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Pharmaceutical Sciences—1974: Literature Review of Pharmaceutics

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This review article is a continuation of the annual review of pharmaceutics begun in 1963. As in past reviews in this series (1–13), the scope has been limited to the overall area of pharmaceutics since other specific subjects in pharmaceutical sciences are pub-

lished elsewhere. The authors have used selected sections of *Chemical Abstracts* as well as 40 journals as the sources for this article.

It is hoped that this review will be of continued usefulness to the pharmaceutical scientist wherever pharmaceutical information is needed. The overall format remains essentially the same as that of the last several years; however, some changes have been made to reflect minor organizational improvements.

GENERAL PHARMACY

A four-part series (14–17) reported on a wide variety of pharmaceutical aspects considered during formulation. Topics discussed included dissolution and absorption of drugs, stability studies, physical pharmacy, microbiology, and tableting. A review article on the development of new drugs on a rational basis discussed the selection of factual leads, molecular modification, and perspectives on drug design (18). Two articles gave the current status of prostaglandins as potentially useful drugs (19, 20). Various properties of camptothecin were reviewed including synthesis, structure, and pharmacological activity (21). The pharmaceutical uses of polymers, both water soluble and insoluble, were discussed (22), and the characteristics and uses of gelatin in pharmacy and medicine were presented (23).

Preservatives—Good manufacturing practice guidelines were reviewed with respect to the prevention of bacterial and other contamination (24). The effectiveness of preservatives and their influences on different containers and on bacterial counts of 45 commonly used compounds in drug manufacturing were also discussed. A modified USP XVIII technique was used to test the efficacy of preservatives in emulsions, and the influence of pH on bacteriostatic activity was stressed (25). The choice of an appropriate preservative and the proper level for a cosmetic product in its final package were reviewed (26). The relationship between the antibacterial activity of glutaraldehyde and pH was studied (27). The antipseudomonal effect of polymyxin and phenylethanol was studied alone and in combination (28). The combination had an additive effect on sensitive *Pseudomonas aeruginosa,* while the behavior of resistant strains indicated that cross-resistance occurs between polymyxin and phenylethanol.

The binding of various preservatives, alone and in combination, to cetomacrogol was investigated (29). Data for the compounds alone indicated that all preservatives combined with two distinct classes of sites on the cetomacrogol micelle. A dynamic dialysis method for estimating the binding of preservatives to nonionic surfactants was studied (30), and Scatchard plots for the interaction of methylparaben and propylparaben with cetomacrogol at 25° indicated that there were two classes of binding sites. The minimum inhibitory concentrations (MIC) of five different mercurials against *Staphylococcus aureus* and *P. aeruginosa* were determined (31). Mercuric chloride was the most efficient bactericide, followed by the phenylmercuric salts; thimerosal was the least active.

Table I—Additional References on Preservatives

Reference	Topic
39	Methods for testing disinfectants and antiseptics
40	Preservation of shampoos and foam bathing agents
41	New preservatives for cosmetic and industrial use
42	Chemical and toxicological factors related to preservatives
43	Interaction of preservatives with surfactants and high molecular weight substances
44	Effects of formulation on preservative availability in fixed oil emulsified systems
45	Physicochemical and bactericidal properties of quaternary ammonium compounds in dispersed systems

A number of papers appeared on the preservation of creams and emulsions (32–37). The effect of ^{60}Co γ-irradiation on oil–water emulsion ointments and hydrogels, both contaminated with two test spores, was investigated (38).

Other papers on preservatives are listed in Table I.

Flavor, Aroma, and Color—Several compounds were classified as to odor type (46), but additional research into the field of olfaction and chemistry is needed to prove a definite relationship between structure and odor. The problems and methods involved in improving the taste and odor of drugs were reviewed (47). The behavior of perfumery ingredients in products was investigated by a new technique involving GLC of perfumery ingredients from product bases (48). The method was used to show how materials behave in soaps and laundry powders after various storage conditions. The formulation of floral perfume bases was given (49), and the perfumery of soap was discussed (50).

Model interaction energy calculations using the monopoles-bond polarizabilities method were used to explain the different sweetness levels in a series of 2-amino-4-nitrobenzenes (51). The taste-masking properties of sorbitol were compared to simple sugar syrup (52). The coverings of the bitter taste of quinine hydrochloride solutions, the salty taste of sodium chloride, and the astringent taste of alum by the two sweetening agents were compared. According to statistical evaluation, the taste-masking ability of sorbitol is equivalent to sugar syrup of the same concentration.

Coloring agents, including their legal requirements, for cosmetics were discussed (53). Another article reviewed the physical meaning of color, the chemical composition of dyes, and general and legal requirements of cosmetic dyes (54). Sixteen pharmaceutical coloring agents were studied with respect to solubility, light fastness, heat resistance, stability in relation to pH and oxidizing and reducing agents, and compatibility with drugs in common use (55).

The influence of the surfactants sodium lauryl sulfate, sodium salts of fatty acid methyltaurides, alkyltrimethylammonium chlorides, and betaines on the coloring of hair was investigated (56). The coacervation of alkyltrimethylammonium bromides by various colorants (tartrazine, amaranth, carmoisine, and

erythrosine), in concentrations of 0.15 and 15 mmoles/liter of the dyes and in the presence of certain salts, was studied (57). Both phase separation and microscopic techniques were used at 5–95°. Phase separation diagrams were prepared, the mechanism of interaction was discussed, and the limits of compatibility of dyes with surfactant were defined.

The influence of sunscreening agents on the color stability of tablets coated with FD&C Red No. 3 and FD&C Blue No. 1 was investigated (58, 59). The sunscreening agent giving the best protection against the fading of the red colorant was 2-ethoxyethyl *p*-methoxycinnamate, but none of the agents gave significant protective action for the blue dye. A general discussion of the stability of coloring agents in pharmaceuticals included the following topics: principal photochemical modifications of coloring agents, methods of measuring color changes, measurement of reflectance, and effects of additives for protection against UV and visible light (60).

Stability—Since fructose is sweeter than sugar (factor 173/100), syrups containing fructose were stability tested at various temperatures and found to be very stable at room temperature and also more resistant to microbial proliferation than normal syrups (61). The browning of dextrates in solid–solid mixtures containing dextroamphetamine sulfate was studied by using diffuse reflectance spectroscopy (62). The changes in the physical and chemical properties of aluminum hydroxide gel prepared by the modified Ivanov method were studied (63). The gel prepared by this method remained practically unchanged after 7 years of storage at 4–37°. The degradation of propantheline bromide in the presence of aluminum hydroxide was studied (64), and the decomposition was more rapid in the presence of aluminum hydroxide than in water. The effect of varying climatic conditions such as temperature, humidity, sunlight, and tropical areas on stability was discussed and examples were given (65).

Solid Dosage Forms—Aspirin tablet stability was studied in various plastic and glass containers, which are more commonly used overseas (66). The amount of salicylic acid in the tablets was determined after the containers were stored at 25° and humidities of 30, 60, and 90%. A series of three articles described various experimental attempts to stabilize aspirin including coacervation, recrystallization, and spraying (67–69). Poly(methyl methacrylate) and silicone oil improved the stability of aspirin in tablets, while the coacervation method using ethylcellulose was the most advantageous.

A study was reported concerning the effects of storage in typical British dispensing containers of the glyceryl trinitrate content in tablets of the British Pharmacopoeia (70). Gitoxin, digitoxin, and cordigit tablets were significantly less active after storage under UV light for 10 hr; however, abicine was not affected (71).

Solutions—Aspirin was found to be extraordinarily stable in silicone fluids (72). Its stability also was improved in a polyethylene glycol base by the use of citric and tartaric acids (73). The effect of six kinds of commercial polyphosphates in preventing the oxidation of ascorbic acid and sodium ascorbate solutions in the presence of Cu^{+2} was studied, and the polyphosphates were grouped in three classes according to their effectiveness (74). Nitroglycerin was stable only at a pH <5 unless alcohol was in high concentration (75).

The degradation of ergotamine tartrate in aqueous solutions was investigated at 100° in the 2.5–4.0 pH range (76). Based on this work, the pH of an injectable solution should be 3.6. The major decomposition products of phenylephrine hydrochloride were determined after storage over a wide pH range (77). Methyl and ethyl *p*-hydroxybenzoates were reported to be stable at pH 4 from 40 to 121°, but considerable hydrolysis occurred at pH 1 (78). The stability of prostaglandins E_1, E_2, and E_3 was studied in solvents useful for clinical trials as well as in solvents used for their isolation from biological systems (79). Tryptophan stability was studied in clear glass and amber vials at 5, 25, and 50°; this compound was found to be more stable in amber vials, decreasing only 4% in potency after 6 months at room temperature (80).

The effect of sodium hydrogen sulfite on the stability of epinephrine (adrenaline) solutions was studied (81). The hypothesis that orally administered lanatoside C was converted to digoxin in the gut partly by gastric acidity and partly by intestinal microflora was tested (82). Significant conversion of lanatoside C to digoxin took place at 37° *in vitro* below pH 3.

Ophthalmics—The kinetics of the hydroxide-ion-catalyzed hydrolysis and epimerization of pilocarpine in aqueous solution were investigated utilizing pH-stat titrimetry and NMR spectroscopy (83). Both hydrolysis and epimerization followed pseudo-first-order kinetics. The stability of *l*-epinephrine solution was strongly influenced by pH, with weakly acid solutions being stable for more than 1 year (84). Hydroxyquinoline sulfate, 0.01%, was found to be a satisfactory stabilizer. A mydriatic eye drop containing 0.5–1.0% cyclopentolate was stable for 1 year (85).

Injectable Products—Isoproterenol was inactivated in the presence of metallic ions and was very rapidly decomposed in Krebs solution, but the solution can be stabilized by the addition of edetic acid (86). A crystal growth study of chloramphenicol and prednisolone in injection suspensions led to the definition and the development of a reproducible method to control particle size and included number of particles to be counted, sample preparation, and method of dilution (87). The effects of pH, buffer components, magnesium and calcium salts, ethylenediaminetetraacetic acid, and a number of antioxidants on the stability of oxytetracycline solutions were studied (88). Formulas containing magnesium chloride, *p*-hydroxybenzoic acid, dimethylformamide, propylene glycol, and sodium sulfite at pH 7.5 were the most stable.

The stability of phenylbutazone sodium injectable solutions was improved in the presence of propylene glycol, sodium metabisulfite, and diethylenetriaminepentaacetic acid (89). The stability of urea solutions, which were heat sterilized to destroy pyrogenic

Table II—Additional References on Stability

Reference	Topic
106	Incompatibilities of intranasal drops and ointments
107	Comparative study of the cardiovascular effect of fresh and air-exposed dihydralazine sulfate–reserpine tablets (Adelphane, Ciba)
108	Effect of physical factors on drug stability
109	Stability of prostaglandins
110	Stability of heroin (diamorphine) hydrochloride and cocaine hydrochloride elixirs
111	Stability of belladonna alkaloid
112	Stability of sulfonamides
113	Method of stabilizing ^{125}I-insulin and ^{125}I-STH (growth hormone)
114	Stability and stabilization of phenothiazine derivatives
115	Solid-state thermal decomposition of *para*-substituted salicylic acids
116	Stability of dispensed medicines
117	Decomposition and stabilization of aminoglycol alkanesulfonates
118	Stability of thiabenzenes
119	Acidic hydrolysis of 2-acylamidobenzamide
120	Physicochemical properties, stabilities, and analysis of iodoxamic acid
121	Stability of rutin in artificial gastric juice
122	Stability of tetrahydrocannabinols
123	Stability of amino acids in a parenteral nutrition solution
124	Hydrolysis of meclofenoxate and its methiodide
125	Coloration and stabilization of aminopyrine preparations
126	Reaction of aminopyrine and iodide compounds
127	Review of stabilities of some common drugs
128	Stability of urokinase preparations
129	Stability of androstenedione 3-enol glucosiduronate in solution
130	Stability of monofluorophosphate and fluoride ions in a dentifrice containing calcium carbonate

impurities, was studied; it was found that urea was partially destroyed (90). One percent solutions of morphine hydrochloride and 2% omnopone in polyethylene injection vials were stabilized by use of 6% glycerin and 0.05% disodium edetate (91). The effect of ^{60}Co irradiation on strychnine nitrate and neostigmine (proserine) injection solutions was investigated; frozen solutions were very stable and the decomposition products were less toxic than the starting compounds (92).

The stability of sulfathiazole sodium and sulfamethazine (sulfadimidine) sodium solutions for injection was investigated (93). Thermal degradation rates of reserpine were obtained by measuring the remaining intact drug and found to follow first-order kinetics at various concentrations (94). Further work by the same investigators included the effects of ionic strength, dielectric constant, inert gas, and stabilizers on reserpine stability (95). A proposed formula contains propylene glycol, phosphoric acid, sodium dihydrogen phosphate dihydrate, and sodium sulfite.

Other stability studies on injectable products concerned Ringer–lactate concentrate in ampuls (96), stability of glaucine hydrochloride (97), and securinine nitrate (98).

Semisolids—The concentration of prednisolone in an ointment was decreased by the addition of phenol and diphenhydramine and, especially, by adsorption to zinc oxide or potato starch (99). The degradation of 1% hydrocortisone in polyethylene glycol ointment USP was investigated at several temperatures (100). Decomposition at the C-17 side chain as well as ring A was followed by two different analytical procedures, and the side chain decomposed at the faster rate. Anthralin was found to deteriorate in zinc oxide paste, but this was remedied by the addition of salicylic acid which reacts with the surface zinc oxide to form zinc salicylate (101).

Several studies appeared on the stability of drugs in suppositories. The stability of chloral hydrate in various bases, including polyethylene glycol and estarine D (102), was studied. The effect of various factors on the oxidation of promethazine suppositories was investigated (103). Stabilized vitamin A in suppositories with massa estarinum C showed a similar but higher stability than vitamin A palmitate (104). The decomposition of hexahydroadiphenine hydrochloride in suppositories prepared with either aged or normal cocoa butter and aged Witespol H_{15} converted the drug to its base and *N*-oxide (105). The mechanism of the decomposition, independent of the type of suppository base, was discussed in detail.

Additional references on stability are given in Table II.

Kinetics—The effect of pH (2.75–9.16) and temperature (40 and 50°) on the hydrolysis of methyl-, propyl-, and *n*-butylparabens was studied at 70° in 0.1 *M* phosphate buffer solution at an ionic strength of 0.3; kinetic constants were calculated (131). The influence of cetrimonium bromide on base-catalyzed hydrolysis of *para*-substituted ethyl benzoates was investigated and led to the hypothesis that the observed rate modifications were dependent not only on the *para*-substituent and the surface pH of the micelle but also on the dielectric constant at the surface of the micelle (132).

The kinetics of the alkaline hydrolysis of benzocaine and some homologs in the presence of a nonionic surfactant were studied (133). It was concluded that these compounds were probably associated with the polyoxyethylene portion of the micelle and that the observed change in the rate of hydrolysis was attributed to both a decrease in the rate of hydrolysis and an increase of solubility within the micellar phase. Ethinyl estradiol did not undergo thermal decomposition at 110° over 72 hr, and decomposition depended on excipients such as lactose, starch, polyvinylpyrrolidone, talc, alcohols, and parabens (134). Thermal decomposition under the conditions established produced estrone, estradiol, and doisynolic acid.

The *in vitro* hydrolysis of oxazepam succinate half-ester by a stereospecific soluble esterase from different animal species was reported (135). The kinetics of hydrolysis of salicylamide were investigated under varying conditions of temperature, pH, and ionic strength (136). The hydrolytic degradation of the drug was found to be first order throughout the entire pH range. The conversion of a steroid oxime, 17α-acetoxy-6α-methyl-4-pregnen-3,20-dione 3-oxime, to the corresponding diketone in acidic media

Table III—Additional References on Stability Kinetics

Reference	Topic
139	Stabilization of aspirin in solid drug forms
140	Degradation of aspirin in methoxypolyethylene glycol 350, 550, and 5000 and unsubstituted polyethylene glycol 400
141	Topochemical decomposition patterns of aspirin
142	Kinetics of hydrolysis of aspirin binary systems of water and organic solvents
143	Kinetics of hydrolysis of (1'-ethoxy)ethyl 2-acetoxybenzoate
144	Stabilities of two aspirin preparations containing aspirin and quinine
145	Hydrolytic decomposition of hexobarbital in frozen systems
146	Oxidative destruction of α-tocopherol and ascorbic acid in methyl linoleate
147	Clinical significance of pilocarpine hydrolysis
148	Kinetics of β-lactamase inactivation of penicillins, and effect of competitive inhibitors
149	Solid-state stability of digoxin as a function of temperature and humidity
150	Decomposition of carbazochrome sodium sulfonate in acid and alkaline media
151	Acid–base catalysis of carbazochrome sodium sulfonate decomposition
152	Kinetics of metronidazole hydrolysis
153	Kinetics and mechanisms of solvolysis of 5-iodocytosine
154	Kinetics and reaction mechanism of phenoxybenzamine decomposition in aqueous and aqueous ethanolic solutions

was found to be first order at 37° (137). The effects of incorporating ester groupings at the oxime function or at C-17 position and modifications in the B ring were also investigated; only the length of the ester chain had a profound effect on the rate constant.

A simple experimental procedure was described to obtain estimates of the activation energy and preexponential factor for drug decomposition from a single experiment (138). A computer program was written involving numerical integration, and the method was illustrated using the decomposition of riboflavin in alkaline solution.

Other general kinetic studies are listed in Table III.

Antibiotics—The stability of procaine and potassium salts of penicillin G in oleaginous systems containing colloidal silica was studied (155). Results indicated that instability of penicillin G in these bases was due to the surface acidity of the silica in conjunction with the ester constituents of the oils. The formation of hydrolysis products of Bulgarian penicillin G was dependent on temperature, pH, and storage time; the development of the degradation products, penicillenic and penicilloic acids, was the cause of allergic reactions (156). The kinetic degradation of methicillin, penicillin V (phenoxymethyl penicillin), and their penicillenic acids was studied in an effort to explain their role in penicillin hypersensitivity phenomena (157).

Another paper also described the kinetics of penicillin stability because of the proposed role of the degradation products in causing allergic response (158). Papers also appeared describing the stability of semisynthetic penicillins and 6-aminopenicillanic acid in aqueous solution (159), as well as carbenicillin degradation in aqueous solutions (160). Three ampicillin studies were concerned with the effect of pH on the stability of ampicillin sodium solutions (161), the stability of ampicillin in aqueous suspension (162), and the stability of betacillin in aqueous solution (163).

Various factors affecting the stability of tetracycline hydrochloride in ointments were studied; included were the effects of preservatives, aseptic processing, light, temperature, and the type of base (hydrophilic or lipophilic) (164). A number of tetracyclines was studied by differential thermal analysis and differential gravimetric analysis (165). A review article on the chemical stability of tetracyclines in aqueous solution listed references on the formation of epimers, anhydro compounds, isomers, and various oxidation products (166). The addition of solubilizers, urea, thiourea, polysorbate 20, and polyethylene glycol 6000 to tetracycline solutions significantly reduced epimerization of the drug (167); it was suggested that occasional kidney damage may be caused by the epimerization.

Stability kinetic studies of oxytetracycline hydrochloride in solutions were performed (168). The effect of different pH's and buffers on the solubility and stability was determined. Also the effect of magnesium, calcium, edetate (EDTA), pyridine derivatives, aromatic oxyacids, water-soluble antioxidants, and inert gases on the stability of the drug in solution was studied. Two stable injection formulations were presented. Another study found that the addition of glycerin, propylene glycol, polyethylene glycol 400, dimethyl sulfoxide, and water was detrimental to oxytetracycline in ointments (169). Rolitetracycline was found to hydrolyze rapidly in dilute aqueous solution (170), and the base was less stable than the nitrate salt. Other workers reported that rolitetracycline was hydrolyzed to tetracycline and 4-epitetracycline in aqueous solutions at 25° (171); both the base and salts were >50% hydrolyzed in 3 hr and the degradation was probably first order. The dehydration kinetics of epitetracycline in solution to form epianhydrotetracycline were investigated (172), and the reaction was found to be first order with respect to epitetracycline and hydronium-ion concentrations.

Table IV—Additional References on Antibiotic Stability

Reference	Topic
175	Decomposition of chloramphenicol stored in frequently opened vessels
176	Effects of aging and relative humidity on drug release of chloramphenicol capsules
177	Physical compatibility and chemical stability of cephapirin sodium in combination with antibiotics and large volume parenteral solutions
178	Stability of frozen solutions of cephapirin sodium
179	Compatibility of antibiotics with gels of semisynthetic and synthetic products
180	Transformation of the factor M of virginiamycin in acid medium
181	Stability of auricular stamycin solutions
182	Stability of nisin preparations
183	Stability of parenteral solutions of cefazolin sodium

Two papers appeared on the intravenous solution stability of amphotericin B stored in 5% dextrose–water solution (173, 174). No appreciable loss in activity was found with the antibiotic alone or in the presence of hydrocortisone and heparin, even when exposed to light; however, sodium and chloride ions were very deleterious to stability of amphotericin, reducing the potency 25% in 4 hr.

Other references relating to antibiotic stability are listed in Table IV.

Vitamins—A number of factors improved the stability of multivitamin oral liquid preparations (184). These factors included the use of glass-distilled water, 0.01% disodium edetate, 0.05% sodium glutamate, and 0.01% cysteine hydrochloride; purification of sucrose with activated carbon; and protection from light and oxygen. Two other articles discussed general vitamin stability in pharmaceutical preparations (185, 186).

The effect of two nonionic surfactants on the aerobic oxidation of ascorbic acid and thermodynamic properties was obtained for vitamin C solutions containing 1% surfactant (187). On storage at 37° and 100% relative humidity, the stability of ascorbate salts was Ca > Mg > Na > K, although they were much less stable than the free acid and the stability was even lower in talc and silica formulations (188). The effect of pH on the rate of coloration of 1% ascorbic acid in 60% sorbitol solution at 37 and 47° was studied, and kinetic constants were calculated (189).

The compatibility of vitamin B_1 preparations in combination with other drugs was studied. Vitamin C did not affect various B_1 derivatives, but those containing B_{12} were decomposed (190). Tablet stability of vitamin U was determined (191, 192), and the effect of fillers on the stability was reported (193). Excipients such as mannitol, lactose, and dicalcium phosphate imparted high stability to vitamin U, but aluminum hydroxide and magnesium hydroxycarbonate had adverse effects on the stability of tablets in storage.

Additional references on vitamin stability are listed in Table V.

Table V—Additional References on Vitamin Stability

Reference	Topic
194	Transformation of vitamin A aldehyde in hydroalcoholic and other aqueous cosolvent solutions
195	Stability prediction of thiamine and L-ascorbic acid in multivitamin tablets and capsules
196	Stability of thiamine, pyridoxine, and hydroxocobalamin hydrochloride in parenteral form
197	Effects of hydrotropic salts on stability of menadione
198	Determination and stability of pantothenates in drugs
199	Compatibility of vitamin B_{12} preparations in combination with other drugs
200	Stability of water-soluble vitamin P
201	Decomposition of L-ascorbic acid in the presence of D-araboascorbic acid
202	Hydrolysis of benfotiamine in aqueous solutions
203	Effect of low storage temperatures on stability of medicinal cod liver oil
204	Stability of parenteral solutions containing amino acids, vitamin B, sugar alcohol, and commercial mineral mixtures

PHARMACEUTICAL TECHNOLOGY

New drug forms resulting from present technological developments, with emphasis on microencapsulation, were reviewed (205). The clinical and design aspects of medicines for oral administration were discussed (206–208). Preparations of gastric antacids were checked for onset and duration of buffer effect against artificial gastric fluid by an *in vitro* test method (209).

Sterile Products—A new sterile products laboratory incorporating the latest developments in the field was described (210), and the anticipated revisions in current good manufacturing practice regulations were reviewed (211).

Several papers concerning particulate contaminant problems were published. An assay procedure utilizing the scanning electron microscope for counting asbestos and other inorganic fibers in fluids was described, along with a method for testing the membrane filter retention of asbestos fibers (212). Examination of 22 sterile solid products for particulate matter using the standard membrane filtration technique indicated that this class of products contained an appreciable number of particles, of which more than 95% are 5–50 μm in size; small volume injections in a similar manner contained approximately half the total number of particles on a per vial basis (213).

Polyvinyl chloride and glass large volume parenteral containers were examined to determine the effects of agitation, storage, and additive handling on the generation of subvisual particulate matter, and it was found that shaking and temperature generated small particles in the polyvinyl chloride containers (214). Particle contaminants from saline and dextrose intravenous solutions were sized and counted using the Prototron instrument (215). Various particle contaminants were identified and these included salt crystals, starch grains, glass fibers, mica flakes, and metal shavings. The general problem of asbestos and other fibers in parenteral solutions was reviewed (216–218), and the particulate contamination of dextran for intravenous use was studied (219).

The incidence and potential for microbial contamination of glass bottle and plastic bag systems used for intravenous fluid administration were estimated from results obtained in a study simulating both hospital and centralized admixture program use (220). Two other articles discussed the microbial contamination of packaged fluids after sterilization (221, 222).

The methods of particle counting in infusion fluids were discussed (223). Another article compared the Coulter counter, the HIAC automatic counter, and a microscopic membrane method in their ability to measure different types and sizes of contamination (224). The use of the Silting index was suggested as an alternative to particle counting (225); this method

Table VI—Additional References on Sterile Products

Reference	Topic
233	Method for aseptic filling of unit dose syringes
234	Preparation of glycerol solutions for intravenous administration
235	Aqueous injection solutions of vitamin A
236	Formulation and stabilization of phenylbutazone sodium injectable solution
237	Limulus test for *in vitro* pyrogen detection
238	Preparation and stability of menadione injection
239	Production of sterile sodium alginate solution
240	Parenteral administration of ethoxypolysiloxane oil
241	Preparation of injectable solution of nivalidine methiodide
242	Solubilization, emulsification, and dispersion with surfactants in parenteral preparations
243	Incompatibility and other problems involved in adding drugs to intravenous fluids
244	Drug additive compatibility
245	Side effects from glucose injections traceable to nitrogen content
246	Behavior of erythrocytes in water–monohydric alcohol solutions
247	Quality control in manufacture of parenteral solutions
248	Control of infusion sets according to requirements in the Nordic Pharmacopoeia

is based upon the tendency of particles to clog a filter, and the flow rate decrease is proportional to the particulate contamination in the test fluid.

Preparative methods for purifying water were described including vapor pressure distillation (226), reverse osmosis (227), ozonation (228), and filtration (229). Removal of pyrogen in physiological saline solution was studied by filtration through Chamberland 25C, Seitz Sheet EKS-I, and activated-carbon Chamberland (230).

A report pointed out the possibility of the precipitation of poorly water-soluble drugs contained in a nonaqueous vehicle when the solution was mixed with human plasma (231). The compatibility of certain vitamins combined with other parenteral solutions was studied (232).

Other papers concerning sterile products are listed in Table VI.

Ophthalmics—The action and uses of a number of topical ophthalmic drugs were discussed (249). The development of radiosterilized tetracycline ointment was reported, and the cost savings feature of cobalt 60 γ-ray sterilization in the final package made it an attractive alternative to conventional aseptic manufacturing and packaging (250). It was found that the amount and rate of drug loss through drainage for a single drop of topically applied ophthalmic solution increased with increasing volume of instilled solution (251). However, the concentration of drug in the precorneal tear film immediately after installation of drug was higher with larger instilled volumes. Ocular absorption of drugs using various vehicle modifications was reported (252, 253). The formulation of a semisolid oleaginous ointment base employing a polyethylene[1], fused micronized silica, and sodium stearate was studied (254, 255).

[1] Epolene C-10, Eastman-Kodak.

Table VII—Additional References on Ophthalmics

Reference	Topic
256	Stability of palmatine eye solutions preserved by a quaternary amine hydrochloride
257	Effect of polyvinylpyrrolidinone on stability of sodium sulsaphiazole eye drops
258	Formulation of a stable pilocarpine hydrochloride solution
259	Determination of steroid level in aqueous humor after application using hydrophilic contact lenses
260	Formulation of ophthalmic suspensions containing steroids

Other references on ophthalmics are listed in Table VII.

Sterility and Sterilization—An approach to the establishment of parenteral solution sterilization cycles was offered (261). A comparative study of seven media and two systems for sterility testing was presented (262). The use of ethylene oxide as a sterilant was the topic of many reports. Articles sterilized with ethylene oxide released the gas at rates depending on materials and methods of manufacture (263). A mixture of ethylene oxide and acetic acid (1:1) was as effective as a mixture of ethylene oxide and carbon dioxide but was more rapidly desorbed. Extracts of polypropylene syringes that had been sterilized with ethylene oxide did not inhibit growth of *Staph. aureus*, were not toxic to mice after intravenous injection, and did not cause hemolysis upon addition to erythrocyte suspensions (264).

Naturally contaminated samples of sodium alginate treated with ethylene oxide showed a significant drop in viable microbe content without affecting viscosity (265). Ethylene oxide sterilization procedures were discussed as potential generators of chemical toxicities by way of an alkylating agent reaction mechanism (266). Detection procedures for ethylene oxide, ethylene glycol, and ethylene chlorohydrin residues in sterilized materials were reviewed, and 65 references were given. The role of packaging on ethylene oxide permeability was reported. Both 100% ethylene oxide and a dichlorodifluoromethane–ethylene oxide mixture were studied in conjunction with the following materials: 4-mil polyethylene, polyethylene/tyvek, paper, and paper/polyethylene terephthalate (Mylar) (267). Both the packaging and the sterilization cycle played a role in effective sterilization using ethylene oxide. It was found that hard and soft polyvinyl chloride as well as cellophane were sometimes more gas permeable for the mixture of ethylene oxide and methyl formate than pure ethylene oxide (268).

A discussion on the principal factors affecting sterilization, *i.e.*, gas concentration, temperature, humidity, and time, was presented and a detailed sterilization cycle was given (269). Various polyvinyl chloride and rubber materials were sterilized with ethylene oxide, and the residual amount of gas was determined as well as the biological compatibility (270). It was found that the desorption rate was markedly faster at 50° than at ambient temperature. The treatment of naturally contaminated materials was inves-

Table VIII—Additional References on Sterility and Sterilization

Reference	Topic
289	Sterilization of polymers for medical devices
290	Dosimetric substantiation of sterilization of radioactive pharmaceutical preparations
291	Review of sterility testing methods
292	Short-time sterilization of glass materials under ultraclean conditions
293	Microbiological sterilizing characteristics of 1,5-pentanediol aqueous solutions
294	Influence of thermal sterilization and storage on quality of nonstabilized and stabilized fixed oils
295	Optimal conditions for sterilization of buffered glucose solutions
296	Continuous automatic sterilization of parenteral solutions
297	Detection of fungi and yeasts in presence of preservatives
298	Sterilization of particulated atmosphere
299	Control of sterile medical equipment
300	Leakage of spray cooling water into topical water bottles
301	Bactericidal capacity of sodium dichloroisocyanurate formulations used for sterilization of infant feeding bottles and teats
302	Aeration of medical plastics
303	Sterility of a sterile powder-filling line

tigated (271), and the inactivation kinetics of ethylene oxide were discussed with respect to concentration, temperature, relative humidity, and other effects (272).

A number of papers discussed radiation sterilization of various plastics. Samples of plasticized polyvinyl chloride were irradiated with 2.5-Mrad doses of γ-radiation from ^{60}Co and 2.8–3.4-Mrad doses of β-radiation from a linear electron accelerator (273). Electron beam sterilization could be used for this plastic if it was not to be in direct contact with blood. Another paper pointed out that γ-irradiation prior to sterilization with ethylene oxide enhanced 2-chloroethanol formation in a surgical, hospital grade, polyvinyl chloride tubing (274). Another study indicated that polymethacrylate, cellulose derivatives, and polytetrafluoroethylene products were unsuitable for radiation sterilization but that polyvinyl chloride, polyethylene, polypropylene, polyethylene terephthalate, polyamides, polystyrene, silicone rubber, and rubber materials were sterilized satisfactorily (275).

Six kinds of polystyrene were irradiated with 4–5 Mrad of γ-radiation from ^{60}Co, and a study of their chemical and physical–chemical properties showed no harmful effect from this treatment (276). The practical application of radiosterilization of an ophthalmic and nasal ointment of neostigmine bromide, 1%, and dexpanthenol, 5%, with ^{60}Co as the radiation source was studied (277). Two levels, 2.5 and 4.5 Mrad, were used; sterility was achieved with the higher dose. The chemical stability of these drugs was satisfactory, but the tubes exhibited gas formation and an increase in volume and leakage. Two papers reported the sterilization of dry ampuls containing chlordiazepoxide hydrochloride (278, 279).

A series of selected colorants composed of eight FD&C dyes, seven lakes, and four D&C dyes was subjected to 2.5 Mrad of γ-irradiation from a cobalt 60 source over approximately 10 hr (280); no changes were found in these materials and they were all shown to be sterile. Another study reported that colorants were not affected by thermal or radiation sterilization, but decomposition occurred when they were tested in an experimental tablet mass (281). Other papers reported on the use of high frequency sterilization (282) and formaldehyde gas as a sterilant (283). Some drugs were decomposed by the high frequency method.

Three papers discussed experiences using biological indicators (284–286). The use of isopropyl myristate as a solvent in the sterility testing of oleaginous-based ointments was investigated (287, 288).

Other references pertaining to sterility and sterilization are listed in Table VIII.

Tablets and Capsules—Content uniformity criteria, including tests currently in the USP and NF, were studied using computer simulation (304). The results were compared with selected tests by variables for reliability, flexibility, and simplicity. Another paper reviewed the quality control aspects of compressed tablets (305). The formulation of effervescent aspirin tablets was investigated (306). Various methods, *i.e.*, sugar coating and press coating, were studied along with other factors to prepare a tablet containing pepsin and pancreatic enzymes (307).

Tablets containing pancreatin and barium sulfate were subjected to the USP XVIII disintegration test with and without plastic disks (308). The same tablets were given to two groups of people, one with normal stomachs and the other with reduced stomachs; the fate of the tablets in the digestive tract was radiographically documented. General background information and some advantages of formulation into soft gelatin capsules were published (309). A review on formulation of products in hard gelatin capsules discussed the rate of dissolution, release of the active ingredient as a function of particle size, porosity of the active ingredient, and addition of surface-active agents, diluents, and lubricants (310).

Additional general references on tablets are: *in vitro–in vivo* correlation and aging studies of commercial hydrochlorothiazide tablets (311), design of tests for content uniformity (312), degree of disintegration and solubility of tablets as characteristics of their high quality (313), and review of apparatus and methods for improving tablet formulations (314).

Comminution, Mixing, Granulating, and Drying—The milling of pharmaceutical solids was reviewed (315). Another report discussed the problem of obtaining fine particle sizes and the measurement of tensile strength, hardness, and breaking strength of particles, as well as the types of mills used (316). Various physical factors affecting blending of solids were presented together with methods of measuring mixedness (317). The mixedness of 10% ^{113m}In–phenobarbital triturations using three different fillers was evaluated (318). A mixture of fine and crystalline lactose was better than crystalline lactose alone or starch (corn) mixed with fine lactose.

The homogeneity of multicomponent powder mixtures was studied, and a numerical value for mix-

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

Reference	Topic
331	Homogeneity of pharmaceutical dispersed systems
332	Measurement of mixing of pharmaceutical powders using indium-113m
333	Review of various aspects of granulation
334	Effects of milling on granulation particle-size distribution
335	Manufacture and stability of tablet containing L-ascorbic acid and ferrous nicotinate
336	Influence of different factors on *in vitro* dissolution rate of tolbutamide from tablets

edness was mathematically derived (319). A twin-shell blender was used to investigate the blending procedures used in mixing aspirin–lactose (1:99) blends (320). Powders having good flow were less apt to show unmixing tendencies, and better blends were obtained when the amount of solvent was limited since this prevented excessive drug migration. A vertical cone mixer was used to mix a single active component, fenfluramine hydrochloride, with a number of diluents used for production-scale tablet preparations (321). The mixing operation was followed by the analysis of the drug in a number of samples equivalent to the final tablet size.

Reserpine was spray coated onto calcium sulfate granules of different porosities, and the relation between the macroporous nature of the granules and their reserpine content was investigated (322). The effect of fines on the physical properties of a starch–lactose granulation and the corresponding tablets was reported (323). An apparatus was made to measure granulating pressure so that it might be related to the amount of binder used as well as to its surface tension (324). Mathematical calculations were made relating power consumption during granulation of viscoplastic materials in a blade-type mixer (325). Mathematical formulations were also derived for calculating the dynamic coefficient of friction for materials used in the wet granulation process in a blade-type granulator, and the accuracy was checked by experimental runs with various drugs (326).

It was reported that compression of a barbital sodium granulate was greatly affected by moisture content (327). Various solvents were evaluated for use in granulating fusidate sodium (328). The relationship between moisture content and the quality of finished tablets of various drugs was investigated (329), and the optimum conditions of drying urodan granules in a fluid bed dryer were studied (330).

Other references on comminution, mixing, granulating, and drying are listed in Table IX.

Powder Characteristics—The flow of powders and granular solids in an excentric tablet press with the punches removed was measured (337), and the results varied widely compared with those obtained with a flowmeter. Six kinds of granules from four powdered materials, lactose, calcium carbonate, barium sulfate, and zinc oxide, were prepared by extrusion and crushing procedures (338). Physical properties were measured and related to flow rate. The influence of particle shape, hygroscopicity, electrostatic charge, and particle size on powder flow was reviewed (339). A statistical study of tablet uniformity in which the drug medazepam was mixed with three fillers at two particle sizes and two dosage levels was reported (340).

The cohesive force effect of magnesium stearate addition (0.2–1.0%) to salicylic acid was investigated (341). An equation was developed to estimate accurately the flow rates of powders from circular orifices in which flow is dependent on orifice opening, specific gravity of the powder, and a fluidity index obtained by the variable rotating cylinder method (342). Magnesium carbonate, encapsulated with various polymers, showed variations in resultant physical properties such as angle of repose and flow and could be tableted (343). The effect of the choice of excipient on the mixture quality of the unmilled drug, cyclopenthiazide, was investigated, and segregation of the drug mixture could be avoided by using wheat or maize starch in place of lactose (344). The effects of certain process variables were determined for the spheronization process (345).

Various methods of measuring the tensile strength of compacted powders were described including transverse compression using squares and disks as well as the direct tensile stressing of lightly pressed powder (346). The failure properties of lactose, calcium carbonate, and ultramarine were determined, and it was found that narrow size fractions behaved as simple powders (347). The packing properties of moist bulk solids were studied using glass powder, potassium chloride, and calcium phosphate (348). Powder bed densities were found to be dependent on the concentration of calcium stearate and the cumulative number of revolutions in a V-type blender (349).

Compression—The compressibility of sulfanilamide granules and starch was studied by means of a rotary tablet machine fitted with strain gauges (350). The effect of various factors including the method of granulation, residual moisture content, and binder concentration was reported. A follow-up study determined the effect of nonionic surfactants on the compressibility of sulfanilamide granules (351). The strength of compressed tablets was markedly improved in the presence of 1% silica (Aerosil), whereas certain cellulosic materials improved disintegration times (352). Photomicrographs of potential tablet disintegrants in polarized light before and after water treatment revealed the relationship between swelling factors and tablet disintegration. A variety of dextrose (Celutab) was found to be suitable for the preparation of tablets containing aspirin, phenacetin, and caffeine citrate by direct compression (353). Physical changes due to high frequency and tray drying of tablet cores containing a strongly moisture binding antibiotic, which had different coatings in selected solvents, were studied (354). Drying was shown to result in improved stability of aspirin-containing tablets.

No constant relationship was found between tablet compressive force and the tablets *in vivo* and *in vitro* properties (355). A timed-release salicylamide tablet

Table X—Additional References on Compression

Reference	Topic
364	Regulation of structural–mechanical properties of tableted substances
365	Factors influencing physical properties of tablets
366	Influence of water content of pharmaceutical powders on compacting phenomenon
367	Compression under constant upper punch pressure, and behavior of particles filling in voids
368	Influence of particle shape on cohesion of particulate solids
369	Influence of tablet weight on compaction pressure–tablet density relationships
370	Effect of rate on pressure of pressing tablets
371	Compaction of chemical–pharmaceutical powders
372	Solid-state distribution analysis of sulfisoxazole tablets
373	Physics of solid state as related to dosage form design
374	Pressure transmission to lower punch during compression of potassium chloride
375	Log-normal distribution of tablet pore diameters

was made using two types of sodium carboxymethylcellulose; compressive force affected release only slightly with one type of the cellulose polymer but was slowed with the other type (356). The dissolution rate and surface area of phenacetin tablets made with wheat starch and talc were investigated (357).

The relationship between compression stress and displacement of the upper punch was studied to clarify the viscous behavior of powder when a compressed sample was recompressed (358). There appeared to be a hysteresis loop in the stress–displacement diagram; from the loop area, loss energy, depending on the viscosity of the sample, was calculated. The relationships among axial pressure, radial die wall pressure, and density changes in beds of powder undergoing compression were studied using a single-punch instrumented tablet machine (359); data were developed for aspirin, sodium chloride, acetaminophen (paracetamol), and sucrose. Tablets formed from dendritic sodium chloride crystals, which had a larger shape index than cubic crystals of the same size fraction, were stronger than tablets formed from cubic crystals (360).

A new method for determining the tensile strength of tablets was proposed utilizing two fulcrums and a knife edge (361). The results agreed well with tensile strength values obtained from diametral compression. A report on the use of an industrial scale compactor compared the results of various granulation procedures using aspirin, potassium chloride, and a sulfonamide (362). The criteria for using different materials for the dies of rotary tablet machines were discussed, and recommendations for the types of steels for press-molding machines were given (363).

Other references on compression are listed in Table X.

Effects of Excipients—A compressible starch (STA-Rx 1500) was compared as a compression vehicle with potato, maize, and rice starches, Dry Flo starch, cellulose (Solka-Floc), microcrystalline cellulose (Avicel pH 101), and anhydrous lactose USP in aspirin tablets (376). The resulting tablet properties were measured; the compressible starch (STA-Rx 1500) was found to be a good vehicle, but magnesium stearate adversely affected tablet properties. The use of potato starch as a disintegrant was reviewed, and water contents were given after drying and after storage at various humidities (377). High concentrations of starch were used in hard gelatin capsules to improve the release of phenobarbital (phenobarbitone) (378).

Two special directly compressible blends of microcrystalline cellulose with starch and calcium sulfate were investigated (379). It was shown that hydroxypropyl cellulose could be a useful binder in direct compression tablet formulations when properly combined with potato starch and lactose (380). It was demonstrated that tensile strength of lactose tablets decreased as the fatty acid composition of tablets increased (381). The presence of glucose in industrial lactose at various stages of purification and the effect of glucose on the quality of lactose for pharmaceutical use were determined (382). The pore structure of tablets made from wet massed granules and from crystalline granules was compared (383). Tablets made from crystalline granules showed a monosized pore structure regardless of granule size or compression pressure. Direct compression formulations containing microcrystalline lactose, dicalcium phosphate, microcrystalline cellulose, and starch derivatives were characterized using an instrumented rotary tablet machine (384).

L-Leucine and L-isoleucine were investigated as tablet lubricants and compared to other widely available lubricants (385). The addition of 5% L-leucine and 1–5% L-isoleucine gave almost the same effect as 1% magnesium stearate. The use of magnesium lauryl sulfate in tableting was evaluated using ejection force and compressibility measurements (386). A calcium carbonate–starch paste granulation was suggested as a diluent for tablets (387).

The effect of the binders, cellulose acetate phthalate, ethylcellulose, and shellac on the release of thioridazine from tablets was investigated (388). The effect of disintegrants and lubricants on the antimicrobial activity of tetracycline hydrochloride and chloramphenicol after tableting was determined (389, 390). These components caused activity losses of these antibiotics to varying degrees.

A method for the rapid evaluation of the effect of excipients on color fading was suggested; it involved the use of a fadeometer to accelerate light-induced fading followed by spectrophotometric evaluation (391). A photographic technique was developed to measure the degree of mottling of calcium phosphate tablets colored with FD&C Blue No. 1 (392). Optimization of the photographic process was described, and mottling values calculated by this method correlated well with the visual appearance of the tablets. Inclusion of wheat and potato starch (20%) in granule formulations reduced mottling and increased elasticity, suggesting that the elasticity of the granules enables them to retain their original shape after deformation under pressure (393).

Table XI—Additional References on Effects of Excipients

Reference	Topic
394	Effect of disintegrating agents on texture of tablets
395	Effects of formulation factors on dissolution rate of sulfamethazine (sulfadimidine) tablets
396	Relationships between amounts of binders and maximum granulating pressure
397, 398	Dissolution and disintegration of experimental phenindione tablets
399	Effects of disintegrant concentration on disintegration and compression characteristics of two insoluble, direct compression systems
400	Evaluation of two types of cellulose for direct compression

Other references on the effects of excipients are listed in Table XI.

Tablet Coating—Acrylate-based products were suitable for the manufacture of film tablets and other coated dosage forms (401). The use of polyvinyl alcohol in preparing tablet coatings with and without sugar was described (402). Drug coating materials soluble in the small intestine were prepared from succinate monoesters or succinate maleate monoesters of cellulose ethers (403). Various quantities of cellulose acetate phthalate were applied to barium sulfate tablets, and the homogeneity of the films was assessed by a statistical study of thickness (404). The results showed a linear relation at constant pH between the resistance time and the quantity of the film applied per tablet.

Cellulose acetate phthalate was used to coat soft gelatin capsules repeatedly by dipping, and the resultant product was resistant to gastric fluid for 2 hr and to intestinal fluid for 20 min (405). A dipping experiment was also successful for enteric coating tablets (406). A fluidized-bed apparatus was used to apply various aqueous coatings such as cellulose acetate in ammonia solution, methylcellulose, and hydroxypropyl methylcellulose (407). The effects of solids loading on moisture permeability of methylcellulose–ethylcellulose films with two mineral talcs and titanium oxide were investigated (408). Water vapor transmission reduction was directly proportional to the amount of either talc added but reached a minimum at an intermediate solids loading value for titanium dioxide.

Table XII—Additional References on Tablet Coating

Reference	Topic
409	Gas permeability through poly(methyl methacrylate) films containing special fillers
410	Technological control of tablet coating
411	Polymer coating of tablets including acrylic tablet coatings
412	Formulation and process considerations of film coating
413	Review of manufacturing control of dragees and coated tablets
414	Review of various coating techniques including compression, film, and sugar coatings
415	Coating with acrylic resins
416	Coating with aqueous dispersions of acrylic resins

Additional references on tablet coating are listed in Table XII.

Suspensions—The techniques of suspension formulation and stabilization were reviewed; the general topics discussed were particle size and shape, surface-active agents, deflocculating agents, and the principles of rheology (417). The flocculation, dispersion, and caking in sulfonamide suspensions by a cationic agent were studied (418). A monolayer adsorption was reported for sulfisomidine, whereas multilayer adsorption was found for sulfadiazine, sulfaphenazole, and sulfameter (sulfamonomethoxine). The effects of two electrolytes, aluminum chloride and monobasic potassium phosphate, as well as two cationic surfactants, on the stability of a monodisperse system of calcium phosphate were investigated (419). The proper flocculating agent and concentration needed were established.

The flocculating properties of xanthan gum on suspensions of zinc oxide, sulfaguanidine, bismuth subcarbonate, and bismuth subnitrate were investigated under various conditions and in the presence of 1% potassium chloride, 1% calcium chloride, 25% ethanol, and 25% ethanol–1% potassium chloride (420). The studies indicated that xanthan gum acts *via* polymer bridging as an effective flocculating agent for some suspensions and that flocculation occurs at polymer concentrations well below those needed to produce a viscous suspending medium.

Additional articles on suspensions are listed in Table XIII.

Table XIII—Additional References on Suspensions

Reference	Topic
421	Effect of proportion of active ingredient added to a pomade suspension on extensibility
422	Effect of excipient on extensibility of pomade suspensions
423	Effect of powder level on extensibility of pomade suspensions
424	Preliminary study of use of glucomannan as a suspending agent
425	Calculation of kinetics of suspension coagulation
426	Homogeneity of pharmaceutical dispersed systems
427	Electrical properties of particle surfaces in pharmaceutical suspensions
428	Coarse dispersions, suspensions, emulsions, and lotions
429	Chloramphenicol (Levomycetin) suspension formulation for treatment of chronic dysentery

Emulsions—A review and discussion with 13 references on the experimental determination of the hydrophilic–lipophilic balance (HLB) value for a system and the selection of an emulsifier were presented (430). Another review with 40 references was given on the HLB, the phase inversion temperature, and the cohesive energy ratio systems for emulsifier selection (431). The problems posed by emulsion manufacture, especially the technical variables involved, were reviewed (432). A technique was described in which the addition of a thickener to an emulsion at the critical HLB allowed the preparation of stable emulsions

Table XIV—Additional References on Emulsions

Reference	Topic
448	Techniques of emulsification and equipment
449	Physicochemical discussion of emulsion instability
450	Structure of emulsions induced by nonionic emulsifiers
451	Review of emulsions in pharmacy including biopharmaceutical and cutaneous absorption aspects
452	Review of medicinal emulsions (146 references)
453	Effectiveness of emulsified sunscreen agents
454	Problems posed by emulsion technology
455	Survey of theory and practice of emulsions
456	Review of emulsions (72 references)
457	Transparent solutions of oils, perfumes, and aromas
458	Emulsion technology
459	Review of emulsions
460	Emulsion theory
461	Microemulsions
462	Microemulsion formation

(433). Linear HLB was defined, and its use in the preparation of emulsions and their evaluation were explained (434).

HLB values were determined by the Huebner method for 24 surface-active agents involving the following groups of compounds: oxyethylenated wool wax alcohols, fractions of liquid lanolin, oxyethylenated castor oil, oxyethylenated C_{10-18} aliphatic alcohols, and oxyethylenated alcohols of sperm whale oil (435). Phase inversion temperatures were determined for mixtures of several systems including cyclohexane–sorbitol–mono- and diglycerides of fatty acids (Arlacel 186) (436). Various methods used to determine the type and stability of emulsions were reviewed including phase coloring, the drop method, the dilution method, the conductivity method, and microscopic examination (437).

The influence of different thickeners on the characteristics of petrolatum emulsions at a critical HLB value was investigated; stable creams and ointments were prepared with stearyl alcohol or with carbomer 961 as adjuvants (438). The properties of emulsions containing liquid paraffin, glycerol, water, and blends of polysorbate 60 and sorbitan monooleate were studied over a temperature range of 25–80° (439). The formation of clear solutions at 70° depended on the polysorbate–sorbitan ratio and oil content, and the micelle diameter (13–45 nm) increased with increasing oil content and decreasing surfactant–glycerol ratio. A similar study was carried out on microemulsions containing sodium oleate, amyl alcohol, water, and liquid paraffin (440). The relative viscosity relationships for some of the microemulsions (440) were determined (441).

Polysorbate 20 and polysorbate 81 were compared as emulsifiers for carbon tetrachloride and C_5, C_6, C_7, C_{10}, and C_{16} saturated alkyl hydrocarbons (442). Microscopic examination and particle-size measurements were made, and polysorbate 20 was found to be a better emulsifier than polysorbate 81 on oil-in-water emulsions as the carbon number of the hydrocarbons in the dispersed phase became smaller. Nonaqueous emulsions of glycerin and mineral oil were formed using anionic, cationic, and nonionic surfactants (443). Although stable emulsions were prepared by employing surfactants from all three groups, more stable emulsions were obtained when ionic surfactants were used.

A method of measurement of the spontaneity of self-emulsifiable oils was developed (444). The system involved light scattering by dispersed oil droplets and collection of the scattered light by fiber optics onto an array of silicon photodiodes. A very stable emulsion of benzyl benzoate was prepared using triethanolamine oleic acid (445). The physical properties and the capacity of gas transport of fluorocarbon emulsions were reported (446). The manufacture and application of essential oil emulsions in microbiology were discussed (447). Thyme and verbena essential oils were used for the study.

Additional references on emulsions appear in Table XIV.

Semisolids—The quality and stability of mass-produced ointments were assessed (463), and the quality of rectal ointment bases was evaluated (464). Paraffin oil gels made with 5% polyethylene as a gel-forming agent were studied (465). The gels have low flow points and a low degree of thixotrophy, and their viscosities are only slightly influenced by temperature. The effect of adding up to 20% of six different sorbitan emulsifiers on the rheological properties of a microcrystalline paraffin and a white wax–cetyl stearyl alcohol mixture was determined (466). There were small differences in the rates of flow, deformations under load, and restoring tendency between the two sample ointment bases and between materials based on solid *versus* liquid emulsifiers.

Approximate solubilities in common ointment bases were given for salicylic acid, chloramphenicol, prednisolone and its hydrate, thiosinamine, and neomycin sulfate (467). Solubilities in components such as yellow petrolatum, emulsifying alcohols, paraffin waxes, and polyethylene glycols 600 and 1500 were also determined. Bubbles formed in ointments during manufacturing and their enlargement during storage were investigated (468). The influence of the concentration of polyethylene oxide of different molecular weights on the rheological index (degree of penetration) was studied (469). The use of propylene glycol in oral preparations, as a dermatological vehicle, and as a parenteral vehicle was reviewed (470). Its physical and chemical properties were given and its toxicology was discussed.

Ointments containing drugs in suspension were studied for dispersity by a photometric method and a microscopic method (471). The former procedure permitted determination of changes in dispersion caused by comminution, generally gave better precision, was simple and rapid, and required less time and effort. Separation of fluid from ointments was investigated by means of a test used for lubricating greases involving cone mesh filtration (472). The experimental data followed a mathematical relationship and correlated well with bleeding that occurred in the container during room temperature storage. The bleeding of hydrocarbon ointment bases was af-

fected by both the dispersing methods and the concentration of polyethylene (473).

The melting characteristics of ointments and creams were investigated by differential thermal analysis, and an interpretation of their structure was made (474). Another paper using similar methodology gave a further explanation of the melting behavior of semisolids (475). Two papers were concerned with the absorption of materials by gel bases. The consistency of petrolatum and polyethylene glycol gels was studied after addition of peanut oil and camphor (476). The amount of water uptake in mineral oil gels after addition of varying amounts of nonionic emulsifier was determined (477). Radiation had a relatively weak effect on yellow petrolatum, with viscosity being significantly reduced and penetrability and exudation being increased (478). With synthetic petrolatum, penetrability decreased and viscosity increased; polyethylene gels were more strongly affected than the petrolatums. The crystallinity of the solid phases in artificial petrolatum containing either paraffin or polyethylene was changed by extraordinary cooling rates (479). In every case where slow cooling was used, the gels showed microcrystalline structure of the solid phase and good ointment properties; these data were obtained by using a polarization microscope.

A general method using the solubility parameters of polymers was helpful for predicting the relative *in vitro* diffusion rate of an agent dissolved in a carbomer-based gel (480). A review on the selection of semisolid formulations, especially of corticosteroid compounds, discussed how to achieve maximum therapeutic effectiveness while maintaining an elegant and stable product (481). Models used in the description of diffusion processes were applied to drug release from semisolids (482). Two models, an exponential model for finite systems and a nonexponential model for semifinite and infinite systems, were evaluated for their suitability in describing literature data for the release of substances from semisolids.

The dynamics of drug release from ointment bases using the system of 2% salicylic acid, petrolatum, sorbitan monooleate, and 10% dimethyl sulfoxide were reported (483). The releases of a wide variety of common antibiotics from 26 ointment bases were studied and bases were recommended for each product (484). The release of benzocaine from oleaginous, absorption, emulsion, and water-soluble ointment bases *via* dialysis through a cellulose membrane to an aqueous sink was studied at 37.5° (485). The release of benzocaine from commercial and experimental preparations was compared. The diffusion of fluorescein from ointment bases containing methylcellulose was reported (486). Topical availability of hydrocortisone from different ointment bases was determined by the stripping method and reduction of erythema; brand products as well as experimental formulations were evaluated (487). In general, polyethylene bases, hydrogels, and petrolatum bases are biopharmaceutically poor vehicles compared to either oil-in-water or water-in-oil emulsions.

The effects of rheological properties of an ointment base and size of salicylic acid particles on its release from the ointment and absorption by skin were determined (488). Both *in vitro* and *in vivo* tests showed that the release rate and absorption of salicylic acid were mostly affected by the particle size and to a lesser extent by rheological properties. The release of papain from various ointments was increased by the addition of 5% sodium lauryl sulfate (489). The addition of 0.1% chlorocresol and 0.1% sodium metabisulfite suppressed oxidation.

Other references on semisolids are listed in Table XV.

Table XV—Additional References on Semisolids

Reference	Topic
490	Comparative vasoconstrictive activity of topical corticosteroid preparations
491	Sensory firmness and viscousness of cream base substances
492	Ointment bases containing methylcellulose solution
493	Alternative base for calamine cream
494	Cosmetic transparent gels
495, 496	Gel structure of ointments
497	Effect of additives on gelatin gel strength
498	Formulation and clinical evaluation of protective epidermal barriers
499	Ointment base containing polyethylene
500	Pastes, liniments, plasters, and similar drug mixtures known by names of their originators

Suppositories—Factors that affect absorption of rectally administered drugs and the considerations to be taken in suppository formulation were reviewed (501). Formulation and pharmacokinetic studies of suppositories, with particular emphasis on factors influencing drug absorption through the anorectal tract, physical–chemical properties, use of surfactants, and active ingredient concentration, were reviewed (502). Cumidin red was used to test the release rate of suppositories made with polyethylene glycols with stearin base and emulsifiers (503). The consistency of lipophilic suppository bases and drug-containing suppositories was evaluated by determination of the cone flow point, the breaking strength, and the disintegration time (504). Zinc oxide labeled with ^{113m}In was used as a tracer to determine the degree of mixing with cocoa butter (505). The degree of drug release from 10 suppository bases was determined using an apparatus consisting of a semipermeable membrane and peristaltic pump to provide circulation of dialyzing fluid (506).

The aminophylline content of commercial and of laboratory prepared suppositories, all kept at 18–27°, was analyzed periodically; all commercial products were chemically and physically unstable (507). The best results were observed in a laboratory composition containing hydroxylamine hydrochloride as a stabilizer in anhydrous suppositories. The preparation of teturam suppositories with fatty bases was reported (508). The oral absorption and rectal absorption of cystamine hydrochloride were compared, and the rate of drug release from various suppository bases was also determined (509, 510). Work on *in vitro* and *in vivo* drug availability from digitalis sup-

Table XVI—Additional References on Aerosols

Reference	Topic
525	Partition coefficients of fluorocarbon propellants in water, normal saline, cyclohexane, chloroform, human plasma, and human blood
526	Suitability of some plastics for preparing parts of aerosol containers
527	Cosmetic aerosol development: semisolid type of pressurized systems
528	Classification of pharmaceutical aerosols
529	Review of gas dispersions (aerosols and sprays)
530	Medicated dry foam for local therapy in infected burns

positories was reported (511, 512). The consistency of suppository bases containing polysorbate 20 and polysorbate 61 was evaluated (513).

Aerosols—A wide ranging review of pharmaceutical and cosmetic aerosols was published (514). An evaluation of inhalation aerosols using a simulated lung apparatus was reported, and the compatibility of ^{14}C-labeled phenylephrine hydrochloride in polyethylene nasal spray containers was presented (515). Pharmaceutical quality control of aerosol foams was discussed (516, 517). A review of aerosol medicinal foams with respect to structure, properties, and classification was reported (518); quick-breaking aerosol foams and their relation to cosmetics also were reviewed (519). Major factors affecting the time for a foam to break were: water–alcohol ratio, total alcohol content, type and amount of surfactant, and type of propellant. The development of pharmaceutical and cosmetic aerosol emulsions was explained, and the type of material obtained, foam or droplets, was dependent on whether the propellant was in the internal or external phase of the emulsion (520). Various factors, such as powder concentration, surface activity, propellant concentration, and orifice diameter, influencing the diameter of solid particles of an aerosol were investigated and a mathematical equation was developed (521).

The development and evaluation of an inhalation aerosol of nitroglycerin were reported (522). An *in vivo* method for determining effectiveness of spray-on bandages containing anti-infectives was developed (523). Standardized, contaminated wounds in guinea pigs served as the testing system, and the inflammatory response of the wounds was evaluated using several indexes including skin temperature, degree of induration, and presence of pus. A multistage liquid impinger was used to determine the particle-size distribution of aerosols generated by six pressurized inhalers containing isoproterenol (isoprenaline) (524). Inhalers of the suspension type had a higher percentage of size ranges likely to penetrate to the lower airways than the solution type.

Additional references on aerosols are listed in Table XVI.

Timed-Release Preparations—Various aspects of pharmaceutical preparations designed to give a prolonged effect were reviewed (531). The report included a discussion of depot preparations, methods of drug molding, biopharmaceutical and pharmacokinetic aspects of sustained release, and release by zero- and first-order kinetics from insoluble matrix compounds. Formulation of oral, long-acting, solid dosage forms was the topic of another article (532).

A number of papers discussed various mechanisms used to obtain controlled-drug release. Further work was reported on preparations obtained by flocculating an acrylic latex with a solution of an amine drug (533). The interaction between methapyrilene and latexes was studied, and it was found that a compressed mixture of the drug and polymer provided sustained release in GI fluids. The influence of shape factors on the kinetics of drug release from matrix tablets was reported in two papers (534, 535). The rate of drug release varied with tablet shape, but rate constants that were independent of shape were included in the expression. Therefore, it was possible to predict drug release from tablets having identical compositions but varying widely in shape and size. The release of salicylic acid and ephedrine was measured *in vitro* after compounding into tablets containing stearyl alcohol, and it was found that release profiles could be described by a nonlinear expression for both cylindrical and biconvex tablets.

Tablets containing quinidine compressed in a polyvinyl chloride matrix were exposed to γ-radiation, and the drug release was then determined (536). The rate of drug release was proportional to the radiation dose and was correlated to the degree of cross-linking of the matrix. Timed release of acetaminophen was observed from spherical polystyrene beads (537). Factors influencing the rate of release of ethynodiol diacetate, a synthetic progestin, from solid silicone polymer vaginal devices were evaluated, and the cumulative amount of drug released was proportional to the square root of time (538). The release of methapyrilene, pentobarbital, and salicylic acid dispersed in films composed of different ratios of hydroxypropyl cellulose and polyvinyl acetate was investigated (539). The results indicated that drug release followed a diffusion-controlled matrix model, where the quantity released per unit area was proportional to the square root of time. Release rates were also proportional to drug concentration but independent of film thickness.

Two articles reported on the use of microencapsulation for sustained or controlled release of a drug (540, 541). The method whereby an injectable product could be prolonged was reviewed (542). Two depot-type vitamin B_{12} preparations were studied *in vivo* over 2 years (543). One preparation gave satisfactory levels when injected once every 8 weeks, but the other preparation required more frequent dosing.

Dissolution studies were made on seven samples of propantheline tablets from six manufacturers (544). Considerable variation occurred between individual tablets of two samples, and one sample exhibited great delay (over 2 hr) in disintegration as compared to 4–34 min for the other samples. The effect of three factors—surfactant type, surfactant concentration, and time—on the release of sulfosalicylic acid from polyvinyl chloride matrixes was studied (545). Drug

Table XVII—Additional References on Timed-Release Preparations

Reference	Topic
550	Availability of phenformin in a sustained-release oral pharmaceutical form
551	Release of salicylic acid and sodium salicylate from tablets
552	Tetracycline sustained-release tablets
553	Nitrofurantoin release from polyvinyl acetate–crotonic acid copolymers
554	Prolonged-action sulfonamide preparations
555	Preparation of sustained-release ferruginous hematinics
556	Sustained-release tablet containing atropine sulfate, scopolamine (hyoscine) hydrobromide, and phenobarbital (phenobarbitone)
557	Delayed release of niacin (nicotinic acid) in compressed tablets
558	Sustained release for fertility control

release was proportional to the square root of time and could be controlled by the use of surfactants. Sustained-release pellets and capsules prepared with polyglycerol esters indicated that these compounds had significant dissolution-retarding properties (546).

A nonirritating coated tablet of potassium chloride containing a dissolution-retarding additive from aqueous solution was developed (547). Retardant materials evaluated were carnauba wax, agar, alginic acid, stearic acid, cellulose acetate phthalate, hydroxypropyl methylcellulose, polyethylene glycol 6000, and cetostearyl alcohol. The sintering of matrix tablets prepared from a vinyl acetate–vinyl chloride copolymer increased the tensile strength of the tablets but also increased the rate of release of potassium chloride from the matrix (548). Electron-scanning photomicrographs showed that sintering at 100° for 1 hr caused the polymer particles, which had been deformed during compression, to regain their shape. The strength of plastic matrix tablets (Duretter) was correlated to their likelihood of being recovered in the feces after administration to human subjects (549).

Other references on timed-release preparations, particularly on specific drugs, are listed in Table XVII.

Cosmetics—*Microbiological Contamination*—The uses of X-irradiation and chemical compounds for the preservation of cosmetic preparations were discussed (559). Chemical preservatives were examined in detail, and a table of dissociation constants of acidic preservatives was given. Various *Staphylococcus* strains were isolated from cosmetic creams and lotions, and the pathogenicity was determined by culturing in various media (560). Larger amounts of *Staphylococcus* with higher pathogenicity were isolated from less expensive products. Factors that affect microbial growth in various cosmetic and toilet preparations were discussed; these included temperature, pH, oxygen, surface tension, and water quality (561). A study concerned with the resistance of bacteria compared the relative merits of "in use" and laboratory methods for the evaluation of antimicrobial products (562).

Formulation and Technology—The uses, properties, and formulations of dermatological skin lotion vehicles were reviewed (563). Cosmetic dermatitis factors were discussed along with case histories of typical cosmetic products causing irritation and allergenic reaction (564). The pharmaceutical aspects of skin therapy including the management of skin disorders, dermatological vehicles, skin penetration, and percutaneous absorption were reviewed (565). Various problems of black skin were considered, and recommendations for lotion formulations were made (566). The relationships of estrogens and androgens to sebaceous gland function and various kinds of hair growth were explained (567). A review article on the substantivity of cosmetic ingredients to skin, hair, and teeth discussed the advantages and disadvantages of substantive effects, various ways of achieving them, and methods for detection and assessment (568). The necessary properties for the obtainment of a protective epidermal skin barrier were given (569). Three classes of formulations were evaluated: a gelled oil, a water-in-oil emulsion, and an oil-in-water emulsion.

By using basic diffusion theory, mathematical models were obtained that correlate moisture loss to the thickness of topical substances during actual field usage (570). Under these conditions, there was a thickness below which the product did not have a perceptible effect on transepidermal moisture loss rate. Two factors, elastic modulus and stress relaxation, were used to characterize the mechanical properties of the stratum corneum (571). Both properties depended on the moisture content of the stratum corneum or the ambient relative humidity. Water vapor absorption and water vapor transmission were also dependent on relative humidity. In another report by the same investigators, it was shown that cosmetic humectants increase transepidermal water loss *in vitro*, and an attempt was made to explain this phenomenon (572). A depilometer was designed to simulate practical use conditions as closely as possible (573). Thus, important formulation variables could be studied quickly; in-use tests gave good correlation with the depilometer findings.

The cuticle of human hair was isolated in bulk by a new method involving vigorous agitation of fibers in water (574). The cuticle fractions were shown to be of high morphological purity using various techniques of electron microscopy, and the significance of amino acid analyses was discussed. Papain and dithiothreitol were used to separate the A-layer and cell membrane complex from human hair cuticle (575). The digestion was followed gravimetrically, and an electron microscope examination of the digested hair sections demonstrated that the components were clearly separated. The gross and fine structures of hair were discussed, and excellent scanning electron microscope microphotographs were included with the article (576). Scanning electron microscopy was used to evaluate hair care products while the hair was still attached to the head (577).

The effect of critical micelle concentration (CMC) on the detergent action of shampoos at equivalent micellization indexes was studied (578). The amounts

Table XVIII—Additional References on Formulation and Technology of Cosmetics

Reference	Topic
588	Technical aspects in preparation of toothpaste
589	Harmful metals in a cosmetic product containing inorganic pigments
590	Efficiency of chlorhexidine in mouthwashes
591	Formulation and properties of lipsticks
592	Shampoo preparation made from diethanolamine salt of synthetic fatty acids
593	Significance of vitamins for healthy and diseased skin
594	Composition of some natural waxes
595	Crystallization of cetyl alcohol from cosmetics
596	Alkaline and acid hand cleaners
597	Skin lotions in aerosol forms
598	Reconstituted triglycerides in cosmetic lotions
599	Poloxamers (Pluronic polyols) in skin lotions
600	Dermatological skin lotion vehicles
601	Progress in perfumery materials
602	Beeswax–borax reaction in cold creams
603	Brominated salicylanilides and their structure–activity relationships
604	Moisturization of stratum corneum
605	Cationic lotion formulation
606	Sunscreen lotions containing various natural oils
607	Skin lotions for black skin
608	Protein derivatives in cosmetics
609	Pearl pigments in skin lotions
610	Lanolin derivatives in skin lotions
611	Fatty acid amido alkyldimethylamines as cationic emulsifiers in skin formulations
612	Use of propoxylates in skin lotions
613	Use of reconstituted triglycerides in cosmetic lotions
614	Skin lotions in aerosol form
615	Dermatological skin lotion vehicles and formulations
616	Cosmetic gel systems from licorice root
617	Vegetable oils in lotions
618	Sucrose esters in skin lotions
619	Nonionic surfactants in skin lotions
620	Formulation of pigmented cosmetic lotions
621	Use of glucam methyl glucoside in skin lotions
622	Carbomer resins in moisturizing lotions
623	Use of fatty alcohols in skin lotion formulation
624	Properties of mineral oils and petrolatums used in skin lotions
625	Alkanolamine use in skin lotions
626	Natural protein from oats in cosmetic formulations
627	Review of solvents used in cosmetics
628	Emulsion formation with mixed nonionic surfactants
629	Gum usage in drug, cosmetic, and food industry
630	Use of natural products in cosmetic and toiletry preparations
631	Panthenol in cosmetics
632	Lecithin composition, properties, and use in cosmetic formulations
633	Isostearics in cosmetic formulation
634	Effect of simple aluminum compounds on mammalian epidermis
635	Technological properties and quality assessment of petrolatums
636	Surfactants and emulsifiers used in dermatology and cosmetics

of surfactants required to clean greasy hair at physiological standards were calculated (579). Two modes of analysis were utilized to evaluate antidandruff shampoos on groups as small as 10 persons (580). One method was subjective, and the amount of scaling was scored on a 0–10 scale; the second method involved the counting of the number of horny cells produced using a hemocytometer.

Two techniques were used to demonstrate the penetration of proteins into hair strands (581). One method involved chemical analyses of hair scrapings, and the other method involved staining cross sections of hair with ninhydrin. A second paper on factors controlling the action of hair spray investigated the adhesion of hair spray resins to hair fibers (582). The properties of the resin and solvent system were important for the ability of the hair to withstand impact and bending.

A standardized swabbing technique was developed to evaluate changes of axillary microflora, and seasonal differences were found in levels of some bacteria (583). A new method of deodorization was suggested; it involved clathrate formation using zinc ricinoleate and 0.1–2% synergistic additives such as polyhydroxylated fatty acids or resin acids (584, 585).

The history of sunscreen preparations was given, and several natural and synthetic compounds were evaluated and compared (586). A new sunscreen containing 4-(3′,4′-methylenedioxobenzylidene)-1-benzyl-2,3-dioxopyrrolidine in combination with mexenone (Uvistat 2211), titanium dioxide, and burnt sugar solution was suitable for patients who display abnormal sensitivity to UV irradiation (587).

Additional references on formulation and technology of cosmetics are listed in Table XVIII.

Packaging—The requirements for quality, packaging, and transportation of active materials and adjuvants used in the pharmaceutical industry were presented (637). Another review discussed the types of materials that should be considered for pourable liquids, sterile products, and semisolid and solid dosage forms in bulk and unit dose containers (638). Use of glass, metal, and plastics was explored; each group was described with reference to their advantages and disadvantages. The progress in the development of child-resistant packaging systems was explored (639). Three papers discussed various aspects of the use of polyvinyl chloride and plastics as packaging materials. Physicochemical control of plastic materials used in the packaging of unit dose drugs was reviewed (640). The toxic effect of various additives used in the manufacture of polyvinyl chloride was discussed (641), and the importance of physical and chemical tests was stressed (642). A paper from the Netherlands reviewed pharmacopeial requirements, including chemical and toxicological testing, of plastic materials used as containers for intravenous injections (643).

The economics of blister and skin packaging were reported (644), and the technology of shrink wrapping, particularly for toiletries, was discussed (645). A comparative test for the evaluation of the tightness of various prescription containers was developed (646). The test consisted of placing a weighed amount of calcium chloride in a container, closing it, and following the weight gain after storage in an 86% relative humidity chamber. Glass vials with lined phenolic screw-capped closures provided the best protection, while polystyrene vials with a child-resistant closure were the least effective. The unit packaging of solid dosage forms, powders, and granules in blisters or flexible pouches was discussed (647). A

new method of hermetically packaging solid drugs was tested and found to be satisfactory (648). The method involved "cold welding" of aluminum foil under pressure. The packaging of suppositories using various plastic materials was reported (649). A survey of cartoning equipment and a buyer's guide to equipment now on the market were presented (650).

Plastic packaging of infusion and injection solutions was discussed, with particular reference to polyethylene, polypropylene, and polyvinyl chloride (651). The major factors involved in the design and manufacture of packaging to preserve sterility of the contents were enumerated; these included the suitability of the packaging material for sterilization, the resistance of the material to bacteria, the type and strength of the package, and the type of package opening (652). Several approaches to meeting the needs of users of small volume, prefilled, syringe products were presented (653). Development aspects unique to small volume, prefilled, disposable syringes were enumerated. Two-compartment injection systems were described together with their inherent advantages for powder or lyophilized formulations (654).

Instruments and Equipment—A continuing series of articles concerned with pharmaceutical engineering presented the fundamentals of laminar flow (655) and the principles of fluidized beds (656). The ideal physical plant conditions of temperature and humidity in a number of specific pharmaceutical operations were presented (657). The quantity and quality of the air in the plant were discussed with respect to particle content and the means of controlling it.

Various papers were concerned with particular pharmaceutical processes such as drying, coating, and metal particle detection. An accurate automatic control for dryers was devised (658). Equipment available for the polymer film coating of tablets by coating pan, fluidized-bed, spraying, and dipping techniques was examined and compared (659). Tablets and granules of any shape were coated using a new machine equipped with two brush rollers (660). Coating material was fed to the brushes by a roller which was in contact with a reservoir; the equipment was capable of coating tablets with as little as 1 mg of coating material/tablet.

A survey of pumping technology was presented, and some recent developments were of particular importance to the pharmaceutical industry (661). An instrument was developed that automatically detected small metallic particles possessing ferro-, para-, or diamagnetic properties (662). A review of the practical applications of spray drying was presented with a detailed description of the spraying agents used (663). A report appeared on the spray drying of aspirin (664). Scanning electron microscope and electron diffraction studies of spray-dried aspirin with methylcellulose revealed that a noncrystalline amorphous sample of the drug was formed at a 70% polymer concentration. Increased amounts of aspirin in the product led to the formation of crystalline products.

The developments in mixing and grinding technology were examined, and machine and design changes were emphasized (665). A Nauta mixer was evaluated by mixing a tablet preblend containing 10% phenobarbital (phenobarbitone), 1% secobarbital (quinalbarbitone), and 1% butethal (butobarbitone) with 88% lactose (666). Each component behaved in a unique manner during mixing, with adequate mixing occurring at different times.

An instrument was described that will produce a standardized skin abrasion test for skin irritants (667). The same degree of abrasion can be reproduced without bleeding. Further work on the evaluation of vaginal odors by means of GLC was reported (668). Refinements in methodology allowed the technique to be sufficiently sensitive to indicate significant ($p < 0.05$) changes in 10 subjects.

Additional references on instruments and equipment are listed in Table XIX.

Table XIX—Additional References on Instruments and Equipment

Reference	Topic
669	Industrial monitoring of particle size of antibiotic powders
670	Comparison of final filtration devices
671	Heat production by ultrasonic equipment
672	Validation and bioengineering aspects of implantable glucose sensor
673	Continuous intragastral pH measurement after administration of antacid drugs

PHYSICAL PHARMACY

Several review articles were devoted to polymorphism where various polymorphs were characterized by X-ray diffraction patterns, IR spectrophotometry, and dissolution rates. Dissolution rate is the most important characteristic in pharmaceutical formulations because it affects the bioavailability of various formulations (674, 675). The thermal analysis of pharmaceuticals including solvation, polymorphism, impurities, interactions, stability, and compatibility was also discussed (676). The relationships of various polymorphic forms of pharmaceuticals to their biological activity were reviewed (677). Phase solubility in combination with IR spectrophotometry was used for studying the polymorphism of progesterone, cortisone acetate, and prednisolone (678).

Upon crystallization from various solvents, barbital, amobarbital, butethal (butobarbital), hexobarbital, and phenobarbital were found to be polymorphic by thermomicroscopy, microsublimation, and X-ray diffraction (679). The effect of polymorphism on the dissolution behavior and GI absorption of chlortetracycline hydrochloride was studied (680). After oral administration to humans, the cumulative amounts of chlortetracycline hydrochloride excreted by two polymorphs were compared. The results suggest that the more soluble β-form was absorbed much faster than the α-form and was more bioavailable than the α-form. Depending on the method of preparation, hydroflumethiazide crystallized as an anhydrous form, a desolvated crystal species, and an ethanolic solvate, which, under normal atmospheric conditions,

converted to the desolvated crystal, losing all except a small fraction of the solvent from the crystal lattice (681).

Two new polymorphic modifications and a solvent-containing form of indomethacin were described and characterized by their thermal data, IR spectra, and solubilities (682). Solid-state studies were done on the polymorphs of methylprednisolone (683). The metastable crystalline form underwent a transformation to a form other than the stable Form I upon exposure to high humidities, moderately high temperatures, or UV radiation.

Cameroni and coworkers studied the polymorphism of progesterone. In their first paper, they reported on the preparation and characterization of the various polymorphs (684). They studied the use of differential calorimetry with various progesterone crystalline forms (685), and the solubility and thermodynamic data of two crystalline forms were also developed (686). The densities, refractive indexes, and X-ray diffraction measurements of four polymorphic forms of sulfanilamide were studied (687). The data suggested that the forms have very similar structures.

Effects of some process conditions on the particle size and polymorphic form of phenobarbital (phenobarbitone) prepared by acid–base precipitation were studied (688). The presence of water profoundly influenced the behavior of the solid product, and the significance of this phenomenon was discussed. More than 20 progesterone steroids and 30 testosterone-type compounds were tested for hydrate formation to evaluate their stability in solutions and in pharmaceutical preparations (689). Hydrates were observed with 21-acetoxypregnenolone, fluorogestone acetate, 4-chlorotestosterone, testosterone, and stanozolol.

A review of mass transport phenomena and models covered passive diffusion, diffusion in an isotropic medium, diffusion through laminated structures, the influence of some specific permeant and barrier properties on mass transport including diffusant solubility as a flux-limiting factor, and factors affecting diffusivity (690). The effect of sodium carboxymethylcellulose on sodium salicylate transport was studied (691). The drug release rate out of the polyelectrolyte solution was found to be faster than that without carboxymethylcellulose. This transport-enhancing action of sodium carboxymethylcellulose was probably due to the electrical charge between the coion and the polyelectrolyte.

By means of a diffusion cell consisting of two compartments partitioned with a cellophane membrane, the influence of surfactants, thickening agents, and pH on the rate of drug transport of three flavonoid compounds was studied (692). Association and complexing of oxytetracycline in its solutions at pH 1.65 were studied by diffusion transport through inert membranes (693). Association occurred in solutions $>5 \times 10^{-3}$ *M*. The diffusion of aerosols was tested at low temperatures where classical Brownian movement theory is not applicable (694). At room temperature, the diffusion coefficient calculated from experimental penetrations agreed with the theoretical coefficients. However, at −16 and −72°, the experimental coefficients were 150–500% greater than the theoretical values.

Table XX—Additional References on Physical Pharmacy

Reference	Topic
697	Physicochemical properties of amitriptyline hydrochloride
698	Physicochemical properties of digitoxin
699	Physicochemical properties of diphenhydramine hydrochloride
700	Physicochemical properties of echothiophate iodide
701	Physicochemical properties of nifurpipone
702	Physicochemical properties of oxazepam
703.	Physicochemical properties of phenylephrine hydrochloride
704	Physicochemical properties of trimethaphan camsylate
705	Physicochemical properties of tolbutamide
706	Physicochemical properties of tropicamide
707	Review of particulate dispersions and colloids
708	Review of nonaqueous systems
709	Dissociation constants of oxazolidines of ephedrine and pseudoephedrine
710	Influence of anions on physical properties of butyrophenone-type molecules
711	Characterization of phenobarbital (phenobarbitone) samples
712	*In vitro* investigations of antacids
713	Potentiometric study of hydrogels of carbomer 940
714	Factors affecting pharmacodynamic activity of drugs in ointments
715	Physicochemical study of phenobarbital–urea system
716	Effect of washing on physicochemical properties of aluminum hydroxide gel
717	Comparison between theoretical and experimental electric dipole moments of selected *N,N*-dimethylaniline derivatives
718	Measurement of drug displacement by continuous ultrafiltration
719	Interconversion of ampicillin and hetacillin *in vitro*
720	Role of physical properties in formulation and manufacture of drugs

Microencapsulation of solid stearyl alcohol particles by complex coacervation was studied (695). Wall thickness decreased with increasing ratios of solid particles and increased as the particle diameters increased. Microencapsulated aspirin with ethylcellulose was examined as to its dissolution rate in pH 1.1–8.3 media (696). The rate was slower in acidic pH. Release of aspirin from the microcapsule was also examined microscopically. Aspirin leached out of the capsule, leaving the capsule membrane almost intact.

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

Dissolution—Phenylpropanolamine hydrochloride was found to be released from a typical wax matrix by a diffusion mechanism (721). After an initial rapid release of drug from the tablet, the amount dissolved was proportional to the square root of time. Dissolution of human gallstones was evaluated in a water solution containing a mixture of limonene with polyoxyethylene hydrogenated castor oil and ethanol; the solution was able to dissolve completely 1.4–3.2 g of cholesterol-containing human gallstones in 2 hr *in vitro* (722). Bile salt solutions slowly dissolved cholesterol gallstones *in vitro*, chenodeoxycholate and

deoxycholate being about fourfold more potent than cholate (723).

Experimental results suggested that various lots of drug formulations that meet compendial dissolution requirements may contain fractions of poorly soluble tablets (724). If the assumption is made that dissolution behavior and drug absorption *in vivo* are related for certain drugs, such formulations give rise to suboptimal therapy. A modification of the compendial test was presented with the objective of increasing the probability of identifying lots containing a fraction of poorly soluble tablets. The dissolution rate of nitrofurantoin from commercial suspensions and tablets containing microcrystalline drug particles and from capsules containing macrocrystalline drug particles was determined at 37° in simulated gastric and intestinal fluids using the stirrer-flask method (725). The dissolution rate of nitrofurantoin from the suspension and capsule dosage forms at pH 7.2 was significantly faster than at pH 1.12. In contrast, the drug from the tablet dosage dissolved in the pH 1.12 dissolution medium at a rate twice that observed at pH 7.2.

A nonlinear expression describing the dissolution of drug particles under sink conditions and low agitation intensity was presented (726). By using the beaker method, the dissolution of salicylic acid particles having a relatively narrow size distribution was followed to nearly complete solution. It was found that the process could be described by the nonlinear expression and that a dissolution rate constant having the dimension of reciprocal time could be obtained. Dissolution rates of salicylic acid in micellar solutions of polysorbate 20 were determined at pH 1–4 (727). At any one pH, as the concentration of the polysorbate 20 was increased up to 12% (w/v), the dissolution rate increased; but the further increase up to 20% (w/v) polysorbate 20 only slightly increased the dissolution rate. At any one concentration of polysorbate 20, the dissolution rate increased linearly as the pH was increased.

The effects of particle size on dissolution and GI absorption rates of drugs were reviewed (728). When the influence of particle size on dissolution behavior of sulfonamides was evaluated, it was found that at a particle size below 300 μm, the lines obtained by plotting dissolution rate *versus* time had positive intercepts; at above 300 μm, the lines passed closely through the origin (729). The findings indicated that the critical particle size is at about 300 μm in the initial dissolution process.

It was shown that dissolution rates and equilibrium solubilities of digoxin samples before and after dry grinding in a mortar mill may influence dissolution behavior (730). The need for a specification for digoxin that not only controls surface area but also exercises some control of the crystal properties was suggested. The influence of the tablet manufacturing method and drug particle size on the dissolution rate was studied (731). The rate of dissolution of the active ingredient was faster with a particle size of 50 μm than for formulations made with particle sizes of 180–200 μm.

Dissolution characteristics of three crystal forms of aspirin were evaluated (732). The dissolution process of the highest melting form could be represented by the general Noyes–Whitney equation, which assumes that diffusion is the rate-controlling process; the dissolution of the lower melting forms did not obey this model so it was necessary to postulate that the interfacial reaction was not instantaneous. Bundgaard (733) claimed that the differences in the rates of dissolution of aspirin were due to differences in the content of the acetylsalicylic anhydride impurity. When using the rotating-disk method, it was shown that the dissolution rate of aspirin was independent of crystal growth, salicylic acid content, habit, and particle size (734). The dissolution of the eutectic mixtures of aspirin and urea, when evaluated in 0.1 *N* hydrochloric acid, was about the same as pure aspirin; in the 35% solid solution, the dissolution was appreciably enhanced (735).

Shah and Ochs (736) designed and evaluated the rotating-filter–stationary basket *in vitro* dissolution test apparatus. An automated procedure for the determination of *in vitro* dissolution rates from two-component (outer layer plus sustained-release core) sulfonamide tablets was described (737). The dissolution rates *in vitro* for film-coated tablets were dependent on the solubility of the film. An automated dissolution rate apparatus, meeting requirements of the USP–NF dissolution test and applicable to various other agitation systems in common usage, was described (738). The equipment allows simultaneous determination of the dissolution *rate of six* unit doses, enabling the evaluation of a statistically significant number of samples.

Dissolution rates of eight products containing levodopa in three strengths, made by two different manufacturers, were determined using a continuous-flow dissolution apparatus (739). Significant difference was observed in the 250-mg capsules made by different manufacturers. A significant difference also was observed in a 250-mg tablet and a 250-mg capsule of the same manufacturer. Comparisons were made between different methods for the determination of dissolution rates of drugs from tablets using the USP XVIII method and the beaker method (740). The reproducibility of the USP method was better than or equal to the reproducibility of the beaker method. Comparisons of dissolution profiles of tablets and capsules were made using the USP, Levy, and three different size magnetic basket methods (741). The five different dissolution methods produced significantly different dissolution profiles at selected times for both the tablets and capsules studied.

By using the USP method and the shaking beaker method, the dissolution rate of methandrostenolone and phenobarbital tablets was studied (742). The USP method gave a greater dissolution rate. A theoretical model of dissolution was developed in terms of the diffusion layer theory (743). This model was programmed on an analog computer, and theoretical dissolution curves were obtained. Experimental dissolution curves were compared with simulated curves, and the fit of the data allowed the estimation of the

Table XXI—Additional References on Dissolution

Reference	Topic
744	Dissolution kinetics of sulfathiazole Form I
745	Method of testing applicability of diffusion layer dissolution model
746	Influence of dissolution rate of lithium tablets on side effects
747	Influence of drug concentration on aggregation and *in vitro* dissolution rate of tablets
748	Use of porous matrix substances to increase dissolution rate
749	Increasing the dissolution rates of some corticosteroids utilizing glass dispersions and partial solid solutions
750	*In vivo* significance of dissolution test procedures for evaluation of drug products
751	Dissolution profile of log-normal powders, and dissolution before critical time
752	Dissolution of lithium and magnesium from lithium carbonate capsules containing magnesium stearate
753	Influence of dispersion method on dissolution rate of digoxin–lactose and hydrocortisone–lactose triturations
754	Thermodynamics of dissolution of salicylamide by a nonionic surfactant
755	Rate studies on dissolution and enzymatic hydrolysis of chloramphenicol palmitate
756	Methods for determination and criteria for expression of dissolution rate
757	Solvent effects on comparative dissolution of pharmaceutical solvates
758	Digoxin tablet dissolution
759	Dissolution rate of aminopyrine–barbital molecular compounds
760	Dissolution–dialysis and absorption aspects of some pharmaceutical systems
761	Dissolution and dialysis aspects of molecular complexes
762	Liquid–liquid mass transfer studies, and their relationship to solid dissolution

drug concentration in the diffusion layer.

Table XXI lists additional references on dissolution.

Solubility–Solubilization Phenomena—Cholesterol solubility in model bile systems was evaluated (763). It was found that there were significant behavioral differences in the rate of solution with the various crystalline forms. The solubility of the equilibrium species, hydrated cholesterol, and of fresh human gallstones was found to be approximately 5 mole %. The surface areas for 73 aliphatic hydrocarbons and alcohols, for which solubility and boiling point data are available, were calculated (764). The solubility of the alcohols and hydrocarbons could be quantitatively related to a combination of the hydrocarbon and hydroxy surface areas of the molecules.

The solubility of antipyrine derivatives was determined in water and several organic solvents (765). Aminopyrine and isopropylantipyrine exhibited solubility minimums near 25 and 15°, respectively, corresponding to a zero heat of solution. The rates of solution in butanol of compressed plates of modifications I–III of sulfanilamide were determined along with the solubilities at various temperatures (766). A method of calculating heats of transition from the rates of solution was also described. Differential scanning calorimetry was used to determine the solubility of the metastable form of testosterone (767).

Selected surfactants, above and below the CMC, were evaluated for their solubilizing effects on suspensions of aspirin crystals (768). Ranked in order of decreasing solubilizing effectiveness were: cetylpyridinium chloride > polysorbate 20 > benzalkonium chloride > polysorbate 80 > dioctyl sodium sulfosuccinate. The effects of sodium chloride and urea, separately and together, were evaluated on the solubility of methyl *p*-hydroxybenzoate in water (769). Sodium chloride decreased and urea increased the solubility. Solubilizers formed soluble and/or insoluble complexes with tetracycline and its derivatives (770). In all cases, oxytetracycline interacted less than tetracycline. The solubilization of the surfactants was assumed to be due to normal micellar solubilization rather than complexation.

The cosolvent capacity of 1,2-propylene glycol, 1,3-butanediol, and 2,3-butanediol in the solubilization of phenylethylbarbituric acid was studied (771). The solubilizing effect of the aqueous dispersions obtained with these polyols was mainly due to the modification of the dielectric constant of the water, with existence of a complex mechanism, rather than to the direct action of the polyol itself. Solubilities of certain barbiturates in poly(oxyethylene) monoalkyl ethers of varying hydrophobic chain length were studied (772). Solubilization increased with the increasing hydrophobic chain length of the solubilizer due to formation of larger micelles. The effect of monosaccharides on the solubility of barbituric acid and its derivatives was studied (773). The solubility of barbituric acid increased with the increasing monosaccharide concentration, the increase being more pronounced in solutions containing galactose. Calcium *p*-aminosalicylate formed an isonicotinic acid hydrazide–calcium chelate in aqueous solution with isonicotinic acid hydrazide (isoniazid) and resulted in monocalcium *p*-aminosalicylate with increased solubility (774).

Other papers concerning solubility–solubilization phenomena are listed in Table XXII.

Membrane Permeation and Release—The per-

Table XXII—Additional References on Solubility–Solubilization Phenomena

Reference	Topic
775	Solubility of amorphous phase of caffeine, theobromine, theophylline, morphine, and heroin (diacetylmorphine) in water
776	Solubility of sulfanilamide in water
777	Solubilization of liquid paraffin by mixed nonionic surfactant system
778	Solubilization of cresol, chloroxylenol, oils, and vitamin preparations
779	Solubilization, emulsification, and dispersion with surfactants in parenteral preparations
780	CMC and solubilizing capacity of some surfactants
781	Solubilization of cholesterol and cholesterol esters by synthetic surfactants
782	Solubilization of perfume oil with HLB principle
783	Effects of polyvinylpyrrolidone on solubility and dissolution rate of allopurinol
784	Thermodynamic parameters for solubilization of some steroids by nonionic surfactants
785	Thermodynamic stability of solubilized solutions
786	Relationship of composition of nonaqueous binary solvent systems and dielectric constant

meability of films of ethylcellulose and polyethylene glycol to caffeine was studied (787). The rate of caffeine transfer across the films increased linearly with the reciprocal of thickness and caffeine concentration. The permeability of plastics, in particular, in relation to drug products with regard to physical factors and to intrinsic and total permeability was evaluated (788). Gravimetric, manometric, and hygrometric methods were used for the permeability evaluation. Comparisons of dimethylpolysiloxane and trifluoropropylmethylpolysiloxane systems were made, using nicotine base as the permeating species (789). The drug permeability through dimethylpolysiloxane was >20 times more rapid than through the trifluoropropylmethylpolysiloxane system.

The permeation of phenylbutazone through polydimethylsiloxane was studied under conditions of varying membrane thickness, stirrer speed, and pH (790). The results were described in terms of the two-phase model of general transport theory and provided experimental evidence of its usefulness. The influence of surfactants on the transfer of salicylate and salicylamide was studied in everted rat intestine (791). Sodium tauroglycocholate, sodium oleate, sodium lauryl sulfate, polysorbate 20, and sorbitan monolaurate increased the transfer rate of both sodium salicylate and salicylamide across the everted rat intestine.

The effects of pH and various substances on the permeation of phenylbutazone through the everted rat intestine and polydimethylsiloxane were studied (792). The classical pH–partition hypothesis was not obeyed. Phenylbutazone permeation rates in one or both membranes decreased in the presence of gelatin, methylcellulose, polyvinylpyrrolidone, skim milk, albumin, sodium lauryl sulfate, polysorbate 80, and cetrimonium bromide. The effects of excipients and various additives on the permeation of chlordiazepoxide through polydimethylsiloxane membranes also were studied (793). No effect on the permeability coefficient was observed in the presence of starch, calcium hydrogen phosphate, gelatin, lactose, silica, sucrose, cholesterol, or porcine mucin. The coefficient increased in the presence of magnesium stearate and decreased with talc, sodium saccharin, skim milk, egg lecithin, beef albumin, egg albumin, polysorbate 80, cetrimonium bromide, and sodium lauryl sulfate, indicating an interaction of these substances with the drug.

The effect of hyaluronidase on the activity of two ointments containing antibiotics was studied by the evaluation of the active transport of sodium through the isolated skin of frog and by the measurement of the current necessary to cancel the electrical potentials of the membrane covered with ointments (794). The antibiotics evaluated were tetracycline, chloramphenicol, neomycin, erythromycin, nystatin, streptomycin, kanamycin, griseofulvin, and penicillin. Interrelationships between skin, vehicle, and drug during penetration into skin were reviewed (795).

The permeation of water vapor through cellulose acetate phthalate polymer films applied in various ways to hygroscopic solid surfaces was determined at several different temperatures (796). The data indicated that the activation energy of the absorption processes was determined by the film, while the method of film application affected the actual rates of permeation at a given temperature.

Models used in the description of diffusion processes were applied to the drug release from semisolids (797). Two models, an exponential model for finite systems and a nonexponential model for semi-infinite and infinite systems, were evaluated for their suitability in describing literature data for release of substances from semisolids. The exponential model derived for finite systems was found applicable in all of the literature cases, while the nonexponential model had restricted applicability. The effects of systematic alteration of vehicle composition on the release rate of drug from their vehicle were studied (798). Equations were developed that quantitatively predicted the rate of transport of a drug across a membrane separating two identical binary aqueous solvents. Separate equations were derived for solutions and for suspensions; they accounted for both the resistance of the membrane and the resistance of the solvent to drug diffusion.

The release of sodium lauryl sulfate and cetrimide from ointment bases containing complex emulsifiers was studied (799). Cetostearyl alcohol blocked the release of sodium lauryl sulfate into agar, but doubling the sodium lauryl sulfate concentration enhanced its release. A stabilized shea butter in the form of an ointment base was developed and found to release medicaments at a faster rate than the British Pharmacopoeia ointment bases. The assessment of release of medicaments by microbiological method and through a dialysis membrane gave promising results (800). The rate of drug release from a gel medium was determined by placing a salicylic acid-containing gel in a 1-cm diameter hole in a ferric chloride-containing agar plate and measuring the colored ring formed. Two gels were used, one based on liquid paraffin and the other on castor oil. The gel based on castor oil was more viscous but released salicylic acid faster.

The effects of various sorbitan surfactants on drug release were determined (801). The drug release increased with increased HLB value and decreased with increased chain length. Effects of polysorbate 80, sorbitan monostearate, water, and physicochemical structure of the ointment on potassium iodide release from lard and white petrolatum were studied (802). Addition of 3% polysorbate 80 retarded potassium iodide release from lard but accelerated the release from white petrolatum. A reverse effect was observed with a 3% addition of sorbitan monostearate. Release of iodine in a potassium iodide solution was studied from ointment bases, comprised of petroleum or a melt of petroleum with sunflower oil and various oxyethylenated aliphatic alcohols as emulsifiers, into an agar gel (803). The bases were water-in-oil emulsions. Release of iodine increased with the increasing water content of the base and decreased with the increasing number of carbon atoms in the hydrophobic portion of the molecule of an emulsifier.

The releasing ability of four different ointment bases containing salicylic acid was evaluated by an *in vivo* test on rats and by four different *in vitro* tests (804). The salicylic acid releases from the various bases in the *in vivo* test decreased in the following order: Unguentum leniens, Unguentum emulsificans hydrosum, Unguentum alcoholum lanae hydrosum, and Unguentum macrogoli.

The effects of small-scale preparation techniques on the diffusion of salicylic acid from various ointment bases were studied (805). The method of mechanical incorporation of the drug in cold petrolatum base, using a spatula, appeared to result in higher rates of salicylic acid diffusion than those encountered with ointments prepared by fusion, regardless of drug concentration and the presence or absence of a surfactant. The drug release pattern of micronized ethynodiol diacetate from silicone devices was investigated in polyethylene glycol containing elution media with a wide range of solubility and partition properties (806). When high drug solubility was maintained, the drug release pattern was matrix controlled. As the drug solubility in the elution medium was decreased, the drug release process shifted from matrix controlled to partition controlled.

The *in vitro* release pattern of nitrofurantoin embedded in polyvinyl acetate–crotonic acid copolymers was studied in artificial intestinal juice (807). *In vivo* studies were also done on conventional and slow-release nitrofurantoin tablets. Both *in vivo* and *in vitro* results indicated that the copolymer with 8% crotonic acid was effective for prolonging the release and excretion of nitrofurantoin. The water solubility and chemical reactivity of hydrocortisone and hydrochlorothiazide were studied, and the type of matrix useful for their preparation as a sustained-release dosage form was determined (808). Acetohexamide incorporated into silicone rubber disks was released into water in microgram quantities for over 6 months (809). Based on these data, these disks were recommended as sustained-release polymeric capsules for acetohexamide.

The effect of some variables involved in the manufacture of nylon microcapsules *via* an interfacial polymerization on the release rate of core material from the microcapsules was evaluated (810). The presence of emulsifiers in the external phase had no significant effect on the release of core material; sodium hydroxide, as an acid acceptor, did not enhance the retentive properties of the microcapsules; and the choice of organic solvent not only affects the release of the core material but may govern the collection method.

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

Table XXIII—Additional References on Membrane Permeation and Release

Reference	Topic
811	Properties and drug permeabilities of poly(vinyl alcohol)–oxystarch membranes
812	Drug permeation through artificial membranes
813	Problems on ocular penetration of antibiotics
814	Correlation between *in vitro* and *in vivo* availability of salicylic acid for membrane transfer from polysorbate 20 solutions
815	Reverse osmosis separation of solutes from aqueous solution
816	Model transport studies utilizing lecithin spherules
817	Rate of dialysis of chemicals through semipermeable membrane with varying concentrations of polyvinylpyrrolidone
818	Influence of surfactants on dialysis of drugs through artificial membranes
819	Release of boric acid from a base with silicone, paraffin, and olive oil
820	Release of salicylic acid, chloramphenicol, and prednisolone from ointment bases
821	Influence of packing on the release of salicylic acid from dimethyl sulfoxide-containing ointment bases
822	Effects of various factors on velocity of drug release from isoniazid repository tablets
823	Drug liberation of meprobamate–dihydroergocristine from retard tablets
824	Influence of solute properties on release of *p*-aminobenzoic acid esters from silicone rubber

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

Interactions of Drugs with Biological Substances—A quantitative comparison of various methods of fundamental binding parameter estimation was presented (825). For optimal reliability, the choice of a particular approach should be made on a critical assessment of the experimental procedure and various calculated statistical criteria rather than on the ease of data treatment. By using nonlinear regression, an improved parameter estimate in drug protein binding studies was devised. In addition, a kinetic approach to drug–protein binding was developed (826). Computer analysis of drug–protein binding data was evaluated (827). A stepwise equilibrium model was recommended as the standard procedure for the investigation of drug–protein interactions.

The binding constants and the number of binding sites for the binding of 11 sulfonamide and seven penicillin derivatives to bovine serum albumin were determined using a fluorescence probe method (828). The results demonstrated that these drugs bind to hydrophobic sites of the serum albumin. New fluorescence probes for drug–protein binding studies were developed (829). The binding of various ingredients was studied, and the results showed that the fluorescence of these acridine derivatives was essentially a combination of fluorescence of acridine and the substitution effects. A dynamic dialysis technique, utilizing a constant flow of buffer solution, yielded the same drug–protein binding information as did equilibrium dialysis (830).

The application of membrane ultrafiltration to the determination of protein binding of drugs was studied (831). Reproducibility between the experiments was good, as was agreement between the binding data obtained by this method and those obtained by equilibrium dialysis. The characterization of drug–protein interactions by classical methods was reviewed (832). Methods discussed were dialysis, ultrafiltration, and gel filtration. The mechanisms of drug–protein interactions also were reviewed (833). The ef-

fects of binding on drug elimination and drug displacement were discussed.

The binding of ascorbic acid and fatty acid ascorbyl esters to bovine serum albumin was studied (834). The analysis of the binding data showed that the albumin possessed a single binding site for these chemicals and that there were marked differences in their binding strength, which increased in the order of ascorbic acid, benzoate, octanoate, and decanoate. The binding of atropine to albumins or γ-globulins from human blood serum was studied (835). The binding significantly increased with an increase in pH above 6.0 or 7.1, respectively. The *in vitro* binding of phenytoin (diphenylhydantoin) to the protein in plasma from 97 volunteers was studied using ultrafiltration (836). The protein binding of phenytoin was significantly decreased in patients with renal disease, hepatic disease, or hepatorenal disease.

Comparative binding of disopyramide phosphate and quinidine sulfate to human plasma proteins was studied (837); the two drugs did not compete for the same binding sites on protein molecules. Glisoxepide, a new antidiabetic drug, was 93% bound by human serum proteins, independent of its concentration (838). When evaluating the competitive binding capacity with phenprocoumon, it was found that glisoxepide did not displace it. Protein binding of indomethacin was studied (839). Binding of indomethacin to human plasma albumin was increased by the presence of phenylbutazone and decreased by the presence of ibuprofen and salicylate. Binding coefficients of various antibiotic affinities to blood protein in a kinetic–biological model suggested that low protein binding was associated with good antibiotic activity (840).

In balanced dialysis experiments, scopolamine hydrobromide interacted with blood serum albumin and γ-globulin (841). An increase in the pH of the solutions from 6.9 to 7.3–7.8 was accompanied by a significant increase in the alkaloid binding with the proteins. The interaction of tolbutamide, glyburide (glibenclamide), chlorpropamide, and tolazamide with serum albumin was studied (842). Glyburide, the most strongly bound of the four compounds, was bound to only one class of sites. The other three compounds were bound to at least two sites. When the interactions of sulfonylureas with plasma proteins were studied, glipizide and glyburide bound to different but closely located sites on the protein with greater affinities (843).

The binding of tolbutamide and glyburide to human serum albumin was examined in varying concentrations of phosphate and tromethamine buffer and in phosphate containing sodium chloride (844). Binding of tolbutamide was affected little by changes in phosphate concentration but was particularly sensitive to the presence of tromethamine and chloride ions. The interaction of tetracycline with human serum lipoproteins and albumin was studied (845). Albumin possessed two binding sites for tetracycline, one a high affinity, low capacity site and the other a low affinity, high capacity site. Tetracycline appeared to dissolve in the lipophilic portion of the lipoprotein molecule rather than to be associated with specific binding sites.

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

Reference	Topic
852	Binding of two β-adrenergic receptor antagonists, alprenolol and metoprolol, to human serum proteins
853	Binding of β-adrenergic receptor antagonists to human serum albumin
854	Binding of *p*-aminohippuric acid, hydrochlorothiazide, and cyclopenthiazide to serum proteins of rats of different ages
855	Spectrofluorometric study of association of ampicillin–lysozyme with diverse medical preparations
856	Binding of antibiotics to a soluble protein from rat liver
857	Influence of binding on pharmacological activity of antibiotics
858	Determination, physicochemical bases, and pharmacokinetic relevance of binding of drugs to plasma proteins
859	Binding of certain antibiotics by blood serum protein
860	Interaction of pharmaceuticals with β-cyclodextrin
861	Plasma protein binding of carbamazepine
862	Binding of chlorpromazine to human serum albumin
863	Binding of diazoxide and benzothiadiazines to human albumin
864	Plasma protein binding of digitoxin and digoxin
865	Comparative study of plasma protein binding of phenytoin (diphenylhydantoin)
866	New approach to determination of protein-bound bilirubin displacement and its applications
867	Doxycycline and albumin-binding capacity of serum from neonates
868	Complex formation between macromolecules and drugs
869	NMR studies of binding of drugs to macromolecules and cellular structures
870	Protein binding of β-methyldigoxin
871	Salicylate interaction with penicillin and secobarbital binding sites on human serum albumin
872	Binding of pyrazolone and pyrazolidine derivatives to bovine serum albumin
873	Binding of (+)- and (−)-Δ^1-tetrahydrocannabinols and (−)-7-hydroxy-Δ^1-tetrahydrocannabinol to blood cells and plasma proteins in humans
874	Effects of drugs on thyroxine-binding capacity of blood proteins
875	Distribution pattern of a series of tricyclic and bicyclic thymoleptics compared with their lipophilic properties and binding to plasma proteins
876	Binding of warfarin sodium to plasma albumin, and its displacement by phenylbutazone
877	Binding of zinc to human serum proteins
878	Circular dichroic investigations into binding of some drugs to human serum albumin
879	Review of plasma protein binding
880	Conformational changes of human serum albumin by binding of small molecules
881	Physicochemical aspects of drug–protein interactions

Nazareth *et al.* (846, 847) studied the binding of L-thyroxine to serum albumins. They studied the use of 2-(4′-hydroxybenzeneazo)benzoic acid to mirror L-thyroxine binding to, and displacement from, serum albumin. Free fatty acid concentrations within the physiological range were found to affect drug

binding to plasma albumin in two ways: at low molar ratios of free fatty acid to albumin, an allosteric effect predominated; at higher molar ratios, there were both allosteric and competitive binding effects (848).

The binding of calcium and magnesium ions to human erythrocyte membranes was investigated (849). At least three different kinds of sites were concerned in the binding of calcium or magnesium to the membrane. Binding of pentazocine to human whole blood, plasma, and blood cells was investigated in 20 normal subjects and 22 patients by means of equilibrium dialysis (850). Plasma protein binding was 56–66% in the control subjects and 48–75% in the patients. In control subjects, 48% of the total amount of pentazocine in whole blood was present in blood cells and 33% was bound to plasma proteins. The remaining 19% was in the plasma water. A constant degree of binding of quinidine to a red blood cell hemolysate preparation was found for a clinically significant range of concentrations at 37° using the method of equilibrium dialysis and ultracentrifugation (851). Quinidine appeared to be bound to a single binding site.

Additional references on interactions of drugs with biological substances are given in Table XXIV.

Interactions of Drugs with Nonbiological Substances—Moorhatch and Chiou (882) evaluated the interactions between drugs and plastic intravenous fluid bags. They studied the adsorption characteristics of 17 drugs, of which three (vitamin A acetate, warfarin sodium, and methohexital sodium) were found to be significantly adsorbed. They also studied the leaching of chemicals from commercial polyvinyl chloride intravenous fluid bags. Absorbances of media such as distilled water, normal saline, 5% dextrose solution, 5% alcohol solution, and aqueous buffer solution with pH values ranging from 3.5 to 9.5 were all quite low within 48 hr of study, indicating insignificant leaching of UV-absorbing material. Absorbances of 0.01–0.04% of polysorbate 20 and 80 solutions were quite high, indicating leaching of a significant amount of chemicals from the bags. The preliminary study indicated that the plasticizer, bis(2-ethylhexyl) phthalate, or other type of phthalate plasticizer may be a major leached chemical (883).

Chloramphenicol seemed to be solubilized by complexation with polysorbate 80 throughout the neutralization range of the interaction (884). Maximum complexation took place at around pH 3.0, the disappearance of the complex began beyond pH 3.4, and interaction ceased at pH 10. The interaction of theophylline with sodium benzoate was examined by NMR (885). Chemical shifts of theophylline protons were determined as a function of sodium benzoate concentration in deuterium oxide at 30°. Signals of both methyl groups underwent significant upfield shifts, indicating vertical or plane-to-plane stacking. The decomposition of aqueous solutions of common antimicrobial agents, sodium metabisulfite, and vitamins was accelerated by storage in polyethylene containers, indicating interactions between the container and its contents (886).

The *in vitro* binding of drugs by colestipol hydrochloride depended not only upon ionic strength, pH, and type of competing ion but also upon whether association could occur with other molecules (887). Where feasible, the initial input ratio of drug to binding agent was equivalent to the ratio if both were administered orally and in therapeutically effective amounts. The water-soluble drugs ascorbic acid, aspirin, salicylic acid, phenobarbital-^{14}C, sulfadiazine, penicillin G, and lincomycin hydrochloride were less than 30% bound to colestipol hydrochloride, while warfarin and tetracycline hydrochloride were bound 59 and 30%, respectively. The interaction of phenobarbital and ethanol given intraperitoneally to mice was studied (888). Dose–response relationships were established for incidence of death, sleeping time, and time of onset of sleep. When the two drugs were administered together, sleep occurred more rapidly than was calculated as likely on the basis of the effects of the drugs given individually. On the other hand, sleep was of shorter duration and the incidence of death was less than anticipated.

The interaction between the preservative 8-hydroxyquinoline sulfate and macromolecules present in tuberculin purified protein derivative solutions

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

Reference	Topic
892	Interaction between preservatives, plastics, and rubbers
893	Interaction between water-soluble phosphated nonylphenol ethoxylate and oil-soluble phosphated fatty alcohol ethoxylate
894	Physicochemical study of khellin–urea binary systems
895	Interaction between chlorpromazine and polysorbate 80
896	Complex formation of nicotinamide with copper (II) in solution
897	Interactions between gelatin–surfactant–water systems
898	Interaction of theophylline and phenobarbital in solution
899	Interaction of insulin with medicinal polymers
900	Interaction of sulfonamides with β-cyclodextrin
901	Complexes of disubstituted sulfonylureas with aliphatic and araliphatic amides
902	Interaction of chloroquine and carrageenan
903	Interaction of cetyltrimethylammonium bromide and sodium dodecylbenzenesulfonate with polyvinyl alcohol
904	Interactions between 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine and sulfonamides in dogs
905	Interactions between sulfinpyrazone and sulfonamides and between oxyphenbutazone and sulfonamides in dogs
906	Interactions of chlorpheniramine–ethanol combinations
907	Relationship of *in vitro* binding of digoxin to its intestinal absorption in rats
908	Adsorption of chlorpheniramine maleate from aqueous solution by activated charcoal
909	Drugs known to react with coumarin-type anticoagulants
910	Solid dispersions for formulation of pharmaceutical compositions containing slightly soluble drugs
911	Complex formation of caffeine by sodium benzoate and sodium salicylate
912	Interaction of atropine sulfate with sodium lauryl sulfate

such as tuberculoprotein, nucleic acid, and polysaccharide were studied (889). The degree of binding was a function of the concentration of these macromolecules. Interactions of iodine with ethylene glycol, diethylene glycol, triethylene glycol, and polyethylene glycols of molecular weight between 200 and 11,000 in ethanol and in carbon tetrachloride were investigated (890). The absorbance of an ethanol solution of iodine at 360 nm increased by the addition of polyethylene glycols. A new peak was observed at 380 nm by the addition of polyethylene glycols of a molecular weight above 300 to the carbon tetrachloride solution of iodine. The complexes of polyethylene oxide with guanidine hydrochloride and with phenobarbital were subjected to differential scanning calorimetry, polarized IR spectroscopy, and X-ray fiber photography, confirming the formations of the complexes; the structures of polyethylene oxide molecules in the complexes were discussed in comparison with a polyethylene oxide–urea complex or with original samples of polyethylene oxide (891).

Additional references on interactions of drugs with nonbiological substances are listed in Table XXV.

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

Interface Studies—Studies were done on surface films of sorbitan esters at the air–water interface (913). The effects of continuous and discontinuous compression methods on the surface pressure–area isotherms were studied. The slower, continuous compression method gave surface pressure–area isotherms that tended toward a smaller area than the faster, discontinuous method of compression. Cumulative results derived from the effects of compression–decompression studies on hysteresis areas, surface pressure relaxation with time from preselected pressures, and recycling experiments were used to explain molecular behavior at the air–water interface (914). A physical model was developed that considered bulk diffusion, interfacial resistance, interfacial area, and oil–water partition coefficient. The model was used to analyze the data obtained from the rate experiments and to determine the interfacial permeability coefficients. Results of the experiments on the transport of sterols from aqueous sodium taurocholate–lecithin and aqueous cholate–lecithin systems into hexadecane strongly suggested that the kinetics of transport of cholesterol, desmosterol, and hydroxycholesterol were interfacially controlled and involved a two-step process. First there was a collision of the solute–micelle complex with the oil–water interface, and this step was followed by the release of the solute from the micelle in a largely polar environment at the interface (915).

Aggregation and interfacial properties of association colloids of benzalkonium chloride and macromolecular colloids of sodium carboxymethylcellulose and guar gum were studied (916). From the data, it seems that a different drag-reducing mechanism existed for sodium carboxymethylcellulose than for guar gum. Sodium chloride significantly reduced the drag-reducing property of sodium carboxymethylcellulose but did not seem to affect drag retention by guar gum. The effects of variations in temperature on drag reduction were different with sodium carboxymethylcellulose than with guar gum.

Table XXVI—Additional References on Interface Studies

Reference	Topic
921	Enhancing effect of calcium ions on transport of cholesterol from aqueous sodium taurocholate–lecithin micellar phase to oil phase
922	Influence of surfactants on structure of solid–liquid interface
923	Wettability of modified silica surfaces
924	Studies on titanium dioxide solutions in presence of surfactants
925	ζ-Potential of magnesium carbonates in inorganic electrolytes
926	Entropy of transfer of molecular benzoic acid from pure liquid to aqueous solution
927	Interfacial phenomena of pharmaceutical systems
928	New apparatus for measurements of dynamic interfacial properties

The interfacial tension of 10 polar liquids against hexane and tetradecane and the contact angle against paraffin, polyethylene, and polytetrachloroethylene were measured (917). Work-of-adhesion values against any one nonpolar phase, calculated from these data, were independent of the polar liquid used. The kinetic and thermodynamic aspects of *in vitro* interphase transfer of sulfonamides were studied (918, 919). Based on the kinetic and thermodynamic parameters, possible mechanisms for interphase transfer of unionized sulfonamides were proposed. The influence of phospholipids on the transport of antibacterial agents across nonaqueous barriers was studied (920). The results indicate that binding of penicillin G and ampicillin with phospholipids occurred at the oil–water interface, which influenced the further transport of the antibiotics through the nonaqueous phase.

Additional references on interface studies are listed in Table XXVI.

Adsorption Studies—The uptake of digoxin and digitoxin by some antacids was studied (929). Magnesium trisilicate showed the highest adsorptive effect, the extent of adsorption being up to 99% for the two glycosides. Antacid preparations containing magnesium trisilicate adsorbed digoxin from a pediatric elixir to the extent of about 95%. The effect of antacids, when concurrently administered with oral digoxin, on the bioavailability of the drug was discussed. Activated charcoal was capable of adsorbing organic vapors commonly used in anesthesia (930). The stability of activated charcoal after the adsorption of halothane was determined despite the passage of high and low halothane free gas flows through the canister.

Physicochemical studies were done on the adsorption of polysiloxane polymers onto hydroxyapatite

Table XXVII—Additional References on Adsorption Studies

Reference	Topic
939	Kinetics of adsorption of radioactive isotopes from ionic solutions
940	Adsorption of hydrocortisone from aqueous solutions using swelling ion-exchange resins
941	Theory of stabilization of spherical colloidal particles by nonionic polymers
942	Investigations into mechanism of adsorption of cationic surfactants
943	Effect of surface reactions of titanium dioxide on usefulness of drug preparations
944	Adsorption of polymers on clays
945	Properties of finely dispersed silicas with specific adsorptivity with respect to given substances
946	NMR studies of water adsorbed on silica surfaces
947	Adsorption of narrow molecular weight fractions of poly(vinyl alcohol) at the polystyrene–water interface
948	Water vapor adsorption by cellulose acetate
949	Adsorption properties of colloidal silicic acids for homologous polyethylene glycols and polyethylene glycol derivatives
950	Effects of manufacturing methods on surface properties of magnesium silicates
951	Determination of specific surface areas of silicates dispersed in dimethyl sulfoxide by negative adsorption
952	Particle size and adsorption properties of aluminum hydroxide used as depositing substance
953	Role of bridging in colloid flocculation
954	GC study of adsorption and intermolecular interactions
955	Use of GC to determine adsorption isotherms
956	Surface reactivity of microcrystalline carbons
957	Adsorption of vapors and gases at high pressures
958	Effect of temperature on adsorption of binary liquid mixtures on silica gels
959	Relationship among adsorbability on carbon black from aqueous solution, protein binding, and pharmacological activities of barbituric acid derivatives and sulfonamides
960	Review of physical adsorption
961	Review of theory of chemisorption
962	Adsorption of vitamin A palmitate into polyethylene from solubilized solution
963	Determination of specific surface by adsorption from solution
964	Determination of specific surface by the Brunauer, Emmett, and Teller method
965	Physicochemical behavior of poly(methacrylic acid) derivatives
966	Desorption of epinephrine (adrenaline) with carboxyl-containing fibers

(931). The molecular configuration of the polymer adsorbed onto a solid surface was essentially a function of: *(a)* the strength of the polymer adsorption onto the solid surface, *(b)* the degree of polymer solvation by the solvent, and *(c)* the extent to which the solvent could compete with the polar anchoring segments of polymer molecules for the surface sites. The adsorption of benzoic acid on sulfamethazine particles was found to be pH dependent (932). At pH values above 4.2, a gradual suppression of the adsorption occurred; at pH 4.9 and above, no adsorption was noted. The effect of sodium citrate on adsorption was attributed to pH and ionic strength effects.

Adsorption of phenothiazines from aqueous solution by silica (Aerosil) was studied (933). The results obtained were compared with the adsorption on carbon black. The adsorption of benzocaine by nylon 6 powder from aqueous solution was examined under varying environmental conditions (934). The extent of adsorption increased with an increase in electrolyte concentration and with pH up to about 4. Increasing temperature reduced the amount of drug adsorbed. In all cases, the adsorption isotherms were linear over the concentration ranges studied. The adsorption of atropine and scopolamine by magnesium trisilicate was studied (935). At relatively low initial concentrations, the adsorption data were shown to fit a Langmuir plot; values for monolayer adsorption were 14.9 and 3.8 mg/g for atropine and scopolamine, respectively.

A method was developed for determining the adsorption rate of water-soluble dyes by soft gelatin capsules (936). This method was used for determining the diffusivities and activation energies of five FD&C water-soluble dyes. The activation energies of these dyes were in either of two groups, which had ranges of 25.1–25.7 and 34.8–36.0 kcal/mole. The adsorption behavior of steroids on silicic acid surfaces was studied (937). Hydrocortisone acetate was bound to the extent of 0.16 mg to 1 g of silica (Aerosil 200) from a saturated solution. The corresponding adsorption value of ethinyl estradiol was 0.26 mg/g of silica (Aerosil 200).

The adsorption isotherms of water vapors on sodium chloride crystals were plotted (938). True adsorption occurred only when the vapor pressure was less than the pressure over saturated sodium chloride solutions at the corresponding temperatures. With great water vapor pressures, a saturated solution film formed on the sodium chloride crystal surface, and the apparent water adsorption was due to isothermal condensation. The true adsorption of water vapor on sodium chloride crystals was caused by physical forces.

Additional references on adsorption studies are listed in Table XXVII.

General Properties of Surfactants—A study of variations of the surface tension coefficient of chlorpromazine aqueous solutions in relation to concentration and UV irradiation showed that the isotherm had an exponential curve characteristic of negative surfactant substances (967). The wetting behavior of aqueous sodium lauryl sulfate solutions on polyethylene terephthalate, nylon 11, graphite, and aluminum powders was studied (968). By using the Washburn equation for the flow of liquid through a capillary, it was possible to calculate, from the rate of penetration, the magnitude of the advancing contact angle, and the work of adhesion between the liquid and the powder. A linear dependence of HLB values of ethoxylated aliphatic nonionic surfactants on molecular weights was found on the basis of two simplifying assumptions. Surfactants of different polyoxyethylene chain lengths attached to the same hydrocarbon chain, and surfactants of different hydrocarbon chain lengths attached to the same polyoxyethylene chain (969).

The chromatography and spectroscopic analytical methods useful for the separation, identification, and determination of anionic and nonionic surfactants in

Table XXVIII—Additional References on General Properties of Surfactants

Reference	Topic
976, 977	Wettability of some low energy surfaces such as air–liquid–solid interface and oils on solids submerged in water
978	Spreading of solid glycerides and phospholipids at air–water interface
979	Calculation of rate of coagulation of hydrophobic colloids in nonsteady state
980	Basis of theoretical correction factors for use with drop weight method of surface tension measurement
981	Colloidal and surface chemical aspects of dosage forms
982	Cloud point determination of nonionic surfactants
983	Properties of aqueous solution of surfactants under high pressure
984	Effect of shape of micelles and temperature on hydration of nonionic surfactants
985	Velocity gradient dependence of flow birefringence in highly concentrated aqueous solutions of anionic surfactants
986	Interrelation of surface and bulk properties of surfactant solutions
987	Alkyl phosphate surfactants
988	Foam concentration of synthetic surfactants
989	Effect of surface phenomena in pharmaceutical systems
990	Temperature variation of surface tension of water–sodium chloride system
991	Temperature variation of surface tension of water
992	Statistical theory of electrical double layer
993	Surfactant and rheological properties of sodium monoalkyl maleate in aqueous solutions
994	Calculation of capillary constant taking into account the contact angle of wetting in a capillary method for determining surface tension
995	Contact angles and their temperature dependence
996	Surface tension and electric potential of aqueous solutions of some sodium sulfonates
997	Wettability of powders

mixtures were reviewed (970). An optical method for the determination of surface tension was described; the method was based on the determination of the slope of the tangent lines to menisci on the plane vertical walls immersed in the liquid (971). The method was independent of wetting phenomena and gave results in agreement with literature data. The surface tension and wetting capacity of biodegradable preparations such as Azolate A_2 and alkyl sulfate or their compounds with metasilicate and sodium tripolyphosphate were evaluated at 480° and a pressure of 20 atmospheres (972). The surfactants had adequate surface tension and wetting capacity at high temperatures and pressures and were thus recommended for use in crude oil extraction from deep-seated strata.

The manufacture of carbohydrate-based surfactants and their use in food, cosmetics, and pharmaceuticals were reviewed (973), as were the softening, washing, emulsifying, and foam-stabilizing properties of surfactants (974). Also reviewed were the various methods used in determining and calculating the HLB of surfactants and oils (975).

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

Micelle Studies—Experiments were done to obtain new information on the solubility behavior of nonionic surfactants in nonpolar media, glycerol, and sorbitan monofatty acid esters (998). The results obtained were discussed on the basis of the thermodynamic functions calculated from the temperature dependence on the critical aggregating or micellar concentration and from the phase diagrams constructed with both the solubility and the aggregating or micellar concentration curves. The effect of the HLB on micelle formation for a homologous series of nonionic surfactants was studied (999). The HLB value increased as the aggregation number decreased, indicating a reduced tendency for micelle formation.

The CMC's of a series of polysorbates were determined using a surface tension method (1000). The CMC values obtained did not vary to any appreciable extent from those determined by other techniques, indicating that the procedure adopted was reliable, simple, and fast. Phase studies and particle-size analysis of solutions formed with nonionic surfactants were evaluated (1001). The micellar size was increased by increasing the oil content and by decreasing the surfactant–glycerol ratio. Also studied were the phase diagram and particle-size analysis of solutions formed with an ionic surfactant. Phase diagram studies were carried out on oil-in-water solubilized micellar solutions containing sodium oleate, amyl alcohol, water, and varying amounts of liquid paraffin (1002). Light-scattering measurements indicated an increase in micellar diameter following an increase in the concentration of liquid paraffin and a decrease in the surfactant–alcohol ratio.

Viscosity studies were carried out on a series of oil-in-water solubilized micellar solutions of liquid paraffin, glycerol, and water and blends of sorbitan monooleate and polysorbate 60 (1003). The effect of the surfactant concentration on the viscosity was discussed in terms of interaction between the polyoxyethylene chains at the surface of the micelles. The micellar properties of the antihistamine drugs diphenhydramine hydrochloride, bromodiphenhydramine hydrochloride, chlorcyclizine hydrochloride, and diphenylpyraline hydrochloride were studied in aqueous solutions (1004). The ζ-potentials of the micelles were calculated from their electrophoretic mobilities, as determined by a dye-tracer technique.

The solution properties of a series of phenothiazine hydrochlorides were studied using light-scattering, viscosity, conductivity, dialysis, and NMR techniques (1005). The aggregates formed were considered to be true micelles, which in water are probably compounds of about 10 monomers vertically stacked with the alkyl side chain and nitrogen group alternating to form an approximately spherical unit in solution. The usefulness of an analytical centrifuge in investigating micellar properties of drugs was evaluated (1006). Various examples of micelle forms of drugs were discussed, as was the working hypothesis that the same binding forces that hold together the aggregate found at high concentrations may be responsible for the binding of monomer to biological structures. The addition of ethanol, propanol, butanol, dioxane, or urea to aqueous solutions of hexaethylene glycol monoundecyl ether, heptaethylene glycol

Table XXIX—Additional References on Micelle Studies

Reference	Topic
1010	Effect of structural modifications on CMC and HLB of various surfactants
1011	Stability of micelles in apolar media
1012	Effect of polyoxypropylene chain length on CMC of propylene oxide–ethylene oxide block copolymers
1013	Study of solvent properties near surface of a surfactant micelle by merocyanine dye
1014	CMC of sodium lauryl sulfate–bivalent metal lauryl sulfate mixtures in aqueous solutions
1015	Influence of micelle formation on internal chemical shift of aromatic protons of solutions of a cationic surfactant
1016	Effect of aqueous alcoholic solvents on counterion binding to cetrimonium bromide micelles
1017	Distribution equilibria in micellar solutions
1018	Dielectric relaxation of micelle-forming anionic paraffin chain salt, sodium lauryl sulfate
1019	Effect of poly(ethylene oxides) on structure formation in aqueous montmorillonite and palygorskite dispersions
1020	Micelle formation by ionic surfactants
1021	Mechanism of micelle formation
1022	Micelle formation of ester-containing surfactants
1023	Effect of counterion on CMC of surfactants in nonaqueous media
1024	Review of CMC of high polymer surfactants in nonaqueous solutions
1025	Nature of species giving spectral changes in an azo dye on interaction with cationic surfactants below CMC
1026	Effect of anions on dissolution and association of nonionic surfactants
1027	Role of entropy and enthalpy changes in micelle formation and solubilization in water–surfactant systems
1028	Review of micelle formation mechanism, cloud point, and phase inversion temperature of various emulsifiers
1029	Review of micelle formation mechanism, and the determination of the HLB of various surfactants
1030	Use of comparative calculation methods during study of aqueous solutions of surfactants, and critical concentrations of micelle formation
1031	Effect of electrolytes on critical concentration of micelle formation and detergent action of sodium lauryl sulfate and sodium laurate
1032	Micellar properties of drugs
1033	Charge transfer phenomena and CMC's of surfactants
1034	Thermodynamics of micelle formation, and prediction of micelle size and size distribution
1035	Effects of electrolytes on micelle formation in solutions of synthetic detergents
1036	Effect of temperature on critical concentration of micelle formation of sodium *n*-alkane sulfonates
1037	Micellar systems in aqueous solutions
1038	Micelle formation of surfactants in mixed solvents
1039	Study of water structure in micellar solutions and mesomorphic gels of potassium laurate–water system by near-IR spectrophotometry
1040	Potentiometric determination of CMC and activity coefficient of cationic surfactants
1041	Determination of critical concentration of micelle formation of surfactants

monodecyl ether, or OP-10 increased the critical concentrations of micelle formation of these surfactants (1007). The alcohols, which stabilized the aggregates of water molecules, decreased the mobility of the surfactant molecules and diminished the number of collisions in unit time.

The kinetics of the formation of sodium lauryl sulfate micelles between 7.5 and 20° were studied by a pressure jump apparatus (1008). The theoretically predicted $1/\tau$ linear increase with increasing sodium lauryl sulfate concentration could not be confirmed, but the relaxation process became detectable at concentrations well below the CMC. Ultrasonic relaxation data were used to determine the kinetics of micellization of ionic surfactants sodium pentyl sulfate, sodium nonane sulfonate, and octylammonium chloride in aqueous solution, and a two-state kinetic model for micellization was used to describe the interchange of monolayers with the micelles by an adsorption mechanism governed by the Langmuir adsorption theory (1009).

Additional references on micelle studies are given in Table XXIX.

Dispersion Stabilization—Mixtures of phosphated nonylphenol ethoxylate, phosphated fatty alcohol ethoxylate, and *n*-hexane formed "oils," which may spontaneously emulsify when added to water (1042). However, the degree of spontaneity and the stability of the resulting dispersions varied according to the constitution of the system. Studies of the equilibrium phase diagrams suggested that the anomalies may be attributed to the presence of liquid crystalline phases of different types formed in the presence of water. The stabilization of emulsions by solid emulsifiers was evaluated (1043). The effects of surface-active compounds, which are often found in hydrocarbon oils, also were studied (1044). The surface-active compounds interacted with the solid emulsifiers and were related to the stabilization of the emulsion by coagulation structure formation. To determine the optimal HLB of oils, oil-in-water emulsions of castor and paraffin oils were prepared with complex emulsifiers, such as polysorbates and sorbitan esters, in appropriate ratios according to the Griffin formula. The optimum HLB depended upon the concentration of the oil phase (20 or 40%) and was not specific for a certain oil.

The stabilization of pharmaceutical suspensions was evaluated by checking the ζ-potential of suspensions of erythromycin propionate and troleandomycin (1045). Rising concentrations of the dispersed phase led to a reduction of the value of the ζ-potential. Suspensions prepared with surfactant solutions with high HLB values characteristically showed high ζ-potential values. Calcium caproate was studied as an emulsifier in the stabilization of xylene in water emulsions (1046). The effect of inorganic electrolytes on the emulsion flocculation was studied by observing ζ-potentials. The potential barriers and stability of the emulsions were high.

Stabilization of disperse systems by surfactants was studied in relation to the formation of structure and electrostatic repulsion (1047). The oil phase was *o*-xylene. The monomers were styrene and vinyl acetate. The emulsifiers used were the ionized sodium salt of butylnaphthalenesulfonic acid and alkyl benzenesulfonic acid and nonionized polyoxyethylated alkyl phenols and polypropylene oxide. Studies of the emulsions showed that the stabilization was due to

Table XXX—Additional References on Dispersion Stabilization

Reference	Topic
1049	Mechanism of formation of so-called microemulsions studied in connection with phase diagram
1050	Antifoam activity of dimethylpolysiloxanes
1051	Mechanism of stabilization of emulsions
1052	Stability of colloidal dispersions, and theory for interaction between particles dispersed in a regular mixture
1053	Effect of electrolytes and surfactants on emulsion separation of colloids collected by synthetic surfactants
1054	Use of hydrocolloids for stabilization of emulsion systems
1055	Phase inversion temperature and cohesive energy ratio systems as modern methods of selecting emulsifiers
1056	Phase inversion temperature of emulsions stabilized with active nonionic surfactants
1057	Dispersive and cohesive actions of surfactants
1058	Review of classification of mixtures and stabilization of disperse systems
1059	Electrokinetic potential and stability of emulsions
1060	Effect of impeller diameter on liquid–liquid dispersion
1061	Stabilization of dispersed systems by nonionic surfactants
1062	Structure of emulsions stabilized by nonionic emulsifiers

the formation of structure at interfaces. By using phase diagrams, the effects of the polarity of oils and the structure of emulsifier on emulsions stability were studied in oil-in-water formulations (1048). The liquid crystal phases, in particular the lamellar phase, formed from the three components of the emulsion appeared to have definite influence on the stability of emulsions.

Additional references on dispersion stabilization are given in Table XXX.

Rheology—The physicochemical principles involved in rheological measurements were reviewed (1063). The use of instrumentation including the Brookfield viscometer, the Brookfield viscometer with Helipath, the Brookfield plate and cone viscometer, and the Rotovisco viscometer were evaluated. Comparative data were presented for typical lotion, cream, and suspension products as measured with each of these instruments. The practical application of such data to formulations, stability, and processing studies was illustrated.

Sulfonamide drug suspensions were aged for 1 year at room temperature, and their rheological behavior was found to be similar to that of freshly prepared suspensions (1064). Drug content and particle-size distributions of aged and fresh preparations were similar. The data obtained from stability controls were in agreement with predictions based on rheological data. When measurements were made with and without the Helipath stand, the flow curves of bentonite gel, determined at 21°, showed that the area and shape of the hysteresis loop were different, emphasizing the importance of considering the basis and exact way by which rheological values were obtained (1065).

The effects of lemon and rose perfume oils, sodium chloride, and various ethoxylated oleyl and lanolin esters on the viscosity of a standard foam bath were studied (1066). Addition of 4% lemon and rose perfume plus an emulsifier sharply decreased the viscosity, while the rose perfume alone caused inhomogeneity. Sodium chloride increased the viscosity, with a maximum viscosity at ~2% sodium chloride. The suitability of the Hoeppler consistometer for testing ointment consistency was evaluated (1067). The Hoeppler consistometer determination of dynamic viscosity gave absolute values (in centipoises). Davis (1068) reviewed the Weissenberg rheogoniometer and digital transfer function analyzer and found them to be the equipment of choice for studies of mucoid fluids and mucolytic activities. Saliva and gastric mucin were useful in *in vitro* systems for screening mucolytic agents. Bottari (1069) reviewed Newtonian, plastic, pseudoplastic, dilatant, and thixotropic flow instrumental methods for the determination of rheological properties and their applications to cosmetics.

Table XXXI—Additional References on Rheology

Reference	Topic
1070	Determination of viscosities
1071	Relationships between kinematic viscosity and concentrations in aqueous solutions of disodium dodecyl phenoxybenzenedisulfonate
1072	Properties and evaluation of oleogels
1073	Rheological properties of feed slurries containing sodium salicylate and salicylic acid particles
1074	Microrheology of disperse systems

Additional references on rheology are provided in Table XXXI.

PHARMACEUTICAL ASPECTS

Antibiotics—The solubilities of the sodium and potassium salts of benzylpenicillin were determined in butanol and in butanol containing 0.5–3% water (1075). Also determined was the hygroscopicity of salts. Results of storage at 82.5 and 95.5% relative humidity showed the degradation products formed faster with the sodium salt. Oxytetracycline preparations in propylene glycol were incubated at 50, 60, and 70°, and changes in color and biological activity were measured at certain time intervals (1076). These data were used to calculate a low limit of antibacterial activity after 3.4–3.6 years of 30%. Appearance of an undesirable intense color was predicted after 4.73 years for the propylene glycol solution.

Polysorbate 80 decreased the biological activity of levorine but not that of amphotericin B, when added at 1.6 mg/mg of antibiotic before a 100-hr storage period at 40° (1077). In experiments with *Torula utilis* cultures, the rate of amphotericin B diffusion from ointments containing polysorbate 80 was greater than that from ointments containing lanolin of wool and wax alcohols. Polysorbate 80 also increased the resorption of the antibiotic by the skin of mice. The use of several flocculants and wetting and suspending agents was studied in the development of an oral troleandomycin suspension (1078). The influence of water, dimethyl sulfoxide, propylene glycol, polyeth-

ylene glycol 400, glycerol, and ethanol on the release of tetracycline hydrochloride from white petrolatum was determined and compared with a tetracycline–urea complex (1079). Water was most effective with tetracycline hydrochloride and dimethyl sulfoxide with tetracycline–urea complex.

Bauer (1080) reviewed the formulation of antibiotics including appropriate dosage form, route of administration, and physiological and morphological conditions at the site of resorption. Also important was the nature of the active ingredient such as its chemical, physical, pharmacokinetic, and toxicological properties. The effects of particle size and shape on the flow and failure properties of procaine penicillin powders were studied (1081). The effects of moisture content and gelatin binding agent on the mechanical and failure properties of an oxytetracycline formulation were also evaluated (1082).

Radiopharmaceuticals—The rapid incorporation of short-lived cyclotron-produced radionuclides into radiopharmaceuticals was reported (1083). Production methods were described for two sterile, pyrogen-free preparations of 10-min ^{13}N and were used clinically. It was found that cobalt 60 was a constant contamination of pharmaceutically prepared iron 59. For research studies, where the iron 59 preparation has decayed several half-lives, establishment of the level of cobalt 60 contamination prior to use seems desirable (1084). The chemistry of ^{99m}Tc, used as a tracer in medicine, was discussed; this information might help achieve a better understanding of the use of radiopharmaceuticals containing ^{99m}Tc and a more rapid development of additional useful formulations (1085). The mechanism of labeling of human serum albumin with ^{99m}Tc was also discussed. Sterile ^{43}KCl was prepared from $^{43}CaCl_2$ by neutron bombardment (1086). The chlorides were taken up in tetralithium edetate (Li_4EDTA), lithium hydroxide was added to pH 10, and the salts were separated on an ion-exchange resin (Dowex 50x12Li^+).

Aulagner *et al.* (1087) reviewed the phenomenon of radioactivity, the detection of and protection against ionizing radiation, the application of radiopharmaceuticals to diagnosis and therapy, and the use of preparations obtained from isotopic generators for organ scanning. The method of preparation of albumin labeled with ^{99m}Tc and its application to other radiopharmaceuticals were discussed (1088). Stability studies were made on 4-iodoantipyrine labeled with iodine 131 when mixed with sodium nitrate (1089). The quantity of sodium nitrate required for stabilization depended on the specific activity of the preparation.

The preparation of ^{113}In-SMAA was described (1090). This radiopharmaceutical was free from side effects and was the most appropriate indium compound for lung scintigraphy. A simple laboratory method of preparation of ^{99m}Tc-labeled iron hydroxide aggregates was described (1091). The formulation was used for lung scanning. The development of radiopharmaceuticals for application in the evaluation of diseases of the kidney and urinary tract was reviewed (1092). A portable, external, two-channel radiotelemetrical GM-detector unit, for measurements of radionuclide tracers *in vivo*, was developed (1093). The equipment was suggested for local tracer studies when continuous long-term measurements are needed.

Table XXXII—Additional References on Radiopharmaceuticals

Reference	Topic
1094	Effect of ionizing radiation on pharmaceuticals
1095	Effect of cobalt 60 γ-radiations on biological activity and some physical and chemical properties of oxytetracycline
1096	Freeze-dried kits for preparing radiopharmaceuticals from technetium-99m
1097	Dosimetrical importance of radiochemical purity of radioactive diagnostic preparations
1098	Radioactive dosage forms
1099	Continuous monitoring of ^{14}C-activity in blood
1100	Survey of radiopharmaceuticals and their current status
1101	Effect of ionizing irradiation on changes in gelatin of pharmaceutical quality
1102	Studies on quality and test method of radioactive iodine-labeled insulin, IgE, and poly(vinylpyrrolidone)
1103	New rapid synthesis of ^{11}C-labeled norepinephrine hydrochloride
1104	Review of radioactive isotopes in pharmaceuticals
1105	Review of radioactive pharmaceuticals
1106	Stability of a stabilizer-free technetium sulfur colloid preparation

Additional references on radiopharmaceuticals are found in Table XXXII.

BIOPHARMACEUTICS

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

As in previous years, the bioavailability of digoxin attracted the most attention in the field of biopharmaceutics. In a series of five papers, Greenblatt and coworkers evaluated the various aspects of digoxin bioavailability. They recommended intravenous digoxin as a bioavailability standard and found that slow infusion was preferable over rapid injection as an intravenous standard in bioavailability testing (1107). They also evaluated the bioequivalence of digoxin as an elixir and a rapid dissolution tablet (1108). A comparison of 1- and 6-day urinary digoxin excretion in single-dose bioavailability studies was made; 24 hr of urine collection was sufficient for single-dose studies of digoxin bioavailability (1109). The same authors also evaluated the digoxin bioavailability in single-dose studies. They compared the intravenous infusion, intramuscular injection, oral elixir, and oral tablet. The area under the 8-hr serum concentration curve correlated with cumulative urinary excretion but showed greater between subject variation. The intramuscular digoxin and digoxin elixir were significantly more bioavailable than the tablet but not sufficiently absorbed to serve as bioavailability standards (1110).

The bioavailability of digoxin tablets and elixir in the fasting and postprandial states was evaluated. In

the same individual, variations in bioavailability between fasting and postprandial states were similar in magnitude to those after repeated fasting administration. Postprandial administration of digoxin did not significantly alter completeness of absorption but altered the rate (1111). In correlating the plasma levels of digoxin in cardiac patients with dose and measures of renal function, it was found that the readily obtainable parameters did not allow accurate prediction of plasma concentration of digoxin in the individual patient, based on the data collected in a panel of cardiac patients. Therefore, serial measurements of plasma concentration of digoxin were necessary in individual patients taking digoxin (1112). The effect of route of administration on the uptake and elimination of digoxin and the relationship of serum digoxin levels to cardiac arrhythmias were investigated in 15 children with congenital cardiac defects who were receiving maintenance doses of digoxin (1113). The highest serum digoxin concentrations were noted 1 hr after oral and parenteral administration. In the limited number of patients studied, there was no apparent relationship between the serum digoxin level and the onset or persistence of cardiac arrhythmias.

Shaw (1114) evaluated the various digoxin tablets marketed in the United Kingdom. He found that they differed markedly in the fraction of the dose adsorbed. Hazards to the patient were not entirely avoided by brand name prescribing, and it was suggested that new pharmacopeial standards were needed for uniform potency. The bioavailability characteristics of a rapidly dissolving digoxin–hydroquinone complex were evaluated, and the complex was found to be faster dissolving than digoxin alone (1115). Four commercially available digoxin tablet brands were characterized by determination of dose uniformity, dissolution rate of digoxin, and tablet disintegration time (1116). Large differences in the dissolution rate of digoxin were observed. Two batches of one brand were found to have a low dose uniformity, whereas the others were well within the pharmacopeial limits.

The comparative bioavailability of two oral preparations of digoxin in healthy volunteers was investigated (1117). They showed no differences with respect to disintegration time, content uniformity, peak serum levels, and cumulative areas under the curve for 8 hr after oral administration of 0.25-mg doses to healthy subjects. Evaluation of pharmacological response intensities showed evidence for variable digoxin absorption (1118). Ball milling or Muller milling digoxin with a 20-fold excess of lactose, sucrose, dibasic calcium phosphate, or microcrystalline cellulose significantly enhanced its dissolution rate (1119). Tablets prepared with such triturations also exhibited superior rates of dissolution. Those prepared with the digoxin–lactose trituration gave plasma levels in rats that were 89.6% of the values from an oral solution of digoxin.

A method was described for the reduction of digitalis glycoside intoxication by rational dosing procedures (1120). Variations in digoxin bioavailability also were evaluated by mean serum digoxin levels obtained 0–6 hr after oral administration of 0.5-mg digoxin tablets (1121). There was a twofold difference in the mean serum peak concentration and the urinary excretion of the two brands studied. Low serum digoxin levels were found in eight institutionalized patients with congestive heart failure despite daily administration, in standard dosage, of a digoxin preparation for 4 weeks (1122). All eight patients developed serum levels within the accepted therapeutic range after receiving another digoxin preparation for 1 week. Analysis revealed that the first preparation did not meet USP requirements of content uniformity. *In vitro* testing demonstrated marked differences in dissolution characteristics between preparations.

Relative bioavailabilities of commercial digoxin tablets were investigated, using a digoxin elixir (Lanoxin) as the most available oral dosage form (1123). Bioavailability of digoxin tablets was calculated from the 0–12- and 0–24-hr areas under the serum level–time curve and from 48-hr cumulative urinary excretion data. Results obtained by the three different methods of calculation were in agreement with each other. Digoxin was reproducibly absorbed from the elixir, as shown by relatively small intrasubject and intersubject variations.

Bioavailability of 14 nitrofurantoin products was evaluated *in vitro* and *in vivo* (1124). All products tested met USP XVIII specifications for drug content, disintegration time, and dissolution rate. Statistically significant differences were observed in bioavailability, as determined from crossover urinary excretion studies in 14 human volunteers. Bioequivalency of generic and brand name chlorpromazine was evaluated (1125). Because of consistent similarities between generic and brand name chlorpromazine for the wide ranges of dimensions evaluated, it was concluded that the two compounds were bioequivalent.

A four-way crossover study was performed to establish the bioavailability of phenytoin (diphenylhydantoin) (1126). Single 100-mg doses of phenytoin sodium were administered as an aqueous solution and compared with a new phenytoin 100-mg capsule and a commercially available 100-mg capsule. Phenytoin capsules from both manufacturers gave plasma levels that were not significantly different at any sampling time. Although phenytoin in solution form was absorbed more rapidly, higher initial plasma levels were produced with the solution form. Plasma level curves of oral doses of naproxen ranging from 125 to 900 mg were studied in normal subjects (1127). Areas under plasma concentration–time curves increased linearly with dose increments up to 500 mg twice a day, but larger doses resulted in a plateau effect. Experiments with tritium-labeled naproxen showed that there was no difference in the fraction of drug excreted in the stools whether the dose was 250 or 900 mg, eliminating incomplete absorption as a factor. Accelerated renal clearance at high doses because of disproportionate increases in the amount of unbound drug appeared to be the most likely explanation for the plateau effect.

The disposition of propoxyphene and its major

Table XXXIII—Additional References on Biopharmaceutics

Reference	Topic
1141	Review of biopharmaceutics
1142	Review on biopharmaceutical criteria for nonoral administration
1143	Review of bioavailability
1144	Bioavailability testing and clinical significance
1145	Biopharmacy and drug effectiveness
1146	*In vitro* evaluation of bioavailability of oral solid formulations
1147	Biopharmaceutics in preformulation stages of drug development
1148	Review of bioavailability
1149	Bioavailability of oral solid dosage forms, and clinical response to drug therapy
1150	Bioavailability and dose–response correlation
1151	Physiological availability of medicinal agents in tablets, and an appraisal of their quality tests
1152	Equipment for studying *in vitro* absorption of orally administered drugs
1153	Bioavailability and pharmacokinetic requirements for registration of new drug products
1154	Corneal penetration of aceclidine into rabbit eyes using perfusion technique
1155	Rate of dissolution and biological availability of coated aspirin
1156	Urinary excretion of amitriptyline *N*-oxide in humans
1157	Comparison of plasma levels of antipyrine, tolbutamide, and warfarin after oral and intravenous administration
1158	Gold kinetics following aurothiomalate therapy
1159	Bioavailability of chloramphenicol in minipigs
1160	Chlorphenesin carbamate serum levels during subchronic administration to normal human volunteers
1161	Bioavailability of clofibrate
1162	Bioavailability of volatile or gaseous compounds after peripheral intravenous dosing
1163	Factors affecting excretion of ^{14}C-dicumarol in rat bile
1164	Di(2-ethylhexyl) phthalate (DEHP) metabolism in animals and posttransfusion tissue levels in humans
1165	Serum levels of gentamicin and tobramycin after slow intravenous bolus injection
1166	Fate of intravenous ^{3}H-glycopyrrolate in humans
1167	Role of sweat in accumulation of orally administered griseofulvin in skin
1168	Correlation of plasma ibuprofen levels with biological activity
1169	Serum levels, excretion, and biotransformation of ketoprofen in animals and humans
1170	Disposition and metabolism of 4-methyl-2-(4-phenylbenzyl)-2-oxazoline-4-methanol in rats and dogs
1171	Bioavailability of methaqualone
1172	Fate of ^{14}C-naproxen
1173	Plasma half-life of niacin (nicotinic acid) in humans
1174	Ocular penetration of ^{14}C-oxyphenbutazone
1175	Equivalence of oxytetracycline tablets BP
1176	Biological availability of oxytetracycline hydrochloride capsules
1177	Use of animal model to predict bioavailability of penicillins
1178	Penicillin blood levels after intramuscular administration of Ampiclox
1179	Biliary excretion kinetics of phenolphthalein glucuronide after intravenous and retrograde biliary administration
1180	Absorption of penicillin V potassium (potassium *S*-phenoxymethyl penicillin)
1181	Biopharmaceutical study of colloidal association of scopolamine *N*-butylbromide and sodium lauryl sulfate
1182	Effect of mucin on bioavailability of tetracycline from GI tract, and *in vivo–in vitro* correlations
1183	Comparison of tetracycline preparations for oral use
1184	Bioavailability of thiazinamium methylsulfate after oral and intramuscular administration
1185	Influence of polymers and pH on transcorneal biophasic availability and mydriatic response of tropicamide
1186	Biopharmaceutical study of vitamin U
1187	*In vitro* testing of drug availability with Stricker apparatus
1188	Penetration of fluorouracil in excised skin
1189	Evaluation of activity of dermopharmaceutical preparations with corticosteroid base
1190	Percutaneous penetration of methotrexate

biotransformation product norpropoxyphene was studied in normal subjects following a single 130-mg oral dose (1128). The peak plasma level of propoxyphene occurred at 2 hr, followed by a rapid elimination with an average apparent half-life of 3 hr. The plasma level of norpropoxyphene reached a peak at 4 hr and slowly decayed with an apparent half-life of 16.8 hr. The data indicated that individual differences in absorption and biotransformation may have been responsible for the substantial variation of the plasma propoxyphene levels seen in subjects receiving the same dose.

A single-dose, crossover, comparative study of 25- and 100-mg spironolactone tablets was undertaken in 39 healthy males (1129). Following a total dose of 200 mg of each dosage form, the primary discriminators for comparing the two dosage forms were found to be the plasma metabolite levels at 3 and 4 hr, peak plasma metabolite level, and total 24-hr area under the plasma level curve. Total serum iodine levels were measured for 24 hr in human subjects following a single, oral, therapeutic dose of organically bound iodine administered as iodinated glycerol (1130). Peak levels were obtained 1–2 hr after administration of a single dose, with a gradual fall to almost basal levels at 24 hr. The experiment with continued dosing for 6 days indicated that once peak blood levels were reached, they continued at this concentration until the drug was discontinued.

The concentration of theophylline in the plasma and saliva of seven normal adults receiving single oral doses of 200-mg theophylline/m^2 of body surface area was determined spectrophotometrically over 8 hr (1131). There was an excellent linear relationship between theophylline concentrations in plasma and saliva over a plasma concentration range of 4–14 μg/ml. The results suggested that theophylline determination in saliva may be a convenient, painless, and noninvasive method for routine monitoring of theophylline levels. To determine bioavailability of theophylline in a new sustained-release form, plasma drug concentration–time curves were determined for five normal male subjects after an intravenous dose of 4 mg/kg and after an oral dose of 700 mg as two oral tablets (1132). The absolute bioavailability of the oral dosage was 77.1 ± 5.4%.

Chrai (1133) studied the influence of precorneal factors on the bioavailability of topically applied drugs. Urinary excretion data were used to determine the bioavailability of crystal forms II and III of sulfameter in humans (1134). Agreement was observed between the ratio of absorption parameters of the two forms determined in the present study and those previously obtained from blood level data. Although the urinary data revealed a significant difference in the rate of absorption of the two forms, no significant difference was observed in the extent of absorption of both forms as indicated by the 72-hr urinary excretion data.

The *in vivo* dissolution rates of prednisolone from five commercially available 5-mg prednisolone tablets were determined in distilled water (1135). A two-way crossover bioavailability study was also preformed in 12 human male adult volunteers, comparing the fastest and the slowest dissolving brands. Statistical analysis of the data for the two brands showed no significant differences between average plasma levels of prednisolone at any sampling time. The results suggested that on the average the *in vivo* rates of dissolution of the two brands were essentially the same. Wagner and Johnson (1136) reviewed the relationship between the rate of drug dissolution *in vitro* and biological availability and suggested that the dissolution rate may be the rate-limiting step in drug absorption, hence limiting its bioavailability from solid dosage forms. Correlation of *in vitro* dissolution measurements with *in vivo* parameters makes it easier to control the factor of bioavailability.

A modified *in vitro* permeability technique permitted the hydration of the stratum corneum to be maintained very close to its natural state (1137). Penetrant molecules were applied by adding a few microliters of acetone solution to the stratum corneum surface. The acetone quickly evaporated, leaving a residue of solid penetrant. The time course of penetration of the solid material through the epidermis was observed as a function of applied dose, mild hydration, and solvent contact time. Remarkedly steady and uniform penetration persisting over several weeks was observed. Diffusion through the stratum corneum rather than sorption of the solid at the surface appeared to be rate limiting.

The development and evaluation of ointment and cream vehicles for a new topical steroid, flucloronide (fluclorolone acetonide), were described (1138). Enhanced drug release and superior vasoconstrictor activity were demonstrated by flucloronide when prepared in vehicles in which it was entirely solubilized. A gel or cream base containing 0.025% betamethasone benzoate was a suitable formulation for topical treatment of steroid responsive dermatoses in comparison with other steroids (1139). The cream was significantly less efficacious than the gel. Percutaneous absorption of escin-^{3}H in mice and rats was studied (1140). A horizontal diffusion was observed in the skin of mice. Only small amounts of escin were found in inner organs, bile, and urine. Higher escin concentrations were detected only in the part of the muscular system beneath the site of application.

Additional references on biopharmaceutics are listed in Table XXXIII.

Effects of Physicochemical Properties—Microcrystals of aspirin of 100 × 25 × 2-μm size, given orally to volunteers, were excreted in urine more rapidly than aspirin crystals of 1000 × 300 × 250-μm size (1191). Apparently, smaller crystals were more readily absorbed by the digestive tract than were larger ones. The influence of three granulometric fractions of aspirin on rectal absorption in rabbits was examined (1192). Particle size of the drug influenced the absorption, as had been established for GI absorption of drugs. A correlation between dissolution rate and release of the drug from suppositories was established. The particle-size effect of sulfathiazole on availability after subcutaneous administration was evaluated (1193). The particle size influenced the absorption and dissolution rates when sulfathiazole was administered as aqueous suspensions subcutaneously.

Structure–activity relationships of some organic hydroxy acids with reference to their choleretic activity were studied (1194). Of the nine hydroxy acids tested, 3,4-dimethoxycinnamic acid was the most potent choleretic. Acids that possessed an unsaturated carbon–carbon bond and a methoxy group possessed a stronger action, and acids that contained a free hydroxy group possessed a weak action. A study was made to determine the relationship between the structure of phenylalkylamines and their psychotomimetic activity (1195). Optimum activity was associated with: *(a)* an isopropylamine side chain, with a *R*-(−) configuration at the carbon atom alpha to the amino group; and *(b)* 2,5-dimethoxy substitution, together with an alkyl or halo group at position 4, which is probably limited in bulk to *n*-propyl or bromo.

The anticancer activities of some dihydrofolate reductase-inhibiting 2,4-diaminopyrimidine derivatives, solapalmitine-related *N*-acylamines, bis(1-aziridinyl) phosphinyl carbamate derivatives, and aromatic nitrogen mustards were correlated with substituent constants (1196). For the 2,4-diaminopyrimidines, activity correlated with Taft's steric constants for substituents in the 5-position, demonstrating that anticancer activity in these compounds was related to the steric bulk of the 5-substituent. The carbonic anhydrase inhibitory activities of 17 sulfonamides were compared with their structures, based on quantum chemical calculations performed within the framework of the extended Hückel theory (1197). Correlations were found between the activity of molecules and the reduced Mulliken overlap populations relative to the SO_2 group. Screening of 300 chalcone, flavanone, flavone, flavonol, and acetophenone derivatives showed that 44 compounds had hypotensive, analgesic, anti-inflammatory, antithrombic, sedative, or antifungal activity (1198). Halosubstituted flavones were more active than corresponding flavanones, but all flavanone derivatives were inactive, suggesting that pharmacological activity was dependent on the presence or absence of a double bond in the 2–3 position.

Table XXXIV—Additional References on Effects of Physicochemical Properties

Reference	Topic
1205	Structure–activity correlations of actinomycins
1206	Structure–activity correlations of β-adrenergic receptor antagonists
1207	Structure–activity correlations of apomorphine analogs
1208	Structure–activity correlations of anti-inflammatory 2-arylbenzoxazoles
1209	Structure–activity correlations of aureolic acid group of antibiotics
1210	Structure–activity correlations of cardioactive steroids
1211	Structure–activity correlations of chlorohydrins as orally active male antifertility agents
1212	Structure–activity correlation in series of compounds related to diphenhydramine
1213	Structure–activity correlations of isoarecaidine derivatives
1214	Structure–activity correlations of mitomycins
1215	Structure–activity correlations of *N*-substituted narcotic antagonists
1216	Structure–activity correlations of pyridine derivatives as myorelaxants
1217	Structure–activity correlations of tricyclic antidepressants
1218	Structure–activity correlations of *dl*-α-tocopherol having different isoprene chains
1219	Structure–activity correlations of zygosporin derivatives
1220	Relation between chemical structure and pharmacodynamic activity
1221	Absorption of iron from ferrous salts
1222, 1223	Review of effect of physicochemical properties on bioavailability
1224	Effect of physicochemical and pharmacokinetic properties of barbiturates on induction of drug metabolism
1225	Comparative study of absorption and distribution of quinidine salts
1226	Effect of physicochemical properties on intramuscular absorption of drugs from oily solutions in rats
1227	Influence of molecular structure on intestinal absorption of fat-soluble vitamins
1228	Relation of drug effectiveness to physicochemical properties
1229	General influence of physicochemical properties on drug–receptor combination
1230	Comparative clinical pharmacology of three ampicillins and amoxicillin administered orally
1231	Physicochemical factors influencing drug absorption from intramuscular injection site
1232	Effects of physicochemical properties on biological availability of drugs
1233	Comparison of availability of ions from sodium salicylate and salicylic acid tablets
1234	Absorption and *in vitro* dissolution of phenytoin and its sodium salt
1235	Comparative serum levels and urinary recovery of cefazolin, cephaloridine, and cephalothin in humans

Based on the theory of quantum statistics, a method was developed for the correlation of drug action and chemical structure (1199). It was applied to the interaction of distinguishable biological receptors and in distinguishable drug molecules. Calculations for several local anesthetic drugs illustrated the usefulness of the method. A Hansch analysis of the anabolic activities in the rat of butyrate to undecanoate normal fatty acid ester of nandrolone was made (1200). Two peaks of activity were observed in plots of organ weight against time for each ester and were assigned to release into the blood from the site injection and from body fat, respectively. Anabolic activities were measured as an increase in weight of levator ani over control weight, multiplied by duration of response. A binomial relationship was obtained between log anabolic activity and the log ethyl oleate–water distribution coefficient. Kasuya (1201) studied the structure–activity relationships of androgens and evaluated the metabolism and target organ uptake of the various compounds.

An aqueous suspension of ampicillin, when compared to ampicillin sodium, yielded a higher and longer lasting blood level and was eliminated less in urine (1202). The bile concentration was two to three times higher than the blood level in rabbits injected with ampicillin intramuscularly. The bioavailability of aminosalicylic acid and its sodium, potassium, and calcium salts was evaluated in humans (1203, 1204). Absorption of aminosalicylic acid and its three salts was essentially complete. Dissolution of aminosalicylic acid appeared to be the rate-limiting factor in its absorption, and the type of salt administered affected the rate of absorption. Although absorption of all four compounds was complete, the areas under the plasma concentration–time curve, or bioavailable drug, were dependent on the rate of absorption. The data presented showed evidence of rate-limited metabolism, especially in the first pass.

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

Effects of Formulation—The effects of formulations in various digoxin preparations were evaluated. Binnion (1236) studied tablets from four different manufacturers and found that the disintegration times for these tablets were different and did not correlate with the plasma levels in subjects who took them. The tablet with the slowest disintegration rate produced satisfactory plasma digoxin concentrations. Another tablet, with slow dissolution rate, failed consistently to produce a therapeutic plasma level. The author recommended that all packages containing digoxin tablets should be labeled with data on their dissolution characteristics but that none should be sold unless these data are consistent with biological availability. Also the *in vitro* dissolution was correlated with bioavailability of various oral digoxin preparations (1237). Plasma concentrations were measured by radioimmunoassay. For rapidly releasing preparations, the dissolution rate did not control absorption. Absorption from slowly releasing tablets was reduced but only partially controlled by dissolution rate.

By using various methods of estimating digoxin absorption, the absolute bioavailability of 0.25-mg digoxin tablets was found to be 62%, and an equivalent dose of digoxin solution was determined to be 77% (1238). Of the various methods studied, the urinary excretion of digoxin was the most valid measure of bioavailability of oral digoxin preparations. The bioavailability and dissolution properties of two commercial digoxin tablets and an elixir were evaluated (1239). The elixir form gave much higher blood levels than either tablet during the first two sampling

times, but the two tablets showed nearly identical blood levels and relative bioavailabilities. A previously reported dissolution rate test method showed wide differences between the two tablets and thus failed to correlate with the similar bioavailabilities observed *in vivo*.

The *Federal Register*, for the first time, reported some guidelines for marketing oral digoxin tablets (1240). It was proposed that digoxin tablets be withheld from distribution until released by the Food and Drug Administration after testing to meet USP XVIII requirements and dissolution tests and that the quantity of digoxin dissolved in 1 hr should not be more than 95% of the assayed amount or that the quantity dissolved at 15 min should not be more than 90% of that assayed amount.

The effect of (−)-Δ^9-*trans*-tetrahydrocannabinol was studied in mice following four routes of administration: oral, subcutaneous, intraperitoneal, and intravenous (1241). For each route, four different vehicles were used: bovine serum albumin, polysorbate 80, polyvinylpyrrolidone, and propylene glycol. The anticonvulsant activity of the parent drug was strongest in the propylene glycol vehicle with subcutaneous and intraperitoneal routes and equal in the propylene glycol and polyvinylpyrrolidone vehicles with the oral route. With these three routes, bovine serum albumin and saline appeared to be inadequate vehicles for studying the anticonvulsant activity of (−)-Δ^9-*trans*-tetrahydrocannabinol.

A correlation between the ear temperature-lowering effect and blood level was investigated in rabbits and dogs after oral administration of two different dosage forms of ethylphenylephrine: an uncoated tablet, which showed a rapid dissolution rate *in vitro*, and a sustained-release capsule, which showed a gradual dissolution rate (1242). Absorption of the drug from the uncoated tablet was more rapid than from the sustained-release capsule. Plasma concentration and urinary excretion of proxyphylline were studied in healthy volunteers after the administration of the drug intravenously and orally as ordinary tablets and slow release tablets of the insoluble matrix type (1243). The rate of absorption from the slow release tablets was limited by the dissolution from the tablets, and the *in vitro* release agreed closely with the calculated absorption. Administration of slow release tablets twice a day for 5 days gave about the same plasma levels as ordinary tablets given three times a day, and the bioavailability was the same from both preparations.

A competitive protein-binding method was used to evaluate two prednisolone preparations: a conventional form and an enteric-coated formulation (1244). Except for the delay due to the coating, they were completely comparable, since maximum levels reached, areas under plasma concentration–time curves, and apparent disappearance half-lives were almost identical. Diethylpropion 25-mg capsules and 75-mg sustained-release tablets were tested in humans under acidic conditions, and the results compared with those obtained previously after administration of the drug in aqueous solution (1245). The bioavailabilities were comparable in each case, and the metabolic fate of the drug was not modified by these pharmaceutical formulations. Under conditions of uncontrolled urinary pH, the recoveries of diethylpropion and all basic metabolites except norepinephrine were greatly reduced.

Table XXXV—Additional References on Effects of Formulation

Reference	Topic
1251	Relative bioavailability of commercial ampicillin formulations in humans
1252	Effects of formulation on aspirin bioavailability
1253	Relative bioavailability of chloral hydrate after rectal administration of different dosage forms
1254	Effects of formulation on clomethiazole bioavailability
1255	Effects of formulation on availability of cyclazocine
1256	Effects of formulation on griseofulvin and riboflavin bioavailability
1257	Effects of formulation on topical bioavailability of griseofulvin
1258	Effects of formulation on isoniazid bioavailability
1259	Effects of formulation on nitrofurantoin bioavailability
1260	Effects of formulation on phenobarbital bioavailability
1261	Effects of formulation on potassium chloride bioavailability
1262	Effects of formulation on procainamide bioavailability
1263	Effects of formulation on sulfadiazine availability
1264	Effects of formulation on theophylline bioavailability
1265	Effects of drug–adjuvant interactions on drug bioavailability
1266	Drug adsorption properties of different activated charcoal dosage forms *in vitro* and in humans
1267–1269	Review of effects of formulation on drug bioavailability
1270	Effects of formulation on bioavailability of injectables

The dissolution rates of oxyphenbutazone in two commercial samples of sugar-coated tablets and one soft gelatin capsule were determined (1246). Clinical trials to compare tolerance indicated that the soft gelatin capsules led to less complaints of gastric irritation. The bioavailability of two experimental ampicillin capsule formulations was greater than 85% of the standard product, indicating that the processes involved in the manufacture of these formulations (dry granulation *versus* direct encapsulation) had little influence on ampicillin systemic availability (1247). In two test panels of 10 subjects each, plasma levels and urinary excretion of two drugs, acetaminophen and nitrofurantoin, were measured to compare bioavailability when the drugs were formulated as commercial tablets and as specially formulated gelatin capsules (1248). No significant differences in the relative efficiency of absorption were obtained between tablets and capsules with either drug.

Pagay and coworkers (1249, 1250) studied the rectal absorption of acetaminophen from an aqueous solution and from several polyethylene glycol base dosage forms. A relationship was observed between acetaminophen bioavailability and the dielectric properties of the vehicles utilized. The *in vitro* dissolution

rates of acetaminophen in these dosage forms were also studied and were somewhat related to the time of occurrence of the maximum urinary excretion rate.

Additional references on effects of formulation are found in Table XXXV.

Absorption Control and Alteration—Segre *et al.* (1271) studied the pharmacokinetic interactions between aspirin and other nonsteroidal anti-inflammatory drugs including naproxen. The results showed that simultaneous oral administration of aspirin and naproxen in humans resulted in a small, but statistically significant, lowering of plasma levels of naproxen. This effect was not mediated by competition for drug absorption but was associated with enhanced renal clearance of naproxen or its metabolites. The bioavailability of digoxin was evaluated in the presence of antacids containing magnesium trisilicate (1272). The results indicated that antacids may impair the bioavailability of the drug.

The effects of 1,25-dihydroxycholecalciferol on calcium absorption, muscle weakness, and bone disease in chronic renal failure was investigated (1273). 1,25-Dihydroxycholecalciferol given for 4–8 days increased intestinal calcium absorption without causing large changes in plasma calcium or phosphate. Effects of caffeine on the absorption and analgesic efficacy of acetaminophen (paracetamol) were studied in rats (1274). There was a dose-dependent decrease in the GI absorption of acetaminophen. The administration of aluminum hydroxide gel delayed and depressed the GI absorption of isoniazid in rats and patients with active tuberculosis, whereas magaldrate had less pronounced and more variable effects (1275). The depressed absorption of isoniazid was probably related to delayed gastric emptying as a result of the presence of Al^{+3} in the stomach.

Tetracycline in aqueous solution containing 50 mg of iron caused an ~80 and ~65% inhibition of iron absorption in subjects with normal iron stores or depleted iron stores, respectively, by complex formation (1276). This effect was decreased when tetracycline was given before and iron was given after the meals. The effects of potassium ion on the intramuscular absorption of some anionic drugs were examined using the rat thigh muscle clearance method (1277). In the presence of potassium ion, a specific and reversible inhibition was noted in the absorption of anionic drugs such as isonicotinic acid, aminobenzoic acid, and sulfa drugs. The effect of ethanol on intestinal absorption of theophylline was evaluated (1278). Theophylline absorption was significantly increased by 5% ethanol and was decreased by 20% ethanol.

The effect of salicylic acid on antibacterial activity and distribution of sulfadimethoxine was studied in rabbits (1279). The antibacterial activity of sulfadimethoxine following intravenous administration of sulfadimethoxine was significantly increased by the concurrent administration of salicylic acid. The effects of the polysorbates on the intramuscular absorption of the water-soluble, micelle-free drugs were investigated in the rat (1280). The presence of a low concentration of the polysorbates caused a pronounced decrease in the absorption rates of drugs, and the reduction was reflected in their plasma levels. Absorption rates of the drug in the muscle were dependent on the concentration rather than the absolute amount of the surfactant. The GI absorption of 1% phenobarbital or phenobarbital sodium, administered orally to rats, was enhanced by polysor-

Table XXXVI—Additional References on Absorption Control and Alteration

Reference	Topic
1290	Absorption of aspirin and acetaminophen (paracetamol) in patients with achlorhydria
1291	Effect of concurrent administration of aspirin and indomethacin on serum concentrations
1292	Effect of acidic drugs on absorption of aminopyrine from rat small intestine
1293	Effect of gastric emptying on absorption of aminopyrine in rats
1294	Effects of drug pretreatment on antipyrine levels in blood and tissue
1295	Effect of nonionic surfactants on absorption of aprobarbital sodium from suppositories in rabbits
1296	Inhibitory effect of high dietary zinc on copper absorption in rats
1297	Effect of salicylate ion on absorption of ^{3}H-dextromethorphan hydrobromide in rats
1298	Digoxin malabsorption due to altered renal function
1299	Absorption of phenytoin (diphenylhydantoin) in humans and its inhibition by phenylbutazone
1300	Effect of phenobarbital on bioavailability of erythromycin
1301	Effect of food on *in vivo* release of propranolol from a polyvinyl chloride matrix tablet in dogs
1302	Effect of sodium cholate on intestinal absorption of sulfa drugs
1303	Absorption studies of sulfamethoxazole in presence of trimethoprim in young adults
1304	Absorption studies of sulfamethoxazole in presence of trimethoprim in humans
1305	Interactive effect of (+)-fenfluramine and dextroamphetamine on feeding in rats
1306	Effect of potassium ion on *in situ* rat intestinal absorption of several drugs
1307	Effect of short-chain fatty acids on intestinal absorption of drugs in rats
1308	Effect of phenylpyrazolone derivatives on gastric emptying rate and drug absorption in rats
1309	Effect of γ-radiation on intestinal absorption of sulfanilamide
1310	Effects of complex formation on drug absorption
1311	Enhancement of drug absorption after administration by an automatic injector
1312	Influence of tablet hardness and food intake on absorption of drugs
1313	Effect of HLB values of surfactants on ephedrine absorption and release from emulsified systems after oral administration to dogs
1314	Effect of dialkylpropionamide on *in vitro* and *in situ* absorption of prednisolone
1315	Effect of nonionic surfactants on absorption of drugs
1316	Effect of drug interactions on absorption
1317	Effect of acid production by stomach on absorption of levodopa
1318	Relation between viscosity of digestive fluid and disintegration time of tablets
1319	Effect of retention time on rectal absorption of aspirin suppositories in children and adults
1320	Availability of three antibiotics after intramuscular injection into thigh and buttock
1321	Effects of dimethyl sulfoxide and trimethylphosphine oxide on percutaneous absorption of corticosteroids in rats
1322	Effect of vehicles on reduction of brain norepinephrine by α-methyltyrosine

bate 80 and sodium lauryl sulfonate, especially at doses lower than the CMC, and was depressed by polyvinylpyrrolidone and methylcellulose (1281).

The effect of polysorbate 80 on the intestinal absorption of nine micelle-free drugs was examined in the rat (1282). Regardless of the ionic nature of the compounds, two levels of the effect were observed, namely an absorption-enhancing effect at a relatively low concentration range and a small inhibitory effect at high concentrations of the surfactant. The effects of surfactants on absorption through membranes were studied (1283). Pentobarbital absorption was enhanced in the goldfish by dioctyl sodium sulfosuccinate and poloxalene.

A prodrug approach to the enhancement of the rate of dissolution of allopurinol was studied (1284). These prodrugs had lower melting points, higher solubilities, and, consequently, greater rates of dissolution than did allopurinol. The prodrug concept was reviewed as a method of overcoming pharmaceutical problems (1285). The effect of food intake and sleep on the absorption of acetaminophen was studied (1286). The rate of absorption of acetaminophen was found to be more rapid in human subjects under fasting conditions than when it was given immediately following food. Differences in absorption rate were confirmed by the excretion rate, but the overall elimination of drug was not affected by urine flow nor was it altered during the sleep period.

The effect of food on the absorption characteristics of nitrofurantoin from a commercial capsule dosage form containing macrocrystalline drug and a commercial tablet dosage form containing microcrystalline drug was assessed in human subjects by a urinary excretion method (1287). In fasting subjects, less nitrofurantoin was absorbed and at a slower rate; lower body levels were obtained when the capsule rather than the tablet dosage form was orally administered. When each was administered with food, the absorption of nitrofurantoin was appreciably delayed. Food in the GI tract produced an increase in the peak body levels of nitrofurantoin from the macrocrystalline form.

The effect of fasting on the oral absorption and excretion of sodium salicylate and aspirin was studied in rabbits (1288). The attainment of the maximum blood levels of these drugs in the fasted rabbits was somewhat slower than in the nonfasted rabbits. However, the extents of absorption were the same in the fasted rabbits as in the nonfasted rabbits. The peak serum levels of amoxicillin and ampicillin were detected 2 hr after oral administration of 500 mg of either drug to a nonfasting subject, the peak values being 5.9 and 2.1 μg/ml, respectively (1289). In contrast, the peak serum level of amoxicillin was found at 3 hr after an oral dose of amoxicillin plus probenecid.

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

Absorption Mechanisms—The effects of surfactants, such as sodium glycocholate, on the absorption and metabolism of the model compounds *O*-benzoylthiamine disulfide and thiamine disulfide were evaluated by both *in situ* and *in vivo* experiments using rats (1323). The *in situ* results indicated that, in the presence of a biosurfactant, the increasing or decreasing effect of a synthetic surfactant on drug absorption and metabolism could be canceled by the possible formation of new mixed micelles consisting of the drug and both surfactants. Results were confirmed by oral experiments using the drug–micellar solution in rats. Based on *in vitro* and *in vivo* studies in rats, it was established that α-tocopherol deficiency affected the passive absorption of barbital, phenol red, and salicylate, probably by altering the GI membrane (1324).

Bromphenol blue and *p*-acetylaminohippuric acid were studied with rats to understand the basic principles of the hepatobiliary transport process (1325). The results suggested that these organic anions were transported from blood into bile by at least two processes (hepatic uptake and biliary excretion) and that the hepatic uptake of these compounds was mainly due to the binding to substances in the liver cells. Atropine sulfate, when recirculated through the rat intestine *in vivo*, was absorbed as a function of pH but not concentration (1326). Similar results were observed when atropine sulfate was instilled in rat intestinal loops for 30–120 min. Thus, atropine did not inhibit its own absorption in the intestine, where the blood vessels are not supplied with cholinergic vasodilators. The difference in absorption at different pH's might indicate that the diffusion of the drug was dependent on the degree of its ionization.

The effects of altered urinary pH on the renal excretion of doxycycline were studied in humans (1327). Alkalinization of the urine resulted in higher cumulative amounts of doxycycline excretion during both single- and multiple-dose regimens. The increased excretion was reflected in larger renal clearances and shorter half-lives for both regimens when the alkaline condition was compared to the control condition. A model was developed to study the GI absorption of drugs and dosage forms in the unanesthetized rhesus monkey (1328). The absorption of an ionizable acidic drug, an ionizable basic drug, and a nonionized drug from the stomach and the intestines was compared. The nonionized form of the drug was

Table XXXVII—Additional References on Absorption Mechanisms

Reference	Topic
1330	Contribution of solvent drag to intestinal absorption of acidic drugs, benzoic acid and salicylic acid, from rat jejunum
1331	Contribution of solvent drag to intestinal absorption of basic drugs, aminopyrine (amidopyrine) and antipyrine, from rat jejunum
1332	Proposed mechanism for gentamicin transport
1333	Sublingual resorption of trapidil in humans
1334	Effect of physiological factors on bioavailability of oral dosage forms
1335	Kinetics of sulfathiazole (norsulfazole) absorption in isolated intestine of rats
1336	*In vitro* hydrolysis and absorption in animals and humans of a new synthetic ester, thiamphenicol palmitate
1337	Review of absorption mechanisms of drugs
1338	Models for studying drug absorption *in vitro*

absorbed faster than the ionized form at any particular site in the GI tract.

A general physical model was described for the simultaneous active and passive transport of conjugated and unconjugated bile acids from nonmicellar solutions in the ileum (1329). It reduced to the passive absorption mechanism in the duodenum and the jejunum. Theoretical computations indicated that the stagnant water layer may be the rate-determining barrier.

Additional references on absorption mechanisms are listed in Table XXXVII.

PHARMACOKINETICS

A modern view of pharmacokinetics was presented, suggesting that both linear and nonlinear systems must be included (1339). Special attention was given to the equations used to describe nonlinear kinetics, the recognition of nonlinearities, nonlinear models, and the fitting of data. Seven guidelines were presented for use in possible future pharmacokinetic studies involving drug kinetics. After reviewing the present status of pharmacokinetics, the methods for pharmacokinetic analysis were outlined (1340). Special emphasis was given to the determination of drug bioavailability from various dosage forms. Use of pharmacokinetics in determining sites of drug action and in determining a clinical metabolic profile was suggested.

The effect of the route of administration on drug disposition was reviewed (1341). The authors suggested that while the first-pass effect is a fairly generally understood phenomenon in the gross sense, it is not commonly appreciated that the rate at which the drug is delivered to the liver can influence the fraction of the administered dose that reaches the fluids of distribution. The drug molecules being absorbed *via* the hepatic portal vein intermix with previously absorbed drug recycling in the hepatic artery. The concentration of the drug returning *via* the hepatic artery is affected by the volume of distribution of the drug into body tissues.

The importance of tissue distribution in pharmacokinetics was discussed (1342). Mechanisms of drug distribution were summarized, and the differences between intracellular and extracellular pH, active transport system for drugs, distribution of drugs between fat and water in adipose tissue, reversible binding of drugs to phospholipids and to various macromolecules including proteins, nucleic acid, and melanin were presented. Examples were presented of pharmacokinetic analysis which influence the practice or principles of practical therapeutics. The action of the organism on the drug was summarized in terms of pharmacokinetic parameters: absorption, distribution, metabolism, and excretion. These parameters were examined with respect to drug accumulation, relation of pharmacokinetic data to therapeutic effects, saturation phenomena, effect of kidney disease, variation of pharmacokinetic parameters in individual patients due to age, pH of body fluids, and states of wakefulness (1343).

A general consideration of cancer chemotherapy was presented, consisting of a brief description of cell kinetics and some biochemical events (1344). Models of local tissue and cell uptake of drugs were presented, including various diffusion and mass transport steps. The complex interactions of saturable transport, cell binding, and other pharmacokinetic parameters on the concentration levels of methotrexate in rat bone marrow and other tissues were studied.

A simple equation was presented by which the first-order rate constant for drug absorption into the central compartment of any linear mammillary pharmacokinetic model can be calculated (1345). No specific knowledge of the distribution or elimination characteristics of the drug was required. The meaning of clearance for drugs that are exclusively eliminated from a peripheral compartment of a multicompartment mammillary system was examined (1346). The utility of the various pharmacokinetic parameters employed to interpret drug elimination was discussed. Practical pharmacokinetic techniques for drug consultation and evaluation were described (1347). Psychotherapeutic drugs were used as prototypes for illustrating some considerations in pharmacist-generated dosage regimens.

Pooling of Michaelis–Menten equations for models having parallel paths for formation of two or more metabolites was discussed (1348). A theory that explains phenomena exhibited by pooled nonlinear pharmacokinetic systems and equations relating pooled Michaelis–Menten constants (V_p, K_p) to microscopic constants (V_i, K_i) were presented. The suitability of this type of pooling for use in pharmacokinetic modeling was discussed, as was the use of pooling concepts in the design of clinical studies. Ballard (1349) reviewed the effect of temperature on pharmacokinetics. He discussed the effects of body and environmental temperature on human physiological changes and physicochemical properties, absorption, distribution, and metabolism of drugs.

Pharmacokinetic parameters of amikacin and kanamycin were compared in a crossover study using healthy adult male volunteers (1350). Apparent volumes of distribution, serum half-lives, and renal clearance were compared and were found to be virtually identical. The pharmacokinetics of intravenously administered amobarbital and its major metabolite hydroxyamobarbital were studied (1351). The metabolism of amobarbital was a saturable process and largely zero order over the entire dose range studied.

Pharmacokinetic studies in amphetamine-dependent subjects, using large intravenous doses, were undertaken to relate measurable pharmacokinetic parameters to the clinical manifestations of amphetamine abuse (1352). Subjects having an acidic urine exhibited a relatively mild psychosis, while the psychotic symptoms were aggravated in patients with an alkaline urine. Chlorphenesin carbamate serum levels during subchronic administration to normal human volunteers were studied (1353). A one-compartment open model appeared to have predicted adequately the equilibrium serum concentrations of chlorphenesin carbamate.

Analog and digital computing techniques were

used to elucidate the pharmacokinetic parameters involved in the metabolism and excretion of diethylpropion and its metabolites in humans (1354). Rate constants for the various processes were evaluated for the complex reaction scheme. The values of the rate constants were used as the basis for discussion of the relative importance of some metabolic routes.

Several papers were presented on the pharmacokinetics of digoxin. During chronic therapy with 0.25 mg of digoxin, mean plasma digoxin levels measured by radioimmunoassay were 0.7 ng/ml and the daily urine excretion of digoxin was about 44% of the daily given dose (1355). When the levels of orally given 0.25-mg digoxin tablets were measured by peak serum digoxin concentration as well as by area under serum digoxin concentration–time curve, the bioavailability of digoxin appeared to be higher in the fasted subjects than in fed ones (1356). After intravenous administration, the pharmacokinetics of digoxin were described by a two-compartment open model. Digoxin was strongly distributed to tissues, as reflected by a mean ratio of k_{el}/B = 9.24 and an average volume of distribution at steady state of 5.95 liters/kg (1357).

Pharmacokinetic design of digoxin dosage regimens in relation to renal function was studied (1358). Calculation of a dosage schedule to produce predetermined steady-state serum concentrations of digoxin was dependent on four major variables: bioavailability, biotransformation rate constant, renal clearance, and apparent volume of distribution. Loading and maintenance doses of digoxin in patients of normal renal function and those with severely impaired renal function were studied (1359). It was found that loading doses for patients with severely impaired renal function should be half those for patients with normal renal function.

A dose–effect curve constructed from ventricular rate slowing and oral maintenance doses for digoxin provided evidence for assuming that occupation theory correctly described drug–receptor site interaction (1360). The influence of allopurinol on drug metabolism was studied in humans. Its administration in conjunction with the anticoagulant warfarin did not alter their dose requirements (1361).

Furosemide, as tablets or aqueous solution, was taken orally by normal subjects during a fast and postprandially (1362). Comparative studies were conducted using intravenous furosemide. No significant differences were found between the tablets and the aqueous solution. During fasting, detectable drug levels appeared in the serum within 10 min. The postprandial studies displayed delayed appearance and low peak serum concentration. Salivary and urinary excretion of lithium was studied in three healthy male subjects after oral administration of two or three different doses (1363). In all individuals, the concentration of lithium in the salivary fluid was 2.2–3.3 times as high as the concentration in plasma. Thus, once the saliva–plasma concentration ratio is established, the measurement of saliva concentrations can provide all of the pharmacokinetic information necessary for rational dosage regimens.

Serum levels of methaqualone were determined in eight unfasted subjects following single- and multiple-dose administration (1364). The data were analyzed by a two-compartment open model. The significance of pharmacokinetic parameters in relation to bioavailability and the biological disposition of single- and multiple-dose methaqualone administration was discussed. Acetaminophen (paracetamol) was administered intraperitoneally or intravenously to male rats (1365). Its availability in the systemic circulation after intraperitoneal administration was 34% of that after intravenous administration. This finding suggested a high first-pass metabolism of intraperitoneally administered drug, which was confirmed using the rat isolated perfused liver.

The absorption of orally administered pivampicillin, an ester that hydrolyzes to ampicillin *in vivo*, was studied in healthy males and compared to ampicillin administered intravenously, intramuscularly, and orally (1366). Renal clearances and serum half-lives for pivampicillin were the same as those for ampicillin. The clinical efficacy, tolerance, and pharmacokinetics of a new aminoglycoside antibiotic, sisomicin, were studied in elderly male patients suffering from complicated urinary tract infections (1367). After intramuscular injection, serum levels of the antibiotic declined, with a half-life of about 3 hr after the initial dose. The pharmacokinetics of thiothixene was studied in psychotic patients on long-term therapy (1368). Drug plasma concentrations reached an early peak following an oral dose and declined slowly thereafter. Despite considerable differences in doses, peak plasma concentrations fell within a relatively narrow range, indicating that, during earlier adjustments of dose to achieve therapeutic control, optimum plasma concentrations were also being achieved.

Matin *et al.* (1369) studied the pharmacokinetics of tolbutamide and found a good linear relationship between tolbutamide concentration in saliva and plasma; salivary levels were 1.2% of plasma levels. The pharmacokinetics and pharmacodynamics of enantiomers of warfarin were studied in humans (1370). In nine subjects, the plasma half-life of *R*-warfarin after a single oral dose was significantly longer than that of *S*-warfarin. Similar pharmacokinetic studies on the warfarin enantiomers were conducted with rats (1371).

There has been a new stress on determining the various pharmacokinetic parameters of different drugs used during the diseased state. Jackson and McLeod (1372, 1373) discussed the dosing concentration of antimicrobial agents when used in patients with renal impairment. They discussed the pharmacokinetics of the following drugs: bacitracin, chloramphenicol, chloroquine, clindamycin, dapsone, erythromycin, lincomycin, neomycin, vancomycin, the urinary tract anti-infectives, sulfonamides, and trimethoprim.

The pharmacokinetics of cefazolin were studied in normal and uremic patients after single and multiple intramuscular doses (1374). In normal subjects, cefazolin gave maximum serum concentrations of 30–50

μg/ml 1 hr after a single 500-mg injection, with a serum half-life of about 2 hr. Higher serum levels were obtained after identical doses to uremic subjects, and serum half-lives increased with decreasing renal function. Also studied were the pharmacokinetics of cefazolin in the presence of normal and impaired renal functions (1375). The mean serum half-life of cefazolin sodium was 1.6 hr in normal patients and about 42 hr in patients with impaired renal function.

The pharmacokinetics of furosemide in normal subjects and functionally anephric patients were studied (1376). The plasma half-life was increased from 29.5 min in normal patients to 80.7 min in anephric patients. The pharmacokinetics of furosemide in advanced renal failure, where the renal furosemide clearance was reduced (1377), were also discussed. The anticoagulant half-life of heparin in human subjects with normal and impaired renal functions was studied (1378, 1379). The anticoagulant half-life of heparin was found to be dose related. The normal renal function group gave a mean anticoagulant half-life of 36.8 min for the 0.6-unit/ml dose and 22.7 min for the 0.3-unit/ml dose. The chronic renal failure population had a mean half-life of 47.5 min for the 0.6-unit/ml dose and a mean half-life of 32.6 min for the 0.3-unit/ml dose.

The pharmacokinetics of metolazone were studied in normal adult volunteers after oral or intravenous administration and after oral administration in patients requiring diuretic therapy for severe renal failure, for moderate renal failure, and for heart disease (1380). Clearance of metolazone from the central compartment was approximately equal to creatinine clearance and ranged from 110 ml/min in normal subjects to 20 ml/min in severe renal failure. The absorption was 64% in normal controls, but as little as 40% of the oral dose was absorbed in some patients. The plasma half-life of phenylbutazone in patients with impaired liver function was studied (1381). Preliminary evidence was presented for a significant correlation between the apparent elimination rate constant of phenylbutazone and the galactose elimination capacity in cirrhotic patients.

Eight volunteers with normal renal function and 11 patients with chronic renal insufficiency were each given propranolol while in the fasting state (1382). Absorption was rapid in both groups. In the patients, propranolol appeared in the serum within 0.5 hr of oral administration and maximum concentrations, with a mean of 154.6 ng/ml, appeared in 1.5 hr; in the control group, maximal concentrations, with a mean of 51.1 ng/ml, developed in 2 hr. The pharmacokinetics of the antibacterial combination sulfamethoxazole and trimethoprim in patients with normal or impaired kidney function were studied (1383). Following oral administration, the elimination rate of sulfamethoxazole and, to a lesser extent, trimethoprim was decreased by renal impairment. Also studied were the pharmacokinetics of 4,5-bis(*p*-methoxyphenyl)-2-phenylpyrrole-3-acetonitrile in normal and polyarthritic rats (1384).

Additional references on pharmacokinetics are listed in Table XXXVIII.

Table XXXVIII—Additional References on Pharmacokinetics

Reference	Topic	Reference	Topic
1385	Pharmacokinetics of acetylkidamycin	1401	Pharmacokinetics of 1β-D-arabinofuranosylcytosine in humans
1386	Pharmacokinetic properties of β-adrenergic receptor blocking drugs	1402	Pharmacokinetics of 1β-D-arabinofuranosylcytosine deamination in several species
1387	Influence of pharmacokinetic variations on the pharmacological properties of adriamycin	1403	Pharmacokinetic aspects of elimination from plasma and distribution to brain and liver of barbiturates in rat
1388	Blood levels, tissue distribution, and clinical effects of adriamycin	1404	Absorption and metabolism of orally administered beclomethasone dipropionate
1389	Kinetics and bioavailability of two formulations of amiloride in humans	1405	Pharmacokinetics of 1-[4,6-bis(allylamino)-*s*-triazin-2-yl]-4-(di-*p*-fluorobenzhydryl)piperazine bis(methanesulfonate)
1390	Urine data analysis for pharmacokinetics of aminopyrine	1406	Pharmacokinetics, drug availability, and clinical pharmacology of bromhexine
1391	Antibacterial activity, absorption, excretion, and clinical applications of amoxicillin	1407	Pharmacokinetics of the diuretic bumetanide
1392	Pharmacokinetics of amoxicillin	1408	Pharmacokinetic study of local anesthetics, bupivacaine and etidocaine, in humans
1393	Distribution of parenteral ampicillin and cephalosporins in late pregnancy	1409	Pharmacokinetics of burimamide and metiamide
1394	Pharmacokinetics of ampicillin potassium in healthy subjects and patients with glomerular renal insufficiency	1410	Pharmacokinetics of butaperazine
1395	Comparative studies on absorption of ampicillin trihydrate and ampicillin potassium	1411	Kinetics of human urinary excretion results for butethal (butobarbitone) and its metabolites
1396	Comparative study of serum concentrations and urinary excretion of ampicillin, pivampicillin, and amoxicillin after oral application to fasted subjects	1412	Butethal (butobarbitone) metabolism in humans: identification of 3-ketobutobarbitone
1397	Absorption, distribution, and excretion of anisodamine	1413	Pharmacokinetics of calcium dobesilate in humans
1398	Relevant pharmacokinetics of antimicrobial drugs	1414	Pharmacokinetics of microdispersed calcium oleate
1399	Pharmacokinetics of antineoplastic preparations	1415	Distribution, metabolism, and excretion of caprylohydroxamic and nicotinohydroxamic acids
1400	Pharmacokinetics and biodegradation of aprindine in humans	1416	Pharmacokinetics of carbenicillin in high dosage

Table XXXVIII—*Continued*

Reference	Topic
1417	Pharmacokinetics of cefazolin compared with four other cephalosporins
1418	Cefazolin plasma concentrations and urinary excretion in patients with renal impairment
1419	Pharmacokinetics and therapeutic uses of cephaloridine
1420	Determination of half-life, clearance, and dialyzability of sodium salt of cephalosporanic acid in humans
1421	Dose equation for continuous intravenous infusion based on pharmacokinetics and its clinical applications on cephalothin
1422	Pharmacokinetics of cephanone in healthy adult volunteers
1423	Pharmacokinetics of chlorpromazine metabolites
1424	Absorption, distribution, and excretion of 6-chloro-5-cyclohexylindane-1-carboxylic acid in rats
1425	Absorption, distribution, and excretion of 8-chloro-6-phenyl-4*H*-*s*-triazolo(4,3-*a*)(1,4)-benzodiazepine in rats
1426	Species differences in metabolism of 8-chloro-6-phenyl-4*H*-*s*-triazolo(4,3-*a*)(1,4)benzodiazepine
1427	Multicompartmental analyses of bi- and triexponential plasma disappearance curves after intravenous injection of ^{14}C-cholic acid, sulfobromophthalein, and ^{14}C-bilirubin, and their significance for quantitative studies of the hepatic excretory function
1428	Distribution and excretion of iodochlorhydroxyquin (clioquinol) in animals
1429	Pharmacokinetics of clonazepam in humans
1430	Pharmacokinetic profiles of clonazepam in dogs and humans and of flunitrazepam in dogs
1431	Comparative pharmacokinetics of coumarin anticoagulants; relationship between distribution, elimination, and anticoagulant action of warfarin
1432	Comparative pharmacokinetics of anticoagulant effect of coumarin drugs in humans and rats
1433	Comparative pharmacokinetics of coumarin anticoagulants; relationship between distribution, elimination, and anticoagulant action of dicumarol
1434	Pharmacokinetics of cyclohexylamine in humans
1435	Distribution of daunomycin and adriamycin in mice
1436	Pharmacokinetics of diatrizoate sodium and iodipamide sodium under hemodialysis
1437	Absorption, excretion, and distribution of 3′,4′-dideoxykanamycin B in rats
1438	Absorption, excretion, and distribution of 3′,4′-dideoxykanamycin B in rabbits and dogs
1439	Pharmacokinetic analysis of 3′,4′-dideoxykanamycin B in pediatric field
1440	Pharmacokinetics of ^{14}C-dimethothiazine
1441	Pharmacokinetics of 4-[3-(dimethylamino)-propylidene]-4,9-dihydrobenzo[*e*]thieno[2,3-*b*]thiepine-10-^{35}S (dithiadene-10-^{35}S)
1442	Metabolic fate of *N*,*N*-dimethyl-*N*′-(*p*-phenoxyphenyl)sulfamide in rats, dogs, and humans
1443	Fate and metabolism of dimethyl sulfoxide
1444	Pharmacokinetic studies of phenytoin (diphenylhydantoin)
1445	Half-life of diphenylpyraline in humans
1446	Diazepam metabolism in normal humans; serum concentrations and clinical effects after intravenous, intramuscular, and oral administration
1447	Diazepam metabolism in normal humans; serum concentration and clinical effect after oral administration and accumulation of diazepam
1448	Pharmacokinetic analysis of 3′,4′-dideoxykanamycin B in humans
1449	Review on pharmacokinetics and bioavailability of digitalis
1450	Absorption, metabolism, and excretion of cromoglycate disodium in nine animal species
1451	Effect of phenobarbital on pharmacokinetics of erythromycin
1452	Pharmacokinetics of fluorocarbon aerosol propellants
1453	Pharmacokinetic studies on flupentixol and flupentixol decanoate in animals and humans
1454	Pharmacokinetics and metabolism of fominoben in humans
1455	Pharmacokinetics of gentamicin in cerebrospinal fluid and eye compartments
1456	Pharmacokinetics of glibornuride
1457	Pharmacokinetics and pharmacodynamics, as well as metabolism, following orally and intravenously administered ^{14}C-glipizide
1458	Pharmacokinetics of glipizide in humans
1459	Pharmacokinetics of radioactively labeled glisoxepide in animals
1460	Pharmacokinetics and metabolic spectrum of glisoxepide in humans
1461	Absorption, distribution, metabolism, and excretion of glycopyrrolate in mice
1462	Pharmacokinetics of glymidine and tolbutamide in acute and chronic liver diseases
1463	Absorption, metabolism, and excretion of ^{14}C-griseofulvin in humans
1464	Absorption and elimination of ^{35}S-gutimine following intraperitoneal administration
1465	Metabolism of heptabarbital (heptabarbitone)
1466	Disposition of hydralazine in humans, and a specific method for its determination in biological fluids
1467	Comparative studies on distribution, excretion, and metabolism of hydroxyzine-^{3}H and its methiodide-^{14}C in rats
1468	Imipramine protein binding and pharmacokinetics in children
1469	Pharmacokinetics of isoniazid in Caucasian race
1470	Pharmacokinetics of isoniazid in humans
1471	Pharmacokinetic and metabolic studies with lanatoside C, α- and β-acetyldigoxin, and digoxin in humans
1472	Pharmacokinetics of levodopa and its metabolites
1473	Hypothesis for rapid attainment and maintenance of lidocaine plasma levels
1474	Pharmacokinetic studies with maprotiline
1475	Pharmacokinetics of menadione and menadione sodium bisulfite in animals
1476	Pharmacokinetic properties of meprobamate in dogs; an example of dose dependency in elimination kinetics
1477	Pharmacokinetic studies after administration of ^{14}C-dipyrone (^{14}C-metamizole) to rats, dogs, and humans
1478	Pharmacokinetics and availability of methanesulfonic acid derivative of dapsone (*p*,*p*′-diaminodiphenylsulfone) in rabbits
1479	Review of pharmacokinetics of methotrexate
1480	Absorption, metabolism, and distribution of ^{14}C-*O*-methyldopa and ^{14}C-levodopa after oral administration to rats
1481	Pharmacokinetics of antimicrobial agent mydecamycin
1482	Pharmacokinetic studies on mydecamycin
1483	Pharmacokinetics of ^{3}H-naftazone in humans
1484	Pharmacokinetics of nalidixic acid: serum and urinary levels with normal renal function
1485	Pharmacokinetics of naloxone
1486	Metabolism of nealbarbital (nealbarbitone)
1487	Absorption of neomycin from alimentary tract of a pig

(continued)

Table XXXVIII—*Continued*

Reference	Topic
1488	Pharmacokinetic and genetic studies of nortriptyline and desipramine in human subjects
1489	Aspects of pharmacokinetics of opiates
1490	Compartmental study on pharmacokinetics of D-penicillamine
1491	Metabolism of D-penicillamine
1492	Pharmacokinetics of dihalo-substituted isoxazolyl penicillins
1493	Pharmacokinetic evaluation of penicillin and cephalosporin derivatives in serum and milk of lactating cows and ewes
1494	Pharmacodynamic and pharmacokinetic study of modern semisynthetic penicillins
1495	Pharmacokinetics of pentazocine and its optical isomers
1496	Analysis of intersubject variation in pentazocine metabolism
1497	Dose and dosage form-dependent pharmacokinetics of phenacetin and its metabolite in humans
1498	Pharmacokinetic studies on 2-phenyl-4-(*p*-chlorophenyl)thiazol-5-ylacetic acid
1499	Urinary metabolites of phylloquinone and α-tocopherol
1500	Metabolism and kinetics of piribedil in humans and rats
1501	Absorption and distribution of 4-prenyl-1,2-diphenyl-3,5-pyrazolidinedione in rats
1502	Excretion of probenecid and its metabolites in bile and urine of rats
1503	Pharmacokinetics of procainamide
1504	Pharmacokinetics as a guideline for procainamide and theophylline dosing regimens
1505	Computerized dosage regimens for procainamide
1506	Pharmacokinetic studies on propanidid
1507	Clinical investigations on pharmacokinetics of propiram-^{14}C fumarate
1508	Chemical study on pharmacokinetics of propiram fumarate
1509	Influence of dose and infusion rate on propranolol bioavailability
1510	Pharmacokinetics of distribution and elimination of sodium di-*n*-propylacetate in mice and dogs
1511	Pharmacokinetic studies on proxyphylline administered intravenously and orally to humans
1512	Pharmacokinetics and tolerance of quinidine sulfate and dihydroquinidine gluconate in horses and dogs
1513	Pharmacokinetic disposition of quinidine in rhesus monkeys
1514	Absorption and clearance of secobarbital, heptabarbital, methaqualone, and ethinamate
1515	Use of a mathematical model of streptomycin pharmacokinetics for providing necessary blood levels under conditions of intravenous infusion
1516	Plasma levels and urinary excretion of K-strophanthoside-^{3}H administered rectally to humans
1517	Pharmacokinetics of sulfadiazine–nitrofurantoin during normal kidney function
1518	Dosage regimens of sulfonamides based on pharmacokinetic parameters
1519	Pharmacokinetic study on metabolism and excretion of sulpyrine in rats
1520	Distribution, excretion, and metabolism of N^1-(2-tetrahydrofuryl)-5-fluorouracil
1521	Pharmacokinetics and metabolism of ^{3}H-thebaine
1522	Pharmacokinetics of thiamphenicol: behavior in acute and chronic hepatic insufficiency
1523	Pharmacokinetics of thiamphenicol: behavior in renal insufficiency under dialysis conditions
1524	Absorption, distribution, excretion, and metabolism of tinidazole
1525	Pharmacokinetic profile of trimethoprim–sulfamethoxazole in humans
1526	Pharmacokinetic studies with trimethoprim and different doses of sulfadiazine in healthy subjects
1527	Absorption and urinary excretion of trimethoprim, sulfamethoxazole, and trimethoprim–sulfamethoxazole
1528	Pharmacokinetics of trimethoprim and sulfamethoxazole in normal subjects and in patients with renal failure
1529	Metabolism of trimethoprim in humans, and measurement of a new metabolite
1530	Excretion of trimethoprim and sulfamethoxazole in patients with renal failure
1531	Similarity of warfarin half-lives in human subjects
1532	Review of pharmacokinetic factors affecting epidermal penetration and percutaneous absorption
1533	Review of pharmacokinetics and dosage regimens
1534	Review of one-compartment open model pharmacokinetics comparing excretion following intravenous administration with and without metabolism
1535	Review of pharmacokinetics of one-compartment open model at constant intravenous infusion and after a single dose
1536	Review of pharmacokinetic and biopharmaceutical fundamentals
1537	Contribution of pharmacokinetics to drug design
1538	Significance of pharmacokinetics in drug therapy
1539	Mathematical aspects of pharmacokinetics and toxicokinetics
1540	Pharmacokinetics in relation to age
1541	Apparent biological half-life values determined by drug administration by methods other than rapid intravenous injection
1542	Mathematical procedures for evaluating pharmacokinetic studies
1543	Dose-dependent drug metabolism during absorptive phase
1544	Pharmacokinetic considerations in clinical drug trials
1545	Pharmacokinetics as foundation for drug therapy
1546	Application of pharmacokinetic principles to elucidation of polygenically controlled differences in drug response
1547	Kinetics of drug–drug interactions
1548	Structural effects in drug distribution using whole animal pharmacokinetics
1549	Statistical estimations in pharmacokinetics
1550	Importance of use of appropriate pharmacokinetic model to analyze *in vivo* enzyme constants
1551	Critical evaluation of use of effective protein fractions in developing pharmacokinetic models for drug distribution
1552	Safe method for rapidly achieving plasma concentration plateaus
1553	Linearity and superposition in pharmacokinetics
1554	Importance of type of dosage form and saturable acetylation in determining bioactivity of aminosalicylic acid
1555	Simulation of blood level of drugs by digital computer
1556	Significance of blood levels of drugs
1557	Design and analysis of comparative blood level trials
1558	Pharmacokinetic consequences of plasma protein binding of drugs
1559	Age-related differences of pharmacokinetic behavior of short-lasting sulfonamides in

Table XXXVIII—*Continued*

Reference	Topic	Reference	Topic
	rats, with special reference to protein binding rate		drug concentrations in blood
1560	Calculation of plasma level *versus* time profiles for variable dosing regimens	1562	Effect of antacids on pH of urine and its effect on kinetics of elimination of certain acidic and basic drugs
1561	Factors causing interindividual variations of		

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RESEARCH ARTICLES

Kinetics and Mechanisms of Degradation of the Antileukemic Agent 5-Azacytidine in Aqueous Solutions

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Abstract □ The hydrolytic degradation of 5-azacytidine was studied spectrophotometrically as a function of pH, temperature, and buffer concentration. Loss of drug followed apparent first-order kinetics in the pH region below 3. At pH <1, 5-azacytosine and 5-azauracil were detected; at higher pH values, drug was lost to products which were essentially nonchromophoric if examined in acidic solutions. The apparent first-order rate constants associated with formation of 5-azacytosine and 5-azauracil from 5-azacytidine are reported. Above pH 2.6, first-order plots for drug degradation are biphasic. Apparent first-order rate constants and coefficients for the biexponential equation are given as a function of pH and buffer concentration. A reaction mechanism consistent with the data is discussed together with problems associated with defining the stability of the drug in aqueous solutions. At 50°, the drug exhibited maximum stability at pH 6.5 in dilute phosphate buffer. Similar solutions were stored at 30° to estimate their useful shelflife. Within 80 min, 6×10^{-4} *M* solutions of 5-azacytidine decreased to 90% of original potency based on assumptions related to the proposed mechanisms.

Keyphrases □ 5-Azacytidine—kinetics and mechanisms of degradation in aqueous solutions, effect of pH, temperature, and buffer concentration □ Hydrolysis, 5-azacytidine in aqueous solutions—kinetics and mechanisms, effect of pH, temperature, and buffer concentration □ Antileukemic agents—5-azacytidine, kinetics and mechanisms of degradation in aqueous solutions

The synthesis of 5-azacytidine (I) was reported in 1964 (1). The compound has antimicrobial and antitumor activities (2–4) and is currently being evaluated clinically in the treatment of human leukemias.

The clinical use of this drug makes it desirable to determine kinetic data on its reactivity in aqueous solutions. Such information is especially important in consideration of its relative instability when compared to cytidine itself. Especially notable are the ease with which the triazine ring hydrolyzes and the lability of the sugar–triazine bond (5). Although most hydrolysis products of I have been identified (5), lit-