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Pharmaceutical Sciences—1971: Literature Review of Pharmaceutics

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Keyphrases ☐ Pharmaceutical sciences—1971 literature review of pharmaceutics ☐ Technology, pharmaceutical—sterility, dosage forms, packaging equipment ☐ Physical pharmacy—dissolution, solubility, permeability, complexation, surface phenomena ☐ Antibiotics—pharmaceutical aspects ☐ Radiopharmaceuticals—pharmaceutical aspects ☐ Biopharmaceutics—drug properties, absorption, pharmacokinetics

CONTENTS

A comprehensive cross section of the research and development efforts in various selected disciplines of the pharmaceutical sciences is presented in this review of the literature. The scope of this endeavor has been limited to a review in the area of pharmaceutics because annual reviews of the literature related to other

Table I—Additional References on Preservatives

Reference	Topic
19	Effect of various surfactants on water-soluble germicidal compounds
20	Effect of various types of modern ointment excipients on the bacteriostatic and fungistatic activity of preservatives
21	Investigation of dimethyldodecylbenzylammonium chloride as an eyedrop preservative
22	Effects of several commonly used insoluble powders on eight preservatives in aqueous solutions
23	Inhibition of the antimicrobial and antifungal activities of sorbic acid by methylcellulose and, to a lesser extent, by sodium alginate, polyvinylpyrrolidone, and tragacanth
24	Brief review of the factors affecting the deterioration of drugs and the incompatibility of the preservative with the other ingredients of a formulation
25	Review of preservatives and the physicochemical aspects of their formulation
26	Use of sorbic acid for the preservation of 13 different drugstore medicinal preparations
27	Use of benzalkonium chloride, chlorhexidine acetate, or phenylmercuric nitrate as preservatives for ophthalmic solutions in the hospital
28	Mixture of 0.07% methylparaben and 0.03% propylparaben inadequate for sterilizing ophthalmic preparations containing 1% resorcinol or 0.5% chloramphenicol
29	Preservation of certain ophthalmic solutions with phenylmercuric borate

areas of pharmaceutical sciences are published elsewhere. This is the 10th annual survey of the series (1–9). To compile it, numerous periodicals and selected sections of *Chemical Abstracts* were abstracted.

The review was prepared to provide an opportunity for reviewing the research of the past year in specific areas of pharmaceutical sciences and to supply a convenient source of references to articles of preferred interest. To maintain continuity, the well-accepted format of last year's review was retained.

GENERAL PHARMACY

Preservatives—A dialysis method was used to estimate the distribution of preservatives between the oil phase and the aqueous phase of an emulsion and the total concentration of preservatives needed to provide a given free concentration in the aqueous phase as determined from a plot of the distribution data on a three-dimensional graph (10). The data obtained from parenteral toxicity studies with benzyl alcohol suggested that the contents of a 30-ml. vial containing 0.9% benzyl alcohol can be given to healthy adults with no problem of alcohol intoxication or toxicity (11). The antifungal activity of methylparaben against *Saccharomyces cerevisiae in vitro* was found to be increased by theobromine sodium salicylate (Diuretin) and procaine, decreased by sodium phenobarbital, potassium guaiacolsulfonate (Thiocol), polysorbates (Tweens), methylcellulose, and gum arabic, and little affected by gum tragacanth or polyvinyl alcohol (12, 13). The capacity to depress the fungicidal effect of methylparaben was directly related to the hydrophilic–lipophilic balance of a surface-active compound. In a similar study of the effectiveness of preservatives in some fluid pharmaceuticals, the activity of both methylparaben and a mixture of methyl- and propylparabens was reported to be highest in citric acid syrup and potassium guaiacolsulfonate syrup (14). The adsorption of benzalkonium chloride onto different filter media during bacteriological filtration depended on the porosity of the filter, on the volume of the solutions used, and on the salts, buffers, and other additives (15). Similarly, the bactericidal activity of benzalkonium chloride in light kaolin suspensions was reduced because of adsorption of the preservative by the kaolin (16). In contrast, the activity of *m*-cresol as a preservative in the suspensions was not affected.

The interaction of a number of commonly used preservatives with the nonionic surfactant, cetomacrogol, was investigated. Binding parameters determined from a Scatchard plot in the concentration range of free preservative necessary for antimicrobial activity were used to calculate the total concentration of preservative needed in the surfactant system (17). Tests of the inactivation of preservatives by the added anion-active surfactants showed that inactivation occurred only after a certain ratio of surfactant to preservative concentration was reached. These ratios were used to determine whether the concentration of preservative is sufficient at a certain concentration of surfactant (18).

Other articles of interest related to the subject of preservatives are listed in Table I.

Flavor, Aroma, and Color—A general discussion of flavoring pharmaceuticals and dietary products, including some of the problems encountered, was presented (30). Flavor, considered by von Sydow (31) to be primarily a psychophysical concept and secondarily a chemical factor, was discussed, together with methods to classify flavor and taste of food products. Organoleptic testing, with particular reference to taste as a production control procedure, was described (32). The difference of tastes associated with D-mannose was found to be solely due to the slight difference in the molecular structure between α-D-mannose and β-D-mannose, supporting the conjecture that taste receptors exhibit a high degree of physical–chemical stereospecificity (33). The characteristics of cold-pressed and steam-distilled citrus essential oils from various sources were established using instrumental analyses (34).

The comprehensive evaluation of the literature in the perfumery materials field by Bedoukian (35) was continued in his 27th annual review. The role of oleoresins in perfumery was discussed, and their imaginative use for creating fragrance compositions with novel effects was proposed (36). Problems concerned with the thermodynamic compatibility of a perfume in a finished cosmetic product, together with the retention of the intrinsic character of the perfume, were explored (37). The stereochemical theory of odors correlates the odor of various compounds with the size and shape of their molecular models, while the vibrational theory relates the odors to certain absorption peaks in their far IR spectra. It may be finally possible to compare the relative success of the two theories of odor specificity directly, since it was reported by Amoore (38) that he intends to apply his stereochemical theory to the same set of compounds that was used as a basis of the vibrational theory. The odor distinctiveness of the enantio-

mers R-(−)- and S-(+)-carvone, the sensory constituents in oil of spearmint and oil of caraway, respectively, was ably demonstrated by several groups of workers (39–42). A representation of sensory impressions by single uniform perfumes as standard reference substances was presented in a review of aromas and fragrances by Zausch (43), in which natural and synthetic olfactory key components were discussed.

The application and usage of colors in pharmaceutical and cosmetic products were reviewed (44). The characterization of nacreous and interference pigments used to impart pearl luster to many items, including cosmetics, was accomplished by measurements of their optical properties which make possible their comparison in terms of quality (45).

Stability—The concentration of nonstabilized tuberculin solutions was found to be greatly decreased by adsorption of the tuberculoprotein to the glass walls (46). The addition of 5 p.p.m. of polysorbate 80 (Tween 80) to the tuberculin solution was reported to prevent this loss in potency. The activity of prostaglandin E_2 solutions for clinical use was found to deteriorate on storage in saline solution. Brummer (47) reported that this can be prevented by preparing these compounds as concentrated alcoholic solutions in ampuls which can be kept for long periods at −20° and diluted with sterile isotonic saline as required within 24 hr. of use. The progression of oxidation of α-methyldopa and its acceptability to interruption by chelation with borate ion were investigated (48). The oxidation product resulting from this chelation with borate ions was shown to be resistant to further oxidation and to be soluble for extended periods of time. In studies on hydroxyethyl starch as a plasma extender, material with higher molecular weight was found to be more resistant to hydrolysis in the blood (49). The mode of hydrolysis was also discussed in connection with the stability of the hydroxyethyl starch in blood. An investigation of the use of sodium carboxymethylcellulose to chelate trace metals, which are frequently the cause of discoloration of medicinal tablets, showed that the discoloration of such tablets was markedly reduced by this agent (50).

In an investigation of the color deterioration of pharmaceutical preparations containing aminophylline, ephedrine hydrochloride, and amobarbital (amylobarbitone), it was found that mixtures containing aminophylline and ephedrine hydrochloride were deliquescent and much less stable than either compound stored separately (51). The observed color changes were accelerated by heat and humidity. Irradiation at 254 nm. of aqueous solutions of 5-ethyl-, 5-propyl-, and 5-isopropyluracil (or their nucleosides) was observed to form uracil or its nucleoside by cleavage of the 5-alkyl substituents (52). Neither the color of the glass ampuls nor the duration of storage was found to have any effect on the antibilharzial activity and toxicity of potassium antimonyltartrate (53). Human plasma stored for 2–5 years in plastic containers was evaluated (54). The overall changes detected suggested that plasma could still be usable after 4–5 years of storage at room temperature, although the use of frozen plasma appeared to be more effective. In a study of particle-size problems, the external surface areas of iodochlorhydroxyquin (Clioquinol), hydrocortisone, and prednisone powders were found to be stable under changes in temperature, relative humidity, and storage time (55).

Stability studies on sulfonamides, reported by Schittenhelm and Hermann (56), showed that their relative instability increased with the increasing aliphatic nature of the side chain and that aromatic character in the side chain and substitution with positive conjugation stabilized the molecule as a whole. In stability studies performed on sterile, unbuffered, 1% solutions of pilocarpine hydrochloride stored in plastic and borosilicate containers at elevated temperatures, it was found that the solutions were stable in the pH range between 3 and 4 (57). The stability of the gel-like product formed from the interaction of salicylic acid with cetrimide in the presence of additives was investigated, and the effect of the additives on the viscosity of the gel-like product was discussed (58). Some of the complexities of making compatibility studies in hyperalimentation solutions were discussed in relation to the problems associated with the experimental design of such a scientific study (59). Stability results indicated that the degradation of tecomine is dependent on the pH of its solution and that antioxidants are beneficial in minimizing its deterioration (60). The major degradation product of methoxamine in aqueous solution under air was found to be 2,5-dimethoxybenzaldehyde (61).

Other papers of interest related to the topic of stability are listed in Table II.

Stability Kinetics—Methods for predicting the stability of a pharmaceutical composition at a given temperature from accelerated stability studies using the kinetics of the degradation reactions and the Arrhenius relationship were reviewed by many authors (99–108). Application of these principles to the prediction of pharmaceutical stability of parenteral solutions was presented by Ho (109) to aid the professional pharmacist in interpreting the current literature on the stability of clinically important parenteral admixtures. For cases where the decomposition of drug is less than 10%, the application of zero-order kinetics in the Gauss–Newton method to accelerated data, including extrapolation to room temperature shelflife, was demonstrated (110). For products whose loss rate constant is related to temperature by the Arrhenius relationship, a single virtual temperature was determined for 30 cities in the United States and elsewhere, at which the loss rate is equivalent to that of the changing monthly pattern of temperature (111). These data were reported to serve as guides in selecting the standard temperature for use in the laboratory stability test protocol of such products. Shelflife predictions for 12 parenteral formulations, extrapolated from short-term accelerated stability test data, were compared with the results of long-term storage tests and were found, in most instances, to be correct (112). The use of an analog computer to simulate and interpret data obtained from linear nonisothermal stability studies was discussed (113). A program for predicting the degradation of lyophilized coenzyme B_{12} (114) and phenobarbital (115) in pharmaceutical preparations was pre-

Table II—Additional References on Stability

Reference	Topic
62	Stability and physicochemical properties of perlapine
63	Resistance of dihydrotriazine pamoate and ethionamide to γ-ray irradiation
64	Effect of some stabilizing agents on apomorphine hydrochloride solutions
65	Degradation of cyclobarbitone in the solid state due to autoxidation
66	Stability of tablet formulations containing aspirin in the presence of various excipients
67	Equation for the evaporation of thermolabile substances relating the decomposition rate to operating parameters of the process
68	Effect of storage conditions on stability of protamine sulfate solution
69	Stabilization of anesthesial ether by various antioxidants
70	Stability of various contraceptive steroids in a tablet formulation at various temperatures
71	Stability of emetine hydrochloride injectable solutions
72	Evaluation of stability of certain medicines kept at ambient temperature for 34 years
73	Thermal stabilities of the reineckates of quinine, betaine, hordenine, and pholcodine
74	Stability of scopolamine in sterile solutions
75	Review of reserpine stability in various drug forms
76	Review of aspirin stability in liquid and solid drug forms
77	Determination of stability of nitrofurantoin in basic solutions
78	Decomposition of *Purpurea* glycosides A and B during storage of tablets
79	Decomposition of amidopyrine–analgin systems
80	Chemical stability of hydrocortisone acetate in various ointment bases
81	Stability and physicochemical properties of flupenthixol dihydrochloride
82	Limited storage stability of a freshly prepared sodium nitroprusside solution
83	Determination of stability of an ophthalmic homatropine hydrobromide solution
84	Rational conditions for storage of some pharmaceutical materials
85	Practical relationships of stability data to expected shelflife of a product
86	Review of effect of electromagnetic radiation on drugs and pharmaceutical preparations
87	Review of hygroscopic properties of norsulfazole and pyramidon and their influence on the stability of drugs
88	Stability of hexahydroadiphenine, ethionamide, and aminophylline in various lipophilic suppository bases
89	Review of stability testing in pharmaceutical formulations
90	Stability of glucose, atropine sulfate, and ephedrine hydrochloride solutions for injection as a function of sterilization conditions
91	Comparative stability study of hypodermic tablets of nitroglycerin packaged in common prescription containers
92	Compilation of incompatibilities of multiple additives to intravenous infusion solutions
93	Physical and chemical incompatibilities of drugs in infusion admixtures
94	Discoloration of amino drugs in solid dosage form induced by lactose
95	Effect of moisture on stability of pyraminal and calcium theobrosal iodide tablets
96	Stability of arginine–malic acid infusion solutions
97	Review of deterioration of pharmaceuticals due to physical and chemical properties of the drug
98	Review of accelerated tests for physical stability of pharmaceutical products

sented, using temperatures of 80, 90, and 100° and requiring only a few days for completion of the tests. The results were comparable to those obtained using lower accelerated temperatures and longer time periods.

In a study of some linear free energy relationships which have been used in ester solvolysis, the use of alcohol and phenol dissociation as a model process for ester solvolysis was explored (116). It was found that correlation of substituent effects with reactivity for acyl-substituted benzoate esters was successfully accomplished using the Hammett equation. However, neither the Hammett equation nor the alcohol and phenol dissociation model was entirely effective in correlating structure with activity when considering a variation in the alkyl portion of the ester molecule. In an investigation of the relative substituent effects on alkaline solvolysis of β-lactams and amides, it was found that substituent effects in the β-lactams could be quantitated using the Taft equation and that a greater sensitivity to polar effects existed in the β-lactams as compared to the model linear amides (117). The kinetics of lactonization of coumarinic acids and hydrolysis of coumarins was elucidated by Garrett *et al.* (118) and Lippold and Garrett (119). The acid-catalyzed lactonization was an apparent first-order reaction, while the coumarin was hydrolyzed by a specific hydroxyl-ion-catalyzed solvolysis. The effect of the substituents on the reaction rates was also described. In a similar manner, the kinetics of hydrolysis of canrenone and lactonization of canrenoic acid were studied (120). Based on the kinetic parameters obtained, maximum concentrations of canrenoic acid salt to maintain elegant pharmaceutical preparations were stated as a function of pH.

The kinetics of drug decomposition for a number of compounds were reported by Pawelczyk and his coworkers (121–125). The decomposition of carbazochrome sodium sulfonate in aqueous solutions was found to be an apparent first-order reaction, and the shelflife of the drug at pH 5.15 and room temperature was estimated to be about 9 years (121). An investigation of the kinetics of autoxidation of sodium sulfanilthiocarbamide in alkaline solution showed that the reaction depended on concentration, pH, and the degree of filling of the reaction vessel (122). The decomposition rate was approximately first order, but at lower concentrations the order of the reaction changed. The photooxidation of sodium nalidixate in alkaline buffer was found to be a zero-order reaction (123). Resistance to higher temperatures and atmospheric oxygen was afforded solutions buffered in a pH range of 8.5–11.0. The degradation of thioridazine in aqueous solutions in the presence of light and air was found to be due to photooxidation, and its reaction rate was dependent on the initial concentration, solutions of higher concentration being more stable (124). Studies of the autoxidation and hydrolysis of sodium phenylbutazone solutions demonstrated that zero-order kinetics were followed in the presence of ammonium acetate, borate, and phosphate buffers under constant oxygen pressure (125). The acid-catalyzed hydrolysis of a number of sulfanilamidopyrimidine derivatives was found to be a first-order reaction (126). The effect of methyl groups substituted at positions 4 and 6 and of methoxy groups at position 5 on the hydrolysis rate of 2-sulfanilamidopyrimidine was also recorded. The hydrolytic degradation of sulfacetamide under anoxic conditions was

reported to be essentially independent of pH over the range of 5–11, but it was subject to catalysis by buffer constituents; below pH 4, specific hydrogen-ion catalysis occurred (127). On the basis of calculated activation parameters, it was concluded that sulfacetamide solutions could be satisfactorily autoclaved provided they were not subsequently refrigerated.

The degradation of a series of imidazolidinone derivatives was examined kinetically (128–130). Upon examination of these results, it was indicated that the 2-substituted derivatives were comparatively unstable and that the substituent introduced into the phenyl ring attaching at the 3-position of the imidazolidinone ring affected the decomposition rate (131). The oxidative degradation of isoniazid catalyzed with Cu^{+2} or Mn^{+2} was examined kinetically, and the mechanism of the reaction was elucidated (132, 133). A few compounds were investigated as stabilizers for the system; it was found that ethylenediaminetetraacetic acid was the most effective, but that citric acid had some effect also. In a somewhat similar study, the degradation of isonicotinic acid hydrazide sodium methanesulfonate was examined in aqueous solution in the pH range of 3.0–9.0, and the mechanism of the reaction was established (134). Sodium hydroxymethanesulfonate was found to be a more effective stabilizer for the system than isoniazid, sodium bisulfite, or formaldehyde.

A series of articles on the hydrolytic behavior of a number of classes of water-soluble corticosteroid derivatives was reported (135–138). The degradation of 16 kinds of hydrocortisone 21-hemiester derivatives in an alkaline aqueous solution was examined kinetically (135). All of the derivatives were found to undergo apparent first-order hydrolysis by the catalytic effect of the hydroxyl ion, a reaction influenced by the steric effects of substituents and the position of the terminal carboxyl group. Eleven different kinds of water-soluble hydrocortisone 21-aminoalkylcarboxylates in an acid aqueous solution were found to undergo hydrolysis by an apparent first-order reaction (136). Data were reported which indicated that the apparent pKa values of the derivatives may have a more important effect on stability than the steric effect of the substituents. Kinetic examination of the hydrolysis reaction of hydrocortisone 21-*o*-sulfobenzoate and 21-*m*-sulfobenzoate in aqueous solution showed that the decomposition reaction of both compounds followed first-order kinetics and that greatest stability occurred at about pH 3 (137). The stability of hydrocortisone 21-sulfate was found to be maximum at around pH 5–6. Kinetic examination of the alkaline hydrolysis of prednisolone 21-hemisuccinate, hemiphthalate, and hemimaleate esters in aqueous solution indicated that the hydrolysis progressed by the apparent first-order reaction catalyzed by the hydroxyl ion (138). It was also reported that the hydrolytic degradation of prednisolone 21-phosphate proceeded by an apparent first-order reaction and that the stability of the drug was greater in the alkaline than in the acid region.

The increase in stability of benzocaine and homatropine solubilized with 3–15% polyoxyethylene lauryl ether and polysorbate 80 was kinetically examined by Hamid and Parrott (139). The logarithm of the specific rate constants for the alkaline hydrolysis of benzocaine and homatropine was linearly related to the percent of the surfactant. Moreover, the specific rate constant for the hydrolysis of benzocaine was linearly related to the reciprocal of the apparent solubility of benzocaine in the two solubilizing agents. The hydrolysis of 4,4′-diformamidodiphenylsulfone was examined kinetically, and the reaction was described as proceeding in two steps, both of which followed apparent first-order kinetics (140). The kinetics of neutral and alkaline hydrolysis of barbituric acid derivatives were elucidated by Garrett *et al.* (141). The degradation of urea in concentrated aqueous solutions was studied at accelerated temperatures, and it was disclosed that the degree of degradation was extremely small and that the overall process conformed to a first- and a second-order reversible reaction (142).

The acid-catalyzed hydrolysis of rifampicin in 0.1 *N* HCl was found to obey pseudo-first-order kinetics, and the heat of activation (19 kcal./mole-degree) was reported (143). The solvolysis of the orally active acetoxymethyl and pivaloyloxymethyl cephaloglycin esters in 10% human serum was found to proceed rapidly to yield the active cephaloglycin (144). The half-lives of hydrolysis of these esters at pH 7.45 and 37° were 5 and 10–20 min., respectively. The effect of cupric ion on the stability and antibacterial activity of benzylpenicillin and 2,6-dimethoxyphenylpenicillin in phosphate buffer solution and phosphate broth kept at pH 5.0 was found to obey first-order kinetics to produce the corresponding penicillenic acids (145). The catalytic and complexing effects of cupric ion on the stability of penicillins were also described. The decomposition of sodium cloxacillin in aqueous solution was described as a function of pH, buffer species, ionic strength, and temperature (146). A rate expression describing four postulated reactions in the overall degradation was also reported.

Other references relative to the subject of stability kinetics are listed in Table III.

Antibiotic Stability—The stability of sodium ampicillin, sodium methicillin, sodium nafcillin, and sodium oxacillin solutions at pH levels from 3 to 10, stored at 25 and 4° for 24 hr., was investigated (170). The semisynthetic penicillins in this study showed a reasonable degree of stability over 24 hr. at the pH ranges and temperatures considered. In a study of sodium ampicillin solutions in the frozen and liquid states, it was found that freezing at from −20 to −78° generally increased the degradation of 1% sodium ampicillin solutions and decreased the degradation of 25% solutions (171). The concentration of sodium ampicillin in solution and the type of vehicle used, but not the pH of the solution, were reported to be the major factors controlling the degradation. Solution stability profiles for the refrigerated and room temperature storage of sodium cephalothin, cephaloridine, potassium penicillin G (buffered), and vancomycin hydrochloride in 5% dextrose, 0.9% saline, and water for injection were reported (172). The relative thermal stabilities of lincomycin hydrochloride monohydrate, lincomycin cyclamate, potassium cyclamate dihydrate, and sodium cyclamate were characterized using differential thermal

Table III—Additional References on Stability Kinetics

Reference	Topic
147	Kinetic study of Fezatione in an ethanolic solution
148	Stability of Levamisole in aqueous solution
149	Photolytic stability of some parenteral solutions in reserpine
150	Estimation of shelflife of solutions of vitamins B_6, B_{12}, and K_3 and glucose by accelerated aging
151	Kinetic examination of stabilities of 3-morpholinosydnonimine and its *N*-ethoxycarbonyl derivative
152	Stability of promethazine hydrochloride complexed with diethanolamine methylmyristyl sulfate in aqueous solutions
153	Kinetics of reaction of primary amines with the food preservative, dehydroacetic acid
154	Kinetics of inactivation of *d*-cycloserine in highly concentrated aqueous solutions
155	Degradation kinetics of parenteral solutions of atropine sulfate, ascorbic acid, and thiamine hydrochloride
156	Evaluation of stability of freeze-dried diphtheria toxoid using degradation kinetics
157	Kinetic examination of hydrolysis of adiphenine and cycloadiphenine
158	Stability of an injectable dexamethasone solution
159	Study of copper-catalyzed oxidation of cysteine
160	Stabilization of procaine hydrochloride solutions with 1,4-butanediol, 1,3-butanediol, or 2,3-butanediol
161	Kinetic study of stabilizing activity of polyols added to aqueous solutions of procaine hydrochloride
162	Kinetic model describing decomposition behavior of germine-3,16-diacetate in aqueous solution
163	Stability studies of nystatin in selected ointment bases
164	Kinetic studies of reversible cleavage of thiazolium salts
165	Degradation behavior of thiamine monohydrochloride and L-ascorbic acid with amorphous silicic acid in multivitamin capsules
166	Thermal degradation of vitamin D_3 in aqueous drinkable solutions
167	Stability of hamycin in 19 different eye ointment bases
168	Kinetic parameters of interaction of penicillinase with penicillins
169	Kinetic study of stability of oxacillin solutions

Table IV—Additional References on Antibiotic Stability

Reference	Topic
186	Review of antibiotics
187	Stability of tetracycline 3,4,5-trimethoxybenzoate in a tablet formulation
188	Effect of vitamin content on tetracycline hydrochloride stability in a formulation
189	Stability of freeze-dried penicilloylpoly-L-lysine preparations
190	Formulation of methicillin solutions with improved stability
191	Stability of thiamphenicol in aqueous solutions and a syrup
192	Hydrolysis of chloramphenicol palmitate by lipase at pH 6.2 as a function of particle size in the crystalline state

analysis and thermogravimetric procedures (173). An evaluation of the effect of protective packaging on the activity of antibiotic-containing tablets and capsules under the conditions of high heat and humidity of a tropical zone was presented (174, 175). A silica gel insert in glass containers was used as protection against atmospheric humidity. The characteristics of a new suppository base suitable for the tropics was also described (176).

The preparation of stable aqueous gels containing neomycin sulfate was accomplished by adsorbing the drug molecule onto a cation-exchange resin prior to incorporation into the gels of synthetic polymers containing polyionic or polar reactive sites (177). The activity of the drug resin was demonstrated, and the binding capacity of the drug for the polymers was determined. The rate of lactose-induced discoloration of neomycin tablets was found to be inversely proportional to the initial hydroxyl-ion concentration of the tablets (178). The browning reaction was retarded or prevented by the addition of sodium bisulfite. In an investigation of the photodecomposition of various tetracyclines, it was learned that calcium tetracycline was the most sensitive and 7-chlorotetracycline was the most stable (179). The stability of tetracycline hydrochloride solutions was found to be increased by the addition of carboxymethylcellulose and, to a lesser degree, by the addition of polyvinyl alcohol or methylcellulose; however, pectin, polyvinylpyrrolidone, and gum tragacanth showed no such beneficial action (180). At therapeutic concentrations of gentamicin and penicillins, no significant inactivation occurred in the serum at 37°; but in infusion fluids, carbenicillin and ampicillin produced a rapid fall in gentamicin concentrations at room temperature (181). It was recommended that where large doses of the penicillin are being administered by continuous intravenous infusion, gentamicin should be given by intramuscular or bolus intravenous injection.

The effect of nonionic surfactants on the stability of chloramphenicol in solution was examined, and it was reported that the stability of chloramphenicol increased with an increasing concentration of either polysorbate 20 (Tween 20) or polyoxyethylene alkyl ethers (Brij 35) up to 0.5%; under the same conditions, either polysorbate 80 (Tween 80) or polyoxyethylene stearic acid esters (Myrj 59) produced the opposite effect (182). Incubated aqueous solutions of chloramphenicol at a pH range of 1–14 were found to yield detectable amounts of *p*-nitrobenzaldehyde (an oxidation product) and arylamine (a reduction product), and evidence was presented on the role of water in this new degradative pathway of chloramphenicol (183). In other studies, the photodegradation products of chloramphenicol in aqueous solutions were identified by Shih (184). Evidence was presented suggesting that chloramphenicol in water under the influence of light undergoes oxidation, reduction, and condensation reactions. A study of one amorphous and three crystalline polymorphs of chloramphenicol palmitate indicated that only the biologically active α-form had a high degree of stability in the solid state or in aqueous suspensions with or without wetting agents (185).

Additional references on antibiotic stability are presented in Table IV.

Vitamin Stability—Stability studies of ascorbic acid in the presence of various flavors indicated that banana caused the least destruction of ascorbic acid while vanilla caused the maximum degradation (193). The other flavors tested that showed appreciable destruction of ascorbic acid were raspberry, cherry, chocolate, and pineapple. A kinetic study of the hydrolysis of ascorbic acid 3-phosphate showed that the degradation followed first-order kinetics with respect to the un-

reacted phosphate (194). The kinetic parameters were evaluated and applied to a mechanistic discussion of the degradation reaction. The anaerobic degradation of aqueous solutions of ascorbic acid in the presence of D-araboascorbic acid was examined kinetically, and a stabilizing effect of D-araboascorbic acid on the decomposition of ascorbic acid was not observed (195). Accelerated stability studies on seven typical liquid multivitamin formulations indicated that thiamine, riboflavin, pyridoxine, niacinamide, and folic acid were fairly stable over normally expected storage periods, but vitamin A and cyanocobalamin in the formulation were highly unstable (196).

A study of vitamin A stability in micellar solution showed that the degradation of vitamin A solubilized with oil by polysorbate 80 depended on the peroxide values of the oil; but when the vitamin A was solubilized by polysorbate 80 pretreated with hydrogen peroxide, the decomposition depended on the peroxide values of the polysorbate 80 (197). The oxidative degradation of ergocalciferol, vitamin D_2, was studied, and the characteristics of the degradation products were described (198). A combination of 0.1% cysteine and 0.1% thiourea was found to provide the most effective stabilization of calcium gluconoascorbate solutions, but lyophilized samples of calcium gluconoascorbate without the use of stabilizers were superior in both color and ascorbic acid content (199). In a study designed to determine the stability of *N,N*-diethylnicotinamide solution, no degradation was detected in samples stored for 2 years and exposed to artificial and natural daylight (200). In an investigation of ointments containing fat-soluble vitamins, ointments containing 5% vitamin F showed a better storage stability when synthetic vehicles such as polyethylene glycol were used instead of vehicles of plant or animal origin (201). The addition of 0.05% hydroquinone or 0.03% α-tocopherol was found to increase the shelflife of the ointment.

Additional references on vitamin stability are listed in Table V.

Table V—Additional References on Vitamin Stability

Reference	Topic
202	Carbonyl-type degradation products of vitamin A palmitate
203	Instability of ophthalmic drops containing vitamins
204	Review of ascorbic acid and methods for increasing its stability in pharmaceuticals
205	Increasing stability of multivitamin preparations derived from natural products
206	Study of folic acid stability in injectables

PHARMACEUTICAL TECHNOLOGY

Progress in the field of pharmaceutical technology was comprehensively reviewed by Chalabala *et al.* (207). Galenical problems in drug development (208) and current aspects of pharmaceutics (209) were also reviewed. Mathematical optimization techniques were demonstrated as an approach to solving pharmaceutical processing problems (210). A review of antacids included a discussion of factors to be considered in their evaluation (211). The solubilization of water-soluble materials, such as aqueous solutions of ascorbic acid, in nonpolar liquids by the use of appropriate surfactants was demonstrated by Morse *et al.* (212). The manufacture and properties of pharmaceutical gelatins, as well as their numerous applications to pharmaceutical products, were extensively reviewed by Jones (213, 214). The properties and pharmaceutical applications of acrylic acid polymers, polyvinylpyrrolidone, and polyethylene glycols were described in a series of review articles (215–217).

The control of microbial contamination in raw materials used in oral and ophthalmic pharmaceutical products was examined (218). In a discussion of the antimicrobial activity of some oral and topical products, many cases were cited in which the activity was destroyed or greatly diminished under conditions of use (219). The detection and control of nonbacterial contaminants in raw materials and in the processing of pharmaceutical dosage forms were also considered (220, 221). A survey of a laboratory building for airborne antibiotics was reported (222), which is indicative of the type of environmental monitoring necessary to assure that other products are not contaminated by antibiotics from this source during their manufacture.

Parenterals—The various factors affecting the solubility of a drug were discussed in relation to developing a parenteral dosage form (223). A report on the thermodynamic and kinetic aspects of parenteral benzodiazepines included a description of solubilization by the use of cosolvents and complexation and showed that stability prediction for the benzodiazepines in solution was possible by means of the Arrhenius relationship (224). The complicating factors which must be considered in manufacturing parenteral radiopharmaceuticals were reviewed and discussed (225). The design of new production processes for hypodermic needles to reduce coring of rubber was reviewed, and the coring effect of the lateral force of entry and the sharpness effect of the new lubricating process for the needle were described (226). The utilization of parenteral hyperalimentation fluids was reviewed; the formulas and procedures for preparing satisfactory solutions were described, along with a discussion of some of the problems encountered (227, 228). A report by Deeb and Natsios (229) indicated that the contamination of hyperalimentation fluids during use occurred more frequently than with other commonly used intravenous solutions but that the risk of contaminating hyperalimentation solutions or other intravenous solutions during preparation in the pharmacy was low when vigorous aseptic techniques were practiced.

A study of particulate matter in intravenous infusion solutions of four manufacturers showed that the amount of particulate matter in solution varied widely among manufacturers and among different solutions made by the same manufacturer; additives and administrative sets contributed to the level of particulate matter, and final filtration sets were effective in removing particulate matter (230). An automatic machine detection of particulate matter in parenteral solutions by image projection was compared with a manual

Table VI—Additional References on Parenterals

Reference	Topic
238	Intravenous formulation of poly(inosinic acid)–poly(cytidylic acid) copolymer
239	Review of pharmaceutical aspects of pyrogenic contamination of parenteral solutions
240	Injectable suspension of Δ^9-tetrahydrocannabinol
241	Review of interactions between closures and liquid pharmaceuticals
242	Sorption of methylparaben from aqueous solutions by Buna S rubber closures
243	Factors affecting the overage needed in containers of injectables
244	Preparation of stable sodium bicarbonate infusion solutions
245	Review of lyophilization procedures for mixtures of incompatible drugs
246	Preparation of a lyophilized formulation of mepicycline
247	Cryoscopic studies of a mixture of aminophenazone and allobarbital
248	Effect of freezing conditions on the lyophilization of pharmaceuticals

inspection method (231). The machine inspection was found to be more reproducible and selective than the visual inspection of a specific set of control ampuls and was considered feasible and practical for further testing of its performance on a production line with the actual product to be inspected. A method of detecting particulate matter in injectable solutions was reported that involved placing an ampul in a liquid whose refractive index approximates that of glass and detecting the particulates by a photomicroscopic method (232).

Rowles *et al.* (233) studied the losses of ^{14}C-labeled benzyl alcohol, phenol, and thiamine hydrochloride from different solutions exposed to natural, butyl, and neoprene rubber closures and the permeabilities of the closures using a technique combining autoradiography and air scrubbing towers. The results showed that: (*a*) natural and neoprene rubber closures sorbed substantially more preservative than the butyl rubber for each solution studied, (*b*) thiamine hydrochloride sorption was low for all solutions and closures tested, and (*c*) solution additives influenced benzyl alcohol sorption but not phenol or thiamine hydrochloride sorption into each of the studied closures. Also, the results of the air scrubbing tower analysis indicated that more preservative was released to the atmosphere by natural and neoprene than by butyl rubber closures. Present knowledge of cleaning techniques for rubber closures indicated that the procedure should start with closures boiled in distilled water in a steam autoclave followed by mechanical washing with detergent (234).

Natural rubber latex vulcanized by irradiation was reported to be more resistant to sterilization and storage than rubber vulcanized with sulfur (235). Freeze drying of four ternary solutions was examined, and the mechanism of collapse during a freeze-drying procedure was discussed in relation to the eutectic temperature and collapse temperature of the solute matrix (236). The conditions for low temperature vacuum drying of sterile parenterals from ethanol were presented for two antineoplastic agents (237). The drying was accomplished at −40° for the first 24 hr., and then the temperature was slowly increased until the final drying temperature of 20°, which was maintained for an additional 8 hr.

Other papers of interest in the category of parenterals are listed in Table VI.

Sterility—The importance of the determination and subsequent reduction of the environmental microbial load in production facilities was emphasized with regard to sterilization and sterility test procedures (249). The benefit of constructing a unitized sterile enclosure around a sterile manufacturing operation, as opposed to installing the operation in an expensive sterile room, was discussed in relation to the elimination of contamination from personnel working in the area (250). In clean-room work, constant vigilance in enforcing rigid clean-room work rules was described as the price of contamination control (251). Factors to ensure microbiological purity of pharmaceuticals were presented as guidelines and methods for use in a pharmacopeia (252).

According to Macek (253), greater emphasis should be placed on the development and use of standardized biological indicators to determine the adequateness of sterilization procedures. The various factors to be considered in developing a biological indicator for control of sterilization processes were discussed by several authors (254–257). These factors included the types of microorganisms on the products to be sterilized, the selection of a suitably resistant microorganism for the sterilization process used, rigid control for the manufacture of the inoculum, proper choice of the vehicles for the test piece, and rigid quality controls of the final biological indicators. An artificial resistance of the biological indicator to ethylene oxide was developed by suspending microorganisms in a mixture of a plasticizer with a film former (258). The degree of resistance established was three times the resistance of freshly harvested spores of *Bacillus subtilis* var. *niger*. The solubility and resistance of the indicator were stable for at least 2 years under ambient conditions.

The results from studying the removal of pyrogenicity from solutions of purified pyrogens and tap waters using ion-exchange resins suggested that the pyrogenicity due to purified pyrogen in solution may be removed or reduced by passage through suitable ion-exchange resins; the pyrogenic activity of tap waters may be removed by passing through a strongly basic ion-exchange resin, and different resins have different effects on various types of pyrogens (259). These data provided additional evidence to support the idea that the ion-exchange method in a sterilizable apparatus may be designed to provide sterile water suitable for use in parenteral products. The characteristics of a highly purified pyrogenic lipopolysaccharide were described; the principal constituents found after hydrolysis were galactose and mannose, plus unidentified fatty acids (260). A sensitive sterility test method for the detection of microbial contamination in petrolatum-based ophthalmic ointments was described by Tsuji *et al.* (261). Two of the authors also reported a somewhat analogous microcount method for petrolatum-based topical ointments containing waxes (262). A collaborative study of aerobic media showed that soybean-casein digest medium was superior to fluid

Sabouraud medium for sterility testing by membrane filtration (263). It was noted that this change was made in the USP XVIII and NF XIII (first supplement).

The level of ethylene oxide retained from the sterilization of polyvinyl chloride, natural rubber, polyethylene, or Teflon tubing that is toxic to tissue was studied (264). Tissue reactions to ethylene oxide in polyvinyl chloride and natural rubber were similar and correlated with the level of retained ethylene oxide. Little ethylene oxide was absorbed by either polyethylene or Teflon. The death of lyophilized *Salmonella senftenberg* and *Escherichia coli* exposed to gaseous ethylene oxide was reported to follow first-order kinetics (265). Other aspects of the investigation indicated that the mode of action of ethylene oxide in causing the loss of cells to reproduce was that of alkylation of the guanosine triphosphate component of DNA. In a study of the safe use of ethylene oxide sterilization of rubber and plastic, it was found that 3–4 hr. of exposure to ethylene oxide at 49–57° and over 50% relative humidity, followed by adequate aeration to eliminate ethylene oxide, ethylene glycol, and ethylene chlorohydrin, was required (266). Ethylene oxide sterilization of contaminated hydrocolloid powder and fast-setting plaster was found to be effective and caused no change in the properies of the impression material (267).

The concept, uses, advantages, and adverse effects of γ-radiation sterilization of products were discussed by Ley (268) and Dietz (269) and were related to the physical facilities by which the sterilization was accomplished. The effect of γ-radiation on the physical and chemical properties of disposable injection needles and disposable plastic syringes was found to be slight, but all plastic parts showed some brittleness after irradiation at doses of 4.5–10 mrads (270, 271). A dose of 10^6 rads of γ-radiation was found to sterilize effectively levorin, nystatin, amphotericin B, sodium levorin, and sodium nystatin, with a potency loss of approximately 10% (272). Dextran (molecular weight 40,000–70,000) was degraded by γ-radiation at sterilizing doses of 1–5 mrads (273–275).

Other papers relative to the subject of sterility are listed in Table VII.

Table VII—Additional References on Sterility

Reference	Topic
276	Loss of chlorhexidine acetate by adsorption onto different filter media
277	Detailed explanation of drug irradiation technology
278	Bacterial contamination of intravenous fluids
279	Effect of ethylene oxide sterilization on several sugars, sulfonamides, barbiturates, and alkaloid salts
280	Inert gas flushing techniques
281	Bactericidal activity of benzyl alcohol in radioactive injectable preparations
282	Heat sterilization of sulfathiazole solutions
283	Pyrogen-free water from filtration of tap water through ion-exchange columns
284	Review of sterilization problems of synthetic biocompatible materials
285	Chronological survey of drug sterilization by membrane filtration
286	Recent developments in irradiation sterilization
287	Discussion of radiation sterilization and preservation of cosmetics
288	Review of the development of ethylene oxide sterilization

Tablets and Capsules—The numerous publications dealing with pharmaceutical technology of tablets and capsules have been subdivided into the following classifications to facilitate the search of the literature: comminution, mixing, granulation, and drying; powder characteristics; compression; effect of excipients; and tablet coating. For a thorough review, consideration of the entire section is advised, since there is an obvious overlap in the subject matter of the subclassifications.

Comminution, Mixing, Granulation, and Drying—Ball milling of 32 kinds of powders was investigated, and the data were reduced to an equation describing the rate of increase of surface area (289). This rate of increase of surface area by ball milling was found to depend on such factors as coherency of powder particles expressed as a function of surface energy, melting point, solubility in water, and true density. In a study of single-impact crushing, it was shown that grain-size distribution and mass-related load energy followed a logarithmic normal function; distributions resulting from different impact energies were interrelated (290). In an effort to improve the efficiency of comminution by jet mills, the flow and comminution by impact of two solid-gas jets were studied for impact angles between 45 and 180°. Best comminution was found for a central impact and for small free distances between the end of the ejector and the impact point (291).

The effects of adding various numbers of Lucite balls as mixing aids on the kinetics of mixing particulate solids in a rotating drug mixer were evaluated, and an empirical relationship between the number of balls added to the mixer and the diffusion coefficient was obtained (292). In a comparison of granules prepared by massing and screening and pan granulation, the action of the pan method was found inadequate to compact calcium phosphate but was highly effective with the less cohesive lactose. On the other hand, massing and screening provided the forces necessary for granulating calcium phosphate but failed to produce a good lactose granulation (293). The use of a fluid bed granulator to prepare tablet granulations was thoroughly explored, and the effects of various process variables on the physical properties of the granulated product were reported (294). In a study of wet granulation, information was obtained on the relationship between the amount of binder and several characteristics representative of the granulation state and properties of the granules; the amount of binder at the flection point of several characteristic curves was almost the same, but the amount of binder at this point was different from the plastic limit measured by another method (295).

The flow rates of some granulated pharmaceuticals were investigated by Danish and Parrott (296, 297) and Danish (298). By using granules of sodium chloride and lactose, an equation was presented relating the flow rate, the diameter of the particles, and the diameter of the orifice. The rate of flow was increased as the diameter of the orifice was increased; but as the size of the particles was decreased, the rate of flow from a given orifice was increased until a maximum rate was

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

Reference	Topic
303	Effect of various granulometries of virginiamycin samples on *in vitro* dissolution rates at 37°
304	Discussion of the wet method of granulation
305	Evaluation of a liquid-phase granulation technique
306	Procedure for uniform granulation by vibration-spray congealing
307	Procedure for spray drying kanamycin
308	Kinetics of drying tableting preparations in a fluidized bed
309	Kinetic evaluation of drying granulated materials in a dense blowthrough layer

obtained, after which further size reduction caused a slower flow rate. In other studies of the effect of concentration and size of lubricant on the flow rate of the granules, these researchers found that at a constant concentration (<1%) in both systems (sodium chloride and lactose) the lubricants having a diameter of 0.0213 cm. were the most effective.

The radial migration of polyvinylpyrrolidone in spherical granules of magnesium carbonate during a controlled drying cycle and its effect on the physical properties of the granule were reported (299). Gum arabic, gelatin, polyvinyl alcohol, sodium carboxymethylcellulose, methylcellulose, and polyvinylpyrrolidone were studied as binders in aqueous slurries of synthetic aluminum silicate or magnesium carbonate which were spray dried (300). The finely agglomerated powders obtained by this procedure showed free-flowing properties and could be readily tableted as opposed to the original powders. According to Fell and Newton (301), only the operational variables of the liquid feed rate affected any of the physical properties of spray-dried lactose produced in an experimental dryer under known conditions. Tablets prepared from spray-dried lactose dried at low inlet air temperatures were found to be stronger than those produced at higher inlet temperatures; this finding was attributed to the high content of the α-monohydrate form of lactose (302).

References to additional literature on comminution, mixing, granulation, and drying are listed in Table VIII.

Powder Characteristics—The effects of particle size and shape on the mixing of powder layers flowing down a chute were assessed; at constant particle size, the amount of mixing decreased with decreasing sphericity; reducing the particle size of the upper layer increased the mixing rate and it was possible to pass into a zone of segregation of the smaller particles (310). In experiments designed for the determination of flow patterns and stress of granular materials on moving beds, it was indicated that: (*a*) granular materials flowing in the center part of a straight column flow down as if stuck together and break up only if the pressure exceeds their static load-carrying capacity, and (*b*) the boundary zone at the wall extends for from four to eight times the particle size and this is the region where abrasion of material occurs. It was further indicated that the height above the bottom where the uniform flow pattern begins to break down due to the orifice was very small when the material was choke-fed into a rotating table (311). A computer analysis of powder flow characteristics from shear test data was developed by Stainforth *et al.* (312), who suggested that this method will produce more reliable hopper design solutions and will determine the essential powder flow properties with the precision necessary for a general classification of flowability.

Table IX—Additional References on Powder Characteristics

Reference	Topic
319	Dynamic shape factors presented as a method of characterizing the shape of particles
320	Determination and application of antibiotic powder characteristics to pharmaceutical manufacturing processes
321	Effect of highly dispersed silicic acids on adhesion of various powders

The flow factor of crystalline and spray-dried lactose was determined by shear cell measurements (313) and compared to the packing properties, the angles of repose, and the flow rate properties into die cavities for the same lactose powders (314). Grading of the powders by these two methods was in good agreement. Considering published data and new evidence which he presented, Harwood (315) showed that both the flow factor and the shear index were in good agreement in predicting an increase in flow properties with an increase in bulk density. However, it was not suggested that the powder would be more free flowing when compacted than when in its normal state. The effect of moisture on the miscibility of powders was determined by measuring the distribution of substances in wheat starch–zinc oxide and talc–zinc oxide binary mixtures (316). In other studies, the relative absorptive capacity of zinc oxide and sulfur powder (previously adjusted to contain 0.2–4% water) was determined for water and a nonpolar liquid, dioxane (317). The absorptive capacity (Enslin number) was found to exhibit a very large drop in value for both solids at only 0.2% moisture content. A study of the influence of viscosity of liquids on the absorbability of a powder showed that the Washburn equation for the Enslin number was valid only within a definite viscosity range (318).

Other articles of interest concerning powder characteristics are listed in Table IX.

Compression—The instrumentation of a rotary tableting machine, including high speed movie photography in polarized light to record the fringes due to the radial stress in the die wall during compaction, was described and evaluated (322). Use of the total information thus obtained was shown to be applicable to establishing compression cycles on a rotary machine. An impact–rebound test method of estimating the hardness of a compact of powdered solid was evaluated by Hiestand *et al.* (323) and was shown to be applicable to the characterization of compacts of organic powders.

The hardness of tablets using microcrystalline cellulose as a diluent was found to be markedly increased by increases in the compression pressure, but the differences in the physical properties of the tablets were found to have very little influence on their disintegrat-

ability (324). A study of the effects of moisture on the compression of particulate material showed that water apparently exerted a boundary lubricant effect in addition to its hydrodynamic properties and, although it had a lower viscosity than light liquid paraffin, it was a more effective lubricant (325). The effect of particle size and the speed of compaction at a given pressure on the density changes in tablets of crystalline and spray-dried lactose was investigated (326). Changes in volume with load were found to be dependent on the particle size, the speed of compression, and whether the tablet volume was determined at pressure or after release of pressure.

The total energy used in compressing sodium chloride tablets was found to be 13.6 cal./tablet, of which 7.5 cal. was required for proper compression and 6.1 cal. for tablet ejection (327). A method for the determination and evaluation of force–displacement curves for the compression of pharmaceuticals, using a small digital computer, was described by DeBlaey and Polderman (328, 329). This method was used in a study of the effect of formulation, processing, and compression on the properties of sulfamethazine (sulfadimidine) tablets containing methylcellulose, potato starch, or gelatin as binders (330). Force–displacement curves were obtained for gross input, elastic deformation, net input, and radial hardness; in each case, tablets containing methylcellulose exhibited different behavior from those containing the other two binders. The disintegration and 50% dissolution times showed anomalies, in that slow disintegrations and dissolution occurred with low compression forces. Tablets formulated with gelatin or starch and compressed at 600 $MNm.^2$ were subjected to *in vivo* experiments using a urinary excretion procedure (331). Dissolution rate and urinary excretion data showed a difference in the availability of drug from the two tablets, both of which complied with the disintegration requirements of the BP.

Additional articles relative to compression are listed in Table X.

Table X—Additional References on Compression

Reference	Topic
332	Theoretical discussion of processes taking place during powder compression
333	Factors influencing the compressibility of substances, including tables of substances classified according to suitability for direct compaction
334	Factors in the manufacture of tablets necessary to assure constancy of physical properties, therapeutic efficacy of the tablets, and economy of the processes
335	Characterization of the compression properties of powders by determination of the work done in forming tablets
336	Influence of compression force of aspirin tablets on their dissolution rate
337	Work required for compressing medicinal tablets described by three independently derived formulas
338	Interpretation of dissolution rate maxima for compressed tablets
339	Preparation of stomachic tablets by a direct compression method
340	Direct compression of isoniazid tablets
341	Discussion of physical properties of compressed tablets in terms of particle-to-particle bonds

Effect of Excipients—The ratio of tablet diluent to drug was reported to have a decided effect on the dissolution behavior of a poorly water-soluble quinazolinone compound at pH 1.2 (342). The dissolution rate increase observed was found to be directly related to the dilution factor in the tablets tested. The changes in the physical properties of hydrochlorothiazide tablets, prepared with acacia, starch, and polyvinylpyrrolidone as granulating agents, after short-term storage at elevated temperatures correlated with the changes upon aging for 1 year at room temperature (343). Acacia was found to be an unsatisfactory granulating agent, because the values of hardness, disintegration, and dissolution times increased with aging. In further studies with hydrochlorothiazide tablets, the influence of polysorbate 80 in several dissolution media used in tablet disintegration and dissolution tests was found to be insignificant (344). The effectiveness of some fatty acids, alcohols, and hydrocarbons as lubricants was evaluated by determining the friction between the die wall and the tablet mass, the rise in temperature on the lateral and upper surfaces of the tablets during tableting, and the amount of ejection force needed to eject the tablets from the die (345–347). The various methods of evaluation all yielded essentially the same results: (*a*) the straight chain fatty acids were the most effective die lubricants and the corresponding alcohols were, in turn, more effective than the hydrocarbons; (*b*) the optimum number of carbon atoms for both fatty acids and alcohol was 18; (*c*) the effectiveness of lubricants increased with increasing melting points; and (*d*) the optimal length of the carbon chain was not found for hydrocarbons.

The effect of different disintegrating agents, lubricants, and surfactants on the dissolving rate and stability of aspirin in compressed tablets was reported by Cid and Jaminet (348–350). Glycolys D was found to be the best disintegrating agent, and the stability of the aspirin was inversely related to the moisture content of the disintegrating agent, being least stable in the presence of Primogel, which had the highest moisture content (348). Lubricants having a weak viscosity caused a greater depression in the rate of dissolution than those having an elevated viscosity (349). The presence of the surface-active agents polysorbate 80, sodium lauryl sulfate, and cetrimonium bromide (Cetavlon) improved the rate of dissolution of aspirin tablets, but this rate was diminished with storage time (350). Another study on the effect of some disintegrants on the properties of aspirin and other drugs showed that the results were influenced by the mode of granulation used, the nature of the disintegrating agent, and the solubility of the active agent (351). With insoluble disintegrating agents, the disintegrating time increased as the solubility of the active agent increased; but with soluble agents, the time increased as the solubility of the active agent decreased.

The effect of the type of starch and its concentration and distribution on the pore structure of tablets was investigated (352). The maximum disintegration of magnesium carbonate tablets was produced when 10% potato starch was incorporated internally and the tablet was compressed to a porosity of 28%. In studies of the mechanism of action of starch and other tablet

Table XI—Additional References on the Effect of Excipients

Reference	Topic
363	Comparative tests of binding substances in tablets containing norsulfazole and lactose
364	Reduction of disintegration times by addition of sodium lauryl sulfate to phenacetin and ethoxid tablets
365	Lubricating properties of polytetrafluoroethylene in compressed tablets
366	Effect of sodium salts of some drugs on the disintegration of starch-containing tablets
367	Influence of alginic acid on stability of pyridoxine hydrochloride tablets and their dissolution properties
368	Influence of ash wood flour and viscosity of binders on dissolution rate of sodium benzoate tablets
369	Utility of ethylcellulose in making tablets of ascophen, meprobamate, pyraminal, and sedaphen
370	Use of Aerosil in tablet formulations of some hydrophobic drugs
371	Influence of the nature and proportion of some adjuvants on physical properties of phenobarbital tablets
372	Physical properties of tablets prepared with formaldehyde–casein or microcrystalline cellulose
373	Discussion of preparation, properties, and application of metal stearates in pharmaceuticals and cosmetics
374	Effect of drug solubility and influence of various disintegrating agents on disintegration time of tablets
375	Dissolution of drugs of low water solubility from tablet matrixes as a function of formulation and manufacturing variables
376	Tablet formulation of methaqualone with improved release of the active ingredient
377	Effect of starch with various binding agents on release of drug from aminophenazone tablets
378	Effect of various lubricating agents on release of aminophenazone from tablets
379	Description of Celutab as a suitable excipient for drug tablets
380	Use of *Cordia myxa* mucilage as a binding agent to prevent capping of amidopyrine tablets
381	Discussion of types of excipients used in pharmacy
382	Study of hysteresis in water vapor sorption and desorption on guar gum
383	Improvement of certain properties of tablets by use of wood flour
384	Use of wood flour as an ancillary substance in direct compression of tablets
385	Study of lubricating efficiencies of powdered polyethylene glycol 6000 for various tablet granulations
386	Investigation of *in vivo* tablet disintegration times with use of $Na^{131}I$
387	Evaluation of drug availability from tablets and capsules by a disintegration test
388	Discussion of several defects in empirically based tests for tablets
389	Hygroscopicity of various preparations of erythromycin
390	Description of a process for manufacturing tablets containing phthalazole, quiniophen, vitamins, bromisoval, and antistrumin
391	Mechanism of action of disintegrating agents in compressed tablets
392	Combined effect of active and inert ingredients in tablets on their porosity, hardness, and disintegration time
393	Diluent, lubricant, and surfactant effects on the release of drug from hard gelatin capsules

disintegrants, neither the effect on mean pore diameter nor porosity was found to be the mechanism of action in the disintegration of tablets under the experimental conditions employed (353). Tests made to determine the effect of starch on the disintegration and dissolution of sodium salicylate tablets indicated that starch markedly delayed the release of the drug and the dissolution of the tablets; the effect was independent of the compression forces used in preparing tablets (354). Tablets of amobarbital (amylobarbitone) made with a vinylpyrrolidone–vinyl acetate copolymer were compared with tablets made with starch as a binder and were found to have better manufacturing properties and a higher dissolution rate which was independent of the compression pressure (355). Polycarboxylic acid ion-exchange resin adsorbates of methapyrilene, dextromethorphan, ephedrine, and pseudoephedrine were prepared and found to reduce the bitterness of the drugs in chewable tablets (356). The use of hydrocellulose prepared from absorbent cotton was found to be an effective disintegrant for tablets when mixed with 20–25% starch or alone at a concentration of 10–12% (357).

A thorough study was undertaken by Newton *et al.* (358) to establish the effect on drug release from capsules produced by adding lactose, magnesium stearate, and sodium lauryl sulfate (each at three levels of concentration) to a 76–105-μm. particle-size fraction of ethinamate filled into capsules at low and high packing density. The results indicated that the effect produced by each additive was dependent on the presence and level of the other two additives. The interaction limited the conclusions, but the indications were that: (*a*) 10% diluent decreased drug release, whereas 50% diluent increased the release; (*b*) the presence of 1% sodium lauryl sulfate was sufficient to enhance drug release; and (*c*) the additive effects were independent of the capsule packing density. The disintegration rate of gelatin capsules was found to be greatly increased by filling with electrolyte solutions (359). Comparative data were presented to show that relatively insoluble drugs from different chemical and pharmacological classes, when formulated in soft elastic capsules, were released faster than from commercially available tablets (360, 361). Faster dissolution from the soft elastic capsules was attributed to the more rapid dispersion of the active ingredients. Exposure of hard and soft gelatin capsules to radiation caused an increase in the disintegration times due to hardening of the gelatin (362).

Other references pertinent to the effect of additives on properties of tablets and capsules are listed in Table XI.

Tablet Coating—The water vapor transmission properties of free and applied polymer films, as well as a method of preparation of the free film, were thoroughly studied (394). The degree to which degradation of ascorbic acid was retarded by cellulose acetate phthalate films and the enteric-coating properties of the film were reported. An investigation of the effects of plasticizers on some physical properties of cellulose acetate phthalate films showed that the addition of plasticizers generally lowered the water vapor transmission rate, water permeation, and moisture absorption but had little effect on tablet disintegration time (395). Examination of some forces responsible for the adhesive process in the film coating of tablets indicated that the surface free energy values are measures of the operative cohesional forces in the tablet surfaces which are effectively interacting with the liquids (396). Such values were suggested as explaining and predicting the adhesion of film coatings to tablet surfaces better than the critical

surface tension values. In research on film coating hydrochlorothiazide tablets, formulations were developed incorporating ethylcellulose and shellac with polyvinylpyrrolidone (Plasdone) films to reduce the hygroscopicity and tackiness associated with film-coating tablets by the pan-coating method (397). The coatings were physically stable and increased the resistance of the tablets to chipping and attrition. The use of gluten, gliadin, and glutenin with an auxiliary substance such as dimethyl phthalate was found to produce suitable enteric coatings on tablets (398). A study conducted to determine the utility of a new polyacrylic acrylate resin as an enteric-coating material for compressed tablets indicated that the resin (Carboset 525) should be considered for this purpose (399).

Additional references on tablet coating are listed in Table XII.

Table XII—Additional References on Tablet Coating

Reference	Topic
400	Review of cellulose derivatives in the manufacture of tablets, emphasizing the use for enteric coatings
401	Microcrystalline cellulose as an adjuvant in the sugar coating of tablets to hasten drying and facilitate use of automatic equipment
402	Solubility of shellac films in artificial gastric and intestinal juices increased by addition of PVP, Span 20, or Tween 20 to the shellac
403	Development of method for coating tablets with hydroxypropyl methylcellulose in a fluidized bed

Suspensions—Recent advances in the rheology of pharmaceutical materials were comprehensively covered in a review by Barry (404). Considerations of powders, suspensions, suspending agents, and other pharmaceutical applications were discussed. The literature describing applications of the Coulter counter for sizing and counting particles in suspensions and emulsions was reviewed, with emphasis placed on the precautions necessary to achieve reproducible results (405). Other reviews (406, 407) considered the theoretical and technical aspects of suspension formulation and the rheology of pharmaceutical thixotropic and antithixotropic dispersions.

Aggregate formation, rheological properties, and suspension stability of chloramphenicol palmitate suspensions prepared by precipitation from solutions containing polysorbate 80 (Tween 80) were found to be dependent on the concentration of the wetting agent (408). At low concentrations of polysorbate 80 (Tween 80), suspensions with a high structural viscosity and a low sedimentation volume were produced due to the formation of coarse particles and large compact aggregates. The rheological properties of tragacanth-stabilized sulfamerazine suspensions were also found to be dependent on the concentration of polysorbate 80 (Tween 80) present (409). The adhesion of particles of a chloramphenicol aqueous suspension to the surfaces of a silicone-treated glass container was found to be inversely proportional to the contact angle of water (410). Thus, surfaces of containers for pharmaceutical suspensions should have a contact angle greater than 90° to inhibit the adhesion of suspension particles. Anionic surfactants and some high polymers were found to prevent this adhesion, while nonionic and cationic surfactants were found to promote it (411).

Rheological studies of sodium kaolinite dispersed with hexadecyltrimethylammonium bromide were conducted; values of yield stress, viscosity, and sedimentation volume obtained for pH values of 4.7, 5.5, and 8.5 were found to be a function of the amount of surfactant adsorbed (412). In a study of Palygorskite clay dispersed with cetylpyridinium chloride at various concentrations, the stabilities, electric polarizabilities, and ζ-potentials of the systems were evaluated; a correlation of the minimum colloid stability to the minimum electric polarizability at a rather high value of ζ-potential was observed (413). The use of low-angle laser light scattering to measure the state of agglomeration of dispersed systems was described (414). The relation of light-scattering patterns obtained in a practical operating procedure was explained in terms of light-scattering theory.

In a study of the sedimentation of powders having low and high surface energies, it was found that the sedimentation behavior of powders having low surface energy depended on the surface tension of the liquid, while the sedimentation behavior of powders having high surface energy depended on the polarity of the liquid (415). The influence of the boundary effect on the rheological parameters for soda suspensions was evaluated (416). The thickness of the boundary layer was found to decrease with an increase in the concentration of the dispersed phase. The use of reflected β-radiation for evaluating the stability of 4% suspensions of barium sulfate, titanium dioxide, and aluminum oxide in water and 0.5–1% aqueous methylcellulose (Tylose) solutions was described, and the results were reported as excellent (417).

Rheological studies on dispersions of guaran by Kassem and Mattha (418) indicated a pseudoplastic flow behavior with highest stability at pH 5–7. In further work on the effect of some additives on dispersions of guaran, the dependency of the relative viscosity of the dispersion on electrolyte concentration was demonstrated (419).

Other papers of interest on the subject of suspensions are listed in Table XIII.

Emulsions—Emulsion stabilization by nonionic surfactants, mainly derivatives of polyoxyethylene glycols, was reviewed in relation to relevant aspects of colloid stability theory (434, 435). In other reviews, the use and possible future development of some rheological techniques in pharmaceutical formulation (436) and various facets of current emulsion technology (437) were discussed in connection with emulsion stability. Rheological and electrophoretic techniques were used by Davis (438) to study the properties of emulsions containing mixtures of anionic surfactant and polyelectrolyte. The addition of potassium arabate to emulsions stabilized by potassium laurate caused increased aggregation through a macromolecular bridging mechanism. Oil–water emulsions aggregated by the hydrocolloid potassium arabate were found to be deaggregated by shear and added surfactant but were unaffected by simple electrolytes (439). Potassium laurate was more effective than hexadecyltrimethylammonium

Table XIII—Additional References on Suspensions

Reference	Topic
420	Effect of temperature of aging on the size of globules (about 17Å) in an aluminosilicate hydrated gel
421	Behavior of ζ-potential of particles as a function of the concentration of sodium oleate, oleic acid, and their mixtures dispersed in water
422	Influence of pH and various inorganic ions on ζ-potential of coagulated kaolin suspension in water
423	Properties of graphite and rutile powders dispersed in aqueous solutions of cationic and anionic surfactants
424	Rheological properties of aqueous suspensions of an abrasive powder using a special viscometer
425	Stable aqueous suspensions of sulfadimethoxine using polyvinyl alcohol and Tween 80
426	Study of the effect of 19 nonionic surfactants on stability of 10% triacetyloleandomycin suspensions
427	Preparation of stable suspensions of sulfadimezine and norsulfazole
428	Preparation, testing, and evaluation of some nonsystemic antacid suspensions
429	Preparation of Asaline and Asalei suspensions with Tween 80 and methylcellulose
430	Rheological properties of xanthan gum, a glucose-derived hydrocolloid
431	Rheological properties of various paraffin chain association colloids in aqueous solution
432	Sedimentation rates of fine powders in air as a function of air pressure and solids moisture content
433	Review of sedimentation retardants, emphasizing the use of different types of cellulose for aqueous, oily, and suppository systems

bromide or polysorbate 20 (Tween 20) in promoting the deaggregation, which was a very rapid process. To test the validity of the concept that aggregation occurred through hydrophobic interactions, the rheological properties of the emulsions stabilized by potassium laurate were measured at different temperatures and in the presence of urea (440). The elasticity of the systems increased with increasing temperature and decreased with added urea, results that are consistent with hydrophobic bonding.

The rheological properties of emulsions stabilized with a combination of ionic or nonionic surfactants (sodium lauryl sulfate and cetrimide) and a fatty alcohol (cetyl or stearyl alcohol) were reported by Barry (441) and interpreted on the basis that a viscoelastic network exists in the continuous phase linking the globules of the dispersed phase and that the nature of this network controls the flow properties of the system. In studying the self-bodying action of alkyltrimethylammonium bromides–cetostearyl alcohol mixed emulsifiers, the strength of the emulsion network in each quaternary series was found to be related to the influence of surfactant chain length on the formation of smectic structures (442). For equivalent concentrations of mixed emulsifiers, the consistencies of the ternary systems and emulsions increased as the quaternary chain length increased. The influence of temperature on the rheology of such mixed emulsifier systems as a function of quaternary chain length was also studied (443). The consistency of each emulsion prepared for the higher quaternary surfactants increased to a maximum as the temperature rose. Maximum consistency was observed at temperatures close to the transition temperature, at which each network melted from the frozen smectic to the liquid crystalline stage.

Distribution characteristics of the dispersed phase of emulsions were estimated from theoretical considerations (444). Comparison of experimental data and calculated data characterizing the fractional composition of sodium stearate, potassium oleate, and ammonium palmitate emulsions in benzene or olive oil showed that the differences of obtained results did not exceed 3–5%. The dielectric properties of water-in-oil emulsions were found to be dependent on the nature of the emulsifier (445). Emulsions stabilized with nonionic emulsifiers showed anomalous dielectric behavior, while the use of magnesium stearate as an emulsifier exhibited a dielectric behavior which can be closely predicted by classical equations for interfacial polarization. Emulsifiers with the same phase inversion temperatures were used to study the effect of the size and distribution of hydrophilic chain lengths of polyoxyethylene nonyl phenyl ether or polyoxyethylene lauryl ethers on the stability of oil-in-water or water-in-oil emulsions (446). Stability against coalescence increased remarkably with the size of the lipophilic and hydrophilic groups and showed maximum stability when the distribution of the hydrophilic groups was fairly broad. The structure of water in microemulsions was studied by electrical, birefringence, and NMR techniques and was found to be in agreement with the proposed mechanism of change in the structure of water from water spheres to water cylinders to water lamellae (447). On the basis of physicochemical studies of emulsions prepared with various types of surfactants, it was reported that low interfacial tension and specific gravity and high viscosity, electrical conductance, and particle size favor emulsification and increase the stability of emulsions (448). An investigation of the processes of settling of suspensions and the phase separation of emulsions, which seem to be similar, indicated that the character of the settling processes was indeed quite different (449).

A test of aluminum hydroxide prepared by different methods as a stabilizer for oil-in-water emulsions indicated that the degree of hydration of the aluminum hydroxide precipitate determined its stabilizing power (450). The stability of emulsions made with pectin, gelatin, agar, gum acacia, and gum tragacanth was examined and correlated to changes in viscosity of the external phase and the hydration process of the hydrophilic colloids (451). The primary cause of stability was not the viscosity of the external phase containing the emulsifier. In a study of the effect of different types of meat protein on the stability of oil-in-water emulsions, a highly significant correlation was found between protein surface activity and emulsion stability (452). In further studies, it was found that increasing the protein concentration or oil phase volume increased the stability and viscosity of the emulsions, and that soy sodium proteinate gave greater stability than gelatin or sodium caseinate (453).

Additional papers on the subject of emulsions are listed in Table XIV.

Ointments and Creams—The formulation and rheology of some oil-in-water creams and an evaluation of the rheological properties of semisolids were reviewed by Barry (469, 470). Some semisolid lipophilic preparations using white soft paraffin were examined by con-

tinuous shear and creep viscometry (471, 472). The creep curves were analyzed to estimate such parameters as storage and loss compliances, and the elastic properties of the white soft paraffins were shown to influence the properties of the ointments made with them. The utility of this type of rheological examination of the ground state of semisolids was discussed in terms of correlation with sensory data for texture profile evaluation. Characterization of the viscoelastic properties of semisolid ointments and creams using nondestructive oscillatory testing was reported by Davis (473). Presentation of the data as a "consistency spectrum" was recommended for pharmaceutical systems which could be applied directly to follow rheological changes in formulation, quality control, storage stability, radiation sterilization, and the action of mucolytic agents. The use of destructive oscillatory testing to simulate the conditions of dermatological usage of semisolid ointments and creams was also described (474). The first-order rate constant for the breakdown of viscoelastic structure under oscillatory shear was shown to be an important parameter in assessing consumer utilization of topical products. Modification of an apparatus and a method for its use in measuring the plasticity of ointment bases in terms of the surface covered by a standard volume of sample under influence of a specific force in a specific time were described (475). Statistical analysis of the results obtained from studies of various ointment bases showed the method to be sensitive enough to detect slight differences caused by only slight modifications in the composition.

The effect of altering the relative amounts of ingredients present in a standard ointment base on the rheological properties was studied; as a result, a composition with improved properties was obtained (476, 477). The rheological properties of ointment-based gels containing microcrystalline paraffin were found to depend on the concentration of the gel-forming solid phase and the nature of the liquid phase (478, 479). Evaluation of antibiotic ointments by three methods based on a gel diffusion test was discussed, with special emphasis on calculating values for the rate of antibiotic release from the ointment (480). An investigation of the immobilization of the liquid phase in a starch–glyceryl–water hydrogel demonstrated the effect of the concentration and type of starch and the concentration of the plasticizer (glyceryl) on the binding capacity for water (481). It was also reported that relatively low temperature (75°) and long periods of heating or high temperatures and short periods of heating produced better gels than those prepared under more moderate conditions. Studies on flow crystallization from a melt showed that cetyl alcohol in liquid petrolatum forms a crystalline gel reticulum, but stirring the melt for 12 hr. with a high shearing velocity while cooling produces a liquid with ideal viscous flow behavior. Theoretical considerations of this mechanically disturbed system were described by Fuehrer (482). The release of tetracycline from petrolatum was found to be independent of the hydrophilic–lipophilic balance value as well as the rheological indexes of the bases and to be influenced by the presence of surfactants (483). However, the surfactants showed no effect on the stability of tetracycline in the anhydrous ointments. The use of an electron microscope in assessing the dispersion of ointment bases was described (484).

Table XIV—Additional References on Emulsions

Reference	Topic
454	Photomicroscopic method for evaluating particle size of liquid–liquid dispersions
455	Effect of indifferent electrolytes on creaming of oil–water emulsions stabilized by long-chain quaternary surfactants
456	Rheological properties of concentrated emulsions based on 5% aqueous methylcellulose and hydroxypropylcellulose
457	Effectiveness of ethylpoly(oxyethylene) esters of fatty acids as emulsifying agents
458	Stability of oil–water emulsions as a function of hydrophilic–lipophilic balance value
459	Direct photomicroscopic observation of emulsion droplets under shear
460	Emulsifier effectiveness of 22 systems found more dependent on concentration than on chemical nature of emulsifier
461	Method for production of peppermint water
462	Research methods used in the selection of an emulsifier for an emulsion system
463	Electron microphotographic study of gradual development of gel structures in oil-in-water emulsion systems
464	Application of hydrophilic–lipophilic balance system to preparation of emulsions
465	Influence of inorganic salt content on emulsifying properties of sodium lauryl sulfate
466	Effect of prolonged ultrasonic irradiation on emulsion systems stabilized with various surfactants
467	Comparative efficiency of some Indian gums as emulsion stabilizers
468	Influence of phase-volume relationship of two immiscible liquids on stability of emulsions stabilized by hydrophilic colloids

The advantages and limitations of improving the activity of high potency topical preparations, in which the drug is in unusually low concentration, by dissolution of the drug in a keratin-penetrating organic solvent and dispersion in the internal phase of an emulsion with a paraffin ointment base were discussed by Senior (485), with a view that this method, demonstrated in the corticosteroid field, may be of value with other topical agents. A study of the interaction of corticosteroid in antimicrobial agents used in topical therapy showed that the activity of fusidic acid and hamycin against some representative bacteria and yeast was markedly inhibited by hydrocortisone (486). The diffusion of atropine from four ointment bases containing water, alcohol, and dimethyl sulfoxide at 1, 2, and 5% concentrations was determined to be a zero-order process after 20 min. (487). The results indicated that, in some instances, the diffusion was affected by the concentration of the liquid additive and the type of ointment base and that the rate constants appeared to correlate with the viscosities of each mixture. In a study on the effect of surfactants on the liberation of drug activity from ointment bases, it was found that the addition of hydrophilic surfactants increased the release of water-soluble citric acid from petrolatum ointment bases and decreased the release of lipid-soluble salicylic acid, while hydrophobic surfactants produced the opposite effects (488). The transfer of citric and salicylic acids through a semipermeable membrane from lipid anhydrous ointment bases was found to depend on the kind of base

Table XV—Additional References on Ointments and Creams

Reference	Topic
493	Determination of factors affecting dispersion of coal tar and its color in ointments
494	Suitability of eye ointments containing drugs comminuted in a vibratory apparatus
495	Rheological studies of suspension-type ointments
496	Hydrogenated castor oil as an ointment base
497	Comprehensive review classifying ointment bases and discussing their role in therapeutic evaluation of ointments
498	Rheological studies of a 10% Ichthyol ointment containing 3% methylcellulose
499	Rheological studies of pharmacopoeia (USSR) ointment bases
500	Rheological studies of 33% sulfur ointment
501	Solution index of vaseline–emulsifier excipients giving physically stable dispersions
502	Resorption properties of some ointment bases containing $Na^{131}I$
503	Autosterilization of contaminated samples of ointments, observed occasionally, found dependent on the type of drug and the ointment vehicle
504	Suitability of products from soapstock as an ointment base
505	Experimental study of pH in ointments described in the Spanish Pharmacopeia IX
506	Polyethylene gel found suitable for use in ophthalmic ointments containing pilocarpine hydrochloride
507	Rheological study of oleaginous ointment bases consisting of bone fat, castor oil, and beeswax
508	Formulations of hydrophobic and lipophobic protective ointments
509	Antiseptic ointment formulation based on tetradonium, a quaternary ammonium compound

and on the kind and concentration of acid (489). The highest transfer rate for citric acid occurred from 15–25% palm-kernel oil ointments, and the highest rate for salicylic acid occurred from 1% ointment using white petrolatum or palm-kernel oil. The highest release of ascorbic acid from the various ointments was shown by *in vitro* and *in vivo* studies to occur when polyoxyethylene was used as a vehicle, but the vitamin was found to be unstable in all vehicles tested (490, 491). Sucrose esters as emulsifying agents in ointment bases were found to be generally useful; but certain substances, particularly acids, were found to be unstable in the presence of the monoesters of sucrose (492).

Other papers pertinent to the subject of ointments and creams are listed in Table XV.

Suppositories—The drug release characteristics of sodium phenobarbital (sodium phenobarbitone) from various rectal suppository bases was evaluated by monitoring the release of sodium ions through a dialysis membrane using a sodium-specific ion electrode (510). The effect of lanolin alcohols and glyceryl monostearate on the release of aminopyrine (aminophenazone), methampyrone (noramidopyrine methanesulfonate), and carbostyril from cocoa butter suppositories was investigated (511). The increased drug release produced by emulsifiers was attributed to the decrease in surface tension. The lipophilic sorbitans (Spans) [alone or in combination with the hydrophilic polysorbates (Tweens)] were found to decrease the disintegration time and, hence, increase the release of aminopyrine (aminophenazone) from suppositories (512). The efficacy of spasmolytic and analgesic pediatric suppositories using fatty bases, as determined by *in vitro* and *in vivo* studies, was also reported (513).

The storage stability of suppositories based on polyethylene oxide was found to be independent of molecular weight, but the breaking strength of the suppositories increased with the molecular weight (514). Some suitable suppository formulations based on polyethylene oxides of different degrees of polymerization were reported. A method for the coloration of suppositories by the means of lakes was described by Schrenzel and Hess (515). Milling of the organic pigments in a sand-grinder was compared with other milling and dispersion methods. The effect of excipients on the properties of some oleaginous suppository bases was noted (516, 517) and the properties of a number of glyceride excipients were also reviewed (518).

Aerosols—Some of the interesting developments in containers and dispensing systems for aerosol products during the past few years were described by Dorland (519). Other reviews of various technological aspects of preparing aerosol products included such subjects as aerosol propellant properties and their effect in products (520, 521), safety of aerosol propellants (522), physicochemical aspects of aerosol systems and their influence on product stability (523, 524), and recipes for aerosol formulations (525–527). The types of aerosol personal products which have been introduced were discussed, and hardware requirements necessary to develop new aerosol products were considered (528). The development of aerosol antiperspirant products, including many of the problems that were overcome, and the current basic formulation designs were reviewed by Rubino (529). The characteristics and mode of operation of deodorant and antiperspirant spray preparations and their effectiveness were also described (530). In a more specific case, the effect of moisture content, polarity, and particle size on the physical behavior of aluminum chlorhydroxide suspensions for aerosol antiperspirant formulations was discussed in relation to current theory (531). Various properties of silicones were described, and the beneficial effect of their incorporation in aerosol cosmetics was emphasized (532).

The transformation of a simple aerosol face cream into a modern fruit cream involved a consideration of the various aspects of cosmetic aerosol manufacture and perfuming problems (533). Several requirements of a perfume designed for use in aerosols were discussed (534), and some reasons for investigating the stability of perfumed compounds in aerosol systems were outlined (535). Aerosol formulations containing a stable, spray-dried, encapsulated fragrance were described and shown to release fragrance upon exposure to moisture under both *in vivo* and *in vitro* conditions (536). It was shown that the release rate could be varied according to the liquid vehicle, the individual test subject, and the stimuli to which he was exposed. GLC was used to follow the stability of synthetic perfume compositions in the presence of ethanol and chlorofluorinated alkanes (537). Under conditions of the study, hydroxycitronellal, nonanal, and undecanal were transformed into diethyl acetals, but the 4-methoxybenzaldehyde and α-amylcinnamaldehyde remained unchanged. Stabilizing agents such as nitroparaffins, olefins, or thiols had no effect upon acetal formation, but 0.01% morpholine or *o*-

tolylbiguanide and 0.1% diphenylamine acted as inhibitors. In another study, addition of nitromethane-stabilized trichloromonofluoromethane to dichlorodifluoromethane was found to improve perfume stability greatly in aerosol systems and reduce corrosion ratings, but it was not effective for aldehydes and acetals (538).

Aerosol formulations of five antinauseant dosage forms for oral inhalation were developed and their performance was evaluated (539). The results indicated that this type of an oral inhalation product was entirely possible and feasible. Centrifugation was used to determine the number of equilibrium phases present in a system of water, mixed emulsifiers, and liquid propellant (540). Three different liquid phases and one liquid crystalline phase were observed. A new portable device for the administration of powdered drugs by inhalation was described (541). A study of its performance indicated a good degree of correlation of dose administration with inhalation into the inspired stream of air.

Timed Release—One layer of a timed-release tablet containing proxyphylline and nitroglycerin was designed to contain a rapidly dissolving initial phase; the other layer, the depot phase, contained the proxyphylline incorporated into the pores of an indigestible plastic skeleton of the matrix in which nitroglycerin was dissolved. *In vitro* and *in vivo* experiments showed that even though the loss of depot action for both drugs upon chewing of the tablet did occur, the nitroglycerin release was slow enough that no toxic side effects occurred (542). The bead polymerization technique for the preparation of timed-release dosage forms for oral administration was tested (543). Agglomeration of the polymer beads during manufacture was prevented by the addition of protective colloids or water and monomer insoluble inorganic powders. The technology for producing injection molded disks of epoxy resins soluble in gastric fluid and a crotonic acid–vinyl acetate copolymer soluble in intestinal fluids was described, and the dissolution rate characteristics of the matrixes were found suitable for timed-release dosage forms (544). These disks did not keep a constant geometrical form during dissolution, so the determined dissolution rate deviated from the expected cube-root law. Encapsulation of lucanthone resinate by the coacervation technique produced a more timed-release product and made possible its compression into tablets (545). Lucanthone was released at a first-order rate from both its encapsulated and unencapsulated resinates, but the calculated half-life was much higher for the encapsulated type. *In vitro* dissolution studies of gelatin coacervate microcapsules of sulfadiazine showed that first-order release characteristics were exhibited by all of the hardened materials (546). The dissolution of sulfadiazine itself was indicated to be the controlling step, rather than the rate of diffusion through the microcapsule wall. The *in vitro* diffusion rate of powdered progesterone-filled silastic implants in the uterus of of rabbits indicated that this type of capsule did not lend itself as a preparation for a sustained hormonal release (547). However, in another investigation, several steroids enclosed in a polydimethylsiloxane membrane exhibited *in vitro* release which followed Fick's law; but when implanted in experimental animals, absorption was increased by increasing the surface area regardless of membrane thickness (548). Several steroid hormones released from implants were considerably more effective than when given in a one-a-day subcutaneous or oral dosage form.

The *in vitro* dissolution behavior of some spray-congealed formulations of sulfamethizole prepared in a lipid–lipase matrix and compressed into tablets was studied in simulated fluids (549). The main portion of the drug was released through the hydrolysis of the substrate by lipase, and the amount of drug released after 1.5 hr. was dependent on the lipase activity. Four methods of preparing timed-release granulations were evaluated; a congealing method in which equal parts of sulfanilamide and melted retardant were mixed to give a uniform suspension, allowed to solidify, and then comminuted, was found to exhibit more retardation of drug release in both alkaline and acid media than any of the other methods (550). It was also found that increasing the particle size from 500 to 1000 μ significantly reduced the release rate due to a reduced total surface area of the larger particles (551). Studies of the variation in the type of dissolution retardant on the release pattern of sulfanilamide were also reported (552). Granulations made with spermaceti or cetyl alcohol using techniques of granulation, congealing, and congealing in chloroform gave more rapid drug release in acid and alkaline pancreatin media than granulations made with hydrogenated castor oil or glyceryl tristearate.

The release characteristics of caramiphen hydrochloride and atropine sulfate from compressed tablets containing carboxypolymethylene (Carbopol 934) were determined by dissolution tests made in both simulated gastric and intestinal fluids (553). Evaluation of the data indicated that carboxypolymethylene (Carbopol 934) may be a useful agent in the preparation of timed-release drug forms. The release of sulfanilamide from long-acting tablets prepared by pressure molding (at three different pressures) of an admixture of lauric or palmitic acid or glyceryl monostearate was monitored potentiometrically in simulated gastric fluid for 10 hr. (554). The release of sulfanilamide with time was found to be linear, but the data for the three pressures studied were not significantly different. Apparently, even the lowest tableting pressure was sufficient to melt and fuse the components. The timed-release properties of tablets containing stearic acid appeared to increase with the increasing concentration of the hydrophobic material (555). In further studies by the same authors, the effect of stearic acid and its glycerol esters on the release of drugs from prolonged-acting tablets was reported (556). The release rates of the retardants decreased in the following order: glyceryl monostearate > stearic acid > glyceryl distearate > glyceryl tristearate.

Other references pertaining to timed release are listed in Table XVI.

Cosmetics—The problem of microbiological contamination of many cosmetic products is a subject of increasing concern to the cosmetic industry. To make the literature references relevant to this critical problem more available, the subject of cosmetics has been divided

Table XVI—Additional References on Timed Release

Reference	Topic
557	Description of a laboratory apparatus for production of timed-release granules by dispersion of a melted, active component into an immiscible liquid
558	Comprehensive review of methods of prolonging the duration of action of drugs
559	Investigation of pesticide–polymer combinations as a means of controlled release of a biodegradable pesticide over an appropriate time period
560	Retardation of *in vitro* dissolution rates of ephedrine hydrochloride and phenformin hydrochloride from tablets compressed with polyvinyl chloride
561	Review of timed-release principle based on an inert plastic matrix
562	Reduced xanthinol nicotinate release by the preparation of tablets with sucrose monopalmitate and magnesium stearate as fillers and shellac as a binder

into the following subclassifications: microbiological contamination of cosmetics and aspects of formulation and technology of cosmetics.

Microbiological Contamination of Cosmetics—A review of the problems of microbiological contamination of topical products by Bruch (563) pointed out the potential danger of causing serious infections and discussed the efforts of the drug regulatory agencies and compendia to control the problem. In discussing the needs for microbiological testing of cosmetics, the types of testing required to assure the microbiological quality of the products were also presented (564). Various means of identifying, controlling, or eliminating microorganisms which threaten cosmetic emulsions were described and included such areas as raw materials, equipment, environment and personnel, packaging and preservative systems (565). A method designed to simplify routine testing for microorganisms in cosmetics was divided into two phases: Phase 1 concerned only the enumeration of organisms present, and Phase 2 involved the determination of the Gram characteristics and identification of the contaminating organisms (566). An investigation of the possible assimilation by various microorganisms of ingredients commonly used in the formation of cosmetic products demonstrated that mineral oil, oleyl alcohol, stearyl alcohol, propylene glycol, isopropyl myristate, 2-hexyldecyl myristate, oleic acid, and stearic acid were utilized as the sole sources of carbon by most of the test organisms. The following materials were not utilized by the organisms: solid paraffin, multiwax, camellian, squalane, silicones, hexadecyl alcohol, polyethylene glycol, and di(2-hexyldecyl) adipate (567).

Boehm and Maddox (568) reviewed the activity of preservatives in a number of typical cosmetic products, with emphasis on the effectiveness of a liquid preservative mixture based on the esters of *p*-hydroxybenzoic acid in protecting cosmetics against a wide range of microorganisms. In addition to the usual capacity test for preservatives, they recommended a modified test claimed to represent the repeated contamination of cosmetics in actual use. Daily applications of a mixture of labeled hexachlorophene and triclocarban in a soap vehicle showed that the amount remaining on the skin after rinsing accumulated and appeared to approach an equilibrium after the fourth application (569). These data were offered as a possible explanation of the observation that the effect of antibacterial soap on the microflora of the skin is related to the number of exposures. The physicochemical, antimicrobial, and toxicologic properties were reported for a new bacteriostat, 2,4,4′-trichloro-2′-hydroxydiphenyl ether, used in skin-care products (570, 571). Phenylethanol was found to enhance the effect of benzalkonium chloride on growing cultures of *Pseudomonas aeruginosa*, and a similar effect was shown for chlorobutanol, chlorhexidine diacetate, chlorocresol, thimerosal (Merthiolate), methyl- and propylparabens mixture, and phenylmercuric nitrate (572). A series, updating information on preservatives previously reviewed, was completed by Gucklhorn (573, 574).

Table XVII—Additional References on Microbiological Contamination of Cosmetics

Reference	Topic
575	Suggested limit on microbial content for cosmetics and measures necessary for compliance
576	Measures necessary to ensure marketing of sterile ophthalmic solutions
577	Studies of γ-radiation sterilization of contaminated organic pigments in eye cosmetics and face powders
578	Significance of pseudomonads in cosmetics
579	Extensive new efforts and developments required for microbial control in the cosmetic industry
580	Review of microbiology of cosmetics
581	Review of preservatives used in cosmetics and discussion of contamination sources
582	Factors to be considered in formulating an ointment with a preservative

Additional articles in the area of microbiological contamination of cosmetics are listed in Table XVII.

Aspects of Formulation and Technology of Cosmetics—In a series of articles, Gucklhorn (583–586) discussed various aspects of cosmetic formulation and manufacture such as filling trials, pilot plant scale-up factors, bulk handling problems, and principles of emulsion production, with the goal of describing some common errors and wasteful techniques that can be avoided. By use of a proposed skin-feel index, it was found impossible to quantitate the skin feel of cosmetics (587). Correlation of this index with the effects of molecular weight, oiliness, polarity, unsaturation, and chain branching was studied for 85 cosmetic emollients, and some definite trends were observed. However, in a separate study, no correlation was found between the spreading of various oils on water (as represented by the spreading coefficients) and the spreading on human skin (588). It was also not possible to draw any conclusions from the spreading values as to the emulsion behavior of the oils. A study of myristyl stearate and isopropyl isostearate for cosmetology purposes showed a behavior similar to the dermal pharmacology of the well-known isopropyl myristate and isopropyl palmitate (589). A review of ethoxylated fatty acid amines in ethylenimine polymers used as emulsifying agents in skin-softening preparations included a discussion of their physical and chemical properties (590). The phase inversion temperature system, a guide to surfactant selection, was applied to polyoxyethylene alkyl ethers, and the effect of distribution of ethylene oxide chain

lengths and surfactant concentration on the phase inversion temperature was described (591). A relationship was also given which can be used in estimating phase inversion temperature for the practical production of an emulsion.

One factor affecting the water absorption properties of lanolin was shown to be the presence of soap or detergent, and a method for determining low concentrations (>0.04%) of five nonionic detergents of the ethoxylated alkyl phenol or ethoxylated linear alcohol type in lanolin or centrifuged wool grease was described (592). The bulk removal of these detergents from lanolin and wool grease by extraction with 45% isopropanol was demonstrated. The factors affecting the rates and extent of penetration of agents into the skin were reviewed and found to be dependent primarily on the physical-chemical properties of the penetrant and secondarily on such factors as pH, concentration, particle size, and vehicles (593). The penetrant was also influenced by physiological variables such as the intact or injured condition of the skin, the skin age, the area of the skin involved, and the blood flow to that area. Some aspects of the role of skin appendages in percutaneous absorption were the subject of a review, which indicated that skin appendages formed the major absorption pathway for brief but variable periods immediately after percutaneous application of the test substance (594). After this, the absorption occurred mainly through the stratum corneum. Active transport did not appear to be involved in absorption *via* the appendages. Examination of the terms used to depict emulsion behavior indicated that use of some of the terms was unwarranted, and an attempt was made to describe substitute terms which would better represent the stability behavior of an emulsion (595). Increasing thermal disorder with the rise of temperature was described as the basic characteristic of the solid state of all fatty chain substances (596). This property is responsible for their polymorphism and is closely related to the interaction with water of all those lipids containing free polar groups.

The unique properties of colloidal polymer microcrystals as suspensoids in water, water-miscible organic solvents, and oleaginous media were reviewed by Battista (597). Unhinged polymer microcrystal dispersions made from the following polymer precursors were described: celluloses, amyloses, chrysotile mineral silicates, collagens, polyamides, polyesters, and polypropylenes. The effects of the presence of polymers and micellar surfactants on the rates of photochemical reaction involving many coloring agents and drugs were discussed, and examples were presented to illustrate the involvement in photoreduction, photooxidation, coupled oxidation–reduction, photodimerization, and triplet–triplet energy transfer reactions (598). A comprehensive review of surface-active sugar esters, a class of substances suitable for cosmetics, by Gerhardt and Liebscher (599–602) included synthesis and purification methods, physicochemical characteristics, cosmetic and pharmaceutical uses, and biological decomposition.

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

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

Reference	Topic
603	Review of fatty bases for cosmetic creams
604	Review of physical chemistry of emulsion stability and suggestions for simple quality control tests
605	Properties of silicones and their uses in cosmetics and pharmaceuticals
606	Potential uses for anabolic steroids in cosmetics
607	Review of properties and uses of white mineral oils for cosmetics
608	Mechanisms of gas bubble formation in cosmetics and suggestions of some possible remedies
609	Discussion of certified color additives for cosmetics
610	Review of action on the epidermis, active agents used, and manufacture of pharmaceutical and medicinal soap
611	*In vivo* study of interaction of ionic surfactants with human epidermis using a bioelectrometric technique
612	Hexachlorophene-induced changes in electrical response specificity of human epidermis for sodium and potassium ions
613	Review of properties and uses of ampholytic surfactants
614	Use of some natural and synthetic phosphoric acid esters as emulsifiers in dermatocosmetic preparations
615	Discussion of properties and possible applications of licorice root derivatives in cosmetic products
616	Review of composition and mode of action of hair lotions
617	Description of physical properties and attributes of 585 Cosmetic Liquid for use in cosmetic formulations
618	Use of polyethylene glycols, fatty acid esters, isopropyl alcohol, ethanol, phytoestrogens, *p*-hydroxybenzoates, and algins in cosmetic applications
619	Use of eosinic acids in cosmetic industry
620	Description of hexadecyl alcohol as an emollient in clear hydroalcoholic products
621	New allantoin derivatives for cosmetic and dermatological use
622	Discussion of pharmacological and cosmetic properties of hydrogenated lanolin
623	Ampholytic surfactants with a betaine structure and their use in deodorant products
624	Utility of Veegum in eye makeup formulations
625	Discussion of guar gum, its properties and applications
626	Discussion of reasons for change from natural to synthetic polymers in some cosmetic products
627	Review of carnauba wax and its amended specifications in the German Pharmacopeia
628	Use of Irgasan DP 300 in personal deodorant aerosol products

Packaging Guidelines for single-unit packages of drugs were presented to encourage manufacturers and packagers to develop new packaging ideas and techniques (629). An investigation of the design and testing of safety packaging for the prevention of accidental poisoning in children was described (630). By considering the requirements for more testing and the problems involved, a need for more action was pointed out. The field of plastics in packaging during the past decade was reviewed by Briston (631). The quality control of high density polyethylene bottles for pharmaceutical products, together with governmental and nongovernmental packaging requirements and proposals, was reviewed and discussed (632). After extended storage conditions of varying temperature and container size, the loss of chlorobutanol from polyethylene bottles was found to be slight in refrigerated solutions, moderate in solutions stored at room temperatures, and excessive in solutions stored at elevated temperature

Table XIX—Additional References on Packaging

Reference	Topic
645	Accelerated testing for drug permeability in polyethylene, polypropylene, and polystyrene containers
646	Light transmission of colored glass containers
647	Review of permeability of plastic packaging materials to gas, water vapor, radiation, and bacterial penetration and sorption phenomena
648	Study group report on hydrolytic resistance of pharmaceutical glass containers
649	Description of use of films and laminates in packaging pharmaceuticals and cosmetics
650	Prediction of loss of drug weight in plastic container by use of permeability coefficients
651	Discussion of absorptive drying of air in packages with solid drying agents
652	Review of corrosion in drug industry, including attack of plastic containers by pharmaceuticals
653	Review of permeability of plastics used in packaging and microencapsulation of pharmaceuticals
654	Problems associated with the various methods of printing and decorating packaging materials
655	Effect of water permeability of container on tablet stability

(633). In addition, it was found that the smaller the container, the greater the loss of chlorobutanol. Polyvinyl chloride was found to be a suitable plastic container for packaging syrups, liniments, and nasal solutions when examined in terms of its properties of permeability and chemical resistance (634). Irradiation sterilization of water for injection in polyethylene ampuls was reported to differ in hydrogen peroxide, dissolved oxygen, oxidizable matter content, and pH from water sterilized in glass ampuls (635). However, no differences in the biological effects of the solution were found.

Differences in the potassium and sodium extracted from vials of injectable solutions [10% glucose, 5% meperidine (Pethidine), 20% theophylline, and water for injection], when heated in an autoclave at 121° for 20 min., were detected by flame photometry (636). There appeared to be a correlation between the mean values of potassium and sodium extracted and the size of the various glass containers. Other studies showed that 10-fold sterilization in an autoclave at 120° for 30 min. had no harmful effects on the glass quality of the infusion bottles (637); but a comparison of the effects of two infusion solutions, 0.9% saline and 5% glucose, on the surface resistance of the glass during sterilization showed a considerably greater manifestation of surface attack on the glass in the presence of saline (638). Procedures for washing parenteral glass containers, which included a rinsing step of either a hydrofluoric acid solution or ammonium bifluoride solution in the washing cycle, were reported by Hinson (639) to increase the effectiveness for removing particulate matter and enhance the chemical resistance of the glass.

Several authors discussed the following subjects related to packaging aerosols: evaluation of polypropylene aerosol bottles containing fluorocarbons and ethanol (640), evaluation of the corrosion of aluminum aerosol containers packed with ethyl alcohol–chlorofluorocarbon systems (641), accelerated aerosol stability tests (642), special fitments for pharmaceutical aerosols (643), and various causes of aerosol valve failure (644).

Other articles related to packaging are listed in Table XIX.

Equipment—Progress in pharmaceutical engineering was comprehensively reviewed by Fowler (656). The topics discussed included size reduction, solid–solid separation, particle characteristics, solids handling, solids mixing, powder compression, and freeze drying. A series of articles designed to provide a broad view of various processing techniques and of the equipment available, together with typical examples of their use in manufacturing pharmaceuticals and cosmetics, was presented by McDonald (657–665). He discussed the following unit operations: mixing and blending (657), micronization (658), separation and filtration (659), molecular distillation (660), metering pumps (661), controlled powder feeding (662), grinding (663), membrane filtration (664), and dust control (665). A system for automatic monitoring and control of an entire tablet-coating procedure was thoroughly described (666).

Instrumentation was described which provides a quantitative measure of granule-crushing strength for use in studies of granule strength as a formulation factor (667). A detailed evaluation of an instrumented pilot plant lyophilizer was found to be almost essential in the development of optimum lyophilization cycles for production equipment (668). The effects of process variables such as binder solution addition rate, air pressure to the binary nozzle, inlet air temperature during the granulation cycle, and binary nozzle position with respect to the fluidized solids in a fluidized-bed granulation technique were investigated (669). It was found that an increase in the rate of addition of the aqueous binder solution to the fluidized bed of powders enhanced the ability of the solution to wet and penetrate the solids and resulted in a larger average granule size, a less friable granulation, a more fluid granulation, and a decreased granulation bulkiness. The effect of the other process variables was also described. An apparatus suitable for the size analysis of certain pressurized sprays by air sedimentation was described, and the effect of formulation variables on the sizing of some powder and liquid sprays was reported (670).

Other references related to equipment are listed in Table XX.

PHYSICAL PHARMACY

Seven different solid phases of fluprednisolone were characterized by IR spectra, X-ray diffraction, melting points, densities, heats of fusion, and heats of solution measurements (678). The existence of two low temperature forms of sulfathiazole was confirmed by the X-ray diffraction patterns and IR spectra. Since both these crystal forms are present in many commercial samples, the author expressed doubts regarding the previously published solubility studies on the drug (679). Polymorphic forms of sodium ampicillin prepared upon recrystallization from various solvent mixtures were identified, and it was shown that the most stable crystal form was obtained from a dioxane–water crystal-

Table XX—Additional References on Equipment

Reference	Topic
671	Evaluation of jet grinders to control particle size in a fluidized-bed denitrator
672	Evaluation of mixing effect of a fluid-bed spray granulator
673	*In vitro* dissolution rate apparatus designed to mimic human digestion and absorption
674	Description of a fluidized-bed apparatus and its evaluation
675	Description of a vortical drier using vitamin preparations
676	Detailed technical description of pneumatic and mechanical methods of transporting solids
677	Methods and machinery for crushing, grinding, or comminution of pharmaceutical materials

lizing solvent (680). The solubility and transition temperatures of two crystal forms of adiphenine hydrochloride were reported (681). A differential scanning calorimetry study dealt with the phase transition temperature and enthalpy of fusion determinations of various alkali metal stearate samples with different thermal histories. Rubidium and cesium stearates were shown to be less sensitive to thermal history than the sodium and potassium salts (682). The use of the term polymorphism to describe solid forms of aspirin which differ in their melting points, heats of fusion, densities, and dissolution rates was questioned (683). Further clarification on this subject suggested that the observed differences in these physical properties of aspirin may be due to polymorphism, crystal habit, or crystal defects (684). The structural differences in solution derived from two polymorphic aspirin forms were demonstrated through pKa values determined in dimethylformamide. The pKa differences were ascribed to differences in intra- and intermolecular hydrogen bonding of the solute (685).

Solvate formation of chloramphenicol and its application to size reduction were investigated by thermal analysis of the crystalline drug solvates. The drug–pyridine (1:1) solvate was shown to be the most suitable solvate for size reduction, since it yielded about 3.0 $m.^2/g.$ specific surface area upon desolvation. For this solvate, a heat of desolvation value of 6.3 ± 0.5 kcal./mole and an activation energy value of 20.6 ± 1.6 kcal./mole were estimated (686). Factors influencing the particle size of the sulfadiazine produced by a solvent change (microprecipitation) method were studied. The most important variables appeared to be the degree of turbulence in the pipeline mixer equipment and the concentration of the drug in the injection solution (687). A microcrystallization method applicable to drugs with greater solubility in glycerin than in water was utilized for aspirin, mebutamate, and quinine sulfate. In this method, the hot saturated solution of the drug in glycerin, while being rapidly stirred, was diluted with cold water. Approximately 80–90% of the crystallized drug particles were below 10-μ dimensions (688).

Experimental microscopic observations of the aspirin crystal growth from a saturated ethanol solution suggested that the step system is the normal process of growth. Two-dimensional spherulites transformed upon heating at 10°/min. into crystals melting at 125° (689). Reversible sorption of the water molecules by the disodium cromoglycate crystals resulted in noticeable changes in the X-ray diffraction pattern, density, and other physical properties. Above 93% relative humidity conditions, the crystal structure collapsed, with the formation of a lyotropic mesophase (690). The kinetics of crystallization of potassium bromide from aqueous solution were studied under different degrees of supersaturation and at different temperatures. The activation energy for the crystallization process was estimated to be 100.9 kJ. $mole^{-1}$, indicating that the rate-limiting step was the incorporation of the potassium bromide on the crystal lattice (691). Crystallization of calcium carbonate from supersaturated solutions showed an initial growth surge due to additional nucleation at the seed crystal surface and in the bulk of the solution. After the initial surge, the rate of crystallization was proportional to the product of calcium- and carbonate-ion concentrations (692).

Flynn and Smith (693) designed and tested a new multifeatured diffusion cell. The cell has a high diffusional area to diffusional volume ratio, precisely controlled stirring planar with the diffusional plane, variable speeds, facile assembly, and other desired features. By using microscope slides for the diffusion grating, a glass diffusion cell was constructed for the determination of absolute diffusion coefficients of γ-ray emitting elements in aqueous solutions (694). The diffusivity of *p*-aminobenzoic acid in methylcellulose gels was studied as a function of polymer type, molecular weight, concentration, and added inert solids. Diffusion data measured as release of the drug from gels separated from aqueous vehicles by a Millipore membrane were fitted to square root of time functions to calculate the apparent diffusion coefficient values (695). Diffusion mechanisms in solid and molten polyethylene were investigated for small molecules like propylene, butane, and neopentane. The diffusion data showed an exponential temperature dependency, with an abrupt change occurring at the melting point of the polymer (696). Based on the dissolution rate theory, diffusion coefficients for the salicylamide–micelle species were calculated from dissolution and solubility data; by using the Stokes–Einstein equation, the molecular weight of the micelle also was estimated. These values were shown to be in good agreement with the values determined by conventional methods (697).

The importance of the partition coefficient as a meaningful and convenient physical phenomenon to match against biological activity was emphasized. The structural relationships between a large number of steroids and their ether–water partition coefficients were explored, and Hansch-like π_e values were estimated for a number of functional groups. The data allow calculation of partition coefficients of substituted steroids from stripped steroid skeletons (698). Partitioning of the antimicrobial drug phenylmercuric nitrate in a gelatin–acacia coacervate system was determined by the antibacterial action of the drug. The method seemed sensitive for the partitioning studies at microgram drug levels found in physiologic systems (699). A general role of the partitioning phenomena in the dosage form design and biopharmaceutical systems was discussed (700, 701).

Table XXI—Additional References on Physical Pharmacy

Reference	Topic
708	Review describing membrane transport, sustained release, dissolution and solubility, surface interactions, complexation, polymorphism, and drug stability
709	Discussion of about 40 crystalline compounds with variations in therapeutic effect due to polymorphism
710	Potentiometric determination of the acid dissociation constants of barbiturates; correlations between normal and methylated barbiturates
711	General discussion on crystallization process, crystal growth, nucleation, and crystal habit modifications
712	Crystal growth of salicylic acid examined in the dry powder state and in ointments after prolonged storage
713	Mechanistic studies of linear single crystal growth rates of sulfathiazole and their inhibition by polyvinylpyrrolidone; preparation and dissolution of high energy sulfathiazole–polyvinylpyrrolidone coprecipitates
714	Phase diagram of cetomacrogol 1000–water–benzaldehyde in the presence of gallate antioxidants
715	Pore size effect in the freeze-drying process; drying rates related to the basic transport properties, thermal conductivity, and pore structure
716	Use of diffuse reflection spectra to determine the specific surface of powdered substances; a linear dependence of the Kybelka–Munk reflection function found with the specific surface of strongly absorbing substances
717	Description and application of scanning electron microscopy in surface studies
718	Surface studies by electron diffraction including theoretical interpretation of the diffraction intensity and discussion of problems in analysis of surface structures, particularly at low energy

The surface free energy values as parameters were considered in the prediction of adhesive bond strengths developed by the film coat on a tablet. These parameters included estimation of critical surface tension by the Zisman technique and calculation of operative dispersion and polar force components of the surface free energies of liquids and solids. On the basis of the free surface energy components, it was possible to explain the strength of the adhesive bond and the qualities of the tablet film coating (702). A review relating lubrication to the properties of surface-active components in forming lubricating boundary layers and dispersant was presented (703). Determination of the disintegration rates of tablets after exposure to reduced pressure environments seemed to confirm the capillary theory of tablet disintegration (704). Disintegration studies in water and in butanol solvents at various temperatures indicated that the disintegration was not related to the swelling process (705).

Rates of water vapor sorption by granular cornstarch were measured gravimetrically. At lower moistures, the sorption occurred by intragranular diffusion; at higher moisture content, the controlling factor was believed to be the dissipation of the heat of sorption. In evaluating the intragranular diffusion coefficient for water in starch, it was suggested to consider the heat of sorption effect along with particle dimensions, swelling, and variable diffusivity (706). A method for the determination of absolute vapor pressures of volatile drugs and drug–adjuvant mixtures was reported. The absolute vapor pressures of methamphetamine, propylhexedrine, and eucalyptol were determined over a range of temperatures. These vapor pressure results were shown to correlate with the concentration emerging in the air stream from a nasal inhaler (707).

Table XXI lists additional references on physical pharmacy.

Dissolution—A mathematical approach for the computation of the temporal variation of pharmacological response intensity from the *in vitro* drug release testing that is functionally related to the *in vivo* drug availability was described (719). Occurrence of progressive changes in the radius of a spherical particle upon dissolution or growth was calculated by the numerical computer integration of a differential equation. The effects of high mass flux, change of solubility with particle size, and change in solution concentrations can all be accounted for during the integration process (720). The dissolution rates of 7-acetyltheophylline pellets were studied in aqueous buffers. This compound hydrolyzed irreversibly in aqueous solution during the dissolution process. Theoretical considerations based on Krevelen's treatment of the rate of gas absorption by a liquid, where the gas reacts irreversibly with the liquid, agreed with the experimental results. According to the theoretical and experimental findings, dissolution rates were shown to be influenced only when the chemical reactions occur at a much faster rate, with the half-lives less than the order of 0.1 sec. (721, 722).

Dissolution rates of 2-naphthol in nonaqueous mixed solvent systems were investigated by Dayal (723) to explore the influence of specific solvation reactions on the diffusion coefficient term in the Noyes–Whitney dissolution rate equation. Theoretical considerations of the mechanism of fluoride uptake by hydroxyapatite from acidic fluoride solution and a physical model for the formation of the Ca_2F_6 layer at the solid interface were presented (724). The kinetics and mechanisms of reaction at the tooth enamel surface in buffered solutions of high fluoride concentrations were determined. The mechanism of the reaction was explained on the basis of simultaneous diffusion, ionic equilibria, and the chemical equilibrium at the moving boundary (725). The dissolution rates of magnesium oxide pellets in dilute sulfuric acid were determined using the rotating-disk technique. Activation energies of 3.6 kcal. $mole^{-1}$ for the diffusion of hydrogen ion to the oxide surface and of 13.0 kcal. $mole^{-1}$ for the chemical reaction at the oxide surface were estimated (726).

The *in vitro* dissolution rates of the six crystalline phases of fluprednisolone compared favorably with the *in vivo* dissolution rates from pellet implants in rats, but only a fair correlation was obtained with the animal weight loss and adrenal gland atrophy (727). A solvent-mediated phase transformation of aspirin crystals to a less soluble crystal form was observed during the dissolution process in aqueous media. The kinetic and thermodynamic parameters of the two crystal forms were determined using a rotating-disk method (728). Dissolution characteristics of four polymorphic forms of phenobarbital (phenobarbitone) were examined; of these, two forms seemed to have equivalent dissolution rates (729).

In a review article (730) and several other publications (731–733), Chiou and his coworkers described solid-solid fast-release dispersion systems and their methods of preparation, classifications, stability, and *in vitro–in vivo* drug release characteristics. Some of the systems described were sulfathiazole–urea, chloramphenicol–urea, and griseofulvin–polyethylene glycol polymers. A similar type of approach was applied to convert liquid drugs into solids by their dispersion in polyethylene glycol 6000 (734). Solid-solid interactions of polyvinylpyrrolidone with hydrochlorothiazide, salicylamide, sulfaethidole (sulfaethylthiadiazole), reserpine, and griseofulvin were studied by diffuse reflectance spectroscopy, solubility, and dissolution rate measurements. The results suggested primarily occurrence of physical adsorption of these drugs onto polyvinylpyrrolidone (735). Release rates of hydroxy and amino derivatives of benzoic acid compounds from polyvinylpyrrolidone tablets were studied. The number of hydroxyl groups, their position with respect to the carboxyl group of benzoic acid, and the tablet compression force were shown to have significant influence upon the drug release rates (736–738). Enhanced solubility and antitumor activity of the drug acronine (acronycine) were obtained with the drug–polyvinylpyrrolidone coprecipitates (739). Physicochemical parameters of a polymer system were evaluated to elucidate their effects on the dissolution of polymer and polymer–drug systems. The systems consisted of four molecular weight fractions of the free acid prepared from the copolymers of ethylene–maleic anhydride and three polymer–drug interaction systems using phenylpropanolamine as the drug. The effects of swelling, molecular weight, and pH on the dissolution of the polymer as well as polymer–drug pellets were studied. Possible application of such systems for regulating dissolution characteristics of dosage forms was suggested (740).

The timed-release rates of drugs from methyl acrylate–methyl methacrylate copolymer matrix tablets were evaluated as a function of drug concentration, compressional force, heating, and exposure of the tablet surface to acetone vapors. Release rates were slower from the tablets exposed to acetone vapors, primarily due to an increase in the tortuosity of the matrix (741, 742). Release characteristics of a steroid drug in solid form dispersed in a silicone elastomer matrix showed an initially linear and then a square root of time dependent release rates. The concentration and particle-size effects on the duration of the linear release suggested that the release was a dissolution- rather than diffusion-controlled process (743). A correlation between the *in vitro* release rates of aspirin from wax-coated formulations determined in the simulated intestinal fluid and simulated gastric fluid and the melting point of the wax was reported (744). Relative *in vitro* release rates of drugs from inert matrixes of various glyceryl esters of higher fatty acids were compared (745–747).

Dissolution characteristics of methylprednisolone were improved by lyophilization in the presence of a small quantity of polysorbate 80. This finding was attributed to the increased surface area and improved wettability of the drug (748). Certain relatively insoluble drugs, when adsorbed on the surface of an inert excipient such as fumed silica by equilibration in an organic solvent, showed faster rates of dissolution. The drugs studied included indomethacin, aspirin, sulfaethidole (sulfaethylthiadiazole), griseofulvin, reserpine, chloramphenicol, oxolinic acid, and hydrochlorothiazide (749). Inhibition of dissolution rates of sulfathiazole and diethylstilbestrol crystals by certified water-soluble dyes was shown to be consistent with the previous results, which had suggested preferential adsorption of the dye at the drug crystal surface (750). In the case of diethylstilbestrol, cationic dyes were shown to be more reactive than anionic dyes (751).

An automated potentiometric titration technique for the determination of *in vitro* dissolution rates of acidic and basic drugs was described by Shah (752). Many common tablet excipients did not seem to interfere with the titration assay. The results obtained by the titration method were confirmed by other analytical tests. The construction of an automated USP XVIII–NF XIII Method I apparatus, with the capability of monitoring six dissolution tests simultaneously, was reported. The system utilizes a commercial spectrophotometer designed to analyze six test samples at programmed time intervals (753). Dissolution rates of aspirin, chloramphenicol, niacin (nicotinic acid), oxytetracycline hydrochloride, phenacetin, phenobarbital, prednisolone, sulfadiazine, and diphenylhydantoin (phenytoin) were evaluated by an automated spectrophotometric method (754). Manual and automated procedures were employed in the assessment of dissolution rates of sulfonamides. Comparable results were obtained by both procedures, with a lesser degree of variability observed upon repeated runs by employing the automated method (755). Dissolution rates of dicumarol tablets were determined using an Autoanalyzer. By using this method, it was demonstrated that the tablet disintegration did not correlate with the dissolution rate (756).

In a previously reported three-compartment dissolution test apparatus, a barrier was placed in the dissolution medium to prevent drug particles from entering directly into the lipid "sink" phase. It was demonstrated that the solid particles do not enter and dissolve into the the lipid phase due to the presence of the aqueous layer around them (757). In a subsequent study using this apparatus, the effects of different pore-size screens, membrane barriers, propeller placement, rate of liquid agitation, temperature, and surfactant were studied in relation to the rate of transport of the dissolved drug into the "sink" phase (758). Equations were derived for the system in which the drug dissolved in the aqueous phase and transferred into a lipid phase may transfer back into the aqueous phase. Based on these equations, it was shown that the "perfect sink" conditions are met only when there is negligible buildup of drug in the aqueous phase and the drug does not transfer back into the aqueous phase (759). The kinetics of dissolution for a nondisintegrating sodium chloride tablet were evaluated in seven different types of dissolution apparatus. The results were used to assess experimental reproducibility and to examine adherence

Table XXII—Additional References on Dissolution

Reference	Topic
762	Preparation of enterosoluble sustained-release pills by drug dispersion in synthetic resins
763	Dissolution of phenobarbitone from gelatin micropellets and the effect of pH on release rates
764	Release of sulfa drugs from various ointment bases determined by dialysis through different membranes and by agar diffusion tests
765	*In vitro* sustained-release rates of chlorpromazine from an insoluble chlorpromazine-polysalt complex in simulated GI fluids did not correlate with *in vivo* results
766	Mechanism for dissolution of a polyphase mixture of a drug and hydrophilic polymer; effect of physiologic components and synthetic substances on wetting and dissolution rates of powdered drugs and development of an appropriate dissolution rate methodology
767	Review of drug release from suppositories and rectal absorption
768	Release rates of salicylates from cocoa butter under simulated *in vivo* test conditions
769	Dissolution of aluminosilicates in hydrochloric acid solutions; dissolution rates of cations and change in specific surface area of residues
770	Automated spectrophotometric recording of dissolution rates directly in terms of percentage dissolution *versus* time
771	Dissolution rates of sodium salicylate tablets monitored by sodium-ion-selective glass electrode
772	Conductometric method for determination of dissolution rates of tablets
773	Examination of dissolution profiles of chloramphenicol capsules and tolbutamide tablets by employing BP disintegration apparatus

of the dissolution process to theoretical rate laws (760). The influence of three-dimensional fluid motion on the dissolution rates of benzoic acid and iodine disks was evaluated. The results were compared with the rotating-disk method. The Reynolds and Peclet numbers were calculated from the experimental results, and these were compared with the theoretical laminar and turbulent flow systems (761).

Additional references on dissolution are listed in Table XXII.

Solubility–Solubilization Phenomena - A structure theory of the thermodynamic behavior of solutions of aliphatic hydrocarbons in water was advanced by considering water molecules at the hydrocarbon–water interface in an asymmetric electrical field, similar to what has been proposed to account for the surface tension of water. Experimental free energy, internal energy, and entropy values were in agreement with the theory, but not the heat capacity value (774). Relative magnitudes of the entropic, regular solution, and specific interaction contributions responsible for the deviations from ideal solubility of polar nonelectrolytes in nonpolar solvents were theoretically estimated. Entropic contributions appeared to account for the deviation from ideal solubility of poorly soluble polar solutes in a series of hydrocarbon solvents. Specific interactions were found to be the dominant factors for the solubilities of polar solutes in solvents possessing acid–base characters. Solvate association constants between various solutes and chloroform or ether were in agreement with the solubility data (775, 776). Solubility differences observed between a crystalline and microcrystalline solid were considered to be due to the difference in their relative entropy of solution (777). The solubility parameters of selected sulfonamides in mixed solvent systems were determined by employing experimentally determined vapor pressure, heat of solution, and solubility data in the Hildebrand equation. The equation was felt useful in prediction of drug solubility where the solubility parameters of the drug and the solvent system are close to each other (778). Solubility, heat of solution, and entropy of solution were determined for four sulfonamides in normal alcohols and in buffered aqueous systems. A two-step solution pathway for the transfer of nonelectrolyte solid solute into solution was described (779).

Synergistic microbiological activity of the combination of two different esters of *p*-hydroxybenzoates was ascribed to the mutual increase in their solubilities. The increase in solubility seems to be due to the existence of more monomeric forms of both the esters in the presence of each other in solution (780). The solubility of a homologous series of alkyl *p*-hydroxybenzoates was evaluated in water–polyethylene glycol solvents. Based upon these results, the mutual solubilization cannot be completely explained by the changes in a dielectric constant of the solvent media (781). Solubility features of the *p*-hydroxybenzoates were further discussed in terms of hydrogen bonding and the interrelation of the molecular symmetry, solubility, and entropy (782).

The effect of various solvents and pH on the solubility characteristics of amino acids were studied in aqueous, alcoholic, and hydroalcoholic solvent systems. The aqueous solubility was found to be inversely proportional to the size of the nonpolar portion of the molecule. In aqueous and alcoholic solutions, an isoelectric band of minimum solubility was formed. In hydroalcoholic solvents, solubility seemed to be dependent on the interaction of the α-aminocarboxylic acid portion of the molecule and, to some extent, on the nonpolar portion of the molecule with each specific solvent system (783, 784). The solubility of sodium salicylate determined in various aqueous mixtures with dioxane, acetone, and alcohols was shown to correlate with the dielectric constant over a wide range of concentration. The possibility of uni-univalent electrolytes existing completely in the associated form in solutions below a dielectric constant of 30 was indicated (785). A correlation between the solubility of phenobarbital and the solvent polarity suggested two solubility parameters corresponding to the associated or monomeric form of phenobarbital, depending upon the solvent system used (786). From the solubility analysis of multicomponent systems, it was concluded that solubility profiles for the mixture of drugs cannot be predicted from individual drug solubility profiles (787). The effect of sodium salts of aliphatic acids on the aqueous solubility of caffeine showed decreased drug solubility by the acid salts up to four carbons, but there was increased solubility with the higher homologous acid salts below the CMC (788). Similar results were also reported for the solubility of certain hydrocarbon compounds in aqueous soap solutions (789).

Mukerjee (790) described the solubilization of benzoic

Table XXIII—Additional References on Solubility–Solubilization Phenomena

Reference	Topic
801	Use of hydrotropic solvents and association colloids for solubilization of drugs in pharmaceutical practice
802	Review of solubilization of drugs by means of polyethylene glycol derivatives of sorbitan monoesters
803	Solubility of L-tryptophan in aqueous solution influenced by addition of alcohols and glycols; correlation of solubility data with adsorption characteristics of alcohols and glycols
804	Effects of dextran, gum acacia, and certain other macromolecules on aqueous solubility of cholesterol, testosterone, progesterone, and diethylstilbestrol
805	Solubility of phenobarbital and hexobarbital determined in ethanol-water and dioxane-water mixtures
806	Solubility and heat of solution of novobiocin in ethanol-water solutions
807	Review of solubilization and its pharmaceutical applications
808	Solubilization of steroid hormones by nonionic Tween solutions
809	Solubility of *trans*-azobenzene, caffeine, and 8-methylcaffeine in aryloxyalkylamine salt solutions
810	Refractometric method for determination of solubilizing ability of surfactant solutions

acid derivatives in the nonionic polyoxyethylene surfactants in terms of two broadly defined loci: (*a*) the hydrocarbon core along with its interface, and (*b*) the polyoxyethylene mantle. The distribution of the solubilized species between the two loci is related to the chemical structure of the solubilizate molecule. An analysis of the distribution model using thermodynamics of small systems was presented. Some consequences of treating the micellar phase as ideal and nonideal solutions were examined (791). Solubilities of a series of compounds of varying polarities in hexadecylpolyoxyethylene monoethers and cetomacrogol 1000 were compared with their solubilities in water, *n*-hexane, and polyethylene glycol. The results suggested that the solubilization of these compounds cannot be adequately described solely on the basis of solubility into separate regions of the micelle (792).

The relative distribution of the solubilized molecule in the micellar regions was further studied by the UV, NMR, viscometric, and osmometric measurements on esters of *p*-hydroxybenzoic acid and other similar compounds solubilized by cetomacrogol 1000 (793, 794). A nonlinear partitioning of phenol between the aqueous phase and the micellar phase of cetomacrogol was accounted for by the Langmuir adsorption isotherm (795). The mechanism of solubilization of water by oil-soluble surfactants in nonaqueous solutions was discussed relative to the heats of solubilization (ΔH_s) calculated from the vapor pressure measurements. The ΔH_s decreased in the order: anionic > nonionic > cationic surfactants (796). Micellar-solubilized testosterone concentrations in *n*-alkyl polyoxyethylene surfactant systems were studied by the dialysis method (797). The concept of gas solubilization in micellar system was considered as a potential method for gas transport in biological systems. Specific anesthetic gases and surfactant systems were studied in relation to the physiological aspects of the gas transport mechanism (798, 799). A linear relationship was shown to exist between the hydrolytic rate constants for benzocaine and homatropine with the reciprocal of their solubility in nonionic surfactant media (800).

Additional studies on solubility–solubilization phenomena are listed in Table XXIII.

Membrane Permeation—The treatment of the membrane transport process by nonequilibrium thermodynamics was compared with the kinetic approach. Both the kinetic and thermodynamic approaches led to similar results; however, the latter approach was felt to be more informative (811). Flynn and Roseman (812) studied the influence of physical adsorption upon the drug permeability through heterogeneous dimethylpolysiloxane membranes. They showed that the permeant adsorption by the siliceous filler dispersed in the membrane was linear with respect to the permeant concentration. The authors felt that such specific binding may influence the drug permeation through cellular membranes and skin, and they suggested application of these principles in the design of drug delivery systems.

Nakano (813) studied the effects of pH, surfactants, adsorbents, and other substances on the permeation of chlorpromazine through a dimethylpolysiloxane membrane. Over the 4.1–6.4 pH range, the transport rate appeared to be a partition-controlled process; in the 6.8–7.4 pH range, it appeared to be a diffusion-controlled process. Permeation rates decreased because of the complexation of the drug with surfactants, bile salts, caffeine, riboflavin, saccharin, milk, *etc.*, and surface adsorption on carbon, kaolin, and talc. Theoretical aspects of the influence of complex formation on transport across a diffusional barrier of three species, partitioning in an association–dissociation reaction, were reported (814) and were employed to rationalize the concentration profile of a reactant species in an inhomogeneous diffusion barrier (815). From the rates of permeation of potassium chloride through a gelatin membrane undissolved by heating, the rate-limiting step in a thin membrane was shown to be the permeation at the membrane interface (816). With the increase in molecular weight of phenothiazines, their permeability through cellulose membrane decreased, which suggested that the process involves diffusion through the membrane pores (817). Depending upon the permeability coefficients of the electrolytes through cellulose acetate membranes, these membranes were classified into two categories as the membranes for which the permeability coefficient value of sodium chloride is either dependent or independent of the presence of other electrolytes. The conditional porosity of the membranes with respect to some ions and organic molecules was calculated (818).

The transport of glucose and urea across two polyelectrolyte complex membranes was explained on the basis of a diffusion model. Binding of urea to the membrane matrix and some unusual behavior were noticed in the boundary layer adjacent to the membrane (819). An expression for the equilibrium membrane permeability was derived in terms of the diffusion co-

Table XXIV—Additional References on Membrane Permeability

Reference	Topic
821	Diffusion transfer of amino acid molecules through ion-exchange membranes
822	Diffusion and reverse osmosis through polymer membranes
823	Permeability coefficients for water and sodium chloride measured in cellulose acetate and nylon membranes
824	Review of permeation of gases, vapors, and liquids through polymeric membranes, and effects of plasticization of membrane on solubility and diffusion of permeant
825	Mathematical description of differential permeation rates for transport in opposite directions through asymmetric membranes
826	Transport properties of a new polymeric dialysis membrane
827	Equation to correct effect of fluid dilution on diffusion through a membrane

efficient, partition coefficient, and thickness of the layer governing the transport process (820).

Additional membrane permeability studies are listed in Table XXIV.

Complexation—The studies reported on complexation phenomena (interactions, binding, *etc.*) were categorized into: (*a*) interactions of drugs with biological substances and (*b*) interactions of drugs with nonbiological substances.

Interactions of Drugs with Biological Substances—A nonlinear mathematical model was formulated to describe dynamics of competitive binding, distribution, and disposal for the binding of hormonal drugs with albumin. The model was simulated on a computer to fit experimental data (828). Hansch (829) used a model system consisting of 1-octanol and water to approximate the role of apolar forces involved in drug–protein interactions. This model seemed to fit the *in vitro* protein binding data. Oleic and palmitic acids, in 2000–4000 μeq./l. concentrations, were shown to inhibit binding of many drugs to serum albumin (830). Phenylbutazone, salicylates, acidic sulfonamides, and other drugs inhibited the *in vitro* binding of urate to human albumin. The *in vitro* urate displacement test may be utilized for screening potential uricosuric active drugs (831). Amino acids, such as histidine and lysine, were shown to compete with albumin, but to a lesser extent with transferrin, for the binding with iron (832). Competition between sulfonamides and thiopental for the binding sites of plasma protein was studied by the equilibrium dialysis method. The results were analogous to the surface adsorption process (833).

The binding of 18 corticosteroid 21-ester derivatives with bovine serum albumin was examined at pH 7.4, 15°; all derivatives were found to follow the Langmuir-type relationship. In the case of hemiesters, a correlation was found to exist between the binding constant and the apparent pKa value, suggesting dominance of the electrostatic forces in the binding interactions (834). The influence of pH upon the binding of sulfa drugs to human serum albumin (835), barbiturates with bovine serum albumin (836), and vitamin B_{12} by human gastric juice (837) was studied. The ionized forms of sulfa drugs and barbiturates seemed to have greater binding affinity than the unionized molecule, while the pH-dependent effect of vitamin B_{12} was shown to be due to the effect of pH upon the intrinsic factor (835–837). On the basis of dialysis and circular dichroism evidence, sulfaethidole (sulfaethylthiadiazole) was shown to exhibit similar binding to both crystalline and fraction V bovine serum albumin. Equilibrium dialysis studies indicated one primary and three secondary binding sites for sulfaethidole, whereas circular dichroism studies detected only the primary binding site (838).

The degree of plasma protein binding of both 5,5-diphenylhydantoin and its major metabolite, determined by the equlibrium dialysis method, showed that the binding of drug to human plasma protein was greater than to the rat plasma protein, but the reverse situation existed for the binding of the metabolite. The importance of these results in terms of the drug response in humans and in rats was discussed (839). Salicylates and phenobarbital (phenobarbitone), but not indomethacin, were shown to bind to human red cells. To predict the extent of drug binding in the circulating blood, therefore, McArthur *et al.* (840) suggested that the *in vitro* results be obtained with whole blood, red cells, and plasma. The binding of dicumarol (bishydroxycoumarin) to human serum albumin was studied by means of spectrophotometry, solubility, and dialysis measurements. The probable site of complexation, the energy of complexation, and association constants were described (841). The substituent effect upon the relative binding tendencies of several coumarin derivatives was reported (842). Dissociation rates of various 17β-hydroxysteroids–β-globulin complexes were determined at 0 and 27° (843). Association constants and the enthalpy and entropy of binding of chlorothiazide to human serum albumin were determined by various methods (844). The types of interactions between a nonionic surfactant and various bile salts or soluble proteins were shown to be predominantly hydrophobic (845, 846).

A dynamic dialysis technique for the evaluation of solute–protein binding was reported. The method is based on the use of radioactive tracers and a dual closed-loop dialysis system (847). A rapid method for the estimation of drug–albumin association constants in human plasma from a single value of its concentration in the plasma was described (848). Based on NMR studies, the alkyl chain of the epinephrine molecule appeared to be the active site for binding with bovine serum albumin (849). Binding of *p*-hydroxybenzoic acid esters (parabens) to bovine serum albumin was determined by the fluorescent probe technique. In this technique, the spectral property of a third component, which fluoresces strongly when bound to protein, was used as an indirect measure for the binding of parabens to serum protein. The aromatic rather than aliphatic portion of the paraben molecule seemed to be the primary binding site (850). A similar test method, utilizing a different fluorescence compound, was reported (851).

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

Interactions of Drugs with Nonbiological Substances—

The crystal structures of sulfanilamide–sulfathiazole (1:1), theophylline–sulfathiazole (1:1), and theobromine–5-chlorosalicylic acid (1:2) complexes were characterized by X-ray diffraction methods. Intermolecular hydrogen bonding in these crystals involves the aromatic amino group of the sulfathiazole in the theophylline complex (870), one of the sulfathiazole oxygens in the sulfanilamide complex (870), and the carboxyl group of the salicylate in the theobromine complex (871). A review article dealt with the subjects of stability constant determinations, effects of solvents, and X-ray analyses of drug complexes, especially of xanthine derivatives complexing with aromatic carboxylic acids (872). By means of NMR chemical shift measurements, the stability constants for benzocaine, procaine, lignocaine, and prilocaine with electron acceptors like 1,3,5-trinitrobenzene were determined. The stability constants for these drugs were higher in comparison to their corresponding simple ring methylated anilines (873). Unlike previously reported results, which were based on partition coefficient studies, NMR data suggested self-association of theophylline in aqueous solution (874). In response to the NMR data, Guttman and Higuchi (875) concluded that the self-association of theophylline may occur to a limited degree in water; however, for the most practical range of concentrations, the associative tendency of theophylline seems rather negligible. The previously reported solubility data on cycloheptylamylose inclusion complexes of barbiturates were correlated with the proton magnetic resonance data to provide direct evidence for the stereospecific complexation mechanism (876).

Solvent effects on the charge-transfer transition energy and association constants of π–π intermolecular complexes were investigated. The transition energy decreased with an increase in the solvent refractive index, while the association constant seemed to be a function of the dielectric constant (877). The formation of UV-detectable charge-transfer complexes between chlorophenyl groups of DDT and its metabolites with tetracyanoethylene was reported (878). The stoichiometric balances and absolute stability constants of atropine, chlorpheniramine, quinine, and other amine drugs with bromthymol blue were determined in chloroform. The results were suggestive of the complexation reaction between amines and bromthymol blue rather than the formation of salts (879). In an effort to explain the solubilizing action of acid amides, a quantum chemical approach involving the linear combination of atomic orbital–molecular orbital (LCAO–MO) method was employed. Based on this approach, it was shown that the acid amides are electron acceptors and form more stable complexes with electron donors than with electron acceptors, and complexation constants are linearly related to energy levels of the lowest vacant molecular orbital of the aromatic acid amides and the π-electron densities of the oxygen atom in acid amide groups (880).

A considerable increase in the aqueous solubility of dicumarol (bishydroxycoumarin) in the presence of polyvinylpyrrolidone occurred due to the formation of a highly soluble drug–nonionic polymer complex, with an intrinsic association constant of about 3×10^3 l./mole at 20°. Equilibrium dialysis, viscometric, and spectrophotometric methods were employed to study the complexation mechanism (881). The influence of counterions upon the complexation of nonionic polymers such as polyvinyl alcohol or polyvinylpyrrolidone with the hydrophobic cations like alkylammonium ions was investigated. As compared to bromide, chloride, and fluoride counterions, the so-called strongly water structure-breaking-type ions (*viz.*, thiocyanate, iodide, and nitrate) induced stronger attraction and complexation, thereby decreasing the polymer solubility (882). Similar phenomena were observed, in which the interactions between nonionic polymers and anionic surfactants were enhanced by the presence of strongly water structure-breaking cations such as guanidinium ions (883). The mechanism of interaction between polyvinylpyrrolidone and anionic surfactants was discussed based on the determination of surface tension, viscosity, solubility, and solubilization (884). The formation of an association complex between sodium lauryl sulfate (dodecyl sodium sulfate) and polyvinylpyrrolidone was studied at varying polymer concentrations. The data suggested occurrence of mixed micelles

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

Reference	Topic
852	Review of nature of drug–receptor complex formation and its importance in drug structure–activity relationships
853	Review of protein binding of tetracyclines
854	Review describing effect of protein binding on distribution and metabolism of a highly plasma protein-bound drug (bishydroxycoumarin)
855	Binding of radioactive label from labeled phenacetin and related compounds to rat tissues *in vivo* and to nucleic acids and bovine plasma albumin *in vitro*
856	Determination of protein–metal-ion binding sites by proton magnetic resonance spectroscopy
857	Binding of dapsone and monoacetyldapsone by human plasma proteins
858	Binding of bupivacaine to maternal and fetal plasma proteins; maternal protein bound approximately twice as much drug as the fetal protein
859	Interactions of levorin and amphotericin B with cholesterol explained on basis of adsorption mechanism
860	Evidence for competitive binding of two sulfas and penicillin G to bovine serum albumin using NMR techniques
861	Accelerated peritoneal dialysis of barbiturates, diphenylhydantoin, and salicylate
862	Dialysis of ephedrine and pentobarbital from whole human saliva and simulated saliva
863	Comparison of protein binding tendency of antibiotics with gel filtration data
864	Protein–polysaccharide interactions in thin films determined by IR internal reflectance spectroscopic studies
865	*In vitro* and *in vivo* binding of 4-(aminoethanesulfonylamino)antipyrine with rabbit serum protein
866	Determination of average binding ratios of taurinophenetidine and its nicotinate in rabbit serum protein
867	Binding of ^{65}zinc by homogenates of rat intestinal mucosa
868	Dissociation constants, molecular weights, conformations, and other physicochemical properties of vancomycin and iodovancomycin and their complexes with specific peptide
869	Relations between chemical structure, lipid solubility, and protein binding properties of tetracyclines

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

Reference	Topic
892	Review of drug–polymer complexation, use of polymers in sustained-action dosage forms, and other pharmaceutical aspects of polymer science
893	Intermolecular reaction of barbiturates with phenols; correlation shown between equilibrium constants and physiological activities of barbiturate complexes
894	Complexation of *p*-aminosalicylic acid and its sodium salt with caffeine, Tween 80, methylcellulose, *etc.*; compounds determined by refractive index, solubility, dialysis, and conductivity measurements
895	Thermal electric osmometric study of self-association and complex formation of some purine and pyrimidine derivatives
896	Interactions of biological macromolecules in coacervate systems
897	Molecular interactions between gelatin and glycerol shown to reduce hygroscopicity of gelatin
898	Review of drug–macromolecular interactions and implications to pharmacological activity
899	Polymeric structures of β-lactam antibiotics
900	Physicochemical properties of gelatin–carboxymethylcellulose complex
901	Properties of gelatin–polysaccharide complexes in organic solvent systems
902	Association constant for chlorpromazine–diethylbarbituric acid complex in water at 30°
903	Interaction of caffeine and theophylline with 9-ethyladenine in deuterochloroform solution; theophylline interacts strongly with 9-ethyladenine, whereas relatively weak interactions observed with caffeine
904	Self-association of morphine sulfate and related salts in aqueous solution studied by conductivity and optical rotatory dispersion measurements
905	Aggregation of chlorhexidine digluconate in aqueous solution from optical rotatory dispersion measurements; a system in which optical activity is centered in the counterion rather than in the aggregate core
906	Complex formation between phenols and quaternary ammonium salts in aqueous solution
907	Behavior of enramycin in aqueous solution; solubility, surface tension, stability in aqueous media, and intermolecular association of drug with nonionic surfactants
908	NMR studies of interactions between cetomacrogol and phenol; phenol solubilized in cetomacrogol micelles appears to accumulate in polyoxyethylene region
909	Interactions between ionic surfactants and nonionic water-soluble polymers; strong interactions occurred between anionic surfactants and the polymer molecule
910	Interactions between methylcellulose mucilage and electrolytes
911	Stability constant for citric acid–methenamine complex determined by potentiometric method
912	Detection and formulation of complex metal ions in aqueous solution by coagulation and charge reversal of lyophobic colloids

at concentrations lower than CMC of the pure sodium lauryl sulfate (885). The nature of the interaction between chlorpromazine and polysorbate 80 was investigated by UV spectrophotometry and by the technique of monomolecular films. The results suggested that the locus of the drug–surfactant interaction is primarily hydrophobic and that the drug has strong affinity for sorbitan monooleate, the more hydrophobic constituent of polysorbate 80 (886).

Solubility analyses and spectrophotometric studies were reported for several metal complexes of thiouracils. Only those tautomerizable thiouracils that can form ionizable sulfhydryl groups seemed to be capable of forming metal complexes. Thiouracil solubility was not significantly different in the presence or absence of metal ions, while the solubility of the precipitating complexes was less than that which can be detected accurately by analytical methods. The data do not support the previous literature proposal, which indicated the formation of a cuprous–2-thiouracil disulfide complex in 2-thiouracil and cupric-ion mixtures (887). Three iron–dextran complexes used as parenteral hematinic agents were studied by electron microscopy, X-ray diffraction, IR, and Mössbauer spectroscopy to examine dimensions and other physical properties of the complexes (888). The structure of several metal complexes of the virus inhibitor 2α-hydroxybenzylbenzimidazole was deduced from spectral and magnetic measurements. In most cases, the virus inhibitor chelates through the tertiary nitrogen of the imidazole ring and hydroxylic oxygen atom (889). Several complexes of copper, with pyridine–carboxylic acid, aminobenzoic acid, and their derivatives were prepared. Physical-chemical properties, structures, and biological activities of some of these complexes were determined (890). Solubilization of certain poorly soluble drugs upon complexation with the neutral xanthine derivative 7-(2-hydroxypropyl)theophylline was utilized as a convenient means for determining ionization constants of the insoluble drugs by potentiometric titration (891).

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

Surface Phenomena—The publications dealing with surface phenomena were subdivided into four major categories. However, because of the obvious overlap among these categories, the reader with a special interest in this field is advised to consider the entire section.

Interface Studies—A correlation was shown to exist, apparently for the first time, between the dielectric constants and the surface tensions of liquids. It may be utilized for the estimation of surface tension of nonhydrogen-bonded polar liquids and nonpolar liquids (913). The interfacial properties of certain homologous benzalkonium chloride compounds (C_8 and C_{10}–C_{19}) were studied. In the presence of excess electrolyte, the surface tension of these compounds adhered to Traube's rule; however, significant deviation occurred in the absence of electrolyte. An "odd–even" chain length effect observed in the equilibrium pressure values of the homologous compounds was rationalized on the basis of their melting points (914). The surface tensions and surface entropies of different molecular weight polyethylene glycols and polypropylene glycols were measured. In these homopolymers, molecular weight appeared to have little effect on the surface free energy, and the increase in free energy on passing from the interior to the surface was mainly due to the heat content, with very little entropic contribution (915). A review of dynamic surface tension dealt with the nonequilibrium surface states, dynamic tension measurements, and the interpretation of dynamic surface tension on the basis of diffusion rate and transfer rate mechanisms (916). The diffusion-controlled mechanism was shown to be inadequate to account for the dynamic surface tension data obtained for dilute aqueous

solutions of monoalcohols, but the data were explainable on the basis of first-order adsorption kinetics (917).

The dynamic properties of monomolecular films of saturated fatty acids ranging from 15 to 20 carbons in alkyl chain length were studied by evaluating the influence of film compression upon surface pressure. When the films were compressed beyond their apparent equilibrium spreading pressure, they exhibited a spontaneous loss in the surface pressure. In general, more stable films were obtained with longer chain length fatty acids; however, odd and even carbon compounds showed distinct differences in the collapse pressure, rate of surface pressure change, and the apparent equilibrium pressure values. From these and other results, it was concluded that the three-dimensional lens formation occurs when the film enters the region of instability before an apparent collapse pressure is reached (918). The surface properties of monolayers of polyvinylpyrrolidone copolymers were investigated. The results suggested that the high compressibility and low cohesion observed can be accounted for by the flexibility of the vinylpyrrolidone residues beneath the surface (919). An equation was derived for predicting the equilibrium spreading pressure of a monolayer spread from a mixed crystal as a function of the composition of the crystal. Although the equation may be useful for estimating the interaction between dissimilar surface-active agents in the monolayer films, more involved mathematical computations appeared to be the major limitations on its application (920). Cholesterol monomolecular films exhibited a loss in surface pressure upon exposure to nitrogen dioxide due to the formation and subsequent desorption of cholesteryl nitrate. This interaction was totally inhibited by prior addition of about 0.75 mole fraction of cholesteryl nitrate ester. An analog computer simulation of the inhibitory process indicated that at least six molecules of the nitrate ester are required for each cholesterol molecule to produce total inhibition (921).

The interaction of 3-methylcholanthrene with mixed films of cholesterol and lecithin was investigated. The extent of interaction between 3-methylcholanthrene and cholesterol in the mixed films was significantly influenced by the competitive interaction between cholesterol and the phospholipid. This may account for the influence of cholesterol and phospholipids on the formation of tumors induced by polycyclic aromatic hydrocarbons (922). The enzymic activity of phospholipase C on tritium-labeled lecithin monolayers was evaluated as a function of lecithin surface concentrations. At lower lecithin concentrations, occurrence of irreversible adsorption and surface inactivation of the enzyme caused a progressive decline in the enzyme activity (923). TLC and surface pressure–surface area (π–A) evidence was presented for the autoxidation of cholesterol monomolecular films spread on an aqueous subphase. Tocopherol, butylhydroxytoluene, stearic acid, dipalmitoyl lecithin, ascorbic acid, and oleic acid inhibited the oxidation (924).

Interfacial barrier-limited transport of some biologically important substances like cholesterol and β-sitosterol across the aqueous polysorbate 80–hexadecane interface was studied. The effects of bulk diffusion, interfacial area, and lipid–water partition coefficient were considered in the quantitative representation of the experimental data. One of the most significant findings of the study was considered to be the possible explanation of the intestinal absorption of cholesterol and β-sitosterol in terms of the interfacial barrier mechanism (925). The transfer of an adsorbing solute across a liquid–liquid interface was considered by taking into account the effects of molecular diffusion in both bulk phases, adsorptive accumulation at the interface, and energy barriers to adsorption and/or desorption. Dynamic interfacial tension data for oil–water systems with interface ages from 0.05 to 1.5 sec. were obtained using a laminar contracting liquid jet. The data indicated the presence of a small net desorption barrier to the transfer of normal and isobutyric acids from oil to water and large barriers to both the adsorption and desorption of 1,5-pentanediol (926).

Additional references on interface studies are listed in Table XXVII.

Table XXVII—Additional References on Interface Studies

Reference	Topic
927	Interfacial tensions between benzene solution of egg-phosphatidylcholine and aqueous bovine plasma; presence of protein in the aqueous phase leads to more rapid adsorption of the phospholipid at the interface
928	State of molecular motion in lecithin bilayers elucidated by nuclear relaxation measurements
929	Discussion on relation between the thermodynamic work of adhesion and mechanical bond strength
930	Review of physical and mechanical properties of surface and interfacial films, and rheological techniques used in drug formulations
931	Electrokinetic potential of oil droplets dispersed in the aqueous solutions of long-chain electrolytes
932	Molecular interactions in thin films of condensed gases
933	Forces across interface between a dipole liquid and a liquid free of permanent dipoles not accountable by the dispersion forces alone
934	Temperature dependence of viscosity of a surface layer at water–*n*-alcohol melt interface
935	Numerical analysis of kinetics of adsorption of certain steroids at oil–water interface
936	Interfacial behavior of liquid quaternary alkylammonium salts at water–benzene interface in terms of monolayer–counterion interactions and solute–solute interactions in benzene phase
937	Adsorption of anionic, cationic, and nonionic surfactants at oil–water interface considered in terms of electrocapillarity theory
938	Adsorption of dodecyl sodium sulfate at silicone fluid–water interface

Adsorption Studies—Organic solute drug molecules without having any cation-exchangeable groups were shown to adsorb on the surface but not into the interior of neutralized montmorillonite. The number of available surface sites was estimated to be about 10^{18}–10^{19} sites/m.^{2} surface area of the adsorbent, while the total number of interior sites was almost 600 times that of the surface sites. The fact that adsorption only occurs at the surface may partially provide explanation for the physiological availability of the adsorbate drug molecules from such systems (939). The nature of bonding between an unionized polar drug molecule and montmorillonite was postulated as an ion–dipole type of interaction (940). Heats of wetting, monolayer capacity, specific surface limiting (maximum) sorbed volume, and

Table XXVIII—Additional References on Adsorption Studies

Reference	Topic
949	Review of IR spectra of adsorbed molecules, physical adsorption, chemisorption, hydrogen bonding, and electronic spectra of adsorbed molecules
950	Review of physical adsorption of gases on solid surfaces including heat transfer by adsorbed air molecules, multilayer adsorption, and motion of adsorbed molecules
951	Review of structural characteristics of systems of idealized packed particles, adsorption, and capillary vapor condensation
952	Review of effect of surfactant adsorption on strength of solids
953	Review of methods for conversion of liquids into solid forms by adsorption and drying and their application in food, drug, and cosmetic manufacturing
954	Differential enthalpies, entropies, and free energies of adsorption in relation to molar refractions, dipole moments, and specific interactions; application of these parameters in gas–solid chromatography
955	Effect of electrolytes on sorption capacity of the colloidal silicic acid "Aerosil"
956	Review describing mechanism of interaction of water molecules with surface atoms of oxides; IR, NMR, and thermal data presented to differentiate between coordinatively bonded water and hydrogen-bonded water
957	Adsorption of long-chain (C_{12}) electrolytes on monazite–water interface; isotherms explained on the basis of hemimicelle formation on monazite surface
958	Adsorption of surface-active agents leading to changes in surface properties of kaolinite–hydromica clay
959	Ion-exchange sorption of dicaine, nupercaine, trimecaine, novocaine, novocainamide, bencaine, and pseudococaine on Dowex 50 (H^+)
960	Adsorption of surfactants on kaolinite clay studied by X-ray diffraction and thermal methods
961	Stabilization of dispersions by adsorbed macromolecules; theoretical derivation of density distribution for segments of adsorbed macromolecules as a function of distance from interface
962	Strongly bound water and its role in structure of clay minerals

energy constants for the adsorption of water and benzene on montmorillonite were reported (941). The adsorption of crystal violet by kaolin, studied over a pH range of 2.5–9.5, showed increased adsorption at higher pH. From the experimental evidence, the principal mechanism of adsorption appeared to be the electrostatic charges arising from cation replacement in the clay lattice, whereas contribution from the charges of the aluminum atom of kaolin seemed to be insignificant in the overall adsorption process (942).

The extent of hydrophobicity of eight local anesthetics was evaluated by their adsorption tendency on carbon black. The results were further correlated with the *n*-octane–water partition coefficient and the nerve blocking potency of these drugs (943). In similar studies, the adsorption of phenols (944) and benzoic acid derivatives (945) on carbon black in aqueous solutions was investigated. The relative adsorbability of these compounds was compared with their partition coefficients, complexation with caffeine, and protein binding tendencies to explain the types of interactions involved in these systems (944, 945). The adsorption of polyvinylpyrrolidone on chloramphenicol particles in aqueous suspension was measured. By assuming that the polyvinylpyrrolidone molecules lie flat on the chloramphenicol particles, the adsorption capacity values indicated formation of two to three surface molecular layers. The increase in polyvinylpyrrolidone adsorption at higher temperatures was attributed to the large positive entropy contribution due to the decrease in the water–polymer interactions at higher temperatures. These results were further extended to evaluate the stabilizing effect of polyvinylpyrrolidone on chloramphenicol suspensions (946).

The pharmacological action of cholestyramine, a quaternary ammonium anion-exchange resin, depends upon its ability to bind bile salts. The adsorption characteristics of the resin toward bile salts, fatty acid anions, and the drug sodium fusidate were investigated. While the rate of bile salt–cholestyramine interaction showed positive temperature dependency, the equilibrium adsorption was essentially temperature independent and irreversible. Strong adsorption of the drug sodium fusidate by the resin appeared to prevent *in vivo* availability of the drug upon concurrent administration of both the resin and the drug (947). Among 39 liquid compounds studied, 20 were shown to be significantly sorbed by nylon. Equilibrium sorption weights and activation energies of desorption were determined by thermogravimetric analysis of the equilibrated sample. Compounds having hydrogen-bonding potential appeared to have a greater sorption tendency with nylon. Application of this thermal test method was recommended for similar types of sorption studies (948).

Additional references on adsorption studies are listed in Table XXVIII.

General Properties of Surfactants—A four-component emulsion system containing water, *n*-octanol, *n*-dodecane, and a nonionic surfactant $C_8H_{17}(OCH_2CH_2)_6OH$ was investigated, particularly in the presence of a liquid crystalline phase of the surfactant. The liquid crystalline phase did not exist in the binary surfactant–water system but was formed only in the presence of the organic liquids. The results were discussed with respect to their significance in the emulsion systems (963). The presence of a liquid crystalline layer at the interface of a stable emulsion was verified, and its role in the emulsion stabilization was discussed (964). A correlation between the surface activity and molecular structure was established for nonionic surfactants having two, three, four, or six branches of the polypropylene glycol–polyethylene glycol chain in their molecule (965). The surface-active properties of a series of polyethylene glycol monoethyl ether esters were determined, and it was shown that esters with 12, 16, and 18 carbon atom chains formed a netlike structure with water, thus failing to obey Traube's rule (966). Zettlemoyer *et al.* (967) reported on the surface-activity measurements of sodium α-sulfo fatty esters by the determination of interfacial tensions at air–liquid, liquid–liquid, and solid–liquid interfaces as a function of surfactant concentrations. The results suggested perpendicular orientation of surfactant molecules at the air–liquid and liquid–liquid interfaces. Rates of adsorption studies indicated that the wetting agents appeared to adsorb about 3–6 times as fast as the detergents.

The hydrophilic–lipophilic balance of surfactants can be determined by the polarity index obtained by GC. A linear relation was shown to exist between the polarity index and the content of different emulsifiers in a mixture, and also between the CH_2OCH_2 group content and the polarity index of ethylene oxide adducts having a similar lipophilic portion. Based on these relations, the polarity index can be calculated from the ethylene oxide content of the adducts plus the polarity index of the lipophilic portion of the adducts (968). The polarity index was shown to be a linear function of the hydrophilic–lipophilic balance values for a given series of nonionic surfactants but not for mixtures of nonionic and ionic surfactants (969). Hydrophilic–lipophilic balance values for different homologous series of sorbitan monoesters and polyoxyethylated octylphenol surfactants correlated with their distribution coefficients (970). The influence of hydrophilic–lipophilic balance values of surfactants upon the release characteristics of ephedrine from liquid emulsions was determined by means of a dialysis technique. The data indicated a distinct influence of the hydrophilic–lipophilic balance upon the drug release rates, and they also suggested the presence of an interfacial barrier in the emulsion (971). From thermodynamic parameters such as chemical potential and internal surface tension values, the distribution coefficient and hydrophilic–lipophilic balance values were calculated for various surface-active substances. The results were further extrapolated to evaluate conditions for the stabilization of emulsions (972). Selection of appropriate emulsifiers on the basis of phase inversion temperature values rather than the hydrophilic–lipophilic balance values was suggested. The variation of phase inversion temperature with the hydrophilic chain length of nonionic surfactants, phase volume, added salts, and optimum temperature for stabilization was considered (973). A similar study also described the application of phase inversion temperature values for quality control and for characterization of nonionic emulsifying agents (974).

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

Micelle Studies—Apparent aggregation numbers for a series of nonionic, anionic, and cationic surfactants in nonaqueous solutions were measured by the vapor pressure depression method. The magnitude of the aggregation number for surfactants having hydrocarbon groups of equal size was: anionics $\gg$ cationics $>$ nonionics in various nonaqueous solvents (986). The dependence of micelle aggregation number on the polar head structure was studied by light-scattering measurements of aqueous solutions of decylalkylammonium salts and related surfactants. According to this study, factors like the mean distance of closest approach of a counterion to the charge center of the surfactant ion, hydrophobic bonding between alkyl groups on adjacent polar heads, and polar head-water interactions must be considered to evaluate the role of polar head groups in the micellization process (987). In a subsequent study, aggregation numbers of heterocyclic surfactants were determined, which led to the conclusion that charge location and hydrogen bonding are additional factors that can affect the polar head's role in micelle formation (988). On the basis of simple geometric considerations and the experimentally determined aggregation numbers, Schott (989) questioned the existence of spherical shaped micelles for surfactants having a single normal alkyl chain as their hydrocarbon moiety.

Table XXIX—Additional References on General Properties of Surfactants

Reference	Topic
975	Effect of detergent concentration on monomer activity in a nonionic detergent solution
976	Hydrotropic and adsorption properties of bisquaternary ammonium compounds and other related cationic surfactants
977	Surface tension, solubility, and refractive index determination of *n*-1,2-alkanediols and *n*-1-alkanols in aqueous solution
978	Interfacial activity of sodium lauryl sulfate in presence of cetyl, cetostearyl, and stearyl alcohol
979	Steric structure of nonionic polyoxyethylene surfactants shown to exert considerable influence upon solubilization and emulsification
980	Modified zonal centrifugal analysis technique for studying role of surfactants in suspensions
981	Effect of cationic surface-active agents on hydrolysis rates of ethyl *p*-aminobenzoate, ethyl *p*-nitrobenzoate, *p*-nitrophenyl acetate, and *p*-aminophenyl acetate esters
982	Structural characteristics of surfactants examined in relation to wetting, emulsification, dispersion, surface tension, and micellar properties
983	Surface tension of anionic and cationic surfactants measured as a function of concentration to determine CMC and adsorption at air–water interface
984	Density, viscosity, refractive index, and light-scattering measurements of aqueous cetyltrimethylammonium bromide solutions; characterization of micellar phases at various surfactant concentrations
985	Solution phase with reversed micelles in the cetyltrimethylammonium bromide-hexanol-water system

Micelle formation by phenothiazine derivatives—*viz.*, promethazine, chlorpromazine, promazine, and thioridazine hydrochlorides, in D_2O and water were investigated by NMR, pH, and viscosity measurements. The magnitude of chemical shift observed by NMR upon micelle formation suggested vertical stacking of the phenothiazine rings, probably in an alternating mode in the micelle interior. The increased dissociation of the hydrophilic $-NH^+<$ groups upon micellization was indicated by pH measurements (990). NMR evidence for the formation of micelles by phenothiazine derivatives was also presented by Ravin and Warren (991).

The decrease in the CMC of sodium lauryl sulfate (dodecyl sodium sulfate) in water upon addition of alcohols (C_2–C_4) was compared with the free energy of transfer of an alcohol molecule from pure liquid to the extremely diluted aqueous solution. Factors affecting changes in the CMC value appeared to be the reduction of free energy of a micelle due to the diluted surface charge density on the micelle, the hydrophobic interaction to the hydrocarbon exposed to water, and the entropy of mixing of a mixed micelle on addition of alcohol (992). Similar studies were reported on the experimentally evaluated effects of the addition of a water-miscible solvent upon the CMC values of surfactants (993–995).

Micellar properties of sodium fusidate, a steroid antibiotic structurally resembling the bile salts, were

Table XXX—Additional References on Micelles

Reference	Topic
999	Review of formation and structure of micelles and solubilization phenomena
1000	Temperature dependence upon CMC of cationic surfactants
1001	Changes in micellar properties of $C_{18}H_{37}NH_3O$-$COCH_3$ in aqueous solution by addition of organic polar substances and temperature
1002	Influence of electrolytes upon CMC of polyoxyethylated nonionic surfactants
1003	Fluorine magnetic resonance studies of micelle structure of fluorine-labeled nonionic detergents as a function of concentration and temperature; thermodynamic considerations
1004	Effect of pH upon aggregation number and charge on *N*-alkylpyridinium bromide micelles
1005	Competition of monovalent inorganic cations at charged micelle and monolayer interfaces of alkaline soap solutions
1006	Molecular motion of counterions in Stern layer of a detergent micelle studied by NMR measurements
1007	Relationship between CMC of ascorbyl monofatty acid esters and number of carbon atoms in fatty acid chain
1008	Dehydrocholate and its metabolites, with the exception of cholic acid, shown to have little micelle-forming capacity
1009	Micelle size and shape of anionic surfactants in aqueous solution; existence of second CMC confirmed

determined by spectral shift, surface tension, and ultracentrifugal analyses. The CMC's, mean molecular areas, and apparent aggregation numbers were estimated as a function of the countercation concentrations. A model for the sodium fusidate micelle structure similar to the previously described model for the bile salt micelle was proposed (996). From spectral properties of mixed micelles of a nonionic surfactant (octoxynol, Triton X-100) formed with anionic surfactants, it was suggested that the micelles of nonionic detergents contain more water molecules in the core than the micelles of anionic detergents (997). Viscosity in the micellar interior (microviscosity) was determined by comparing fluorescence depolarization of 2-methylanthracene when dissolved in the micellar system and in the American white oil 35 (mineral oil USP), the latter being used as a reference with known viscosity. The results on microviscosity measurements on certain cationic surfactants and mixed micellar systems led to the conclusion that micelle interiors are similar in nature to aliphatic hydrocarbon solvents (998).

Table XXX provides additional references on micelle studies.

Dispersion Stabilization—This section includes some basic studies reported on the stability of dispersed systems (*e.g.*, emulsions, suspensions, and colloids). For some of the practical stability aspects of these systems, however, the reader is advised to refer to the previously discussed sections under *Pharmaceutical Technology*.

Bernstein *et al.* (1010) reported on the kinetics of emulsion coalescence by recording changes in the particle number and size distribution with time. Treatment of the experimental data by plotting the reciprocal of the cumulative number of particles greater than a specified size as a function of time was rationalized on the basis of theoretical considerations. For rapid reaction systems, the slopes of these Smoluchowski-type plots were directly related to the Smoluchowski rate constants. A maximum rate constant for coalescence of 4.0×10^{-12} cm.^{3}/sec. ($\pm 5\%$) was observed in studies over a 10-fold range of oil concentration, a 100-fold range of surfactant concentration, and a six-fold range of electrolyte concentration (1010). The stability of an oil–water emulsion containing a nonionic detergent was enhanced by the addition of a long-chain alcohol, which was attributed to the increase in the interfacial viscosity by alcohol addition (1011). The influence of salt addition upon stability and interfacial tension in similar types of emulsion systems suggested that the entropic forces are the main stabilizing forces in these emulsions (1012).

The asymptotic principle of the interaction of solids in liquid media was applied to certain case examples related to the molecular structure of microheterogeneous systems (1013). The effect of hydrodynamic interaction between neighboring colloidal particles upon coagulation rates did not seem to explain the existing discrepancy between the experimental and theoretical coagulation rates (1014). Hesselink *et al.* (1015) presented a theory regarding the stabilization of dispersions by adsorbed macromolecules. The theory considers volume restriction repulsion due to the decrease of configura-

Table XXXI—Additional References on Dispersion Stabilization Studies

Reference	Topic
1017	Mechanisms and general principles governing colloid stability
1018	Review of dielectric properties of dispersed systems
1019	Method for determination of critical concentration of a dispersed phase
1020	Review of electrical double-layer theory, electrodes and electrode reactions, thermodynamics of surface phases, diffuse double-layer theory, and compact layer theory with and without adsorption
1021	Effect of mechanical agitation on dispersion of an organic phase into aqueous continuous phase
1022	Effect of some anionic detergents on stability of emulsions stabilized by partially flocculated sols
1023	Theoretical consideration of selective coagulation on the basis of Derjaguin–Landau–Verwey–Overbeek theory of colloid stability
1024	Steric stabilization of colloidal particles; factors influencing stability of polyethylene oxide-stabilized dispersions
1025	Spontaneous colloidal dispersion of colophony and silver in water explained by presence of structurally weakened boundaries between microregions
1026	Promotion of mechanical coagulation by addition of sensitizing electrolytes; kinetics of coagulation process not explained by Smoluchowski theory of bulk coagulation
1027	Prevention of mechanical coagulation by surface-active additives
1028	A minimum amount of turbulence required to obtain mechanical coagulation at either solid–liquid or liquid–air interface
1029	Structure formation in aqueous colloidal systems determined by paramagnetic probe method
1030	Electrokinetic potential measurements of kaolinite in aqueous suspensions yielding information about ionic environment of particles and possible surface interactions
1031	Review of electrokinetic potential, streaming potential, electroosmosis, and electrophoresis of aqueous dispersed systems and their measurements

Table XXXII—Additional References on Surface Phenomena

Reference	Topic
1032	Dynamic surface tension measurements of surfactants (hysteresis curves) by Cahn apparatus
1033	Critical surface tension of human skin before and after extraction of surface lipids estimated as approximately 22–30 dynes/cm.
1034	Use of surface tension and film weight measurements in preparation and development of new surfactants
1035	Surface tension and cohesion in kaolin–electrolyte–water system; results explained in terms of structure of electrical double layer and hydrated water layer
1036	Surface tension balance for evaluation of dynamic properties of surfactants, such as role of lung alveolar surfactant in lung mechanics
1037	Surface area determination of magnesium hydroxide suspensions by adsorption of different dyes and iodine on solid particles
1038	Surface areas of amorphous calcium phosphate and crystalline hydroxyapatite determined by nitrogen adsorption measurements; specific surface area of crystalline hydroxyapatite samples about 2–4 times that of amorphous calcium phosphate samples

tional entropy of adsorbed loops and tails on the approach of a second particle, an osmotic repulsion due to the mixing of the adsorbed polymeric clouds when two particles approach each other, and van der Waals' attraction between the particles. The adsorbed macromolecules are described by a random-walk model, and there is no "bridging" between particles by the macromolecule. According to this theory, in general, stabilization will be enhanced by long adsorbed chains and an extreme size distribution, a high amount of polymer adsorbed, a good solvent, a low Hamaker constant, and a small particle size (1015). Based on theoretical considerations, it was shown that the type of flocculation, either isotropic or anisotropic, depends on the particle radius, ζ-potential, and electrolyte concentrations. The relation of kinetic energies to repulsive energies of colloidal particles indicated that the floc growth by attachment of new particles at the end of the floc is favored in "stable" sols, leading to anisotropic flocculation (1016).

Table XXXI provides additional references on dispersed systems. Additional studies of a general nature involving surface phenomena are provided in Table XXXII.

Rheology—A modification of the Gauss–Newton method for nonlinear regression analysis was applied in describing the flow behavior of non-Newtonian systems. Some of the original data employed in the derivation of the structure equation of the non-Newtonian flow gave a better fit upon reevaluation by the nonlinear regression analysis (1039). In a theoretical study on the rheological properties of suspensions showing time-independent non-Newtonian behavior, it was assumed that the bonds between particles are broken gradually with an increase in shear stress or shear rate. A differential equation derived on the basis of this model was compared with other existing equations for the flow behavior of suspensions (1040). Equations describing the concentration dependency in coherent suspensions on the Bingham yield value, plastic viscosity, and plasticity were presented (1041).

Table XXXIII—Additional References on Rheology

Reference	Topic
1046	Rheological and electrokinetic properties of kaolinite suspensions studied as a function of pH and in the presence of long-chain quaternary ammonium compounds
1047	Particle motion in sheared suspensions; existence of closed, limiting, and open external streamlines around liquid drop in shear flow confirmed experimentally
1048	Principles of minimum energy dissipation applied to obtain lower bounds on intrinsic viscosity of a polymer molecule consisting of *N*-spherical beads
1049	Hydrodynamic forces on touching spheres along line of centers exerted by a shear field; theoretical considerations applicable for analysis of floc stability at high shear rates
1050	Viscosities and CMC of aqueous soap solutions having C_7–C_{12} carbon chain lengths
1051	Shear properties of thin liquid films measured between optically smooth rubber and glass surface
1052	Viscosity and local liquid structure of dimethyl sulfoxide–water mixtures
1053	Rheological properties of sodium carraghenate hydrogel considered suitable for its use in cosmetics
1054	Setting behavior of precipitated magnesium hydroxide suspension evaluated by viscosity measurements
1055	Rheological properties of monoglyceride–water systems existing in isotropic, mesomorphic, and dispersed phases
1056	Stress waves propagation in viscoelastic nonlinear dispersed medium; measurements of angular frequency of perturbation and other rheological properties
1057	Rheological behavior of water–clay–enamel–electrolyte system

Continuous shear and creep viscometry were used to investigate the effect of work softening and recovery on the rheological properties of four grades of white soft paraffin BP. The data indicated that the loss of consistency during working and recovery after working were mainly viscous phenomena (1042). The kinetics of the rheological properties of acacia solutions prepared from the USP grade material were investigated with respect to preservative, temperature, and pH. Apparent first-order rate constants, calculated by computer analysis of the data, showed an Arrhenius-type relationship (1043). Organogels prepared from aluminum stearate and liquid paraffin were examined by using a rotating viscometer fitted with a cone and plate. The flow curves were characterized in terms of plastic viscosity, apparent viscosity at fixed rates of shear, and the estimated area of the hysteresis loop. Thixotropic behavior and the recovery rate were influenced by the temperature as well as by the aluminum stearate concentration (1044). Structure formation in gelatin gels were studied as a function of gelatin concentration, temperature, and addition of urea, using optical rotation and light-scattering measurements (1045).

Additional references on rheology are provided in Table XXXIII.

PHARMACEUTICAL ASPECTS

Antibiotics—A review of β-lactam antibiotics dealt with the description of physical–chemical properties, structural relationship to biological activity of β-lactam antibiotics, and inactivation of penicillins and cephalosporins by bacterial enzymes (1058). Kinetic

evidence was presented for the existence of a metastable oxazolone–thiazolidine intermediate in the isomerization of benzylpenicillin methyl ester to methyl benzylpenicillenate in aqueous solution (1059). The effect of urine pH on the antibacterial activity of several antibiotics and other antibacterial agents against *Escherichia coli* was tested in human urine samples. The result suggested that the antibacterial therapy of urinary tract infection requires the maintenance of the proper urinary pH level, depending upon the type of drug administered (1060). The *in vitro* antimicrobial effect of kanamycin and gentamicin in combination with various other antibiotics was examined. Combinations with either ampicillin, chloramphenicol, or tetracycline showed a synergistic effect, with optimum concentrations equal to from one-half to one-sixteenth of the minimum inhibitory concentration (MIC) of kanamycin or gentamicin and from one-half to one-eighth of the MIC of the second component (1061).

Griseofulvin dispersed in polyethylene glycol 6000, prepared by the melting or solvent method, was found to be completely and rapidly absorbed after oral administration to two human subjects. The absorption from commercially available micronized drugs was irregular and incomplete (1062). The chloramphenicol–urea binary system was shown as a simple eutectic mixture and not a partial solid solution as previously proposed by other workers. The increased rate of *in vitro* dissolution and *in vivo* absorption of chloramphenicol from such a system was explained on the basis of particle-size effect (1063).

Radiopharmaceuticals—The preparation of radiopharmaceuticals labeled with ^{68}Ga, such as ^{68}Ga-ethylenediaminetetraacetate, ^{68}Ga-citrate, and ^{68}Ga-ferric oxide colloid, was described. Procedures were suggested for maintaining and testing the sterility and apyrogenicity of ^{68}Ga elutions from the generator (1064). The need for cleanliness, sterility, and the use of aseptic techniques in the preparation of radiopharmaceuticals was stressed in a review article (1065). The deposition of the $^{99}Tc^{m}$-sulfur colloid in the rubber plunger of a disposable syringe was studied. About 10% deposition was found when the incubation was delayed in the syringe for more than 15 min. (1066). The stability, purity, and shelflife of several radiopharmaceutical compounds were investigated (1067, 1068). The decomposition products of aqueous solutions of radiopharmaceuticals after irradiation with ^{60}Co γ-rays were determined as a function of concentration, additives, intensity of radiation, and absorbed energy dose (1068).

Additional references on pharmaceutical aspects are listed in Table XXXIV.

Table XXXIV—Additional References on Pharmaceutical Aspects

Reference	Topic
	Antibiotics
1069	Microbial content determination of 261 batches of nonsterile antibiotic U. S. market samples, showing all to be of acceptable hygienic quality
1070	Rapid percutaneous drug absorption occurring upon application of tincture of ^{14}C-siccanin (a new antifungal antibiotic) to the rat skin
1071	Review of chemical structure of tetracyclines, their intestinal absorption, serum concentration, and protein binding
1072	Calculation of approximate rate of continuous intravenous infusion to maintain required antibiotic level
1073	Combination of ampicillin and nalidixic acid found nonsynergistic, nonadditive, and nonantagonistic in *in vitro* testing
1074	Synergistic *in vitro* bactericidal activity of trimethoprim–sulfamethoxazole combination
	Radiopharmaceuticals
1075	Survey of preparation of radiopharmaceuticals, particularly $^{99}Tc^{m}$ compounds
1076	Improved binding and stability of $^{99}Tc^{m}$–iron hydroxide macroaggregates by preparation under vacuum and storage at 4°
1077	Review of radioactive isotopes in pharmacy in reference to nuclear medicine and radioactive pharmaceutical products
1078	Review of radiopharmaceuticals, emphasizing radioactive materials used for diagnostic purposes
1079	Metal-binding abilities of radioprotective organic thiosulfates
1080	Review of use of isotopes in metabolic tracer studies, autoradiography, biological half-life, and drug distribution studies

BIOPHARMACEUTICS

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

A comprehensive survey of the generic equivalence and inequivalence of oral products was presented. The need to establish generic equivalence among commercial products by performing adequate bioavailability tests and establishing correlation between the *in vitro* test results with *in vivo* data was emphasized (1081). Several examples of the biological inequivalency among drug products were cited to illustrate that the "chemical equivalency" of the drug dosage forms may not guarantee their "therapeutic equivalency" (1082). A general discussion regarding the biological availability information which may be required by the FDA for new, old, and future products was presented (1083). An approach toward the accumulation and presentation of biological availability data for filing new drug applications was described (1084). The role of official compendia in establishing required standards for the assurance of bioavailability of drug products was discussed (1085).

Several studies were aimed toward the development of theoretical and *in vitro* test models as a means to elucidate *in vivo* drug absorption mechanisms. A diffusional model, described by Stehle (1086), dealt with the steady-state transport of neutral, weakly acidic, and weakly basic solutes in the three-phase ("mucosal" aqueous–lipid–"serosal" aqueous) system. The important feature of the model was the inclusion of aqueous diffusion layers in series with the lipid membrane. Theoretical aspects of this three-phase model in conjunction with the pH-partition theory of drug absorption were experimentally verified (1086). In similar test systems, but considering only one barrier phase, four first-order rate constants for the reversible drug transport across the lipid barrier were determined (1087, 1088). *In vitro* data were correlated with the *in*

vivo absorption rates across gastric, intestinal, and rectal regions of the rat GI tract (1088). The transport rates of 19 drugs were determined in a similar test system, and the results were correlated with the *in vivo* drug absorption rates in humans and in rats (1089). Permeation characteristics of a polymeric model biomembrane were examined for the transport of salicylic acid from aqueous pH 2.0 solution through the synthetic biomembrane into the aqueous pH 7.4 medium. The data indicated the transport of mainly unionized lipid-soluble species through the membrane (1090). Transport rates for a series of benzoic acid analogs across the biomembrane were shown to correlate with: (*a*) *in vivo* absorption, (*b*) reciprocal of water solubility, and (*c*) log partition coefficient of the substituent group on benzoic acid (1091). Development and testing of another polymeric model biomembrane, which appears to mimic the *in vivo* drug absorption by the passive diffusion process, were reported (1092).

The pharmacokinetic and chemical kinetic processes were simulated by means of computer-generated plots. The procedure involved successive approximation of smooth computed curves, displayed on a video display system, to the experimental data points by systematized parameter variation (1093). This type of approach was employed for evaluation of serum concentration of orally administered cephalexin (1094). Analog computer simulation of drug distribution and elimination rates, using an open two-compartment system, was shown to be in reasonable agreement with the experimental excretion data (1095). A digital computer program suitable for solving differential equations involved in various simultaneous kinetic processes was described (1096). A nomographic method (1097) and an approximate analog computer program (1098) were reported for the estimation of appropriate multiple-dose regimens. Numerical methods were described for the solution of differential equations involved in the multicompartment pharmacokinetic models. Application of this method to a one- or two-compartment model, while considering nonlinear protein binding of the drug, suggested that the binding should result in detectable nonlinearity in the log C *versus* time plot only when the binding sites approach saturation condition (1099). A one-compartment model was considered as too simple to account for the preferential distribution of drugs into body fluids. A multicompartment model may be simulated by the flow of water through a series of vessels with varying outflow rates (1100).

Currently used pharmacokinetic models assume that the drug administered both intravenously and orally initially enters the same vascular pool. However, literature data suggest that although a drug is completely absorbed, the total area under the plasma level curve after oral administration may be considerably less than the corresponding area following intravenous administration. This has been explained on the basis of a "first-pass" effect in the liver. The significance of this effect in the design of clinical studies was discussed (1101). Estimation of pharmacokinetic parameters by fitting blood level data to a pharmacokinetic model may be subject to considerable error (1102). One such parameter, namely biological half-life, can be utilized for the calculation of the exact dosage pattern, provided factors such as protein binding, pH of the urine, and variability among subjects are considered in estimating biological half-life from the pharmacokinetic model (1103). Gibaldi and Weintraub (1104) showed that the premature termination of pharmacokinetic studies may yield erroneous underestimates of biological half-life.

Table XXXV—Additional References on Biopharmaceutics

Reference	Topic
1105	Review of use and limitation of pharmacokinetic models in drug metabolism studies
1106	Summary report of the First International Symposium on Biopharmacy and Pharmacokinetics
1107	Review of factors influencing drug release rates and their relation to body disposition and observed pharmacological response
1108	Review of drug interactions and their effect on drug absorption, distribution, metabolism, or excretion; tabulation of drugs that may be involved in such interactions
1109	Review of movement of drugs across biological membranes presented as a refresher course in pharmacology
1110	Review of absorption of drugs presented as a refresher course in pharmacology
1111	Rational design of drug dosage form based on biological half-life, frequency of dosage, and duration of effect considerations
1112	Review of pharmaceutical profiling and drug action; new knowledge and evidence
1113	Review of aqueous and lipid solubility, partition coefficient, dissociation constants, surface tension, and electronic properties of certain new drugs as they relate to pharmacological drug activity
1114	Review of drug polymorphism and related solubility, reactivity, stability, and biological activity
1115	Review of biological and *in vitro* availability
1116	Technique for oral administration of tablets to rats
1117	Use of partial fraction theorem for obtaining inverse Laplace transforms in pharmacokinetic analysis
1118	Kinetic aspects of biological membrane transport processes
1119	Hemolytic behavior of human erythrocytes in sodium and potassium buffers
1120	Drug distribution in blood and abdominal organs after administration *via* a peripheral vein, portal vein, and aorta in dogs
1121	Portal vein blood sampling method for intestinal drug absorption studies in rats
1122	Review of pharmacokinetic and other factors influencing drug metabolism and its clinical implications
1123	Review of chemistry, toxicology, pharmacodynamics, and mechanism of action of biguanides
1124	Use of a membrane model (RESOMAT) for *in vitro* drug release rates and absorption studies
1125	General discussion of bioavailability and some principal aspects of current bioavailability studies
1126	Use of Laplace transform for solving differential pharmacokinetic rate equations
1127	Model for estimating drug availability which mimics rat gastric absorption

Additional references on biopharmaceutics are provided in Table XXXV.

Effects of Physicochemical Properties—Relative rates of enzymatic hydrolysis of soluble lincomycin esters in dog serum and in simulated intestinal fluid were determined by Taraszka (1128). The significance of these rates in terms of *in vivo* drug activity was discussed. The enzymatic hydrolytic rates of several 1-, 2-, and 3-methyl-2-hydroxyquinolizidines were found uncorrelatable with the duration of corneal anesthetic activity of these esters (1129). The feasibility of achieving

desired timed-release action by the enzymatic hydrolysis of fatty acid ester derivatives of acetaminophen was investigated. Based on *in vitro* enzyme hydrolysis rates and *in vivo* blood levels evaluated for a series of fatty acid esters of the drug, a suitable timed-release dosage form was developed (1130).

Hansch and his coworkers established correlations between the biological data available in the literature on congeneric series of antifungal (1131), hemolytic (1132), and fibrinolytic (1133) agents with their hydrophobic and electronic parameters. In a number of examples, antifungal activity closely paralleled with the antibacterial and hemolytic activity, suggesting that the membrane perturbation may be responsible for the biological activity of these fungicides (1131). A mathematical treatment describing extrathermodynamic structure–activity relations for various sets of congeners causing hemolysis was presented, and the similarity of these equations to those correlating antibacterial action and narcosis was discussed (1132). The relative rates of oxidation of drugs by rat liver microsomes were shown to be a function of their octanol–water partition coefficient (1134). Regression analyses by a modification of the Free–Wilson technique were applied to the phenethylamines as substrates of biosynthetic enzymes of sympathetic transmitters. It was shown that the substitution contribution to the activity of unsubstituted phenethylamine was additive with the use of logarithmic activity data; in certain cases the substituent effects were related to the Hammett σ and the hydrophobic constant π values (1135).

The antimalarial activities of chloroquine and its analogs were subjected to regression analyses by employing hydrophobic, steric, and electronic parameters in the free energy related structure–activity model. The results suggested that hydrophobic or steric properties of the terminal amine group of the four-carbon side chain along with the charge on nitrogen are important in the biological activity of these compounds (1136). Correlations between the hydrophobic, electronic, and steric parameters with biological activity were established in cases of leucomycin and lincomycin antibiotics (1137), CNS active cyclic urea and cyclic thiourea derivatives (1138), CNS active lactams and thiolactams (1139), quaternary ammonium antitumor agents (1140), androgenic steroid esters (1141), and *N,N'*-bis(dichloroacetyl)diamines and substituted naphthoquinones for their inhibition of mitochondrial electron-transport activity (1142). The lipid solubility of cardiac glycosides was closely correlated with the rates of metabolism in the isolated guinea pig liver, whereas only the polar drug metabolites were excreted in the bile (1143, 1144).

The rate of penetration of quinine, salicylic acid and its derivatives, barbital, and lithium across the vitreous barrier of the rabbit eye was shown to be the function of both the lipid solubility and dissociation constant of these drugs (1145). The local anesthetic activity of 4-substituted benzoic acid β-diethylaminoethyl esters was correlated with the carbonyl frequency, saponification, σ-values, and protein binding properties, but not with the pKa, solubility, partition coefficient, or surface activity (1146). The mechanism of bactericidal action of several homologous series of quaternary ammonium compounds was investigated in terms of their interfacial properties, adsorption at the interface, and permeation through a protein–phospholipid film (1147). For a series of tetracyclines, it was shown that with the increased lipophilicity of these compounds, their activity against Gram-negative bacteria decreased, whereas the activity against Gram-positive bacteria was not influenced by the lipophilic characteristics (1148).

A method for calculating relative total molecular energy as a function of its geometry was utilized in predicting structural requirements for biological action of muscarinic agents, cholinergics, nicotinic agents, histamine, and α-adrenergic agents (1149). Although it is now possible to calculate electronic indexes of the drug molecule by means of a high-speed digital computer and the Schröendinger equation, it was viewed that the Free–Wilson method using regression analysis holds more immediate promise in the drug design with optimum biological activity (1150). A review of quantum perturbation theory and linear free energy relations in the study of drug design was presented by Cammarata (1151). He concluded that judgment on the value of physicochemical approaches in the study of drug action should be reserved until their full potential can be realized. Representation of the lipophilic parameter π in terms of molecular electronic indexes was demonstrated for a series of benzoic acid and phenoxyacetic acid derivatives (1152). A relationship between partition coefficient and other measures of lipophilicity, notably polarizability and the molar attraction constant, was described on the basis of regular solution theory (1153). Quantum perturbation molecular orbital theory, combined with multiple-regression techniques, was employed to estimate relative variation in perturbation energy ΔE_i for a family of tetracyclines. The ΔE_i values were in good agreement with the bacteriostatic activity of these compounds and were consistent with the hypothesis that the bacteriostatic action is a consequence of an inhibition in protein synthesis by the association of the antibiotic with a ribosomal site (1154). The interdependence between frequently used parameters in establishing correlations with the biological activity was examined. It was shown that σ, π, and E_R values are not linearly related, whereas significant correlations were found for π and molecular volume, refractivity and molecular volume, and aliphatic π and Taft's aliphatic E_s values. These correlations were considered important for providing guidelines in understanding biological mechanisms of drug action and in drug molecular design (1155). Snyder (1156) presented a review of the electronic, steric, and biochemical properties of psychedelic drugs in relation to their biological activity. The influence of steric and electronic factors upon the activity of several hallucinogenic drugs was evaluated (1157).

Additional studies on the effects of physicochemical properties on drug absorption are listed in Table XXXVI.

Effects of Formulation—The influence of particle size on solubility, GI and dermal absorption, toxicity,

and therapeutic effectiveness of a number of drugs was reviewed (1177). In another review article, the standards established for particle size in several pharmacopeias and the relation between particulate state of a drug and the therapeutic effectiveness were discussed (1178). Phenobarbital suspensions containing drug particles of different size ranges were administered intramuscularly to beagle dogs. The data suggested that the biological availability of phenobarbital in terms of the duration of action can be controlled by the drug particle size (1179). The influence of particle size upon GI absorption and physiological availability was shown for 1-benzenesulfonyl-5,5-diphenylhydantoin (1180) and for nitrofurantoin drugs (1181). Oral administration of aspirin in the solution form yielded 30% faster drug absorption in humans than by administration of the drug in tablet form. The peak levels were reached in 30 min. after administration of a solution as compared to 60 min. after the tablets (1182).

Variation in the physiological availability of chloramphenicol among different solid dosage formulations and their dissolution characteristics were evaluated (1183, 1184). In one study, significant differences in the apparent absorption rate and peak serum concentration in humans were observed among 14 different commercial oral chloramphenicol preparations; the differences were correlatable with the *in vitro* dissolution rates of these products (1183). However, in another study, no such correlation between absorption and dissolution rates of chloramphenicol tablets was obtained (1184). Considerable differences in the drug availability were observed upon oral administration of chloramphenicol to dogs in capsule and in solution forms or by intramuscular injection (1185). The bioavailability of lithium carbonate from a capsule dosage form was shown to be equivalent to that of the solution but was considerably less from a timed-release tablet dosage form (1186). The dissolution characteristics of two capsule formulations of sodium diphenylhydantoin were studied under varying *in vitro* test conditions. The dissolution rates of these formulations correlated with their bioavailability characteristics in humans (1187). The *in vitro* dissolution rates of eight brands of sulfadiazine tablets were compared with the blood and urine levels obtained by these brands. The time required for 10% of the drug to dissolve measured by the *in vitro* test did not correlate with the *in vivo* results (1188). In a similar study, *in vitro* dissolution rates of eight sulfisoxazole tablets were compared with their *in vivo* availability. In this case, the time required for 20% of the drug to dissolve from these samples showed a rank order correlation with the *in vivo* results (1189).

The rate of absorption and bioavailability of warfarin in humans following oral administration of the tablet dosage forms were assessed by pharmacokinetic and statistical analyses of the plasma concentration data. It was shown that the rate of absorption was about twice as fast from the five 5-mg. tablets as from the one 25-mg. tablet, and the relative absorption from one 25-mg. tablet was only about 80% that of the five 5-mg. tablets. Furthermore, it was shown that the *in vitro* dissolution rates of different brands of warfarin tablets correlated with the *in vivo* rate of drug absorption (1190). A protocol for comparing physiological availability of 10 dosage forms of acetaminophen was presented, with specific details on toxicity of the drug, safety precautions, experimental design, and dosage regimen. The blood and urine levels of acetaminophen in 10 human subjects obtained according to this protocol established bioequivalency among a control solution, eight lots of tablets, and an elixir (1191). The bioavailability of nitroglycerin in man from a controlled-release tablet form was mathematically correlated with the *in vitro* dissolution rate (1192). Timed-release tablet formulations of prednisolone phosphate (1193), alprenolol (1194), and a new anorectic agent 4′-chloro-2-(ethylamino)propiophenone (1195) were prepared and tested for their prolongation of *in vitro* and *in vivo* drug release characteristics.

Various aspects of percutaneous drug absorption, including histology and physiology of skin, nature of vehicles, factors influencing the rate of absorption, and methods for evaluating percutaneous absorption, were

Table XXXVI—Additional Studies on Effects of Physicochemical Properties

Reference	Topic
1158	Review of structure–activity relationships in peptides
1159	Review concerning conformations of peptide antibiotics in solution and their biological activity
1160	Review of structure–activity correlation of amphetamines
1161	Review of physiological and physicochemical bases of drug interactions in man; aspects of physicochemical factors, dose-dependent metabolism, and competitive protein binding
1162	Review of pharmacokinetic properties of sulfonamides in relation to certain physicochemical parameters
1163	Influence of molecular weight of hydroxyethyl starch on its physicochemical and biological properties
1164	Passage of sulfonamides through human placenta during early pregnancy correlated with the physicochemical properties of the drug
1165	Review of relation between chemical structure and pharmacological activity of drugs
1166	Relationship between antioxidant activity and antihemolytic activity of vitamin E derivatives *in vitro*
1167	Review concerning hydrophobic, electronic, steric, quantum chemical, and thermodynamic parameters in drug design
1168	Physicochemical factors influencing drug absorption
1169	Review of factors influencing rate of drug absorption and physical characteristics which affect therapeutic quality of raw material (surface, polymorphism, solvates, salt forms, *etc.*)
1170	Effects of substituents on hydrolysis of *N*-acyltryptamines in rats
1171	Hemolytic potency of tricyclic amines (phenothiazines) correlated with ATPase inhibition, surface activity, and partition coefficient
1172	Structure–activity relationships in 4-aminoquinoline antimalarials
1173	Evaluation of hydrophobic or van der Waals' forces in relation to binding of a series of *N*-alkyl-substituted normeperidine homologs to acylcholinesterases
1174	Angina-protecting effect of chromone-2-carboxylate salts increasing with increase in pKa of the base drug
1175	Relative absorption of theophylline, quinine, ephedrine, tolazoline, antipyrine, amidopyrine, *etc.*, in rats correlated with R_f values determined by partition chromatography
1176	Effect of chain length and ring substitution on metabolism, distribution, and biological action of amphetamines

discussed (1196). The penetration of fluocinolone acetonide and fluocinonide steroids through human abdominal skin and across a membrane was investigated as a function of the propylene glycol–water vehicle composition. Terms from the flux equation describing the passive transport of the two steroids across a membrane were shown to be useful in predicting the optimal composition of the vehicle (1197, 1198). In a similar study, a rank order correlation was obtained between the *in vitro* release of fluocinonide from topical creams, the percentage of drug solubilized, and the *in vivo* drug response. The results demonstrated the significance of vehicle composition, drug solubility in the vehicle, and the usefulness of *in vitro* release tests in predicting vehicle efficacy (1199). The composition of the vehicle and drug solubility were considered as important factors in the absorption of glycol salicylate from ointments upon topical or rectal administration (1200). The rate of penetration of salicylic acid and resorcinol through isolated human abdominal skin was studied as a function of drug solution concentration in aqueous and organic solvents (1201).

An *in vivo* isotope technique was employed to evaluate the role of petrolatum, water, and sodium lauryl sulfate upon the percutaneous absorption of sodium chromate, cobaltous chloride, and mercuric chloride in guinea pigs. Absorption was higher from aqueous media and by the use of surfactant than from petrolatum (1202). The percutaneous absorption rates of sulfanilamide-^{35}S from an aqueous bentonite ointment base, hydrogenated castor oil, and a mixture of lanolin and petrolatum were compared. The extent of drug release obtained from these vehicles were in the order: hydrogenated castor oil > bentonite base > lanolin–petrolatum mixture (1203). The absorption, excretion, and biotransformation of dimethyl sulfoxide obtained after topical application of dimethyl sulfoxide, 80% gel, to humans were investigated. Approximately 25–40% of the total dimethyl sulfoxide applied was absorbed within 30 min. Dimethyl sulfoxide was transformed into dimethyl sulfone and dimethylsulfide; the former was excreted in the urine and the latter was eliminated in expired air (1204).

A hydrophilic corneoscleral lens (Hydron), composed of ethylene dimethacrylate–2-hydroxyethyl methacrylate copolymer, was used as a drug delivery system in the treatment of corneal disease. The diffusion coefficient for the drug pilocarpine hydrochloride through the lens of $\sim 1.6 \times 10^{-7}$ cm.^{2}/sec., with the permeability coefficient ranging from 1×10^{-7} to 5×10^{-6} cm.^{2}/sec., was reported (1205). The penetration of fluorescein eyedrops into human aqueous humor was measured to determine the effect of vehicle viscosity on the rate of penetration. Methylcellulose gave increased penetration independent of the viscosity, whereas only higher viscosity polyvinyl alcohol was effective in producing rapid drug penetration (1206). A number of surface-active agents increased the penetration of fluorescein eyedrops into the eye, with up to a fivefold increase obtained by the mixture of polysorbate 20 (Tween 20) and polyoxyethylene alkyl ethers (Brij 35) surfactants (1207). Since the hypertonic fluorescein eyedrops are immediately diluted in the human eye, drug penetration is not facilitated by the administration of hypertonic eyedrop solutions (1208).

Additional studies on the effects of formulation are listed in Table XXXVII.

Absorption Control and Alteration—This section of biopharmaceutics is comprised of studies related to control and alteration of drug absorption by coadministration of drugs or a drug with other chemical agents, disease, blood flow, fasting, route of administration, and age.

The role of bile salts in the intestinal absorption of drugs was investigated by considering: (*a*) the interactions of bile salts with biological membranes and their influence upon drug absorption, (*b*) the effect of bile salt administration on bile flow, and (*c*) the influence of bile flow on the absorption of a poorly water-soluble drug, sulfadiazine. It was shown that the permeability of the biological membrane to drugs is influenced by the adsorption of a conjugated bile salt, sodium taurodeoxycholate, to the membrane (1239). The absorption of sulfadiazine was determined in rat intestine loops *in situ* under four experimental conditions—*viz.*, control, bile duct ligation, sham bile duct ligation, and sodium dehydrocholate-stimulated bile flow. Enhanced bile flow increased the absorption of the drug about 50%, apparently by increasing the solubility and dissolution rate of sulfadiazine. The results suggested that bile plays an important, although not critical, role in the absorption of sulfadiazine (1240). The effect of bile upon absorption of L-thyroxine and L-triiodothyronine was measured in washed loops of rat intestine *in vivo*, both in the presence and in the absence of plasma protein. The data indicated that bile contains a small molecular weight substance which competes with plasma protein for thyroxine binding, or that bile may reduce the binding capacity of thyroxine with plasma protein (1241). Although the bile components, taurocholic acid and glycocholic acid, enhanced the absorption of salicylates through the rat digestive tract, the secreted bile juice and cholic acid had the opposite effect of inhibiting their absorption (1242).

The passive transfer of several drugs across the everted rat intestine can be significantly decreased by the presence of materials causing tissue fluid uptake—*viz.*, glucose and xylose (1243). This was further confirmed by the results showing the influence of hypotonic and hypertonic solutions on the passive drug transfer across the everted rat intestine (1244). Additional studies concerning potassium-ion inhibition of drug transfer across the everted rat intestine substantiated the proposed mechanism that polar drug molecules traverse through intercellular channels existing between the mucosal epithelium cells. In the presence of agents like glucose and potassium ions, which cause tissue fluid uptake, the drug transport is inhibited by the narrowing of the apical portion of the intercellular channel (1245, 1246).

The absorption of soluble antibiotics in the presence of surface-active absorption promoters was studied in the doubly ligated stomach, in the ligated small intestine, and in the intact GI tract of the rat. The results suggested that in the intact GI tract, rapid but transient

Table XXXVII—Additional References on Effects of Formulation

Reference	Topic
1209	Review of drug interactions in the pharmaceutical preparations
1210	Relation between absorption from various formulations and the dissolution process; use of a "Sartorius dissolution apparatus"
1211	Rate and extent of oral absorption of norsulfasol in rabbits from hydrophilized and oil emulsified preparations
1212	Potassium absorption from sustained-release tablets
1213	Continuous release of cyproterone acetate from subcutaneous silastic capsules tested for fertility control in male rats
1214	Development of a two-layer sustained-release nitroglycerin–proxyphylline tablet; buccal and oral absorption studies
1215	Dissolution rates of drugs from tablets after simulation of different modes of intake: (*a*) tablets swallowed whole, (*b*) after disintegration in water, and (*c*) after chewing
1216	Effect of formulation of anagestone acetate on progestational proliferation of rabbit uterus after oral administration
1217	Serum salicylate levels in rats following administration of salicylic acid and sodium salicylate suppositories
1218	Dissolution rates of eight brands of acetaminophen tablets determined by three *in vitro* dissolution test methods; *in vitro* rates not completely correlatable with *in vivo* blood level and urinary excretion data
1219	No significant differences found in phenylbutazone metabolite blood levels after oral administration of drug in tablets or in solution forms
1220	Physiological availability of solid dosage forms of phenylbutazone; correlation of *in vivo* availability with *in vitro* dissolution parameters
1221	Influence of physical–chemical properties of drug, formulation interactions, and urinary pH upon biological activity of drug; experimental data presented for several drugs
1222	Serum levels following administration of indomethacin suppositories to humans were about 60% that of the serum levels obtained with capsules
1223	Halogenated salicylanilide solubilized by nonionic surfactants shown to be biologicaly active upon appropriate dilution of drug solution with water
1224	Release of boric acid, paraformaldehyde, sulfathiazole, chloramphenicol, and other active drugs from powder mixtures of drug with highly dispersed colloidal silicon dioxide determined by agar-dish method
1225	Use of colloidal silicon dioxide in wound dusting powder superior in *in vivo* testing to use of talc
1226	The dog as a quantitative model for evaluation of nondisintegrating sustained-release tablets found satisfactory; specific limitations of the model discussed
1227	Oral administration of thiamine and riboflavin in highly viscous solutions to humans not influencing rate and extent of absorption
1228	Percutaneous absorption of salicylic acid 2-hydroxyethyl ester ointment ~3.6% in 1 hr. after topical application to human subjects
1229	Lipid-soluble and water-soluble *N,N*-dialkylnicotinamides, when employed as topical drug vehicles, increasing skin penetration of active drugs
1230	Transcorneal biphasic availability of tropicamide; quantitative approach for evaluation and design of ophthalmic drug vehicles
1231	Aluminum hydroxide gel preparations, evaluation of sedimentation rates, antigen binding, and macrophage reactions in experimental animals
1232	Potency of chlordiazepoxide, diazepam, medazepam, and nitrazepam in mice after intraperitoneal injection of drugs in various vehicle solvents
1233	Plasma levels and urinary excretion after intramuscular injection of triamcinolone acetonide
1234	Absorption of sulfonamides from several types of suppository bases
1235	Salicylate absorption from six different suppository bases
1236	Effect of vehicle dielectric properties on rectal absorption of acetaminophen
1237	*In vitro* and *in vivo* studies of sulfonamide uptake and absorption from suppositories
1238	Excipients for rectal and parenteral administration of antibiotics and their *in vitro–in vivo* drug release characteristics

promoted absorption occurs in the duodenum–small intestine portion, with little contribution from promoted gastric absorption (1247). The rate of absorption of *p*-aminohippurate and D-xylose across the isolated rat intestine was retarded by tetracycline, whereas absorption was promoted by calcium chelating agents (1248). Simultaneous administration of aminopyrine with antihistamines was shown to yield increased absorption of aminopyrine in the rat intestinal tract (1249). Similarly, administration of aminopyrine with barbital yielded increased blood levels of aminopyrine in rabbits, possibly due to an increased stomach emptying action of barbital (1250).

The influence of food on the oral absorption of phenobarbital was studied in rats. The presence of food decreased the initial rate of absorption, primarily due to slowed gastric emptying (1251). The effect of various foods on the absorption of neomycin from the GI tract of mice was reported (1252). Various high carbohydrate, high protein, and high lipid test meals were administered concurrently with acetaminophen tablets to human subjects to study the effects of foods on the GI absorption of this drug. Although the rate of drug absorption was influenced by the type of test meal administered, the total amount of absorption at the end of 9 hr. showed little difference among test meals (1253). Levy (1254) showed that the systemic availability of acetaminophen, when administered as such, is essentially the same as when administered in the form of its precursor acetophenetidin. These results suggested that the extent of inactivation of acetaminophen during absorption from the GI tract is relatively minor. The reason for the potentiation of reserpine taken orally as reserpine–bile acid coprecipitates seemed to be due to physicochemical factors rather than to pharmacological factors (1255). Succinic acid in 1.1-g./day amounts, administered orally on alternate days, increased the oral absorption of iron in subjects made anemic by frequent phlebotomy. About 20.9 and 13.5% of the administered iron were absorbed when given with and without succinic acid, respectively (1256).

The effects of nonsystemic GI drugs—*viz.*, cholestyramine, an antacid mixture, and psyllium mucilloid, upon the oral absorption of warfarin were studied by concurrent administration of warfarin with the nonsystemic drugs. Cholestyramine resin significantly decreased the plasma levels of warfarin, but the antacid and psyllium colloid did not alter plasma levels of warfarin. *In vitro* experiments demonstrated significant binding of warfarin to cholestyramine above pH 5.5

Table XXXVIII—Additional References on Absorption Control and Alteration

Reference	Topic
1263	Glycine conjugation and accumulation of benzoic acid in rat intestinal tissue
1264	Salicylate and acetanilide transfer across rat intestinal musculature after edetic acid treatment
1265	Effect of surfactants on intestinal permeability to glucose *in vitro*
1266	Intestinal glucose absorption depressed in humans and dogs by phenethylbiguanide or butylbiguanide
1267	Inhibition of lactose hydrolysis by dietary sugars studied in rat intestine
1268	Effect of protein diet upon urine pH reflected in the excretion rate of amphetamine
1269	*p*-Aminosalicylic acid impeding GI absorption of rifampicin in man
1270	Review of reduction of drug action due to decreased bioavailability and pharmacological incompatibility by interactions between drugs
1271	Dicumarol inhibiting active transport of galactose through rat intestine sac
1272	Absorption of molecular compounds of aminopyrine through rat intestine
1273	Kinetics of increased vascular permeability induced in rat skin by serotonin
1274	Penetration of procaine hydrochloride through inverted gastric sac of rat reduced by increase in drug concentration and Tween 80
1275	Factors affecting drug absorption, including gastric emptying, intestinal motility, food, viscosity, blood flow, and drug interactions
1276	Review of potential dangers inherent in concurrent administration of two or more drugs
1277	Urinary excretion of bucolome in healthy adults being delayed by concurrent dosage of aspirin
1278	Elimination of phenacetin and phenazone by man before and after treatment with phenobarbital; elimination rate of phenazone being increased by 40% after treatment with phenobarbital
1279	Effect of neomycin on absorption of glucose from small intestine of rats and on morphology of intestinal mucosa
1280	A cholecalciferol metabolite found highly active in promoting intestinal calcium transport
1281	Calcium in divided doses producing greater absorption than a single daily dose
1282	Kinetics of intestinal iron absorption in rats, and influence of cobalt upon iron absorption
1283	Effect of fever on iron absorption
1284	Absorption and metabolism of guanethidine in hypertensive patients requiring different doses of drug
1285	Absorption, distribution, and excretion of cephalothin, cephaloridine, cephaloglycin, and cephalexin in normal subjects
1286	Complex formation between calcium phosphate and acidic phospholipids involved in migration of calcium ions from aqueous to organic phase
1287	Complexation of novocaine with polyvinylpyrrolidone prolonging analgesic action of novocaine
1288	Effect of aminopterin on lipid absorption, depression of lipid-reesterifying enzymes
1289	Effect of 2-(diethylamino)ethyl 2,2-diphenylvalerate hydrochloride on gastric emptying rate and absorption rate of sulfacetamide in rats
1290	Buffer constituent effect on transfer of salicylate and acetanilide across *in vitro* rat intestine
1291	Influence of various drugs on connective tissue permeability in rats
1292	Effect of methyl phenyldiazenecarboxylate on cation transport and permeability of rat lens studied *in vitro* using ^{86}Rb
1293	Intracutaneous absorption of hydrocortisone from guinea pig skin increasing with increasing concentration of dimethyl sulfoxide
1294	Effect of surfactants on GI absorption of acetylsalicylic acid in rats
1295	Inhibition of the active intestinal glucose absorption after oral and intravenous administration of tetracycline to rats
1296	Enhanced absorption of atropine sulfate, aminopyrine, and sodium salicylate attained in rats by oral administration of relatively dilute drug solutions
1297	Penetration of phenazone, sodium salicylate, tetraethylammonium, and phenolsulfonphthalein across inverted rat gut greater in 10-day-old rats than in 30- or 120-day-old animals
1298	Influence of blood flow on absorption of urea, methanol, and ethanol from jejunum of rats
1299	Normal and surfactant-promoted absorption of vitamin B_{12} from ligated stomach and intact intestine of rats
1300	Absorption and excretion of rifampicin in newborns and children

(1257). Levodopa, when given with L-phenylalanine, decreased the absorption of L-phenylalanine in nine patients with Parkinson's disease. However, levodopa did not affect the plasma disappearance curve of intravenously injected L-phenylalanine (1258). The absorption of tetracycline, oxytetracycline, methacycline, and doxycycline in human subjects was considerably impaired by the simultaneous administration of 200 mg. ferrous sulfate. The mean serum levels were about 40–90% lower when administered with ferrous ion (1259). Chelation is usually considered to be the mechanism responsible for the decreased absorption of tetracycline and other antibiotics in the presence of antacids containing polyvalent cations. However, it has been demonstrated that tetracycline absorption can be reduced to a similar extent by a nonchelating sodium bicarbonate antacid. This effect of sodium bicarbonate appeared to be due to slower dissolution of tetracycline in less acidic gastric media, which leads to decreased drug absorption. Any substance or condition that may elevate gastric pH may decrease dissolution and, hence, absorption of tetracycline (1260).

It has been shown that the protein binding of drugs occurring in eye fluids and tissues has a profound effect on the transport and distribution of drugs in the eye. Consequently, competitive inhibition of this interaction may yield shortened lag time to drug therapy, lower dose requirements, and fewer side effects. These concepts were substantiated by experimental studies showing increased biological activity of drugs in the rabbit eye due to competitive inhibition of drug–protein interactions (1261). Such a mechanism was also attributed to the enhanced phenobarbital narcosis by having other drugs compete for the serum protein binding sites (1262).

Additional references on absorption control and alteration are given in Table XXXVIII.

Absorption Mechanism—The disappearance of salicylic acid and certain other drugs from the *in situ* rat gut lumen was found to be monoexponential, while certain highly lipid-soluble drugs exhibited biexponential disappearance in the same preparation. Experiments with an *in vitro* three-phase model for drug absorption suggested that monoexponential disappearance from

the lumen can be expected when there is negligible accumulation of drug in the membrane, whereas the biexponential disappearance suggests appreciable accumulation of drug in the membrane (1301). A theoretical basis was developed for the performance of drug absorption analysis from the data obtained from the observation of the time course of pharmacological response intensity following single, multiple, or continuous dosing of a drug by any route of administration. This approach was applied for the interpretation of mydriatic response in rabbits obtained upon intravenous infusion of tropicamide (1302) and for the absorption of tridihexethyl chloride following oral and ophthalmic administration (1303).

Bile acid and fatty acid uptake from micellar solutions by intestinal cells failed to reflect the incremental free energy changes expected for permeation that is rate limited by cell membranes. However, altering the size of the diffusing particle or the thickness of the unstirred layer did change the uptake. These observations suggested that the unstirred water layer is the rate-limiting barrier for intestinal absorption of lipids from micellar solutions (1304). The rate of diffusion of drugs through stationary water layers as the rate-limiting process in their action at membrane receptors was verified by the study of contraction response of guinea pig ileum to drugs and the depolarization of the rat isolated sympathetic ganglion to acetylcholine in the presence of eserine. Diffusion half-times measured in pieces of ileum were 4.13 for acetylcholine, 3.60 for carbamylcholine, and 1.01 sec. for potassium chloride. The equivalent thicknesses of the stationary layer calculated from these values were, respectively, 93, 87, and 70 μm. (1305).

The permeability of rat tongue epithelium was investigated to provide information on the accessibility of free lingual nerve endings to chemical stimuli. The rate of penetration from both the rat tongue epithelium and rat skin increased with the increase in the ether–water partition coefficient of the penetrant. In general, the tongue epithelium appeared to be as effective a barrier to chemical penetration as the skin (1306). The buccal absorption of 31 aromatic and aliphatic acids and 10 basic drugs in human subjects showed a parabolic relationship with the logarithm of octanol–water partition coefficient. The optimum partition coefficient for maximum buccal absorption was in the range of $10^{4.2}$–$10^{5.5}$. The log of the permeability constant of a series of alcohols and steroids was linearly related to the log of the partition coefficient measured in three different solvent systems (1307). Ho and Higuchi (1308) provided a rigorous application of the physical model approach, apparently for the first time, to the mechanistic and quantitative interpretation of the *in vivo* buccal absorption of drugs. The results of Beckett and Moffat[1] on the buccal absorption of *n*-alkanoic acids were shown to be in excellent agreement with the theoretical considerations. A self-consistent, biophysically meaningful factor of 2.33 was estimated for the buccal lipoidal membrane–aqueous incremental partition constant for a methylene group. A model involving protein binding proposed for the buccal absorption of drugs was found consistent with the *in vivo* results (1309). The extent of buccal absorption of 16 *p*-substituted acetanilides showed a parabolic relation to the analgesic activity. The correlation appeared slightly better than that between log partition coefficient and analgesic activity (1310). The buccal absorption of five barbiturates was determined over the pH range 3–9. No correlation between the absorption and chloroform–0.1 *N* HCl partition coefficient was apparent, suggesting that the adsorptive power of the buffer–buccal membrane interface may represent more exactly the real affinity of the membrane for barbiturates than the partition coefficients with chloroform (1311).

Additional references on the absorption mechanism are provided in Table XXXIX.

Table XXXIX—Additional References on the Absorption Mechanism

Reference	Topic
1312	Review of permeability of physiological barriers with respect to drugs
1313	Review of mechanisms of drug absorption, displacement, excretion, biotransformation, and enzyme induction
1314	Absorption of some organic compounds from biliary system of rats
1315	Screening of antimitotic drugs for topical effectiveness by intravaginal and intrarectal testing
1316	Review of factors influencing percutaneous absorption and pathways of metabolic transformation of hydrocortisone by skin tissue
1317	Cholesterol and bile salt influxes across brush border of rabbit jejunum
1318	Isolation of dimethyl sulfoxide-soluble components from human epidermal preparations; a possible mechanism of action of dimethyl sulfoxide in effecting percutaneous migration phenomena
1319	Transport of phenols across isolated human skin lipid barrier
1320	Diffusion of sodium shown to occur exclusively in extracellular space of bovine lens cortex
1321	Absorption rates of drugs administered intramuscularly governed by blood flow rather than diffusion coefficient of drug
1322	Surface and interfacial properties of some phenothiazine analogs, and role of lecithin in promoting cation transport through lipid cell membranes
1323	Absorption of oleic acid by guinea pig gallbladder
1324	Mechanism of cobalt and iron absorption in proximal and distal portions of intestine
1325	Decomposition of chlorpromazine during absorption in rat intestine *in vivo* and *in vitro*
1326	Specific physiologic mechanisms underlying role of lymphatics in absorption and distribution of drugs
1327	Mechanism of GI absorption of pteroylmonoglutamic acid in man and effect of intraluminal pH on drug absorption
1328	Pharmacodynamics and biotransformation of pentaerythritol tetranitrate in man; rapid deesterification of pentaerythritol tetranitrate to mononitrate after oral ingestion
1329	Calcium absorption in rat intestinal loops shown to occur both by active transport and by diffusion process
1330	Extent of digitoxin absorption in man from stomach, duodenum, and upper jejunum
1331	Absorption of warfarin from stomach and small intestine
1332	Selective permeability for fructose from small intestine of rat and rabbit
1333	Route of absorption of intraperitoneally administered drugs studied by following drug appearance rates in liver and in systemic circulation of rats

[1] *Added in press:* A. H. Beckett and A. C. Moffat, *J. Pharm. Pharmacol.*, **20**, 2395(1968).

Table XL—Additional References on Drug Absorption

Reference	Topic
1350	Comparative effects of orally administered iron antianemics
1351	Absorption, distribution, and excretion of ^{14}C-kebuzon and ^{14}C-trimetazone in rats
1352	Establishment of dosing schedules for steady blood levels of quinidine in prolonged therapy
1353	Absorption of erythromycin from rectal suppositories
1354	Absorption, distribution, metabolism, and excretion of ^{14}C-labeled rifampicin in the rat
1355	Blood, bile, urine, and fecal levels of sulfiodizole administered to animals and humans
1356	Absorption, distribution, and elimination of metronidazole in rats after oral administration
1357	Absorption and excretion studies of nitrofuran derivatives
1358	Absorption studies of orally administered ^{3}H-thalidomide in rabbits and rats
1359	Intestinal absorption of rutosides
1360	Absorption and excretion of 12 hypnotics in man and animals
1361	Absorption studies of metoclopramide in rabbit
1362	Absorption, distribution, and excretion study of propranolol in rat, dog, and monkey
1363	*In vivo* absorption studies of α-carboxy-3-thienylmethylpenicillin in mice, rats, dogs, and squirrel monkeys
1364	Absorption and excretion of α-carboxy-3-thienylmethylpenicillin in man
1365	Comparative study of absorption and excretion of pivampicillin and ampicillin
1366	Absorption and excretion in man of α-amino-*p*-hydroxybenzylpenicillin
1367	*In vivo* evaluation of α-amino-*p*-hydroxybenzylpenicillin in animals
1368	Excretion of sulfaguanidine, sulfadiazine, antipyrine, and aminopyrine in human eccrine sweat
1369	Absorption and excretion behavior of ^{35}S-encephabol in man and rat
1370	Studies of absorption, distribution, excretion, and metabolism of piromidic acid in man and animals
1371	Serum and sputum levels of some antibiotics of patients with cystic fibrosis or with bronchiectasis
1372	Comparative enteral absorption of some cardiac glycosides in rat using *in vivo* and *in vitro* methods
1373	Intestinal absorption of sodium ferric gluconate
1374	Comparative studies on absorption of some tritiated cardiac glycosides in rats and guinea pigs
1375	Absorption of some phosphorylated pyridoxines in humans and animals

Drug Absorption—Encapsulated bunolol-^{14}C was found to be absorbed quickly by dogs (1334). The peak blood level 1 hr. after treatment corresponded to 4.6% of the dose. In a study of the oral administration of ^{3}H-ouabain, the amount administered was found to be linearly related to the amount absorbed across the intestinal wall in the guinea pig (1335). Plasma levels and urinary excretion of disodium cromoglycate after inhalation by human volunteers were determined (1336). The powder that reached the lungs was absorbed rapidly, with plasma levels reaching a peak concentration 20 min. after inhalation. Total deposition in the lungs of about 7.5% of the dose was indicated, as contrasted to about 1% absorbed by oral administration. An orally administered aqueous solution of toxogonin produced dose-related blood levels of oxime which were lower than those found with similar doses of 2-pyridinium aldoxime methochloride (1337).

An investigation in children of the absorption of amorphous and polymorph A forms of chloramphenicol palmitate suspensions made with polysorbate 80 showed that both forms were absorbed (1338). Although the absorption of the amorphous form was definitely superior, the polymorph A form in suspension with a surfactant was also absorbed to a considerable extent in children, maintaining blood levels of chloramphenicol for a prolonged period. The lack of significant absorption of cephaloridine in rats was apparently due to its low rate of absorption by the small intestines and rapid degradation in the lower intestine (1339). Cephalexin, which was less susceptible to this enzymatic degradation, was found in studies of human subjects to be absorbed rapidly from the intestines, and peak blood levels were reached in 30 min. In another study of cephalexin in adults and children, the drug was found to be almost completely absorbed after oral administration and was well distributed in the tissues, with a partition coefficient of 1 in children and 0.3–0.4 in adults (1340). The absorption and excretion of the calcium salt of phosphonomycin were studied in man after single oral doses ranging from 250 to 2000 mg. (1341). Peak serum concentrations were observed about 2 hr. after injection. Repeat oral doses showed early cumulative effects, reaching a plateau after an interval which appeared to be related to frequency of dosage.

A study of the absorption of propoxyphene napsylate from tablets, capsules, and a suspension formulation, as measured by plasma levels in 10 human male subjects, revealed that the tablet and capsule were equivalent solid dosage forms (1342). In addition, it was observed that tablets of propoxyphene napsylate and aspirin with and without phenacetin and caffeine tended to produce higher plasma propoxyphene concentrations than did tablets containing only propoxyphene napsylate. In another study, plasma propoxyphene concentrations were determined for four normal male subjects given equimolar doses of propoxyphene napsylate and propoxyphene hydrochloride, and the resulting curves were evaluated by a hybrid principal component–analysis of variance technique (1343). No differences between the plasma concentration curve of the orally administered salts could be detected.

An investigation of GI absorption of atropine in man showed that 90% was absorbed in the proximal part of the small intestine (1344). The main absorption of a quaternary anticholinergic compound [piribenzil methyl sulfate (Acabel)] in volunteers was found to be localized in the upper part of the small intestine and amounted to 10–20% of the given dose (1345). Contrary to *in vitro* studies, no evidence was found *in vivo* of its decomposition in the proximal part of the digestive tract. The anorectic, cloforex, when given orally to man and dogs, was decomposed in the GI tract to chlorphentermine and then absorbed (1346). From the data for the renal elimination of chlorphentermine, it was concluded that 30–50 and 50–70% of the oral dose was absorbed in the dog and man, respectively.

The dermal absorption of hexachlorophene from solutions used to wash infants in a hospital was reported (1347). The mean hexachlorophene levels in the umbilical cord rose from 0.022 to 0.109 p.p.m. at the time the infants were discharged from the hospital. No percutaneous absorption following topical application of neomycin sulfate ointments to normal male volunteers was detected by Panzer and Epstein (1348). All

urine and blood samples were found to be negative for neomycin by a sensitive bioassay. Little or no percutaneous absorption of boric acid from topical preparations applied to the intact skin of the dorsal surface of rats was reported (1349). When application was made to damaged skin, the ointments caused boric acid excretion 4–8 times that found in control rats, and an aqueous jelly formulation caused a 34-fold increase.

Other references on drug absorption are listed in Table XL.

Pharmacokinetics—The kinetics of drug absorption in goldfish were examined, using a two-compartment reversible model to describe the occurrence of pharmacologic effect of 4-aminoantipyrine-induced overturn (1376). The results of this investigation suggested that 4-aminoantipyrine-induced overturn in goldfish was absorption rate limited. Based on the experimental conditions of a single luminal perfusion of an intestinal loop, equations were derived which described the dependence of blood flow on the disappearance of a substance from the intestinal lumen and its appearance in the blood and the serosal bathing fluid (1377). Two different four-compartment models were used as the basis of the derivation. Pharmacokinetic parameters were developed to characterize the effects of phase-nonspecific chemotherapeutic agents which attach irreversibly to cell receptors, and a log-linear relationship which evolved was shown to relate the fraction of surviving cells to the drug level–time integral at the pharmacologic site (1378). A new nonlinear pharmacokinetic model was elucidated, and specific application was made to *in vivo* studies of methylene blue conducted in dog, rat, and man (1379).

Serum levels of penicillin activity following intramuscular administration to humans of sodium ampicillin solution, three ampicillin trihydrate suspensions, and sodium dicloxacillin solution were examined kinetically by Doluisio *et al.* (1380). The experimental data at all times agreed with the computer-generated lines when the analog computer was programmed with a kinetic model that depicted absorption as two successive first-order steps. Pharmacokinetic studies involving serum levels at a low rate of intravenous infusion of chloramphenicol and the excretion rate of the drug through the renal system permitted a mathematical derivation of the excretion rate, existing at any given point of time, when chloramphenicol was transferred from the renal system to the urine (1381). Other studies conducted after oral administration of a drug were reported, implying almost complete enteral absorption of chloramphenicol. The 100% absorption of rifampicin when given orally on an empty stomach with no food for the next hour was reported, together with a discussion of factors influencing the kinetics of its elimination (1382). Pharmacokinetic studies of daunomycin in man showed the short plasma half-life to be 0.75 hr., the long plasma half-life to be 55 hr., the apparent volume of distribution to be about 1000 l., and the relative volume of distribution to be 580 l./m.[2] (1383). The disposition of phosphonomycin following intravenous administration in man was found to be adequately described by a two-compartment open model (1384). The pharmacokinetic parameters derived from serum concentration data were found to predict correctly the urinary excretion profile for the same individual.

A novel approach to a pharmacokinetic examination of halothane in man involved a unique 54-detector whole body counter to follow the uptake, distribution, and excretion of a single breath of halothane-^{82}Br (1385). The sum of two exponentials, resulting from a compartmental analysis of the data with the SAAM[2] program, provided an excellent fit. Plasma lidocaine levels in humans receiving 50 mg. of lidocaine hydrochloride as an intravenous bolus over a 1-min. period or 100 mg. over a 2-min. period were interpreted in terms of a two-compartment open model (1386). By assuming linearity between the infusion rate and the plateau concentration, an intravenous infusion rate of 40 mcg./kg./min. was calculated to produce a plateau concentration of 4 mcg./ml. Since subjective symptoms typical of lidocaine were noted in some cases after a 500-mg. oral dose when the blood levels of lidocaine were lower than those following intravenous administration, it was suggested that they may, in part, be due to a metabolite formed during the first passage of the drug through the liver (1387).

Some pharmacokinetic parameters related to the absorption and disposition of fenoprofen administered orally as calcium and sodium salts in man were evaluated, using a two-compartment open model to analyze the plasma concentration data (1388). The bioavailability, distribution, and elimination of fenoprofen were reported to be independent of the salt form of the drug. The comparative pharmacokinetics of orally administered chlorphenesin carbamate and methocarbamol in man were evaluated by Forist and Judy (1389), using a one-compartment open model. No statistically significant differences were found between estimates of mean lag times, half-lives for absorption, and times for attainment of maximum serum concentrations for the two drugs, but the mean biological half-life for chlorphenesin carbamate, 3.14 hr., was significantly greater than the value of 1.20 hr. obtained for methocarbamol. The decline of serum levels in man after oral administration of ethchlorvynol was found to be biphasic; when the data were interpreted in terms of a two-compartment model, the rate constant for elimination was calculated to be 0.13 hr.$^{-1}$ (1390). The indomethacin analog, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, was found to be well absorbed after oral administration to the dog and rat, and the plasma half-lives were 1–2 and 4 hr., respectively (1391).

The pharmacokinetics of multiple diazepam ingestion (10 mg. three times a day for 2 weeks) in psychiatric patients were evaluated (1392). It was reported that the half-life of accumulation was equal to the half-life of elimination in a single one-compartment model and that approximately 94% of the plasma level was reached after a time interval approximately equal to four times the half-life. A study of the disposition of intravenous and oral doses of demoxepam in the dog revealed that: (*a*) the disposition was adequately de-

[2] NIH-SAAM-22 program coder [M. Berman and M. F. Weiss, Users Manual for SAAM (Simulation, Analysis and Modeling)], NIA-MO, NIH, Bethesda, Md., 1967.

Table XLI—Additional References on Pharmacokinetics

Reference	Topic
1403	Multicompartmental analysis of glucose kinetics in normal and hypoglycemic cows
1404	Pharmacokinetic behavior of 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine in man following oral administration
1405	Pharmacokinetic behavior of 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine in man and in rabbits following intravenous administration of sodium salt
1406	Intestinal absorption and distribution kinetics of practolol in rats
1407	Significant effect of blood drainage in the pharmacokinetics of enteral absorption
1408	Michaelis–Menten kinetics of renal tubular secretion of *p*-alkylated mandelic acid in rats
1409	Pharmacokinetic studies with tritiated helveticosol-acetonide in man
1410	Distribution and elimination kinetics of warfarin following intravenous administration in man
1411	Comparative kinetic behavior of triphenylmethane dyes in biliary excretion
1412	Comparative kinetic behavior of xanthene dyes, fluorescein and bromosulfophthalein, in biliary excretion
1413	Saturation of glucuronide formation in man and its implications on excretion of salicylate
1414	Discussion of drug distribution and pharmacological effects in multicompartment systems
1415	Review of pharmacokinetics
1416	Review of kinetics of drug distribution in the body
1417	Review of applications and limitations of radioisotope methods in pharmacokinetic studies
1418	Review of radioisotopes used in interrelating pharmacokinetic and pharmacodynamic parameters in man
1419	Consideration of concentration-dependent rates in a multicompartment drug model
1420	Derivation of an equation for calculating effective serum concentration of a drug based on assumption of exponential absorption and exponential elimination of administered drug
1421	Discussion of pharmacokinetic models in biopharmaceutics
1422	Rate of transfer of clindamycin and 1′-demethyl-4′-depropyl-4′-pentylclindamycin by everted rat intestine
1423	Blood level kinetics of carbenicillin
1424	Pharmacokinetics of penicillin G, penicillin V, oxacillin, and ampicillin
1425	Dose-related changes in kinetic rate constant of rifampicin and confirmation of interference between rifampicin and bilirubin
1426	Pharmacokinetics of gentamicin sulfate in normal subjects and patients in terminal renal failure
1427	Kinetic evaluation of oral absorption of different ampicillin preparations in beagle dogs
1428	Pharmacokinetic studies of ampicillin and hetacillin in man
1429	Absorption, distribution, and excretion kinetics of *p*-chlorobenzenesulfonamide following oral administration in rats, dogs, and humans
1430	Effects of a single oral dose on the pharmacokinetics of sulfametopyrazine
1431	Review of the factors concerned in pharmacokinetics of barbiturates
1432	Pharmacokinetics of ^{35}S-labeled sulfamethoxazole with 2-^{14}C-labeled trimethoprim in man and their distribution in rats
1433	Tinidazole and metronidazole pharmacokinetics in man and mouse
1434	Pharmacokinetics and pharmacodynamics of a diuretic, fursemide, in normal males
1435	Review of pharmacokinetics of chemotherapeutic drugs in relation to age
1436	Review of pharmacokinetics of coumarin and vitamin K
1437	Review of drug excretion kinetics
1438	Review of distribution and metabolism in man of some narcotic analgesics and some amphetamines
1439	Kinetics of absorption and elimination of amphetamines in normal humans
1440	Pharmacokinetics of 2-sulfanilamido-3-methoxypyrazine in children
1441	Review of pharmacokinetics in chemotherapy
1442	Absorption, distribution, excretion, and metabolism in rats of a new diuretic, meticrane
1443	Review of intestinal absorption, transport, activation, and action on cellular receptors of the D vitamins and on the cellular calcium transport system
1444	Review of *in vivo* methods used for investigating absorption kinetics of drugs
1445	Pharmacokinetics of radionuclides and their mathematical treatment with models
1446	Review of kinetics of heparin
1447	Pharmacokinetic behavior of propylhexedrine in rats
1448	Pharmacokinetic study of cobalaminsulfonic acid, hydroxycobalamin, and cyanocobalamin in man
1449	Pharmacokinetics of tritiated acetyldigoxin and *k*-strophanthin in terminal renal insufficiency
1450	Review of urinary excretion as a measure of drug absorption
1451	Simple graphic method for determination of transfer function in a pharmacokinetic multicompartment model
1452	Pharmacokinetic study of methocarbamol-^{14}C in rat, dog, and human

scribed by a two-compartment open model; (*b*) oral demoxepam was apparently well absorbed; (*c*) the rate of elimination varied between dogs, with a half-life of 10–20 hr., but with an individual dog it did not appear to be greatly influenced by the route of administration; and (*d*) elimination proceeded primarily by biotransformation, with excretion of intact drug limited to 10% in the urine and less than 2% in the feces (1393).

A pharmacokinetic analysis of lithium carbonate absorption in man was used to estimate the pharmacokinetic parameters in a two-compartment model for orally administered drug (1394). It was also reported that lithium carbonate in the capsules studied was as available as in the solution (standard), but the drug in the delayed-release tablets was not completely available. The pharmacokinetic properties of fenclozic acid were established in the rat, mouse, guinea pig, monkey, and man after oral dosage and also in the dog, calf, sheep, and horse after intraveous administration (1395). The biological half-life of fenclozic acid varied between 3 hr. in the monkey and 118 hr. in the horse; in the guinea pig, rat, dog, and man the half-life was in the range of 26–31 hr. The disposition of intravenously administered radioactive potassium canrenoate in man was studied, and the elimination of the total radioactivity in the plasma was found to occur in three phases, with half-lives of 0.073, 0.85, and 43.31 hr., respectively (1396). A pharmacokinetic model was presented to predict the detailed distribution and excretion of methotrexate in several mammalian species over a wide range of doses (1397). The rate and extent of levodopa absorption and excretion following intravenous and oral administration of 2-^{14}C-levodopa to acutely and chronically treated dogs were investigated (1398). The efficiency of absorption of total radioactivity was calculated to range between 83.0 and 92.0%.

The *in situ* absorption kinetics of sulfaethidole and barbital from the rat stomach and intestine were reported; with both drugs, absorption from the intestines was found to proceed 10 times faster at a given pH than from the stomach (1399). In all cases, significant transport of ionized drug was noted. In a study of the effect of urinary pH on amphetamine metabolism, the half-life of tritiated amphetamine in the plasma of persons with acid urine (<pH 6.0) was 8–10.5 hr., whereas in persons with alkaline urine (>pH 7.5) the half-life was 16–31 hr. (1400). Urinary excretion of ephedrine in man, without pH control but with adequate urinary flow, was studied following oral administration of ephedrine sulfate (1401). The urinary excretion data were adequately described by the two-compartment open model with first-order absorption and lag time, and the average elimination half-life of ephedrine was 5.99 hr. estimated from the β-values obtained by exponential fitting. The urinary excretion of phentermine, mephentermine, and chlorphentermine in man under normal and acidic conditions of urinary pH was evaluated after oral administration of phentermine and chlorphentermine hydrochlorides and mephentermine sulfate (1402). Phentermine and mephentermine were recovered almost quantitatively within 24 hr. from the subject under acidic urine control; but under similar conditions, only about 35% chlorphentermine was recovered.

Additional references on pharmacokinetics are listed in Table XLI.

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