62**, 580(1973).

(1278) B. Duhm, W. Maul, H. Medenwald, K. Patzschke, L. A. Wegner, and H. Oberste-Lehn, *Arzneim.-Forsch.*, **22**, 1276(1972); through *Chem. Abstr.*, **78**, 11719c(1973).

(1279) T. Tobin, S. Dirdjosudjono, and S. I. Baskin, *Amer. J. Vet. Res.*, **34**, 951(1973); through *Chem. Abstr.*, **79**, 100391c(1973).

(1280) A. J. Atkinson and J. M. Shaw, *Clin. Pharmacol. Ther.*, **14**, 521(1973).

(1281) J. Simiand, P. Eymard, B. Ferrandes, M. Polverelli, and A. Troussier, *Ann. Pharm. Fr.*, **31**, 205(1973); through *Chem. Abstr.*, **79**, 87323k(1973).

(1282) C. J. Jones, D. K. Luscombe, and P. J. Nicholls, *J. Pharm. Pharmacol., Suppl.*, **25**, 139P(1973).

(1283) J. Fabre, P. Kalfopoulos, and M. Rudhardt, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 29(1972); through *Chem. Abstr.*, **79**, 142998m(1973).

(1284) C. T. Hardesty, N. A. Chaney, and J. A. R. Mead, *Cancer Res.*, **32**, 1884(1972); through *Chem. Abstr.*, **78**, 23843b(1973).

(1285) R. S. Bourke, C. R. West, G. Chheda, and D. B. Tower, *ibid.*, **33**, 1735(1973); through *Chem. Abstr.*, **79**, 87317m(1973).

(1286) A. Joergensen and C. G. Gottfries, *Psychopharmacologia*, **27**, 1(1972); through *Chem. Abstr.*, **78**, 11747k(1973).

(1287) Z. Kopitar, R. Kunert, and V. Heinz, *Arzneim.-Forsch.*, **23**, 311(1973); through *Chem. Abstr.*, **79**, 73438q(1973).

(1288) Z. Modr, K. Dvoracek, O. Schmidt, and A. Necaskova, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 163(1972); through *Chem. Abstr.*, **79**, 38658q(1973).

(1289) E. Schulz, K. Koch, and F. H. Schmidt, *Eur. J. Clin. Pharmacol.*, **4**, 32(1971); through *Chem. Abstr.*, **78**, 11417c(1973).

(1290) G. Rentsch, H. A. E. Schmidt, and J. Rieder, *Arzneim.-Forsch.*, **22**, 2209(1972); through *Chem. Abstr.*, **78**, 105863x(1973).

(1291) N. Gerber, R. Seibert, D. Desiderio, R. M. Thompson, and M. Lane, *Clin. Pharmacol. Ther.*, **14**, 264(1973).

(1292) J. Metz, T. Stau, and R. Taugner, *Verh. Deut. Ges. Inn. Med.*, **78**, 1570(1972); through *Chem. Abstr.*, **79**, 27049r(1973).

(1293) B. Kamper, S. Leodolter, G. Hellmann, and G. Hertting, *Arzneim.-Forsch.*, **23**, 721(1973); through *Chem. Abstr.*, **79**, 132774w(1973).

(1294) A. K. Knirsch, D. C. Hobbs, and J. J. Korst, *J. Infec. Dis., Suppl.*, **127**, S105(1973); through *Chem. Abstr.*, **79**, 73816m(1973).

(1295) A. Traeger, H. Noeschel, and J. Zaumseil, *Zentralbl. Gynaekol.*, **95**, 635(1973); through *Chem. Abstr.*, **79**, 87259u(1973).

(1296) B. B. Gaitonde, B. J. Vakil, M. R. Samuel, N. L. Chabria, and R. A. Kamath, *Indian J. Med. Res.*, **60**, 1674(1972); through *Chem. Abstr.*, **79**, 416w(1973).

(1297) G. A. Ellard and P. T. Gammon, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 45(1972); through *Chem. Abstr.*, **79**, 100376b(1973).

(1298) B. E. Cabana and J. G. Taggart, *Antimicrob. Ag. Chemother.*, **3**, 478(1973); through *Chem. Abstr.*, **79**, 27405d(1973).

(1299) P. D. Thomson, K. L. Melmon, J. A. Richardson, K. Cohn, W. Steinbrunn, R. Cudihee, and M. Rowland, *Ann. Intern. Med.*, **78**, 499(1973); through *Chem. Abstr.*, **79**, 27483c(1973).

(1300) T. W. Redding, A. J. Kastin, D. Gonzalez-Barcena, D. H. Coy, E. J. Coy, D. S. Schalch, and A. V. Schally, *J. Clin. Endocrinol. Metab.*, **37**, 626(1973).

(1301) I. Amon, H. Hueler, and K. Amon, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th*, **1**, 111(1972); through *Chem. Abstr.*, **79**, 38666r(1973).

(1302) P. G. Welling and A. M. Monro, *Arzneim.-Forsch.*, **22**, 2128(1972); through *Chem. Abstr.*, **78**, 105861v(1973).

(1303) J. Rieder, *ibid.*, **23**, 212(1973); through *Chem. Abstr.*, **78**, 143624c(1973).

(1304) B. Alexanderson, *Eur. J. Clin. Pharmacol.*, **4**, 82(1972); through *Chem. Abstr.*, **78**, 11416b(1973).

(1305) F. Sjoqvist, *Muenchen. Med. Wochenschr.*, **114**, 1600(1972); through *Chem. Abstr.*, **78**, 11359k(1973).

(1306) F. Sjoqvist, *Minerva Med.*, **64**, 866(1973); through *Chem. Abstr.*, **79**, 96868u(1973).

(1307) F. Planas-Bohne, *Arzneim.-Forsch.*, **22**, 1426(1972); through *Chem. Abstr.*, **78**, 23833y(1973).

(1308) P. Naumann, H. Lode, and E. Reintjens, *ibid.*, **23**, 218(1973); through *Chem. Abstr.*, **78**, 143625d(1973).

(1309) J. Vessman, B. Alexanderson, F. Sjoqvist, B. Strindberg, and A. Sundwall, *Benzodiazepines*, **1973**, 165; through *Chem. Abstr.*, **79**, 27539a(1973).

(1310) E. Csanyi and I. Elekes, *Advan. Antimicrob. Antineo-*

plastic Chemother., Proc. Int. Congr. Chemother., 7th, **1,** 1015(1972); through *Chem. Abstr.,* **79,** 38406f(1973).

(1311) M. Brunaud and J. Vindel, *ibid.,* **1,** 919(1972); through *Chem. Abstr.,* **79,** 27178g(1973).

(1312) G. Bodem and C. A. Chidsey, *Clin. Pharmacol. Ther.,* **14,** 26(1973).

(1313) C. F. George, T. Fenyvesi, M. E. Conolly, and C. T. Dollery, *Eur. J. Clin. Pharmacol.,* **4,** 74(1972); through *Chem. Abstr.,* **78,** 11730z(1973).

(1314) A. Tacquet, B. Devulder, G. Lelievre, P. Duchatelle, and F. Wambergue, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th,* **1,** 71(1972); through *Chem. Abstr.,* **79,** 38659r(1973).

(1315) W. P. McCann and P. A. Palmisano, *Res. Commun. Chem. Pathol. Pharmacol.,* **5,** 17(1973); through *Chem. Abstr.,* **78,** 143623b(1973).

(1316) L. E. Davis, B. A. Westfall, and C. R. Short, *Amer. J. Vet. Res.,* **34,** 1105(1973); through *Chem. Abstr.,* **79,** 132788d(1973).

(1317) B. von Lehmann, S. H. Wan, S. Riegelman, and C. Becker, *J. Pharm. Sci.,* **62,** 1483(1973).

(1318) S. Fontana, M. Ariano, and G. Olivari, *Riv. Farmacol. Ter., Suppl.,* **2,** 83(1971); through *Chem. Abstr.,* **78,** 11421z(1973).

(1319) F. Lodi, E. Marozzi, G. Barbi, and C. A. Maggi, *Farmaco, Ed. Prat.,* **28,** 105(1973); through *Chem. Abstr.,* **78,** 106233d(1973).

(1320) R. Bergleiter and M. P. Liedtke, *Deut. Gesundheitsw.,* **28,** 1268(1973); through *Chem. Abstr.,* **79,** 143012x(1973).

(1321) R. Denk, E. Brode, H. Kummer, M. Traut, and W. Breckwoldt, *Arzneim.-Forsch.,* **23,** 187(1973); through *Chem. Abstr.,* **78,** 154676x(1973).

(1322) T. Kitakaze, K. Ito, and Y. Ogawa, *Chemotherapy (Tokyo),* **21,** 224(1973); through *Chem. Abstr.,* **79,** 73465w(1973).

(1323) H. Nolte and H. Buettner, *Chemotherapy (Basel),* **18,** 274(1973); through *Chem. Abstr.,* **79,** 73818p(1973).

(1324) K. Mashimo, Y. Kato, O. Yajima, I. Nakayama, M. Tomizawa, and H. Ideuchi, *Chemotherapy (Tokyo),* **21,** 246(1973); through *Chem. Abstr.,* **79,** 87313g(1973).

(1325) K. Fukaya, G. Tomori, T. Komoriya, and O. Kitamoto, *ibid.,* **21,** 273(1973); through *Chem. Abstr.,* **79,** 87476n(1973).

(1326) J. Rieder, M. Fernex, E. Schwartz, E. K. Brodwall, T. Bergan, A. Blumberg, P. Cottier, G. Locher, and W. Scheitlin, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th,* **1,** 79(1972); through *Chem. Abstr.,* **79,** 38661k(1973).

(1327) C. A. N. Davis, L. E. Davis, and J. D. Baggot, *Amer. J. Vet. Res.,* **34,** 425(1973); through *Chem. Abstr.,* **79,** 27210m(1973).

(1328) L. J. Saidman and E. I. Eger, II, *Clin. Pharmacol. Ther.,* **14,** 12(1973).

(1329) C. K. Simon, E. U. Moesinger, and V. Malescyzk, *Antimicrob. Ag. Chemother.,* **3,** 445(1973); through *Chem. Abstr.,* **79,** 27535w(1973).

(1330) E. R. Garrett and H. J. Lambert, *J. Pharm. Sci.,* **62,** 550(1973).

(1331) M. B. Roberfroid, P. A. Dumont, R. DeNeys, and F. Rollmann-Gregoire, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th,* **1,** 127(1972); through *Chem. Abstr.,* **79,** 87298f(1973).

(1332) D. G. Perrier, *Diss. Abstr. Int.,* **34,** 2748B(1973).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the **Operations Division, Syntex Laboratories Inc., and the* ‡*Institute of Pharmaceutical Sciences, Syntex Corporation, Palo Alto, CA 94304*

ˣTo whom inquiries should be directed.