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REVIEW ARTICLE

Pharmaceutical Sciences—1969: Literature Review of Pharmaceutics

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This review of the literature represents a comprehensive cross section of the research and development efforts in various selected disciplines of the pharmaceutical sciences. It is the eighth annual survey of the series (1–7). To compile it, numerous periodicals and selected sections of *Chemical Abstracts* were abstracted.

The review was prepared with two purposes in mind. Primarily, it was to provide an opportunity of reviewing the research highlights of the past year in the field of pharmaceutical technology. Secondarily, it was to supply a convenient source of references for anyone interested in the studies carried out in a specific area. The format was slightly altered from that of previous years; tables were included as a new approach to covering articles of preferred interest in specific areas.

GENERAL PHARMACY

A philosophical review article was published describing the effect of pharmaceutical research on science and society in general (8). Several review articles appeared on governmental control of the pharmaceutical industry in various countries (9, 10). These included a description of the origin, development, and application of the National Drug Code in the United States, as well as the quality control procedures for sampling, stability, and packaging required for pharmaceutical products in Turkey. The Food and Drug Adminstration (FDA) outlined its viewpoint on microbiological control of topical and internal preparations where sterility is not a requirement (11). The primary sources of possible contamination were viewed as being the raw materials, water supply, processing operations, equipment and plant facilities, and employees. Microbiological tests on finished products, to be most meaningful, should include tests for *Salmonella*, *Pseudomonas*, and coliforms. Several other interesting papers described the factors responsible for microbiological contamination of cosmetics and proprietaries (12, 13). The authors believed the training of employees and equipment cleanliness to be the most important factors contributing to microbiological contamination. The articles also contained a brief discussion of the numerous known contaminating organisms, and they described methods to control or decrease their levels.

The optimum pH for many commonly used ophthalmic drugs was presented, along with a discussion of preservatives and buffers suitable for use in ophthalmic preparations (14). The use of macromolecules such as methylcellulose and polyvinyl alcohol in preparing artificial tears and lubricants for contact lenses was discussed in detail (15). Clinical tests indicated that these macromolecules are most effective on the corneal epithelium at a concentration of 1.5%. Another paper reported the formulation and method of preparation

Editor's Note: The scope of this article has been limited to a review of the literature in the area of pharmaceutics because reviews of the literature related to other areas of the pharmaceutical sciences are published elsewhere annually.

Table I—References for Some Relatively Nontechnical Discussions Related to Pharmaceuticals

Reference	Topic
18	Review of local anesthetics
19	Review of antihistamines
20	Review of antiepileptic drugs
21	Review of phenothiazine tranquilizers
22	Review of diabetes and hypoglycemic agents
23	Review of antifertility agents
24	Review of over-the-counter (OTC) antacids
25	Review of sleep-aids and other OTC sedatives

of a stable sulfacetamide ophthalmic solution by avoiding heat sterilization or tyndallization during manufacture (16).

The physiology of the nose and the influence of physical and chemical factors on the penetration of medicaments through the nasal mucosa were outlined (17). The effect of vasoconstrictors, wetting agents, and pH on the duration of drug activity was investigated in guinea pigs.

Other papers of interest in general pharmacy are given in Table I.

Preservatives—The water-solubility and surface-tension-lowering properties of a series of homologous quaternary ammonium compounds were reported to be directly related to their antimicrobial effectiveness (26). Other investigators found no direct relationship between disinfectant effects and other properties of a series of amphoteric surfactants (27). Various alcohols were compared for *in vitro* antimicrobial effectiveness; *n*-propanol was the most effective when used alone, while *n*-butanol, *n*-propanol, and ethanol were very effective when combined (28). Dimethylsulfoxide (DMSO) was shown to inhibit completely the growth of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus megaterum* when used in concentrations of 15% or greater (29). Polyethylene glycol 300 reduced the viability of certain spores with or without the presence of heat (30). The ability of certain organisms (mainly *Pseudomonas* species) to degrade parabens and limit their bacteriostatic effectiveness was demonstrated (31). The action of surfactants on the effectiveness of a wide variety of preservative agents was reported in several articles (32–35). In most cases, the effectiveness of the preservative was shown to decrease after a certain critical concentration of the surfactant was exceeded. The effectiveness of chlorobutanol, chlorohexidene, phenylmercuric nitrate, and polymyxin B sulfate appeared to decrease in the presence of methylcellulose and carboxymethylcellulose (36). In the presence of the latter gum, only phenylmercuric nitrate retained its bactericidal activity. A combination of phenylmercuric nitrate and phenylethyl alcohol was observed to be more effective in preserving fluorescein solutions against *Pseudomonas* comtamination than either of the two agents used alone (37).

Several halogenated naphthol derivatives were tested at different levels in liquid pharmaceutical preparations for effectiveness against 20 different organisms (38). All derivatives were active at levels of 20–50 mcg./ml. against most organisms except *P. aerugenosa*, *Proteus vulgaris*, and *Micrococcus caseolyticus*. The loss of phenylmercuric nitrate and phenylethyl alcohol from solution due to their adsorption by the dropper attachments of ophthalmic packages was described (39). The rubber, nylon, and plastic components tested in this study appeared to adsorb phenylmercuric nitrate more than phenylethyl alcohol. The effect of the electrical charge of a preservative on its bactericidal effect in atropine solutions was used to explain why cationic quaternary compounds are so much more effective than anionic preservatives (40).

Basic mathematical models were suggested for calculating the concentration of preservatives in the aqueous phase of emulsion systems (41). The total concentration of the preservative, the oil–water partition coefficient, the oil–water ratio, and the concentration of the emulsifier were all shown to affect the concentration of the preservative in the aqueous phase, which is the controlling factor. The use of phenylmercuric salts to preserve cosmetics and other ointments was the topic of several interesting papers (42–44). The sensitivity to various preservatives commonly used in cosmetics was also investigated (45). Less than 2% of contact allergies were caused by sorbic acid, but group reactivities were noted with various quaternary compounds and the parabens.

Other papers of interest on preservatives are described in Table II.

Flavor, Aroma, and Color—The effect of formulation and chemical modification on the flavor, odor, and color of drugs was reviewed by several authors (54, 55). The effect of the viscosity of pharmaceutical syrups on the bitter taste was studied using narcotine as the test drug (56). The results of this experiment, obtained organoleptically, indicated that the more viscous vehicles are better able to mask bitterness. The steric requirement of sweet-tasting compounds or molecules was described, based on the differences in sweetness observed between D- and L-sugars and amino acids (57). It was proposed that these steric requirements must be met at the chemoreceptor site if the compound is to have a sweet taste.

A method was devised for quantifying perfume formulations for use in a computer so that fragrances can be classified and reproduced (58). Two interesting papers described the stability of aldehyde-type fragrances and the effect of stabilizers on perfumes present in soaps (59, 60). The maximum rate of color change of a drug solution occurs when the solution is irradiated with light of a wavelength near that of the absorption peak

Table II—Additional References on Preservatives

Reference	Topic
46	Review of disinfectants
47	Review of disinfectants
48	Test method for measuring disinfectant stability
49	Review of preservatives useful in cosmetics
50	Review of microbiological control of cosmetic products
51	Review of disinfectants used in soaps and detergents
52	Review of preservatives useful in ophthalmic preparations
53	Effect of heat and preservatives on spores of *B. stearothermophilus*

of the drug being tested (61). The amount of color change was shown to be independent of the volume of the solution and of the concentration of the drug under constant light intensity.

Stability—Changes in the anionic product of water, in polarity of nonaqueous solvents, and in pK were considered to be the three main factors affecting drug stability during antibacterial heat treatment (62). The effect of ultrasonics on the degradation of aspirin and other drugs in mixed solvent systems was investigated (63, 64). These studies indicated that the application of ultrasonic energy to a system undergoing degradation increases the rate of degradation but does not necessarily change the kinetic order of degradation. It was postulated that the rate changes are due to an increased number of molecular collisions as a result of the addition of ultrasonic energy. The effect of light, oxygen, and humidity on the stability of various oils and drug systems was outlined in a series of papers (65–73). Studies on the stability of phenylephrine in aqueous solution indicated that this compound deteriorates more rapidly at an alkaline pH because of the formation of free radicals, followed by chain-type reactions (74). The discoloration of the phenylephrine was found to depend on the pH and the temperature; it is due to the presence of 5-hydroxy-*N*-methylindoxyl formed by oxidative cyclization of the parent compound (75). The racemization of *l*-phenylephrine was shown to occur readily at a pH lower than 2 (76). This racemization is first order with respect to the phenylephrine concentration and is catalyzed by the hydrogen-ion concentration. The decomposition of pilocarpine in aqueous media was shown to occur in a reversible first-order reaction (77, 78). The decomposition is general, acid/base catalyzed, the products showing pH characteristics comparable to those of other lactones. The effects of sterilization and storage on the stability of aqueous solutions of pilocarpine, atropine, and scopolamine also received attention (79). No appreciable decomposition was noted as a result of the storage of solutions that were unbuffered or contained benzoic acid, while almost complete decomposition was noted in solutions containing phosphate buffers. The photolytic decomposition of sulfacetamide was shown to be of zero order and inhibited by the addition of sodium thiosulfate or by lowering the pH and dielectric constant of the vehicle (80).

The stability and mechanism of degradation of therapeutic methane sulfose derivatives were investigated using ^{14}C-labeled materials (81–83). The addition of antioxidants was shown to retard the color formation resulting from the degradation of *p*-aminosalicylic acid solutions (84). Aqueous solutions of acetylsalicylic acid prepared by the addition of polysorbates were shown to be more stable than similar solutions solubilized by the addition of ethanol (85). Stored under varying conditions of heat, light, and moisture, aspirin tablets showed the least amount of decomposition when prepared with tricalcium phosphate and talc (86). Similar tablets prepared with sodium alginate or polyvinyl pyrrolidinone showed the greatest amount of decomposition after storage for 3 months. The stability of cycloserine, determined in solution as well as in tablet dosage forms stored in various containers, was shown to be very poor

Table III—Additional References on Stability

Reference	Topic
105	Review of stability of drugs in solution
106	Review of chemical changes occurring during storage of drugs
107	Decomposition and stabilization of sulfacetamide in drug preparations
108	Instability of atropine and chloramphenicol in aqueous solution
109	Stability of aqueous solutions of amylbarbital (Barbamyl)
110	Decomposition of barbiturates with unsaturated substituents
111	Effect of impurities on stability of *p*-aminosalicylic acid
112	Decomposition of diethylaminoethyl salicylate hydrochloride
113	Decomposition of aminophenazone tablets
114	Stability of amethocaine hydrochloride solutions
115	Stability of phenoxybenzamine in parenteral solutions
116	Stability of galenical digitalis compositions
117	Stability of angiotensinamide in aqueous solutions
118	Stability of bromoform syrup
119	Stability of hydroxymersalyl-^{203}Hg in storage
120	Stability of inulin labeled with ^{131}I
121	Stability of dyes with gelatin
122	Polyurethane degradation in some physiologically active media

in the presence of water or humidity (87–89). The stabilizing effect of antioxidants on procaine hydrochloride solutions was clearly demonstrated by Moraga *et al.* (90). In solutions buffered to pH 7.9, the specific rate constants for chlorothiazide decomposition were observed to decrease with increasing concentrations of organic solvents such as ethanol, propylene glycol, and acetone (91). The effect of micellar binding on the enzymatic hydrolysis of arylsulfate esters was demonstrated by Baxter and Kostenbauder (92); although acid-catalyzed hydrolysis of the aryl sulfate ester was enhanced when the substrate was bound to the surface of the micelle-forming surfactant, the enzyme-catalyzed hydrolysis of this substrate exhibited a marked overall inhibition when the substrate was bound to the same surfactant. Deviations from first-order kinetics were observed at temperatures below $-9°$ for the hydroxyl ion-catalyzed decomposition of hexobarbital (93). Rate increases occurred in frozen solutions that were as much as 42 times the calculated rates in supercooled liquid solutions at the same temperatures. These increases were partially explained by the increased concentration of the reactants which takes place in the liquid regions of the partly frozen solutions. Similar increases in rate of degradation as a result of freezing have been reported for adrenocorticotropic hormone (ACTH) in human plasma (94). The stability of various antibacterial agents in culture media was shown to affect their activity *in vitro* (95). To be effective against bacteria, these drugs, which are hydrazone derivatives, have to release isoniazid upon decomposing in the culture media. The effect of oxidation on the stability of lecithin, Erolan (wool alcohols DAB7), lemon oil, and methoxy mercurate oils was outlined in a series of papers (96–99).

The instability of benzocaine in throat lozenges was reported to be due to the reactivity of the primary amine group (100). Corn syrup, citric acid, and natural cherry flavors, three commonly used excipients of throat

lozenges, were observed to be incompatible with benzocaine. The stabilizing effect of the *ortho*-hydroxyl group on the acid and base hydrolysis of amides was shown in a comparison of salicylamide to benzamide and other *N*-substituted derivatives (101). Benzamide was even less stable in alkaline than in acid media. The stability of the phenolate ions may result from a resonance effect, with consequent resistance to nucleophilic attack by hydroxyl ions.

Studies carried out on dilute prostaglandin solutions indicated that the F series compounds are very stable in an alkaline pH, while those of the E series are rapidly inactivated. In an acid pH, however, the members of the E series are more stable than those of the F series (102). Contact with various types of rubber stoppers was shown to affect the stability of benzalkonium chloride solutions (103). Autoclaving of carbachol solutions buffered at a pH between 5 and 6 had no effect on drug stability, while a similar amount of heat applied to unbuffered solutions caused 5–10% decomposition (104).

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

Stability Kinetics—An apparatus for determining the stability of drugs under nonisothermal conditions was described (123). Details were presented for devices that allow programmed automated control of temperature, light, and pressure within the apparatus. The employment of the stirred-flow technique to develop mathematical equations for complex kinetic runs was described by Taylor (124). A computer program for chemical kinetics was used to update kinetic experiments and to correct the laboratory procedure used in these experiments (125).

In a comparative study of three methods for predicting the stability of aspirin and ascorbic acid solutions, the direct application of chemical kinetics at accelerated temperatures and the use of the Arrhenius equation gave predicted shelflife values that coincided with those obtained experimentally after storage at 25° (126). Maulding *et al.* (127) were able to predict the compatibility of aspirin with various tablet excipients, based on the hydrolysis rates of aspirin observed in aqueous suspension of the excipients.

Hydrocortisone hemisuccinate degradation was observed to occur in consecutive first-order reactions, the ester hydrolysis being facilitated by way of an intramolecular attack. The formation of a species devoid of the 17-dihydroxy acetone side chain subsequent to the formation of the steroid alcohol was confirmed in the experiments (128).

The light-catalyzed oxidation rate of chlorpromazine was shown to depend on the pH of the solution (129). The rate of decomposition was observed to be much slower in vehicles whose pH is between 2 and 6 than in more alkaline vehicles. The pH profile for the degradation of hydrochlorothiazide solutions was determined by several investigators (130, 131). The pH of maximum stability for this compound was observed to occur at 2.5. The kinetics of dihydroergotamine methanesulfonate were observed to be first order, the pH of maximum stability occurring at pH 2.5 (132). The heat of activation of this reaction was calculated to be 12–13 kcal./mole. The autoxidation of sorbic acid in citric acid-containing solutions was shown to be accelerated by very low concentrations of the ferric or cupric ions but inhibited by higher concentrations (133). The acid degradation of aldopentoses to furfural and the further degradation of furfural were observed to be first-order functions of the acid and pentose concentrations (134). Although the heat of activation was the same for all of the aldopentoses tested, the order of reactivities did vary. The steric positioning of the hydroxyls in the reactive forms was postulated to be the controlling factor in the rate of reaction. The rate of inversion of sucrose in aqueous solutions of some strongly dissociated acids was investigated by Pethybridge (135). GLC was used to study the kinetics and characterize the acid hydrolysis of acacia polysaccharides (136). The acid degradation products were shown to consist largely of galactopyranose units (present equally as end groups), 3–6 linked branch points, and chain units.

Alkaline hydrolysis was used by Sun and Connors (137) to identify low molecular weight aliphatic esters. They obtained rate constants characteristic of the entire ester molecule. The hydrolysis of monostearin in aqueous media was noted to follow first-order kinetics and to decrease as the pH decreased (138).

Hydrolysis caused by enzyme systems was the topic of several papers. The pH effects of trypsin catalysis of *N*-benzoyl L-alanine methyl ester were thoroughly investigated (139). The kinetic results in acidic pH's suggest that a group, presumably the imidazole function of a histidine residue, is involved in acylation and deacylation, while those in basic solutions suggest that another group, presumably the $-NH_3^+$ function of a terminal isoleucine, controls the activity of the enzyme at different stages of complex formation. Dittert *et al.* (140) found that pseudocholinesterases present in human plasma were primarily responsible for the enzymatic activity of the plasma on the hydrolysis of 4-acetamidophenyl-2,2,2-trichloroethyl carbonate.

The hydrolysis of acylcholines in both acidic and basic solutions was evaluated in the presence of borate buffers (141). In acidic solutions, acylcholines with longer hydrocarbon chains were considerably more stable than those with shorter chains. In basic solutions, acylcholines degraded in a first-order manner below the critical micelle concentration (CMC) but not above. This phenomenon was postulated to be due to the formation of an anionic fatty acid which complexed with the undegraded cationic acylcholine, thus repressing hydrolysis. The effects of pH and buffer concentration on derivation of rate equations for the hydrolysis of ethyl glucuronate in phosphate buffers received attention in a very interesting paper (142). The kinetics of *meso*-inositol hexanicotinate were investigated in acidic solution to determine the gastric stability of this substance as a possible explanation of its absorption from the gastrointestinal tract (143). The compound hydrolyzes 10 times faster than other nicotinic acid esters in acid solution. The kinetics and mechanism of the reaction between hydroxylamine and succinamide or ethyl acetate were thoroughly investigated by Notari (144–146) in a series of papers. The rate of formation of 2-dimethylaminoethanethiol propionate from propionic anhydride

Table IV—Additional References on Stability Kinetics

Reference	Topic
150	Kinetics of esterification of phthalic anhydride with model alcohols
151	Kinetic study of nucleophilic addition of diethyl phosphate to benzylideneanilines
152	General acid catalysis of the dichromate ion
153	Degradation of phenylsulfonyl-5,5-diphenylhydantoins
154	Kinetics of hydrolysis of phosphatidyl choline and lysophosphatidyl choline
155	Hydrolysis of isothiocyanic acid in strongly acidic solution
156	Kinetics of hydrolysis of *N*-benzylidene halogenanilines in aqueous methanol solutions
157	Kinetics of chloropyramine decomposition
158	Review of hydrolysis of barbituric acid derivatives
159	Kinetics of synthesis of hydroxysulfonated fatty acid esters
160	Kinetics of acetylcholinesterase inhibition by atropine
161	Thermodynamics of the hydrolysis of adenosine triphosphate

and 2-dimethylaminoethanethiol was observed to exhibit a pH dependency which could be explained by assuming the thiol anion to be the attacking species (147). Differences observed in the kinetics of propionyl thiocholine iodide and 2-dimethylaminoethanethiol propionate were attributed to the stabilization of the hydrolysis transition state by a protonated nitrogen at a lower pH and by the quaternary nitrogen atom at a higher pH (148). The rapid stop-flow system was utilized to study the kinetics of the oxidation of cystine by 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole (149). The rate constants were determined, and the mechanism of reaction was postulated for this system.

Other kinetic papers of interest are listed in Table IV.

Antibiotic Stability—The kinetics and mechanism of degradation of ampicillin were investigated by Hou and Poole (162). The pH rate profile in buffer solutions showed a minimum at a pH of 4.85, while at zero buffer concentrations the maximum stability was shifted to a pH of 5.85. Similar studies were carried out with regard to hetacillin decomposition (163). It is clear that hetacillin initially decomposes to ampicillin, the decomposition rate being greatest in the presence of phosphate ions and least in the presence of the citrate ion. The mechanisms and rates of catalysis of penicillins by the cupric ion and aminocatechols were investigated by various workers. The cupric ion–penicillin complexation was postulated to occur at a catalytic site which promotes the rapid degradation of the antibiotic in the presence of the metal (164). The catecholamines were observed to catalyze the hydrolysis of penicillin in neutral pH by a mechanism similar to that postulated for several hydrolytic enzymes (165). The antigen which causes penicillin allergy may be formed by aminolysis of the antibiotic *via* a mechanism involving its decomposition in the presence of poly-L-lysine and tris(hydroxymethyl)-aminomethane (166). Subsequent studies indicated that poly-L-lysine catalyzes the hydrolysis of penicillin to penicilloic acid as well as the aminolysis of the antibiotic by tromethamine (167). Differential thermal analysis was used to identify stearic acid as the inactivating component in tablets of sodium dicloxacillin (168). This method also indicated the incompatibility of stearic acid with penicillin G and sodium oxacillin but not with ampicillin. The results were substantiated by chemical analysis after storage of the combinations at accelerated temperatures. Anionic surfactants were observed to increase the stability of penicillin in ophthalmic solutions and ointments, while cationic surfactants did not appear to have such an influence (169).

Chloramphenicol in solution was observed to decompose faster at pH's above 8, particularly when exposed to light (170). The effect of polysorbate 80 (Tween 80) on the acid hydrolysis and discoloration of chloramphenicol was reported in a series of interesting papers (171, 172). The mechanism of solubilization of chloramphenicol by polysorbate indicated that the palisade layers of micelles are responsible for the solubilization and will hinder the degradation of the antibiotic, especially at alkaline pH's. The addition of polysorbate 80, however, was observed to accelerate the color formation of chloramphenicol solutions, primarily because of contamination by trace metals found in the surfactant.

The kinetics of hydrolysis of antimycin A in solution was reported to follow classical consecutive first-order kinetics (173). The addition of ascorbic acid was demonstrated to prevent the oxidative decomposition of tetracycline due to air, light, and the presence of riboflavin (174). The rates and mechanism of catalysis of streptovitacin A were discussed in an interesting paper by Notari and Caida (175). The dehydration of this antibiotic gave rise to anhydrostreptovitacin A, with no evidence of the formation of the phenolic product.

Additional references on antibiotic stability are presented in Table V.

Vitamin Stability—The influence of various additives on the stability of vitamin A was considered in various papers. The aluminum salts of fatty acids were shown to stabilize vitamin A in mixtures with tocopherols and lecithin (180). Proteins, as found in gelatin, enzyme-hydrolyzed casein, and ground nut protein, displayed a protective action for vitamin A, even in the absence of antioxidants (181). Dextrose and sodium benzoate, however, increased the autoxidation of vitamin A under similar conditions. The influence of water on the stability of anhydrovitamin A in ethanol was investigated (182). The stability was shown to be universally proportional to the water content of the ethanolic solutions.

The addition of chelating agents and the purging of oxygen from the vehicle were shown to stabilize thiamine bromide solutions for use in ampuls (183). These ampuls, after sterilization and storage for 2 years at 20°, still met official potency limits. Thiamine hydrochloride tablets were observed to degrade in a pattern in which an apparent equilibrium was reached (184). The amount of thiamine at equilibrium depends on the

Table V—Additional References on Antibiotic Stability

Reference	Topic
176	Review of stability and incompatibilities of various antibiotics
177	Stability of various penicillins in animal foods
178	Shelflife of chloramphenicol solutions
179	Effect of storage on biological activity of streptomycin solutions

Table VI—Additional References on Vitamin Stability

Reference	Topic
204	Review of methods of stabilizing vitamin preparations
205	Degradation of thiamine solutions
206	Effect of sterilization temperatures on vitamin D_3 injections
207	Review of stability of ascorbic acid solutions
208	Compatibility of vitamin K with various drugs

amount of moisture present and exhibits a minimum at a 5.5% moisture content. The model proposed for such a system presumes that the thiamine dissolved in the water adsorbs on the cellulose and that the thiamine present in the monolayer degrades totally, whereas the thiamine in layers beyond the monolayer does not degrade. The kinetics and mechanism of degradation of various thiamine derivatives were outlined in a series of very interesting papers (185–187). The stabilities of these different derivatives were compared with those of thiamine under similar conditions.

Various flavors present in vitamin B_{12} solutions were found to exert a significant influence on their stability (188). Vitamin B_{12} suppositories were reported to be stable when prepared by coating the microgranules containing the vitamin prior to their incorporation into the suppository mass (189).

The kinetics of cupric chloride-catalyzed autoxidation of L-ascorbic acid were found to be related to the polarity of the solvents employed (190). The ionization of ascorbic acid to the ascorbate ion, which is affected by the solvent polarity, was postulated as one of the factors controlling the rate of degradation of the vitamin in solvents of different polarities. The cupric-ion catalysis of ascorbic acid solutions was hindered by 2% sucrose or 0.1% citrate in the presence of commonly used preservatives (191). The action of Complexon III (ethylenediaminetetraacetic acid) on the stability of L-ascorbic acid solutions was demonstrated to be potentiated by the presence of acetic, citric, tartaric, metaphosphoric, oxalic, and hydrochloric acids (192, 193). Ascorbic acid monostearate was shown to have greater stability than free ascorbic acid, especially in alkaline solution (194). The thermal degradation of thiamine and ascorbic acid combinations in aqueous solutions was investigated (195). Thiamine exerts a protective action on ascorbic acid only in aqueous solutions and not in the presence of citrate or phosphate buffers.

The stability of vitamin D_2 in the solid state was the subject of a very thorough investigation by Takahashi and Yamamoto (196–202). In the presence of calcium phosphate and talc, the vitamin was shown to isomerize readily, yielding isocalciferol and isotachysterol. The isomerization was observed to be catalyzed by surface acid on the excipients. Storage of the powders under conditions of high humidity increased the stability of the vitamin, since the surface acidity was decreased by the absorption of moisture. Further investigations indicated that vitamins such as ascorbic acid, thiamine hydrochloride, and pyridoxine hydrochloride, which have a high surface acidity in the dry state, behave in a similar manner.

The effect of polysorbate 80 and sodium lauryl sulfate on the photolytic degradation of flavine mononucleotide was investigated through measurement of the electron-spin resonance of semiquinone, an intermediate degradation product (203). The degradation was observed to follow first-order kinetics in the dark, both additives accelerating the formation of the semiquinone derivative.

Other references pertaining to vitamin stability are given in Table VI.

PHARMACEUTICAL TECHNOLOGY

A series of review articles on the current aspects of pharmaceutics discussed a wide number of topics, including drug release and absorption, drug solubility, preservatives, chemical stability, physical stability, and packaging (209–212). Other articles outlined the general concepts involved in the formulation of products containing corticosteroids or hormones having polypeptide structures (213, 214) and reviewed the possible incompatibilities of these hormones with the excipients present in various dosage forms. Schumacher (215) presented a very thorough review of the bulk-compounding technology utilized in the preparation of liquids, suspensions, emulsions, and ointments. The main trends in pharmaceutical research and development were also aptly reviewed (216).

Parenterals—Possible contamination of parenteral products by the packaging components was the topic of several interesting papers. Contamination with heavy metals from ampul glass as a result of washing was eliminated by an acid rinse followed by a wash with deionized water (217). Zinc ions eluted from rubber stoppers were shown to affect the stability of dextran solutions (218). White rubber stoppers were shown to elute more zinc than black butadiene acrylonitrile rubber stoppers (219). Atomic absorption spectrophotometry was used to detect amounts of silicone removed from disposable plastic syringes by distilled water washes (220).

The factors influencing the turbidity occurring in parenteral solutions containing polysorbate 80 and benzyl alcohol were pointed out (221). The turbidity was determined to be a function of the concentrations of the components and the temperatures to which they are exposed. The use of benzyl benzoate in preparing solutions of steroids in peach oil was described (222). Such oil solutions of hydroxyprogesterone capronate and androstenediol dipropionate did not show the presence of crystals after 1 year of storage at −26°.

A closed system of incorporating nitrogen into vials was found to be much more effective than conventional systems for preventing the degradation of the active agent by aerobic oxidation (223). The advantages and methods employed in the nitrogen flushing of products stored in metal containers were discussed (224).

A new stratified lyophilization technique and an example of the use of this technique in preparing ACTH preparations with prolonged action were described in two interesting papers (225, 226). The presence of isonicotinic acid hydrazide was shown to decrease significantly the potency of streptomycin and *p*-aminosali-

cylic acid after freeze-drying (227). Solutions prepared without the hydrazide but under otherwise similar conditions showed no losses in potency. Injectable solutions of sodium sulfathiazole in a 10% sorbitol solution stored under nitrogen were shown to be stable after storage for 14 months at 37° (228).

Other papers of interest in the category of parenterals are given in Table VII.

Sterility—A very complete review of the different techniques utilized for sterilization was presented by Doyle (233). The advantages of the continuous sterilization technique were presented in two excellent papers (234, 235). Such sterilization is accomplished in towers in which carrier-conveyor baskets filled with containers pass through a succession of zones where the temperature is regulated by water, steam, and air. This method was postulated to be superior to the classic autoclave method.

The efficiency of gaseous sterilization was described by several authors (236, 237). A nonexplosive mixture of ethylene oxide and methyl bromide was shown to be effective against a variety of spores (238). Sterility was achieved in 2–48 hr., depending on the object to be sterilized and the conditions applied. The adsorption and desorption of ethylene oxide on rubber, polyethylene, and polyvinyl chloride objects were investigated (239). It was shown that the adsorbed gas remains as a residual for prolonged periods of time unless desorption is accelerated by heating. Ethylene oxide-sterilized plastic medical devices showed no significant toxicities 24 hr. after sterilization (240). The disinfectant action of peracetic acid and formaldehyde on equipment was also demonstrated in a series of interesting papers (241–243). Complete sterilization of microbes was achieved with a 0.5% peracetic acid solution in 1–30 min.

The bacteriological aspects of sterilization by the use of γ-radiation were reviewed, with emphasis on the mechanism of action and the factors influencing the radiation resistance of bacteria and other microorganisms (244). The specific uses of radiosterilization in pharmaceutics were reviewed by several authors (245, 246). A dose of between 2.5 and 4 mrad sterilized all solutions tested. Physical as well as chemical changes were observed in certain cases, especially when aqueous solutions were irradiated. Similar losses in potency were described after irradiation of aqueous solutions of atropine, morphine, and lidocaine (247). The amount of degradation was increased by an increase in the radiation and by a concentration of oxygen above the irradiated solution. Sterilization of hydrocortisone and chloramphenicol ophthalmic ointments by γ-radiation did not cause any change in the physical or chemical properties of the ointments but did increase the number of free radicals present (248). No changes in characteristics or properties of surgical appliances, especially those of biological origin, were observed after irradiating them with 2.5 mrad (249). This radiation level gave complete sterility of all products tested. Changes induced in fats and glucose solutions as a result of heat sterilization were described in two papers (250, 251). These changes were reportedly caused by the high temperatures required.

Table VII—Additional References on Parenterals

Reference	Topic
229	Chemical resistance tests on Indonesian ampuls
230	Use of homemade detergents in cleaning ampuls
231	pH and resistance of liquids used in injectables
232	Review of incompatibilities of numerous injectable drugs

Methods of sterilizing objects by the use of steam as well as by dipping them into chemical preservative solutions were studied (252, 253). Although these techniques can be used to sterilize Plexiglas objects and polyethylene hypodermic syringes, none is capable of sterilizing rubber stoppers.

Various techniques for sterility testing of pharmaceutical products were described in two review articles (254, 255). The membrane filtration technique was considered the method of choice for determining the bacterial content of liquids. The significance of sample size and sample ratios in sterility testing of drug products was discussed in a very interesting paper (256). To eliminate preservative or drug effects in testing parenteral solutions, the optimum sample size is 10 ml. and the optimum dilution in the culture medium is 1:64. Thioglycollate was deemed an unsatisfactory medium for general sterility testing, especially when only a small amount of contamination is present (257). This medium was felt to be reliable only for the detection of *Proteus* species.

Tablets and Capsules—Some of the controls and testing methods used in tableting were outlined in an excellent article by Sinotte (258). Special consideration was given to the potential for automatic testing and the advantages and disadvantages of automating these processes.

The concepts of comminution and its effects on the properties of powders thus ground were briefly reviewed in several papers (259, 260). The factors affecting the efficiency of grinding during jet milling were studied for the grinding of calcite using a 20-mm. diameter jet mill (261). These experiments evaluated the effect of the feed rate of the solids, the injector nozzle pressure, and the grinding nozzle diameter on the particle-size distribution. Several new techniques for measuring particle size of powders were investigated. An average particle-size-measuring technique was developed, giving standard deviations of approximately 2.5%, based on the observation that the bulk volume of powders needed to form a single layer on an area of fixed size is proportional to the average particle size. This method requires the use of calibration curves for different types of solids and is less applicable to powders and very small nonspherical particles which do not pack reproducibly (262). The use of an attenuated light beam passing through a settling suspension of particles was utilized to develop theoretical curves for determining the size distribution and specific surface of the powder being investigated (263).

The effect of particle shape on the angle of repose, bulk density, and rate of flow through an orifice was investigated using sand (264). In all size ranges in which

there is an increasing departure from the spherical, the angle of repose increases while the bulk density and flowability decrease. The rate of flow of a powder through a circular orifice was reported to be a function of the particle size, bulk density, cohesiveness, tensile strength, and shear index of the powder. Different methods of measuring cohesiveness and the effect of glidants and particle size on cohesiveness of a series of powders were demonstrated (265). In the case of granular solids passing through a circular orifice, differences due to shape, density, porosity, and friction of particles could be eliminated by using the term for bulk density instead of particle density in the flow equation (266). The packing properties of powder particles in centrifugal fields were investigated using calcium carbonate and aluminum oxide powders (267, 268). The results supported the assumption that the bulkiness of a fine powder is the product of the forces of interparticle adhesion and the external forces acting on the individual particle. The use of a shear cell has been proposed to measure the cohesiveness and tensile strength of powder as well as the mechanistic behavior of such powder under shear (269, 270). Some of the processes considered are plastic deformation and structural changes such as consolidation or dilation, blockage to resist continuation of motion, and particle orientation, all of which occur in the powder bed. Utilizing this apparatus, a relative shear force and index of retention value can be defined.

The effect of lubricants and surface-active agents on the flow of powders was evaluated. Studies on a capillary vibroviscosimeter indicated that the addition of surface-active additives lowers the viscosity of a flowing powder. The magnitude of this effect, however, was decreased by increasing the vibration rate (271). The viscosity and the angle of repose increased and the packing density decreased with an increase in temperature above 100°, a level at which moisture has a negligible effect on the adhesiveness of powders (272). Lubricants were observed to reduce the angle of repose of powders and to improve their flow characteristics (273). With the addition of ultrafine solid additives, the adhesive forces of strongly adhesive materials were decreased and those of less adhesive powders were increased (274). These results were interpreted to mean that an ultrafine additive roughens the surface of a powder particle enough to increase its friction coefficient and to decrease its adhesion forces.

Based on a diffusion model, Hogg *et al.* (275) developed a quantitative theory to describe the mixing of particulate systems in which one component is present in trace quantities. The theoretical expressions derived to predict the rates of mixing of identical components, both as spherical and as angular particles, agreed with the data obtained. Three probability distributions were defined governing particle movement within a horizontal drum mixer (276). A relationship for the diffusion coefficient, based on the probability distributions, was derived from Fick's first law. The frequency of collisions resulting in particle movement was determined by the interaction between mixer speed and load. The average distance that a particle travels is affected by mixer load but not by speed. The convective and surface mixing of tracer particles of a granular material over a horizontal blade moving relative to a bed was investigated (277). The horizontal movement is determined by the blade height and immersion and the relative velocity of bed to blade and gravity, while the vertical movement is also affected by the particle diameter. The relationship between sample weight and the coefficient of variation as a mixing index and mixing ratio was examined in a V-shaped mixer, utilizing different mixing ratios (278). In the case of adhesive ingredients such as salicylic acid, the charging point and the size of the diluent were found to have a marked effect on the mixing rate. Such phenomena were believed to be due to differences in adhesive force between the same and different kinds of particles or between the particles and the walls of the mixer.

The physical and mechanical factors affecting the compression of tablets were described in a wide range of papers. The powder segregation that occurs during die filling consists of the finer particles ("fines") filtering through to the bottom of the moving powder mass, where it builds an inner mound of fine rich material on the bottom of the die and an excess of coarser material at the periphery of the die cavity (279). This segregation is lessened when the amount of fines is decreased, the rate of die fill is increased, or the height from which the powder falls is increased. The pressure on the die wall was observed to increase with a decrease in the hardness value of the material being compressed (280). The maximum compression force required for tableting granules was dependent on the granule size, although the energy required for tableting was similar for all sizes (281). The smaller granules were observed to decrease the time of the first compression phase. Experiments with an automated tablet press showed that for the limited range of dimensions applicable to most pharmaceutical tablets, there exists a common linear relation between the applied compaction pressure and the force lost to the die wall per unit area of apparent die wall contact during compression (282). During tablet compression, pressure is believed to be transmitted in two directions: along the compression and along the die wall (283). A model was presented to show the phenomena which occur during repeated compressions; this model illuminates some facts about the internal structure of compression-molded substances and illustrates the need for lubricating agents (284).

The physical and mechanical factors utilized in preparing directly compressed tablets were discussed (285). Modification of the specific gravity of the compressed material was observed to modify its other characteristics. The tableting properties of directly compressible starch, STA Rx 1500 brand of starch, and a material derived from beets were also described (286–289). The fluidity and compressibility of these materials made them especially useful for direct compression. The effects of hydroxypropyl methylcellulose, carboxymethyl dextran, starch dextrans, xylitol, talc, and cyclamic acid on the properties of tablets were discussed by a great many authors (290–302). Polytetrafluoroethylene was successfully used as a lubricant in the compression of powders as well as being bonded to the tips of punches to reduce the adhesion between them and the

tablets (303). The properties of Aerosil (pyrogenic silica) and its use as a glidant were discussed. In some of these studies the addition of Aerosil increased the disintegration time of tablets prepared from inorganic salts (304–306). The crystalline form as well as the granular character of lactose was observed to affect the properties of tablet formulations (307). In a thorough investigation, dicalcium phosphate, calcium sulfate, and magnesium carbonate were compared with glucose and sucrose as diluents in the tableting process, the relative merits being judged by the quality of the finished tablets (308). The optimum tableting pressure for these materials was determined, and the effect of this pressure on the required ejection force and the tablet properties was discussed. Under the experimental conditions, the inorganic salts were clearly superior to glucose and sucrose as diluents. In tablets prepared with polyethylene glycol 4000 as a binder, not only the active ingredient used but also the granulation procedure and the moisture present in the powder mixture were observed to affect the hardness and porosity (309).

The effect of various materials on the disintegration times of tablets was well documented (310–318). In general, additives were placed into three classes: those acting as capillary-forming agents, as in the case of starch; surface-active agents such as Tween 80; and swelling agents such as ultraamylopectin. The latter two types were more effective than starch in lessening the disintegration time of certain hydrophobic materials. The mechanism of tablet disintegration was discussed on the basis of cohesive and adhesive properties of the particles. For a tablet to disintegrate, the dispersion of the particles caused by the penetration of water must overcome the forces binding the particles through cohesion and adhesion (319). The inhibitory effect of magnesium stearate on the penetration of liquids into tablets was found to be roughly proportional to its concentration in the tablets (320). With tablets of sulfamethazine, high-viscosity binders prolonged dissolution and hydrophilic binders shortened it, although both types of binders gave similar disintegration times (321). The dissolution rates in both cases were shown to be directly proportional to the amount of binder added. The particle size of aspirin after disintegration from tablets was shown to be different from that used in preparing the tablets, even in the presence of starch. Large particles were broken, while small particles were observed to be agglomerated and partially aggregated to larger particles, thereby negating the therapeutic advantage of finely divided aspirin (322). The effect of tablet form on physical properties was the subject of an interesting paper (323). It was noted that the disintegration time of tablets was dependent on the surface area, flat tablets disintegrating somewhat more rapidly than convex tablets. The breaking strength of convex tablets, however, was found to be greater than that of flat tablets. Taking all factors into consideration, the authors concluded that strongly convex tablets are often preferable.

The porosity, pore-size distribution, and water permeability of several different coating powders used for subcoating sulfathiazole tablets were evaluated (324). Powders consisting of acacia, sucrose, titanium dioxide, talc, calcium carbonate, and Aerosil formed the coatings that were considered to have the best properties. Exclusion of Aerosil from this powder resulted in the formation of a more compact coat having fewer and smaller pores. Polyvinyl acetal diethylamino acetate was investigated for use in preparing a gastric-soluble protective coating for tablets (325). The effectiveness of this material, which is soluble in a wide variety of organic solvents and aqueous solutions of pH less than 5.8, was determined *in vivo* by obtaining blood levels following the administration of coated triacetyloleandomycin and barium sulfate coated tablets to dogs. Other coating materials evaluated with regard to their properties and physical stability on aging were those consisting of zein, polyvinylpyrrolidinone, sodium carboxymethylcellulose, cellulose acetate phthalate, Polyox WSR 205, and WRS 301 (water-soluble resins) (326–328).

The manufacture, filling, and coating of hard-gelatin capsules were very capably reviewed by Jones (329). The transfer of water vapor through capsules and the experimental equilibrium water constants were determined for encapsulated starch and microcrystalline

Table VIII—Additional References on Tablets and Capsules

Reference	Topic
333	Comparison of methods of determining specific surface of powders
334	Influence of particle size on fluidity of binary mixtures of starch with various pharmaceuticals
335	Comparison of adhesive forces of different pharmaceutical powders by centrifugal method
336	Method proposed for the efficient separation of spherical from nonspherical particles
337	Photographic study of the two-dimensional flow of steel balls
338	Influence of physical properties of particulate solids on the rate of mixing and segregation
339	Comparison of microhardness and elastic modulus of crystalline pharmaceutical materials
340	Significance of formulation on the lower punch pull-down force required in rotary tablet machines
341	Review of formulation variables and tableting factors on weight distribution of tablets
342	Encapsulation of liquid and solid aerosol particles to form dry powders
343	Review of theory and operation of granulation of pharmaceuticals
344	New methods of granule production
345	Effects of granule size on homogeneity of tablet weight
346	Effects of moisture on tablet manufacture
347	Effects of storage on dissolution of aspirin tablets
348	Expansion of compressed starch tablets due to moisture sorption
349	Review of absorbable tablets
350	Determination of the optimum weight of tablets
351	Formulations for soluble tablets for preparing eye drops
352	Formulations for the manufacture of sodium *p*-aminosalicylate tablets
353	Use of urea in preparing tablets of benzalkonium chloride
354	Processing of urea inclusion compounds into tablets
355	Review of various coating materials for use in tablets and capsules
356	Preparation of subcoatings in the manufacture of coated tablets
357	Use of shellac and seed lac as enteric coatings for tablets
358	Review on color coating of tablets
359	Characteristics of Farmoids in sugar coating of drugs
360	Use of synthetic dyes in tablet making
361	Review of polymers useful in preparing capsules soluble in intestinal fluids

cellulose stored in closed containers (330). The equilibrium constants and the estimated values calculated from the sorption isotherms of these substances were observed to be in good agreement. Capsules were evaluated for filling characteristics after being filled with cornstarch or lactose, with or without Aerosil as a glidant, by a semiautomatic ring-filling method. On powders without Aerosil, the coefficient of variation of the dose showed that filling by a screw auger was more accurate than by a flat one. The powders containing Aerosil exhibited maximum deviations between 0.1–2% of the glidant (331). The use of a shellac coating on capsules of pancreatic enzymes to prevent dissolution in gastric fluids was evaluated both *in vitro* and *in vivo* (332). This coating inhibited release of the enzymes for at least 2 hr. in artificial gastric juice, yet the enzymes were released in less than 1 hr. when placed in synthetic duodenal fluid.

Further references of interest in the field of tablets and capsules are given in Table VIII.

Suspensions—The effects of the nature of the suspended solids, surface charge ζ-potential, and shear rate on the properties of dispersed systems were thoroughly reviewed in several excellent papers (362–364). A rotational viscosimeter was used to measure the apparent rheological properties of rapidly settling suspensions (365). Using this data, a generalized correlation between the viscosity of the medium and the viscosity of the suspension was developed to predict the apparent viscosity of such rapidly settling suspensions. Measurements were presented on kaolin suspensions, which confirmed that interaction between the suspended particles, macromolecules of the suspension media, and electrolytes influences the flow behavior and stability of the suspensions (366). The adsorption of ions on the surfaces of suspended particles, by changing their distribution in an electrical field, influences their coagulation, flocculation, and sedimentation characteristics through the formation of electrical double layers. The sedimentation and flocculation of dispersed phases were investigated utilizing suspensions of calcium carbonate (367). The volume of immobilized medium present on the particle surface varied, depending on the kind of suspending medium; the larger the volume of the immobilized medium, the greater was the effect on structural viscosity. In a review of the mechanism of flocculation and floccule sedimentation, it was pointed out that theories applicable to colloidal systems must be modified when paracolloidal particles are present (368). The existence of order in dilute colloidal suspensions due to long-range electrostatic forces was shown by the measurement of diffraction of light caused by such suspensions (369).

The effect of the concentration and the shape and size of the solid on the settling of a suspension was outlined in several papers (370–372). Numerical data obtained by utilizing such a model system compared well with the actual experimental data obtained using aluminum oxide suspended in salt solutions.

The rheology of kaolin suspensions was the topic of many interesting papers. The curves of yield stress *versus* pH were shown to exhibit a maximum for sodium kaolinite at pH 5.75, for aluminum kaolinite at pH 7.95, and for the acid form of kaolinite at pH 7. The maximum appeared to occur at the zero point of charge of the kaolinite edges, which is partly dependent on the ionic environment in which the clay is prepared (373). The kaolin–water system was used to illustrate techniques for determining the electrophoretic mobility of particles in suspension (374, 375). These data were used to show the relation between the salt flocculation value of a suspension and its electrophoretic mobility.

The viscosity of various kaolin suspensions was observed following the addition of a basic aluminum chloride complex (376). After addition of only small amounts of the complex, the clays still showed individual differences; but at higher concentrations, common trends could be distinguished, indicating that the adsorption of the complex masks the individual surface characteristics of the kaolin particles. The negative surface charge of kaolin was shown to increase during oven drying of suspensions of kaolin containing a soluble phosphate (377). The viscosity of certain kaolin–water systems was correlated with the montmorillonite content of kaolin (378). Transition from low viscosity to high viscosity occurred when the montmorillonite content exceeded 5%. Adsorption of hexadecyl sulfate by kaolinite crystals was postulated to occur on edges of the tabular kaolinite crystals, forming a bimolecular layer which causes the edges to become negative and deflocculation to occur (379). The rheological behavior of other clay systems was also extensively investigated. The electrical double-layer theory was used to analyze an idealized clay particle system, with the purpose of describing the mechanical stability in terms of attractive and repulsive forces (380). The general pattern of behavior of the model was shown to be compatible with the behavior of the clay mass. The chemical factors involved in the flocculation of clay slurries were pointed out by Slater *et al.* (381). For a polymer to act as an effective flocculant by the "bridging mechanism," it must have a certain extended configuration in solution which is influenced by pH, ionic strength, and polyvalent counterions, and the polymer must be adsorbed on the mineral by multiple functional groups. In various systems, this attachment may occur by electrostatic attraction, hydrogen bonding, dipole interaction, or even covalent bonding. The use of polyacrylamine and polyvinyl alcohol in flocculating and increasing the structural strength of bentonite suspensions was pointed out (382, 383).

Factors affecting the long-term settling characteristics of clay suspensions were described in an interesting article (384). Temperature and concentration were shown to affect greatly the settling characteristics of the clays tested. Layering formed most readily in aqueous vehicles having a low viscosity and density. A mechanism was postulated for the deflocculation of clays in nonaqueous systems by the addition of amines and amino acetates (385). The partition of the amine between the clay and the organic liquid was measured, and this was considered an important factor in the deflocculating efficiency of the amine.

The effect of surfactants on the stability of suspensions of bentonite, polyethylene, carbon black, and kaolin was the subject of several papers (386–389). In most

Table IX—Additional References on Suspensions

Reference	Topic
396	Condensation stability of dispersed systems
397	Review of factors affecting the stability of pharmaceutical suspensions
398	Review of theory of dielectric dispersion of colloidal particles
399	Review of the formation of dispersed systems and spatial structures of these systems
400	Comparison of techniques of measuring particle size of suspensions using microscopically calibrated glass beads
401	Spatial distribution of particles in a suspension
402	Flow behavior of kaolinite suspensions
403	Use of sucrose esters as suspension stabilizers
404	Electrostatic forces between clay and cations as calculated and inferred from electrical conductivity
405	Thixotropy of clays
406	Influence of monomolecular nonionic agents on the behavior of drug suspensions
407	Effect of surface and particle size of solid phase on sedimentation of talc and zinc oxide suspensions
408	Effect of solid-phase concentration and mixing ratio of a second solid on the sedimentation of talc and zinc oxide suspensions
409	Effect of manufacturing conditions of sulfonamide and chloramphenicol suspensions on their physical properties
410	*In vitro* studies of antacid suspensions
411	Effect of magnetic treatment on sedimentation volume of montmorillonite suspensions
412	Sugar-containing suspensions of chloramphenicol
413	Crystal growth studies involving phase transitions in aqueous suspensions

cases, unstable hydrophilic particles can be stabilized by the addition of surface-active agents. The temperature for optimum stability of these systems, however, was shown to increase as the chain length of the surfactant used was increased. The relation between the extent of dilatancy and colloidal stability of suspensions was studied utilizing polysodium methacrylate as a dispersing agent (390). The colloidal stability of this system was varied by changing the degree of dissociation of the acid groups of the polymer. The extent of adsorption of the dispersant was found to correlate well with the viscosity measurements. The increase in viscosity could result from an increase in flocculation due to shear. The pH of maximum stability and the maximum ζ-potential were observed to occur between 7 and 10 for titanium dioxide suspensions (391). This system has an isoelectric point at pH 3, when surface hydroxyls on the titanium dioxide surface are completely neutralized. Above pH 10 the ζ-potential of this system once again drops, with a resultant decrease in stability. The stability of aluminum hydroxide in normal alcohols and toluene stabilized with surface-active agents was postulated to be due to the double-layer electrostatic repulsion forces on the gel (392). The effect of impurities on the charge of aluminum oxide in aqueous suspensions was also determined (393). The ζ-potential of the less pure oxide was greater, resulting in increased structural characteristics of the suspensions. The impurities on the surface of the aluminum oxide particles were postulated to increase the thickness of the firmly bound layer, consequently increasing the effective particle radius and lowering the amount of dispersive medium.

The effects of ultrasound on the properties of suspended solids were demonstrated in two interesting papers (394, 395). Ultrasonic energy was shown to have a greater effect on larger particles than on smaller particles. A logarithmic relation was demonstrated between the increase in solid surface and the concentration of suspended solids. Increasing the viscosity of the dispersing medium appears to reduce the increase of solid surface, while the addition of surfactant enhances it. The maximum increase occurs in the region of the CMC of the dispersed system. Ultrasonic energy may increase the solid surface by reducing the particle size of some materials and the agglomeration of others.

Other articles of interest relating to suspensions are described in Table IX.

Emulsions—Review articles were published on emulsion theory and practice, recent advances in emulsion processes, and critical factors affecting emulsion systems (414–417). A computer was utilized to solve the fundamental flocculation-rate equations, including the effects of polydispersity and the particle–particle potential energy barrier (418). These calculations were based on the assumption that the only rate-limiting process is the passage of particles over the primary electrical barrier to the flocculation of the suspension. The description of a Coulter counter technique for obtaining size distribution of oil-in-water emulsions was presented (419). Although this method compares well with other measuring techniques when certain precautions are taken, it has the same disadvantage of being rather laborious.

The flow characteristics of oil-in-water liquid petrolatum emulsions were investigated using a cylinder-type viscosimeter (420). The shear rate–shear stress curves showed a hysteresis loop which changed from a dilatant to a thixotropic form in accordance with change in distribution of particle size and state of aggregation of the emulsion. The increase in the fineness of particle size of the dispersed phase was shown to increase the viscosity of the emulsion (421).

The distribution of surfactant between the water and oil phases at the point of immersion was a contributing factor in the type of emulsion formed (422). Placing more surfactant in the aqueous phase was shown to favor the formation of an oil-in-water emulsion. No relation was observed between the rate of coalescence of oil droplets in an oil-in-water emulsion and the interfacial tension (423). Although the stability of the oil drops differs from the so-called "emulsion stability," the rate of coalescence of drops was observed to correlate with such stability. The effect of the hydrophilic-lipophilic balance (HLB) of the emulsifiers on emulsion stability was investigated by a number of workers (424–429). The size of the emulsion droplets changed remarkably with temperature and HLB of emulsifier. The droplets coalesced more readily when close to the phase-inversion temperature, and relatively stable oil-in-water emulsions were obtained when the phase-immersion temperature was 20–65° above the storage temperature of the emulsion. At optimum stability, emulsions are relatively insensitive to changes in HLB values but are quite sensitive to the phase-inversion temperature of the system being investigated.

Table X—Additional References on Emulsions

Reference	Topic
442	Relation between composition of emulsion and its viscosity
443	Continuous oil phase emulsion and inversion
444	Studies of density gradient in certain oil-in-water emulsions using mechanical γ-ray analysis
445	Structure determination of superfat oil–water emulsions
446	Mechanism of emulsification with special reference to solid stabilized emulsions
447	Evaluation of hydrogenated lanolin, a new oil–water emulsifier
448	Characteristics of ethoxy polysiloxane oil emulsions

The stabilization of oil-in-water emulsions by the use of nonionic detergents was investigated in a series of papers by Elworthy and Florence (430–432). The higher stability obtained by increasing the glycol chain length of the emulsifier was not due to a raised surface potential but was ascribed to entropic effects. The rate of coalescence of the emulsions was related to the ζ-potential, surface concentration, and polyoxyethylene chain length. In these systems, the adsorbed film was observed to increase the attractive forces between particles. The apparent CMC determined from the interfacial tension–concentration curves were higher than those obtained at the air–water interface. The effect of cationic detergents on emulsions stabilized by acacia and sodium alginate received attention (433). The ζ-potentials and particle sizes were obtained so that the interaction energies could be calculated for these systems. By utilizing the observed degrees of aggregation, the van der Waals constant was estimated and the binding parameters, numbers of binding sites available, and free energies of absorption were calculated. Emulsions prepared with Carbopol (water-soluble resin) neutralized with hexylamine and 2-ethylhexylamine were noted to give stable emulsions, while other shorter or longer chained amines yielded poorer emulsions (434). These results were rationalized on the basis of polymer confirmation and HLB. The use of lecithin, starch phosphate, gelatin, and other hydrophilic colloids as emulsifiers was evaluated in a series of papers (435–437). The viscosities, ζ-potentials, and stabilities of these emulsions were determined. The temperature effects and the effects of adding electrolytes or hydrophilic colloids to solid, stabilized, kerosene–water emulsions were studied (438). Large quantities of electrolytes were observed to have a deteriorating effect, which was ascribed to chemical changes taking place in the stabilizers. The addition of hydrophilic colloids led to better emulsification and finer dispersion. This behavior was attributed to the formation of a protective layer which hinders coalescence of the oil droplets. The use of mixtures of surfactant fatty alcohol emulsifiers to stabilize oil-in-water emulsions and alter their consistency from fluid to semisolid was described (439). A mechanism involving the formation of a viscoelastic network in the continuous phase was proposed to explain this self-bodying action.

Peterson (440) thoroughly reviewed factors affecting nonaqueous emulsion systems and their stability. Anionic emulsifiers are best suited for the preparation of stable emulsions; glycerin appears best at low emulsifier concentrations. Measurement of particle size after long periods showed that such emulsions have good stability during aging. The factors affecting the formation of microemulsions and their resulting properties were outlined in an interesting paper (441). The presence of excess electrolyte in the aqueous phase was shown to inhibit microemulsification. Microemulsions in systems based on soaps are strongly cation dependent, while those prepared with dodecyl sulfate are independent of the nature of the cation. Changing of the water–emulsifier ratio was observed to have no effect on either the total interfacial area or interfacial stoichiometry of the microemulsion tested.

Other articles related to emulsions are presented in Table X.

Ointments and Creams—Ointment bases were classified according to their properties in several interesting review articles (449, 450). Lipophilic and hydrophilic ointments, the first two classes, were further subdivided according to the chemical composition of the bases. Diphilic ointments, the third class, were divided into those containing emulsifiers and emulsifier-type bases.

Rheological measurements were made on a number of ointment bases over a wide range of temperatures (451, 452). The addition of a small quantity of complex material to a paraffin ointment base was shown to change its behavior from elastic to viscoelastic. These viscoelastic materials were all assessed in creep testing, where fundamental parameters were provided and the rheological behavior was represented by mechanical models. There was a distinct difference between the behavior of creams prepared with ionic and nonionic soaps. Lipophilic emulsifiers, such as wool fat alcohols, were noted to reduce the yield value and thixotropy of petrolatum, but complex emulsifiers had the opposite effect (453, 454). The effect of soaps on the yield value and consistency of oil-in-water emulsion ointments was also carefully evaluated (455). The use of stearic acid–sodium lauryl sulfate combinations in these systems led to the formation of creams, which were actually fluids without a gel structure, while cetyl alcohol–sodium lauryl sulfate or cetyl alcohol–sodium stearate combinations formed ointments with a measurable rigidity. The internal structures of ointments prepared with bentonite, ichthyol ointment prepared from petrolatum and methylcellulose bases, sulfonamide ointments, and zinc paste were evaluated using various rheological testing methods (456–462). In most cases, a thixotropy was observed which changed markedly at higher temperatures, approaching the idealized state. Regeneration of the inner structure was usually observable by 24 hr., although the time varied, depending on the surfactant present in the ointment system.

The use of the newer surfactants and emulsifying agents in the preparation of emulsion ointments was thoroughly reviewed by Goldenberg (463). The effect of various emulsifiers on the emulsion system of creams was also studied (464). This paper described the preparation of an ambiphilic cream system, one that can be diluted with either water or oil and still give a stable emulsion. It also listed the properties of other creams prepared with different emulsion systems. The ad-

vantages of methylcellulose as a base in preparing various ointments was reviewed (465). Although active materials were observed to penetrate the skin to a greater extent in ointments prepared with methylcellulose than in those prepared from other commonly used bases, too great an amount of methylcellulose in an ointment should be avoided, because it may interfere with the healing of wounds by the formation of a film. The use of polyhydric alcohols, sodium lauryl sulfate, cetyl alcohol, decaglycerol esters, sugar esters, and other complex esters in preparing ointments of various types was also considered (466–470). The viscosity and some of the other properties of ointments prepared from these materials were measured and further described in these papers.

A method was demonstrated for measuring the particle size of solid pharmaceuticals present in ointments (471). This technique consists primarily of mixing the ointment with a solvent in which it is soluble and then filtering and measuring the size of the insoluble particles remaining behind. For meaningful results, however, the solvent utilized in this technique must not dissolve the solids present in the ointment. To compare the wettability of ointments by liquids of different surface tensions, the contact-angle kinetics of various ointments were investigated (472). The contact angle was observed to change characteristically with the properties of the ointments and the surface tensions of the liquids being evaluated. The water-absorptive properties of lipophilic bases and the dehydration kinetics of hydrogels were also investigated (473, 474). The absorptive properties of starch, talc, and zinc oxide dispersed in petrolatum were evaluated in terms of absorptive rate and capacity. The effect of sample area and air flow on the kinetics of dehydration of hydrogels was evaluated. The dehydration was observed to proceed in two separate steps, a zero-order followed by a one-third-order rate.

In vitro as well as *in vivo* methods for evaluating ointment bases were reviewed in an interesting article (475). The specific evaluation of drug release from ointment-type dosage forms was described by a number of authors. Skin penetration of methyl nicotinate was observed to occur rapidly from water solutions because of hydration of the skin, but was markedly slower from more viscous vehicles which reduced the hydration of the skin (476). The drug-releasing properties of ointments were demonstrated, using a diffusion membrane prepared from freshly removed skin of the rabbit (477). The ointment being tested was placed on the skin, which was carefully stretched over the opening of a diffusion cell, and the amount of drug that penetrated the membrane was determined in 3 hr. The results obtained by this technique for procaine and pentachlorophenol ointments were compared with those obtained using a cellophane membrane. The use of an agar plate technique to study drug release from ointments was also widely investigated (478–480). In general, the release of antibiotics from emulsion-type ointment bases containing surface-active agents or those of nonoleaginous consistency was greater than that observed from oleaginous bases. The interactions between hexachlorophene, polysorbate 20 (Tween 20), and polyethylene glycol 4000 were demonstrated by the hindered release of the antibacterial agent in the presence of the two surfactants.

Table XI—Additional References on Ointments and Creams

Reference	Topic
487	Review of the physiology of skin and methods of measuring skin moisture
488	Review of the effects of emollient emulsions on the moisture of skin
489	Application of silicone fluids in ointments and their uses
490	Use of magnesium oleate as emulsifier in ointment bases
491	Rate of diffusion of cations from various ointment bases
492	Isotropic gel phases in surfactant–oil–water systems
493	Comparative studies of physical properties of various ointment bases
494	Properties of soft white paraffin

The properties and usual components of transparent gels were carefully reviewed by Hynniman and Lamy (481). A special technique to observe the structural features of such gels utilizing the electron microscope following a freezing step to prevent changes in micelles was reported (482). Such techniques are necessary, since the components of such gels and emulsions are very difficult to observe microscopically. The use of polyvinyl alcohol in preparing transparent gels was discussed, as was the stability of various antibiotics in these gel systems (483–484).

The microbiological contamination of antibiotic ophthalmic ointments was examined (485). It was determined that 8 of the 114 batches tested were contaminated. The disadvantages of chlorohexidine as a preservative in nonstick ointments containing anionic surfactants was pointed out (486). The interaction of this preservative with stearic acid soaps and other anionic surfactants completely eliminates its antimicrobial activity. Further disadvantages of chlorohexidine are its inability to control certain *Pseudomonas* strains and its lack of fungistatic activity.

Other articles of interest relating to ointments and creams are described in Table XI.

Suppositories—The use of new suppository bases consisting of hydrogenated coconut oil and beef fat fractions was described (495). These bases compared favorably with cocoa butter and synthetic lauric acid glyceride bases and were shown to be nonirritating. The characterization of Witepsol, a new synthetic suppository base, was reported (496). This material was observed to contain di- and triglycerides, some monoglycerides, and an unidentifiable strong polar substance. A modified glycerin suppository was proposed, based on its different water absorption, solubility, hardness, and ability to release medication (497). The effects of varying the glycerin, gelatin, and sodium stearate contents of these suppositories were reported. The addition of saponins to oleaginous suppository bases was shown to increase greatly the liberation of triphthazine from them (498).

The release of medication from suppository bases received wide attention during the past year. In an excellent paper, Weiss and Sciarrone (499) described

Table XII—Additional References on Suppositories

References	Topic
510	Use of penicillin in rectal suppositories
511	Use of antioxidants to stabilize nystatin in suppositories
512	Review of uses of pressed suppositories
513	Preparation of two-layer suppositories
514	Preparation of polystratified suppositories
515	Proposed tests for weight variation of suppositories

the diffusion of salicylates across a hydrophobic membrane from cocoa butter to an aqueous layer. The release of the drug at the surface was observed to be controlled by diffusion. However, the transfer across the interface is a function of the partition coefficient; consequently, as the partition coefficient decreased, the release rate appeared to approach a limiting value. The release of chloramphenicol from suppositories prepared from different type bases was determined by an agar plate diffusion method (500). Although all of the bases tested gave similar antibiotic release after 2 hr., the suppositories prepared from polyethylene glycol bases showed a considerably better release after 8 hr. The water solubility of the drug was an important factor in the release from fatty-type suppository bases (501). The addition of viscosity-inducing agents such as Arlacel 161 or aluminum stearate or Aerosil had an inhibiting effect on the release of very soluble drugs but only a slight effect on difficult-to-release drugs. The addition of emulsifiers with increasing HLB values was observed to increase the release of soluble drugs from cocoa butter or Witepsol-type suppository bases (502). Optimum release occurred when the HLB value was greater than 10. The effect of the solubility and particle size of aminophenazone on its release from Witepsol suppositories was evaluated (503). As expected, release was most rapid when the drug was in solution and least when it was incorporated as large agglomerates. The effect of surfactants in increasing the absorption of triphthazine from fatty bases was ascribed to their surface tension-reducing properties (504, 505). Similar results were obtained with regard to the rectal absorption of oxytetracycline (506). Fatty-type suppository bases prepared with oil–water emulsifiers showed the greatest absorption, while similar bases prepared without the emulsifiers gave poor absorption of the antibiotic. Intermediate values were obtained with polyethylene glycol-type bases.

The complexation of anionic dyes with quaternary ammonium salts produces a material capable of coloring fatty base suppositories (507, 508). Such techniques must be utilized, because most common dyes are insoluble in the fatty acid glycerides and behave as pigments. The use of various carotenoid dyes, which are fat and oil soluble, to color fatty-type suppository bases was also presented (509).

Further articles of interest on suppositories are presented in Table XII.

Aerosols—Many papers published during the past year reviewed the principles and components of aerosol systems (516–527). These papers discussed operating principles of aerosols, components such as valves, containers, dispensing mechanisms, typical aerosol formulations, filling techniques and equipment, propellants, and the many uses of aerosol products.

The kinetic theory of aerosols and droplet formation during coalescence were discussed in great detail in several papers (528–532). Equations were derived for the solution effect on droplet growth, generalizing this effect as a function of the mean ionic activity coefficient. Two processes were postulated to occur during liquid coalescence: drainage from the drop and Rayleigh disturbance. Interfacial tension and the viscosity of the dispersed phase were concluded to be contributing factors to drop coalescence.

The advantages of carbon dioxide as an aerosol propellant, especially for foods and cosmetics, were described (533, 534). Mixtures of branched-chain aliphatic hydrocarbons were proposed (535). These propellants, which are odorless, water resistant, noncorrosive, and physiologically inactive, may be used in a wide variety of sprays.

The effect of particle size, surfactants, and propellant on the depth of penetration of propyliodone in dogs was studied (536). Greater depth of penetration into the lungs was obtained with powders in the 0.5–10-μ range, although concentration, ratio of propellants, and type of surfactants were also important factors. A cascade impactor was employed to measure the formulation factors influencing the particle size of dexamethasone phosphate aerosols (537). The aerosol particle was capable of being reduced in size by reducing the size of the drug particle, adding a surfactant, reducing the diameter of the spray orifice, increasing the propellant vapor pressure, and increasing the propellant temperature.

The effects of nonionic emulsifiers, buffers, and HLB values on the stability of emulsions used in aerosol foams were investigated (538). Factors affecting aerosol foam appearance were pointed out in an interesting paper (539). Prevention of aerosol propellant loss to the atmosphere will minimize foam wetness, while an increase in the amount of product ingredients in which the propellant is soluble and a lowering of the viscosity of the system will allow a rapid rise of bubbles and an improvement in the percentage of product that can be extruded as a suitable foam. Unusual aqueous aerosol foams and pearlescent aerosols were reported in other papers (540, 541). These new and unusual aerosal systems may find uses in the near future.

The incompatibilities of the components of the aerosol container with its contents were pointed out in several papers (542, 543). Some incompatibilities were those between the contents and the rubber or resin present in the valves and gaskets. The most serious consequence of such incompatibilities is the loss of propellant. A technique was described to test the swelling effects of aerosol contents on gaskets (544); this closed system equilibrates in 24 hr. and gives reliable results in 2 or 3 days.

Several authors evaluated techniques for sterilizing aerosols (545, 546). Sterile filling, bacterial filtration of the vehicle, γ-radiation, and incorporation of ethylene oxide into the gases were all tested for their effectiveness in producing sterile aerosols. Only the ethylene

oxide method was completely successful in producing a sterile product. The main disadvantage of this technique is its possible toxic effects if the aerosol is to be used in inhalation therapy. Other problems associated with the testing of aerosol products were discussed (547–549). The biggest problems were considered to be sterility of the product, corrosion of components, and chemical decomposition during storage. For determination of the propellants, a pressurized liquid-sampling technique and a gas chromatographic analytical method were proposed (550). Another paper described the use of cloud point titration to determine the propellant content of aerosols (551). As shown by tests on 10 commercially available aerosols, the dispensing efficiency of nonmetered topical spray aerosols is very low (552). The pickup efficiency of these aerosols was observed to decrease with an increase in the target distance or in the temperature of the aerosol and to increase with an increase in the nonvolatile content. The formulation, propellant systems, and storage conditions were shown to affect the uniformity of the dose dispensed by different metered valves, above and beyond the normal variation produced by the valves themselves (553).

The toxicological testing of aerosol products was reviewed from both the standpoint of skin and membrane reactions and the dangers of respiratory retention (554). Also discussed was a quantitative method of evaluating the chilling effect of topical aerosol sprays (555). The drop in temperature was observed to be a function of exposure time and to follow first-order kinetics. The chill index was determined and used to compare the chilling effects of commonly used aerosol propellant systems.

Further papers of interest relating to aerosols are presented in Table XIII.

Table XIII—Additional References on Aerosols

Reference	Topic
556	Freezing of droplets of aqueous solution aerosols
557	Effect of soluble surface-active agents on aqueous aerosols
558	Retention of Freon (fluorocarbon refrigerant) in poly(*N*-cyanoacrylate)-sprayed films

Sustained Release—Several articles were published dealing with the terminology, the biopharmaceutical and technical aspects, and the advantages of sustained-release dosage forms (559–561). Equations for the kinetics of the liberation of drugs from sustained-release tablets were developed (562). These equations, which consisted of simplifications of Higuchi's equation for the case where a solid drug is incorporated in a solid matrix, were developed for low-solubility drugs. A method for measuring the permeability of water vapor through a polymer film by a radioisotope dilution technique was reported (563). This method was shown to be rapid, precise, and sensitive and also applicable to the investigation of other parameters which influence the permeability of water vapor.

The application of various epoxy resins in the preparation of pharmaceutical dosage forms was thoroughly investigated (564–566). The addition of basic and acidic curing agents was observed to influence the solubility of the resins in basic and acidic buffers. The type of resin, size of beads, and concentration of drug used were shown to affect the release of the drug. Hydrocortisone, pentobarbital, and papavarine were used as model drug substances in these experiments. Kornblum (567) reported a spray-drying technique which provides a free-flowing powder with decreased dissolution rate after compression into tablets. Since this technique gives good reproducibility of drug release after tableting, it offers another method of preparing sustained-release products.

The chronology of development of a prolonged-action dosage form of proxyphylline was described in detail (568, 569). *In vivo* results indicated that tablets prepared by mixing the active ingredient with a synthetic lipid prior to tableting (embedded tablets) gave the best clinical results. The use of coated tablets did not give as suitable clinical results. *In vitro* comparison of these same formulations showed the liberation of the proxyphylline from the embedded tablet to be dependent on the particle size, the drug concentration, the pH, and the enzyme activity of the solvent system. The release from the coated tablet was much more rapid and was independent of pH and enzyme activity.

The ability of ethylene glycol monomethacrylate gel to hinder the release of drugs saturated in it was described (570). The *in vivo* plasma salicylate concentrations obtained following the administration of oral gels saturated with sodium salicylate confirmed this property of the gel. The effect of gel particle size on the release of the salicylate was shown. Poly vinyl acetate was used to coat micropearls of ascorbic acid to hinder their release (571). These coated granules slowly released ascorbic acid *in vitro* over 20 hr. in gastric and intestinal fluids. *In vivo*, ascorbic acid blood levels were obtained for periods of up to 20 hr. With tablets of ascorbic acid compressed with amyl sodium polyethylene, the release of the vitamin was shown to be inversely related to the degree of compression (572). This effect was postulated as being due to the differences in microstructure obtained by different forces of compression. In the case of *N,N'*-dibenzylethylenediamine ampicillin, the chemical modification was considered to prolong the release of the active drug (573). When administered intramuscularly once daily, this antibiotic had a bactericidal activity equivalent to orally administered ampicillin trihydrate given four times a day. Subcutaneous injection of zinc protamine glucagon gave a prolonged action compared with zinc glucagon suspensions administered to dogs under similar conditions (574). The differences in duration of action were believed to be caused by differences in the composition of the suspension media used.

Bolton (575) presented a method for calculating the release pattern of sustained-release products when more than 1-hr. release rates must be determined. This method is useful whenever hourly assays, as required by the Wiley method, are undesirable.

Other articles of interest related to sustained release are given in Table XIV.

Cosmetics—The trends in cosmetics and toiletries were well reviewed in several articles covering new cosmetic materials, testing methods, and types of prepa-

Table XIV—Additional References on Sustained-Release Preparations

Reference	Topic
576	Preparation of sustained-release oxytetracycline micropills
577	Apparatus for determining release from prolonged-activity solid dosage forms
578	Long-acting tablets containing soluble drugs incorporated into hardened castor oil
579	Use of carboxypolymethylene as an excipient in slow-release tablets
580	Interaction of cellulose acetate phthalate with organic and inorganic cations to form a film soluble in intestinal fluid but insoluble in gastric fluid
581	Application of solid coatings by pressure to hinder drug release
582	Comparison of regular- and slow-release ± 1-(4-hydroxyphenyl)-1-hydroxy-2-butylaminoethane sulfate (Vasculan) tablets

rations useful in cosmetics (583–586). The use of silicones in shampoos, hair sprays, hand lotions, aerosols, quick-breaking foams, toothpastes, and shaving creams was discussed (587, 588). Formulations were given for the types of silicone preparations used in these various products. The properties and uses of fatty acid lactylates were pointed out in a series of interesting articles (589, 590). The use of these materials in deodorant sprays, hair preparations, and shampoos was described. Brandau (591) discussed the various types of surfactants currently used in cosmetic preparations and presented formulations for shampoos, lotions, gels, and skin cleansers utilizing such surfactants. The foaming and surface-tension changes induced by several fatty acid sulfate ethers were described (592). Irritation studies of these materials in the rabbit eye indicated their lack of irritability and possible usefulness in shampoos. Materials which may be used as emollients were broken down into four general classes: hydrocarbons, vegetable fats, animal fats, and fatty alcohols. The properties and advantages of each group were discussed in an interesting review (593).

A series of articles pointed out the use of various materials, such as hexadecyl alcohol, metallic stearates, and vitamins in cosmetics (594–596). The properties of each of these materials, as well as typical cosmetic formulations, were described for each class of compounds. The use of zinc salts in cosmetics and as astringents was also discussed (597). The chemistry and biology of these compounds were thoroughly studied. Blake reviewed the application of radioisotopes in cosmetic research (598). The application and detection of such compounds were covered in detail. The use of tallow and coconut fatty acids to prepare soaps was discussed (599). The soaps were evaluated for their ability to dissolve, slush, lather, and swell. The effects of different ratios of these materials on the properties of the soaps were described.

In a series of articles (600–604), Gucklhorn fully outlined the advantages and disadvantages of the various preservatives used in cosmetic preparations. The bacteriologic spectra and reactions of the parabens, halogenated salicylonilides, organic mercurials, essential oils, sorbates, and other commonly used preservatives were discussed. The antibacterial and antimycotic activities of undecylenic acid and mono- and diethanolamine were determined against a wide variety of organisms (605). Since all of these materials exhibit some antibacterial activity, formulations containing them were presented. In view of the nutritive properties of cosmetics, they are best prepared using bactericidal rather than bacteriostatic preservatives. The bactericidal levels of certain commonly used preservatives were described (606). UV light at 253 μ was utilized to purify water prior to its use in preparing cosmetics and pharmaceuticals (607). This UV method of sterilization was shown to be completely effective if carried out properly.

The use of the scanning electron microscope in cosmetic research was described (608). This instrument, which scans the topography of skin and nails, may be used to investigate the effects of cosmetics on skin. Various viscosimeters and their application in studying the rheology of cosmetics were also discussed (609).

Review articles on hair preparations and shampoos described typical formulations and laboratory techniques (610, 611). Amphoteric surfactants were described which give additional hair-conditioning properties to shampoos (612). The perfuming of soaps and a technique for determining the minimum odor intensity were discussed in several other interesting articles (613–615).

Packaging—During the year, many articles were published covering the use of plastics in pharmacy and pharmaceutical packaging. Varsano and Gilbert (616–618) had a series describing the effects of preservatives, pH, and temperature on plastic packaging materials. The biological effects of plastics and of drug–plastic interactions, along with newer packaging innovations involving plastics, were also reviewed. The properties of polystyrene, polypropylene, polyvinyl chloride, vinyl resins, and other general considerations relating to the use of these materials in pharmaceutical packaging were discussed (619–622). The interaction between silver nitrate solutions and polyethylene containers from various sources was investigated (623). Storage of these solutions in plastic containers resulted in the precipitation of silver particles and an increase in pH. Preservatives containing free hydroxyl groups were prone to adsorption by polyvinyl chloride containers (624). The solute composition and pH of the solute were also shown to be contributing factors. The stability of fatty oils in plastic containers, a measure of their oxygen permeability, was investigated (625). Hot, humid storage conditions were shown to cause clouding of neutral oils stored in plastic containers. Comparisons of various plastic and glass containers with regard to influence of pH, oxygen permeability, and catalytic action of the surface were ably made by Houta and Lenpin (626). The influence of plastic materials on the pH of water is nearly negligible compared with that of glass. The permeability of plastic material to oxygen has no substantial effect on the stability of easily oxidizable substances, although certain plastics are affected by strong oxidizing agents. The alkalinity of glass containers was the subject of several detailed articles (627–629). The importance of this alkalinity on liquid pharmaceuticals was pointed

out. The ions eluted from different types of glass following acidic or basic attack at 121° were also described.

The protective properties of packaging materials, the properties of rubber, its permeability to water, the permeability of glass to light, and the resistance of aluminum ointment tubes to corrosion were discussed (630).

The effects of sterilization on leaching from stoppers composed of natural rubber, IR-25, butyl rubber, POV-30, and polycarbonates were investigated (631). None of the material leached from these stoppers affected the medicinal or physicochemical properties of the solutions being sterilized. The use of polyethylene or cellophane liners over rubber closures of multiple-dose injection vials to protect the solutions was investigated (632). Although this technique was successful in protecting ascorbic acid or sodium sulfadiazine solutions, it was unsuccessful in protecting phenol solutions from the rubber stoppers.

EQUIPMENT

A thorough review of pharmaceutical engineering was presented in several articles (633–636). The engineering aspects and the equipment used in drying, analyzing particle size, and mixing of solids and liquids were described in these reviews. A comprehensive review of methods of mixing and of mixers utilized in the mixing of liquids was presented by Skidmore (637). The advantages and disadvantages of each system were pointed out in this excellent paper. An apparatus for adding suspensions or solids to reaction mixtures was evaluated (638). Wray (639) presented an excellent account of the uses of an instrumented rotary tablet machine. The effects of compression forces on tablet hardness, disintegration time, and tablet weight were given. The characteristics of good and bad formulations, as determined by the instrumented tablet machine, were described. The advantages and disadvantages of new tableting equipment were pointed out (640). The Industrial Pharmaceutical Technology Section (APhA Academy of Pharmaceutical Sciences) standards for tableting tools and the proposed inspection program for such tools were detailed (641).

A description of the concept of laminar flow and the equipment necessary for such systems was presented (642). The effectiveness and limitations of horizontal and vertical laminar flow systems were shown. The equipment used for color measuring and matching was described (643). The use of spectrophotometers for reflectance data and the tristimulus colorimeter to take into account the light source and color sensitivity of the eye was reviewed.

Filling equipment for tablets and ampuls was described in detail in two papers (644, 645). The ampul-filling equipment utilized an automatic magnetic logic setup which gave very reproducible filling volumes.

PHYSICAL PHARMACY

Yang (646), in studying polymorphism in sulfonamides, suggested that the *para*-amino group, the acidic N^1-hydrogen atom, and the oxygen of the sulfonamide group are implicated in the various hydrogen-bonding arrangements that distinguish one polymorphic form from another. Functional groups attached to the N^1-position which serve as electron-withdrawing or electron-furnishing substituents apparently influence the strength of the hydrogen bonds formed and hence the tendency of compounds to exist in more than one crystal form. Through IR spectral studies, the physiological activity of the α-form of chloramphenicol palmitate was shown to be due to the weak intermolecular hydrogen bonding of the alcoholic hydroxyl groups. The β-form of this compound showed a very strong intermolecular hydrogen bonding of the alcoholic hydroxyl groups and is said to be physiologically inactive (647). Haleblian and McCrone (648) reviewed the applications of polymorphism in the pharmaceutical industry. Their publication discussed the preparation of physically stable dosage forms, the possible differences in chemical stability with various polymorphs, the absorption of compounds exhibiting polymorphism, the tableting of polymorphic compounds, and methods of studying polymorphism. Rosenstein and Lamy (649) discussed the pharmaceutical aspects of polymorphism and suggested that the more energetic polymorphic form of a drug may be considered the form of choice in dosage form development.

Using an electrostatic model, Ladd and Lee (650) suggested that the process of hydrate formation takes place in two stages: (*a*) expansion of the anhydrous crystal and accommodation of gaseous water molecules, and (*b*) water–ion interaction. The maximum hydration of dimethylsulfoxide (DMSO) in aqueous solution at 25° was investigated by the deviation of experimental values of fluidity, dielectric constant, refractive index, density, and molar refraction from values calculated by linear interpolation between the values of the two pure liquids as a function of mole fraction. The maximum deviation in fluidity and dielectric constant occurred at the ratio of 3 water molecules per DMSO molecule, which was the maximum hydration (651).

The application of calorimetry to simultaneous determination of equilibrium constants and enthalpy changes for reactions in solution was discussed, and data were presented supporting a more optimistic evaluation of the calorimetric method (652). A calorimetric method was also employed to study proton ionization from aqueous solutions of protonated amines. Resulting enthalpy values were combined with pK values to calculate entropy values. The effect of hydrocarbon chain length and branching on entropy and enthalpy values for proton ionization from primary and secondary aliphatic protonated amines was described by a simple linear equation (653). Michaelis and Higuchi (654) demonstrated the influence of temperature on the distribution ratio of pharmaceutical ammonium species paired with various anions and between aqueous and organic phases, and they determined the thermodynamic parameters associated with these extractive processes. These authors concluded that, unlike transfer of uncharged solute molecules, ion-pair transfers involving inorganic anions appear to be largely entropically controlled. The process of movement from water to chloroform of dextromethorphanium halides, for

example, involved a material increase in ordering. Less polar organic phases tended to lead to less negative entropic changes.

Based on the principle of the higher kinetic energy of water particles in Brownian movement relative to the kinetic energy of particles dissolved in water, Wolkowski (655) presented a new hypothesis for the osmotic mechanism; it explains the principle of water penetration from lower pressures to the higher pressures which exist in solutions of higher concentration. Kostenbauder *et al.* (656) described the unique permeability characteristics of nylon film which make it a useful membrane for conducting dialysis studies or separations that are not readily accomplished with the semipermeable membranes more commonly employed for these purposes. The authors indicated that the permeability of nylon to drugs is not that exhibited by a porous membrane nor that of many nonporous membranes. Nylon is relatively impermeable to small molecules and ions such as water, urea, and sodium chloride; but many less polar, high-molecular weight nonionized species, as well as such ionic compounds as cetyl-, dodecyl-, and ethylpyridinium bromides and sodium naphthalene sulfonate, diffuse readily through nylon films (656). The diffusion rate of sennoside A through a cellulose membrane into water increased, irrespective of the temperature conditions under which diffusion took place, when the membrane was irradiated with ultrasound. These results were consistent with the hypothesis of boundary-layer disruption at the phase interface (657). Rushing discussed the osmotic properties of aqueous solutions of certain divalent salts of disulfonic acids (658).

Repta and Higuchi (659) described the preparation and chemistry of an unsymmetrical monomolecular crystalline anhydride of citric acid, and they suggested possible uses of this compound in pharmaceutical formulations.

Dissolution—Dissolution testing assumed increasing importance during the past year. Studies of three different lots of diazepam tablets revealed no correlation between the rate of disintegration and the rate of dissolution. Increased stirring rate and solvent volume, however, did accelerate the dissolution rate, as did the addition of polysorbate (Tween) (660). Tawashi (661) reviewed the current concepts of crystal dissolution and how dissolution rates and release patterns of drugs are related to such parameters as the cohesive forces in the crystal, which in turn are affected by crystal imperfections or defects. These defects explain some of the discrepancies between experimental and calculated yield strengths. Crystal defects included grain boundaries and cracks, lattice flaws, vacant sites, and foreign atoms outside the regular geometric pattern of the crystal. Other important factors noted in the review were crystal polymorphism, crystal impurities, dosage form additives, processing, and compaction, all of which may act to alter the dissolution rate of the dosage form.

In studying dissolution rates of high-energy polyvinyl pyrrolidone (PVP)–sulfathiazole coprecipitates, Simonelli *et al.* (662) demonstrated the apparent solubility and rate of solution of sulfathiazole from compressed tablets containing PVP to be greatly increased if sulfathiazole was previously coprecipitated with PVP.

Table XV—Additional Dissolution Studies

Reference	Topic
672	Proposed model for analyzing simultaneous phase change dissolution phenomena using *p*-hydroxybenzoic acid and phenobarbital, which change to the respective hydrates during dissolution
673	Minimizing loss of effective surface area during *in vitro* dissolution of sustained-release cellulose acetate phthalate pellets suspended in a turbulent flow field
674	Dissolution of dicoumarol tablets of different crystal properties
675	Parameters of theoretical importance in drug dissolution technology
676	Effect of the nonionic surfactant cetomacrogol on the rate of solution of powdered griseofulvin in water
677	A modified USP disintegration apparatus for use in measuring the dissolution rate of chloramphenicol capsules
678	An automated apparatus for measuring the dissolution rate of solid dosage forms at constant volume under sink conditions maintained by continuous elimination of the solution and replacement with fresh buffer
679	Dialysis method for determining the effects of compression forces and tablet additives on the dissolution rate of sparingly soluble dosage forms
680	Review of the history of dissolution studies and the methods used
681	Dissolution apparatus in which agitation is provided by a flow of liquid maintained by a peristaltic pump
682	Review of the current methods employed in evaluating the rate of drug release from solid dosage forms, and a description of a new apparatus employed for the determination of dissolution rates
683	Influence of polymer molecular weight and solvent pH on solvent penetration and polymer swelling in compressed disks of a series of polymer-free acids derived from ethylene maleic anhydride resins

The increase noted was found to be a function of the chain length of the PVP used as a coprecipitate and the sulfathiazole-to-PVP weight ratio of the coprecipitate powder mixture used to compress the tablet. Similarly, Bates (663) showed that a 1:6, reserpine–PVP, coprecipitate had a 200-fold increase in dissolution rate over that for pure reserpine. This was due to the reduced particle size and, consequently, to the increased surface area of the reserpine in the coprecipitate.

The relative rates of dissolution and solubilities of three polymorphic forms of chloramphenicol palmitate in a 35% tertiary butanol–water mixture and two polymorphs of mefenamic acid in dodecyl alcohol were measured. The thermodynamic relationships involving the transition of the metastable polymorphs to the stable one were examined; the significance of the energy differences between the polymorphs and their absorption, as reflected by blood levels in humans, were discussed (664).

An IR-attenuated total reflectance spectrophotometric technique was employed to demonstrate the surface reversion of methyl prednisolone Polymorph II to Polymorph I in the presence of water. The process was shown to occur rapidly enough to account for the slower than expected dissolution rates of nondisintegrating pellets of Form II in water. The unusual effects of agitation upon the dissolution rate of Form II pellets were thus explained (665).

A marked increase of dissolution rates and attainment of supersaturation of griseofulvin were found when the drug was dispersed by fusion or solvent methods in

matrices of polyethylene glycol (PEG) polymers, pentaerythritol, pentaerythrityl tetraacetate, or citric acid. Although the exact physical nature of the dispersion systems was not determined, it was suggested that some griseofulvin is molecularly and/or colloidally dispersed in the PEG polymers due to their highly viscous and supercooling effect, which would retard the nucleation and growth of griseofulvin precipitation during the solidification process. Pentaerythritol and pentaerythrityl tetraacetate are believed to form limited or completely solid solutions with griseofulvin. The griseofulvin–citric acid mixture forms a glass, and the resultant glass solution may represent a new class or physical modification of drugs exhibiting a strikingly fast dissolution rate of griseofulvin (666).

A column-type method was described for the assessment of the dissolution behavior of solid dosage forms. The method, which is based on the mass transfer between solid and liquid phase in an exchange column, was shown to avoid certain disadvantages of the commonly used beaker methods employing fixed liquid volumes. Because of its reproducibility and the absence of arbitrary external parameters, the method appears to be useful for a meaningful study of dissolution kinetics (667).

Two samples of commercial aspirin with no crystallographic or solubility differences did, however, exhibit different thermodynamic activities, as determined by the effects of agitation and temperature on intrinsic dissolution rates. The metastable form was capable of rapid reversion to a more stable form, depending on the conditions of study (668).

Wagner (669) showed that, under sink conditions, the percent dissolved value at time t may simply be equivalent to the percent surface area generated to that time; if this is so, the percent dissolved–time data may best be described by a distribution function, and the parameters of the distribution may best be employed to describe the data. Simulated percent dissolved–time data, generated by means of the logarithmic normal distribution function, were shown to yield apparent first-order plots. Hence, apparent first-order kinetics, derived from *in vitro* dissolution tests on conventional tablets and capsules, may be artifacts in some cases. In the special case when surface area of drug available for dissolution decreases exponentially with time after some lag time, t_0, first-order kinetics appear applicable to the dissolution data. The new method of examining dissolution-rate data is capable of providing characterizing parameters of greater potential utility than conventional treatments used previously. Gibaldi *et al.* (670) showed that dissolution from constant-surface pellets into micellar solutions followed first-order kinetics in agreement with theory. A method for determining the apparent zero-order rate constant for dissolution from constant-surface pellets, which does not require maintenance of sink conditions, was also suggested.

Low (premicellar) concentrations of polyoxyethylene lauryl ether and lysolecithin markedly enhanced the dissolution rate of salicylic acid powder, while pepsin and gastric mucin were without effect. The same surfactants enhanced the dissolution rate of aspirin from a tablet dosage form but were without effect on the dissolution rate of the drug from a capsule dosage form. Good correlation was observed between the surface tension of the polyoxyethylene lauryl ether solutions and the dissolution rates of aspirin from the tablet dosage form in these media. The authors discussed the relevance of these data to design of *in vitro* dissolution tests (671).

Additional studies on dissolution are provided in Table XV.

Table XVI describes references on the measurement of particle size.

Table XVI—Additional Studies on Measurement of Particle Size

Reference	Topic
684	Review of the advantages and disadvantages of methods employed for determining the distribution of particle size
685	Millipore's combination microscope, TV camera, and computer for the determination of particle size
686	Determination of particle size of water and salt solution aerosols by the dye film technique

Additional references on physical pharmacy are provided in Table XVII.

Solubility—Paruta (699) in determining the solubilities of methyl-, ethyl-, propyl-, and butylparabens in a series of normal alcohols, noted that these compounds have a dielectric requirement of about 14 with another postulated to exist at about 30. These compounds exhibited a good parallel solubility in the various alcohols, indicating a similarity of interactions in the dissolution

Table XVII—Additional Studies on Physical Pharmacy

Reference	Topic
687	Two FORTRAN programs for the IBM 1620 computer which permit determination of the pH of weak acids and bases and salts of these species in aqueous solution at 25°
688	Limitation on the validity of the additivity of molar attraction constants on a functional group basis
689	Dissociation kinetics of methyl red in dilute aqueous solution
690	Acid dissociation constants of barbiturates as determined by pH measurement
691	Dissociation of aminomethanesulfonates in aqueous solution; role in the complex equilibria of neutral solutions of sodium colistimethate
692	Correlation of percentage composition of hydrochloric, perchloric, phosphoric, and sulfuric acids in aqueous solution with molarity, molality, activity coefficient, water activity, and Hammett acidity function
693	Occurrence of complete erythrocyte hemolysis in water–amide solutions and prevention with sodium chloride at low amide concentrations
694	Sodium chloride equivalents and freezing point depressions at various aqueous solution concentrations of 30 different medicinal substances, with isosmotic concentrations of the soluble materials
695	Lithium and sodium chlorates in water and in water–dioxane solvents: the higher solvation of lithium chlorate, as determined using a vapor pressure method, and the major role of dioxane in the solvation of both electrolytes
696	Sodium and lithium chlorates in water: diffusion coefficients and hydration numbers
697	Review of the principles and concepts of ionic motion
698	Isotonic buffer mixtures of pharmaceutical interest: tonicity and pH at 37°; discrepancies between freezing-point depression and vapor-pressure osmometer data

Table XVIII—Additional Studies of Solubilities

Reference	Topic
710	Measurement of dissolved oxygen in water–glycol mixtures in which the glycol has either a hydrophilic group or both a hydrophilic and hydrophobic group
711	Effect of temperature on the solubility and rheology of an ascorbic acid–water–polysorbate system
712	Solubilization of *p*-dimethylamino anil of phenylglyoxal nitrile by cationic surfactants, and effect of electrolytes on micelle formation
713	Review of methods for dissolving insoluble drugs
714	Linear increase in chloramphenicol solubility with concentration of solubilizer once the CMC is reached
715	Review of the solubilization of drugs
716	Use of Tweens (polysorbates) to increase the extraction of rose oil from the rose flower without altering the quality of the oil
717	Solubilization of sulfamethoxypyridazine using a mixture of polyethylene glycol 300, water, alcohol, and piperazine
718	Review of pharmaceutical solvents and solubilizers
719	Increase in aqueous solubility of various drugs by use of polyethylene glycol 400
720	Relationship between the CMC of the surfactant and its ability to solubilize benzyl alcohol or naphthalene
721	Effect of water hardness on the solubilizing activity of linear alkylbenzenesulfonates
722	Formation of micelles by aerosol OT in all nonaqueous solvents studied except methanol, as determined by ultracentrifugation, light scattering, and viscometric techniques
723	Review of the theory of solubilization and stabilization of drugs
724	Increase in solubility and bacteriostatic activity of salicylic acid by use of Tweens (polysorbates), Spans (surface-active agents), polyethylene glycols, propylene glycol, and various mixtures of these nonionics
725	Solubilization of camphor using a pentaerythritol oleate polyethylene glycol ether
726	Review of solubilization and its use in pharmacy
727	Solubilization of water by oil-soluble anionic surfactants: micellar interaction between water and cation of surfactant
728	Solubilization of water by oil-soluble cationic surfactants: ion-dipole interaction between water molecule and halogen anion

process. In aqueous solutions of dioxane, these same *n*-alkyl parabens had a dielectric requirement of about 8–10. Two-phase systems were found for certain of these paraben derivatives over a given composition range of the binary solvent mixture, suggesting the production of a solvate between the paraben and a fixed composition of the binary mixture, thus forming a biphasic system in equilibrium (700). Similar conclusions relative to solvate formation were drawn from an investigation of the solubilities of *n*-alkyl parabens in binary mixtures of ethanol and water. With the latter solvent system, a dielectric requirement of 29–32 was suggested for *n*-alkyl parabens (701).

Several interesting papers dealing with micellar solubilization were published in the past year. Oil-soluble surfactants were studied as solubilizing agents for water-soluble food dyes in the solvent perchloroethylene. In the absence of water, no solubilization of dye occurred; but above a minimum water-to-surfactant ratio, the dye was soluble to a measurable degree. The author concluded that the CMC decreases linearly with an increasing water-to-surfactant ratio (702). The solubility of testosterone, methyltestosterone, and testosterone propionate in aqueous solutions of ethoxylated cholesterol was determined and found to be greatest for the propionate derivative. Based on the UV spectral characteristics of the three steroids in aqueous solutions of the surfactant, which were similar to those in various polyethylene glycols, the mechanism of solubilization was reported to involve association of the steroid with the polyoxyethylene portion of the surfactant (703). Wan and Hwang (704) showed that the solubilities of a series of alkyl gallates in water and in cetomacrogol solution increased with a decrease in alkyl chain length. The solubilities of the short-chain gallates in benzaldehyde increased, while those of the long-chain gallates decreased with chain length. The comparative antioxidant efficiency in solubilized systems appeared to be related to the distribution ratios, and that in emulsified systems to the solubility of the antioxidant in the aldehyde. Thakkar and Hall (705) attempted to explain the anomolous initial supersaturation observed in solubilized systems of testosterone and concluded that the behavior was related to conversion of the anhydrous crystal form to a hydrate crystal form. In studying the solution behavior of the anhydrous form, the authors noted that the peak solubility time in surfactant solution was either increased or decreased relative to water, depending on the concentration and type of surfactant used.

Using ultracentrifugation and viscometric techniques, the behavior and state of aggregation of barium dinonylnaphthalene sulfonate in toluene, toluene–methanol, and methanol were studied, and methanol was shown to diminish the size of sulfonate and carboxylate micelles in nonaqueous solutions (706).

Phenobarbital USP, when crystallized slowly at room temperature from 50% aqueous acetone, dissolved faster in single crystal as well as in powder and tablet form than did an anhydrous form of phenobarbital crystallized in a similar manner from a saturated solution of 85% ethanol. With heat or upon storage in a dry atmosphere, the hydrated crystal form was converted to the anhydrous crystal form (707).

Guess and Jones (708) showed that the degree of solubility of ethylene oxide in plasticizers is a function of the chain length of the plasticizer hydrocarbon moiety. They concluded that the degree of polarity of the plasticizer might, therefore, be a great factor in controlling the solubilization.

The solubility of free modified cellulose polymer films was found to be decreased in the presence of certain FD&C and D&C red dyes. These same dye-containing polymers, when employed as coatings on riboflavin tablets, retarded the tablet disintegration time and the riboflavin dissolution rate. Riboflavin urinary excretion studies confirmed that the dyes may adversely affect *in vivo* product performance (709).

Additional studies of solubility are listed in Table XVIII.

Complexation—Higuchi *et al.* (729) reported a study of some of the methods available for the experimental measurement of hydrogen-bonding interactions in the formation of complexes and the means of determining the association (equilibrium) constants from the experimental results. An attempt was made to develop suitable methods for the quantitative analysis of hydrogen-bond-

ing data so that useful estimates of association constants could be made *a priori*. The study also showed the effect of a nonaqueous solvent on the value of the association constant, and a method was provided whereby an estimate of solvent interaction could be calculated. A critical evaluation of the utility of thermal methods for the detection of possible interactions between the solid components of pharmaceuticals was reported. Phase diagrams were constructed for a number of binary systems. Using thermal methods, interactions were detected with deoxycholic acid–menadione, quinine–phenobarbital, theophylline–phenobarbital, and caffeine-phenobarbital systems(730). Evidence for the interaction of procaine and procaine amide with ATP in aqueous solution was found by means of optical rotation and NMR measurement. The aromatic components of drug and nucleotide molecules were shown to associate through hydrophobic bonding with vertical stack formation rather than through horizontal bonding (731). A simple and general procedure for calculating the statistical factors of mixed ligand complexes was presented. It was noted, for example, that the formation of a mixed complex, MAB, from a metal ion, M, in the presence of equal concentrations of Ligands A and B, is always favored, on a statistical basis, over the formation of MA_2 or MB_2. Thus, there is an enhanced probability of bringing together two different ligands, or a small substrate molecule and an enzyme, *via* a metal ion—a fact which may have great biological implications, particularly as regards the multimetal–multiligand systems in biological fluids (732). Spectroscopic studies on complexation between caffeine and benzoic acids were reported. The relation between the free energy change and the pKa for benzoates suggested that direct electrostatic forces between the carboxyl group in the benzoate molecules and the nitrogen of the 7-position in the caffeine molecule play a dominant role in the complexations (733). The physical and chemical properties of complexes of mono-, di-, and triethanolamine with bentonite, kaolin, and other clays were reported. A triethanolamine–bentonite complex having optimum swelling characteristics at pH 7 gave good stabilization of aqueous suspension. Electrolyte concentrations greater than 1% decreased the stabilization effect of the complex (734). Polli and Frost (735) investigated the role of PVP as a stabilizer for hexylresorcinol in a compressed tablet. While the presence of PVP was shown to be responsible for the color stability of hexylresorcinol, the antimicrobial activity of hexylresorcinol was found to be reduced in the presence of PVP. This reduction in activity was apparently due to the molecular interaction between hexylresorcinol and PVP, and indicates the need for biological evaluation of complexes whenever their formation is suspected. The apparent stability constant of the salicylic acid–caffeine complex was studied in a medium of varying polarity. The salicylic acid and caffeine interacted very strongly in the nonpolar solvent, presumably by hydrogen bonding, but their interaction was minimal in the moderately polar solvents. Because the complexes differ in the organic and aqueous phases, they are not likely to penetrate the phase boundary when the caffeine and salicylic acid are allowed to partition between these phases (736). By this means, Krivis and Rabb (737) reevaluated the Cu–isonicotinic hydrazide system and obtained evidence for the formation of a Cu (I) species rather than a Cu (II) species. The reduction of Cu (II) to Cu (I) and the subsequent formation of an isonicotinic hydrazide complex with the latter ion may be the critical reaction responsible for the therapeutic efficacy of isonicotinic hydrazide. The stability constants and the enthalpies of formation of complexes of caffeine and sodium salts of aromatic acids showed that the stability of the complex is the most important factor in the solubilization of caffeine by these salts (738). The interactions of ergotamine tartrate and caffeine between pH 1 and 6.65 demonstrated that there are marked changes in the solubility of the alkaloid with increased caffeine concentration. Caffeine enhanced the dissolution rate of ergotamine tartrate by a factor of 3 at gastric pH (739). The degree of sorption of chlorobutanol-^{14}C by polyamide and polyethylene was determined using scintillation spectroscopy. The magnitude and rate of sorption were measured, as well as the standard chemical potentials, heats of sorption, and standard entropy values (740).

Additional references on complexation are provided in Table XIX.

Surface Phenomena—To aid the reader in locating areas of specific interest, the authors of this review have subdivided the various publications dealing with surface phenomena; however, because of the obvious overlap in subject matter, the reader who needs a thorough review is advised to consider the entire section.

Interface Studies—The absorption of cellulosic ethers at lipid–liquid/water interfaces was studied in order to clarify the role of polymers in depressing the rate of drug transfer. Carboxymethylcellulose lowered the interfacial tension only when the lipid was nonpolar and the aqueous phase was acidic. Hydroxypropylcellulose markedly depressed the interfacial tension regardless of the polarity of the lipid phase or the pH of the aqueous phase (777). Air–water interface adsorption studies were conducted using seven members of a homologous series of *N*-alkyl betaine zwitterionic amphiphiles. The standard free energies of adsorption were calculated and resolved into separate contributions from polar head groups and methylene groups in the alkyl chain. The data were compared with previously published data for the same compounds undergoing micellization (778). A similar study was made of the properties of monolayers of normal alkyl betaines at the air–water interface. Condensation of the films at pH 4.5–6 was ascribed to the formation of the zwitterions, but there was no indication that an anionic species is produced on alkaline substrates. The entropies and enthalpies of spreading suggest that there is intramolecular neutralization of charges between N^+ and COO^- groups in each molecule (779). The adsorption of cetyltrimethylammonium bromide at different concentrations of the liquid paraffin–water interface was measured by an interfacial tension-lowering technique as well as by an emulsion technique. The experimental data on adsorption appeared to fit both the Freundlich and Langmuir adsorption isotherms (780). On the basis of previous work on interface potentials in amino acid solutions, a structural scheme of interactions between nonpolar radicals and water molecules was sug-

Table XIX—Additional Studies on Complexation

Reference	Topic
741	Zein as a model substance in studying the interactions of proteins and detergents
742	The adsorption of cyanocobalamin on talc in the presence of pyridoxine and thiamine, and the use of talc as a lubricant in tablets of these vitamins
743	The employment of simulated absorbance data to demonstrate the effects of 2:1 molecular complexes on formation constants and absorptivities calculated for 1:1 donor–acceptor interactions
744	Decrease of urotropine–water interaction with increase of the ionic radius of the alkali ion, suggesting its hydration
745	Spectroscopic studies of the triethylamine–iodine systems showing the advantages of the Benesi-Hildebrand method for the determination of equilibrium constants
746	*In vitro* binding of neomycin and its analogs by fatty acids, showing the marked loss of neomycin activity when the interaction results in the formation of a precipitate
747	The effect of magnesium ions on an ascorbic acid monostearate–nicotinamide complex
748	Formation of a 1:1 association compound by chlorpromazine and ninhydrin, as determined by a spectrophotometric method
749	Unique spatial orientation of flufenamic acid and other *N*-arylanthranilates with respect to serum albumin, even when the drugs are bound to the same site
750	Increase in solubility of aromatic hydrocarbons in water by complexation with caffeine
751	Interaction between salts of primary aliphatic amines and hydrophilic organic colloids like sodium carboxymethylcellulose dependence on pH, ionic strength, and chain length of the amine
752	Interactions between colloidal silicic acid containing a sorbed water layer and drugs such as 8-hydroxyquinoline sulfate and quaternary ammonium compounds
753	Spectrophotometric studies on the interaction of acacia and sodium alginate with certain preservatives such as parabens, benzoic acid, salicylic acid, and sorbic acid
754	Interaction between some thiamine derivatives and styrene–maleic anhydride copolymer
755	Polyvinyl alcohol was shown to solubilize benzocaine, phenobarbital, and thymol through complexation by polyvinyl alcohol
756	Single crystal X-ray diffraction methods for obtaining the crystalline and molecular structure of a 1:1 association complex between 5-chlorosalicylic acid and theophylline
757	The formation of an acridine–triphenylmethane dye complex as a possible explanation for the therapeutic interference by such dyes with the action of the acridines
758	The relationship of the anti-inflammatory activity of ethacrynic acid and *n*-ethylmaleimide to the binding properties of their sulfhydryl groups
759	The role of complex formation with water-soluble steroids in the increased *in vitro* activity of water-insoluble polyene-type antibiotics
760	The role of van der Waals-type forces and charge-transfer forces in the strength of a PVP–iodine complex, as determined by a spectroscopic method
761	Improvement in color stability of aqueous sodium erythrosin solution over a broad pH range as a result of complexation with PVP
762	Interaction of thiodiphenylamine with sodium and copper chloride and sulfate solutions
763	Binding of enzyme inducers to histones and nucleic acids
764	Computer program for calculation of stability constants of metal complexes of amino acids and penicillin derivatives from pH values, using known relations
765	X-ray diffraction study of the structure of polymorphism of protein–lipid–water phases
766	Increase in serum vitamin B_{12} binding capacity in women receiving oral contraceptives
767	Possible inactivation of carbocaine and lidocaine by complexation with phospholipids
768	Binding of calcium, sodium, and potassium ions to acid polysaccharides
769	The influence of 36 different drugs on the binding of promazine to bovine serum albumin
770	The predominantly zwitterionic form of aqueous pyridine carboxylic acids and hydroxypyridines as a cause of their lesser complexing tendencies toward 8-methoxycaffeine as compared with corresponding benzene derivatives
771	A solubility technique used to demonstrate the forces involved and the differences in interaction between β-cyclodextrin and 11 pharmaceuticals in aqueous solution
772	Apparent association constants used to estimate the binding of thyroxine to proteins
773	Preferential complexation as the mechanism whereby certain barbiturates prevent the association of riboflavin and adenine derivatives in chloroform solution
774	Increase in the solubility of rutin and quercetin as a result of complex formation with starch
775	Description of the kinetics of intramolecular hydrogen bonding in methyl and ethyl salicylaldehyde by means of an ultrasonic absorption method
776	Review of the binding forces between molecules and an introduction to the theory of adhesion

gested. The aqueous molecules are spontaneously oriented at the interface, with nonpolar substances forming a maximally dense monomolecular layer. This layer forms a basis on which other layers can be formed by hydrogen bonding (781). An apparatus and technique to obtain accurate surface pressure measurements were described, and a single valid surface pressure area per molecule curve was constructed for an insoluble cationic film spread from pure water onto a substrate of sodium chloride solution. With this curve and the results obtained by a crystal spreading method, it was shown that the old criteria for assessing the reliability of the π times area results for an expanded film are invalid and that the spreading of solvents is a major source of error (782).

Additional studies on interface phenomena are described in Table XX.

Surface Tension Studies—Zettlemoyer and Rao (800) reported that the DuNuoy procedure for measurement of surface tension of anionic sodium α-sulfo fatty acid ester surfactants did not give reproducible values, thus indicating that the equilibrium surface tension is too variable for a given solution using this testing procedure. The surface thermodynamic properties of a series of alcohols (C_6–C_{18}), cellosolves, and carbitols were derived from surface tension measurements at various temperatures. A systematic variation of thermodynamic properties with respect to chain length and change in temperature was observed with the alcohols and cellosolves (801). The surface tension of pure liquids was shown to depend on the miscibility of the phases and the orientation of the molecules at the interface. As a function of temperature, the surface tension isobars were concave at elevated pressures but were straight lines at lower vapor pressures. The temperature coefficient of surface tension is affected by the decrease in surface tension resulting from an increase in the saturated vapor pressure and by

Table XX—Additional Studies on Interface Phenomena

Reference	Topic
783	The adsorption of surface-active agents at a liquid–liquid interface
784	Spreading at the solid–oil–water interface
785	Properties of interfacial films of colloidal electrolyte–protein complexes
786	Effects on surface pressure and surface potential of the addition of glycerol to the aqueous substrates of various monomolecular films at the air–water interface
787	Review of the practical application of the monomolecular films formed at air–water interfaces
788	The kinetics of adsorption at the oil–water interface as determined using a suspended-drop tensiometer
789	Ionized monolayers of surfactant at oil–water interfaces
790	Measurement of the attractive forces at liquid–solid interfaces
791	Surface pressure relaxation and hysteresis in stearic acid monolayers at air–water interfaces
792	Review of the intermolecular and interatomic forces at interfaces
793	Determination of the interfacial surface during mechanical mixing of immiscible liquids
794	Review of the work on the properties of water-insoluble soap films at surfaces and interfaces
795	Measurement of the adsorption of sodium dodecyl sulfate at toluene–water interfaces using an interfacial tension-lowering method
796	Review of the discrepancies in the data reported in the literature on solid–liquid interfaces
797	Measurement of electrocapillary phenomena at oil–water interfaces, including the interaction between surfactants and dyes
798	The effect of lysolecithin on lecithin monolayers at air–water interfaces
799	The adsorption of stearic acid on silica and alumina and of decanoic acid on magnesia

the increase in the mobility of the liquid phase molecules with increasing temperature (802). A method was described for substituting a dynamic measurement of surface tension in aqueous solution for the usual static measurements. The dyanmic method shows a time-dependent accumulation of surfactants and a change in the surfaces prior to their reaching equilibrium (803). The influence of temperature and added electrolytes on the dynamic surface tension of sodium dodecyl sulfate solutions was examined by an oscillating jet method. An increase in temperature increased the initial rate of surface tension lowering but had little subsequent effect. Addition of electrolytes increased the subsequent rate but had little effect on the initial rate (804).

Additional references on surface tension studies are provided in Table XXI.

Wetting and Contact Angle Studies—The minimum depth of free energy corresponding to an equilibrium in thin liquid films was determined by measuring the contact angle between the film and the bulk solution. The significance of this angle and its relationship to conventional contact angles were discussed and an experimental method for measuring it was described. Results were also provided for solutions of sodium dodecyl sulfate containing sodium chloride (821). Shafrin and Zisman (822) reported on a new class of surfactant compounds designed to adsorb on solids to improve adhesion of liquids, resins, and protective coatings. Shortening the aliphatic chain from chlorphenyldodecanoic to chlorphenylacetic acid influenced the wettability properties but also permitted use of solvents such as water. A technique was developed for measurement of contact angle in the transition zone between very thin and thick liquid films, based on the Wilhelmy plate technique for measuring surface tensions of liquids. Results were obtained at 25° for films stabilized with sodium dodecyl sulfate in varying amounts of sodium chloride (823). Equations were derived which described the thermocapillary flow of liquid films spread on hydrophilic surfaces and consisting of two layers having different rheological properties. The layer adhering to the solid surface was presumed to exhibit viscoelasticity and the top layer to exhibit Newtonian flow patterns. Dimensionless velocity gradients were established according to layer thickness (824). A theoretical formula was presented for the spreading of a spherical droplet on a smooth rigid surface, based on the assumption that spreading is impelled by surface tensions at the interface and retarded by viscous flow of the droplet. Equations were also derived to predict the rate of spreading and change of contact angle with time (825).

Additional references on wetting and contact angle studies are provided in Table XXII.

Micelle Studies—Frank and Zografi (832) stated that di-(2-ethylhexyl)sodium sulfosuccinate, when dissolved in various hydrocarbon solvents, was capable of solubilizing large amounts of water, whereas closely related compounds such as the di-*n*-octyl and di-*n*-hexyl derivatives exhibited negligible solubilizing capacity. Using light-scattering techniques, the authors measured the micelle size of these three compounds in *n*-octane and

Table XXI—Additional Studies on Surface Tension

Reference	Topic
805	Review of the classification and testing of wetting agents
806	The effect of purity on the surface tension behavior of a homogeneous nonionic detergent
807	The suggested absence of significant inflections in the variation of the surface tension of pure water with temperature
808	Surface tensions of solutions of polydimethylsiloxanes in toluene and tetrachloroethylene at room temperature
809	Equations showing the relationship between surface tension and surfactant concentrations and the effect of temperature on this relationship
810	The variation of surface activity with concentration of surfactant and CMC for cetylpicolinium compounds
811	Mathematical equations for formulating the force between two spheres in contact due to the presence of a pendular ring of liquid
812	The surface tension and viscosity of liquids according to the transient state theory of liquids
813	Review of surface tension theory
814	Review of surface tension
815	Review of the surface tension of liquids in meniscuses with small radii of curvature
816	Dependence of surface tension on surfactant concentration
817	Mathematical equation for the surface tension of water–ethanol–methanol solutions
818	Relation of the purity of sodium dodecyl sulfate to surface tension equilibrium time
819	Calculated thickness of the surface layer of liquids, based on thermodynamics and the theory of Brillouin, which relates surface tension to layer thickness
820	Changes in surface tension during mixing of different types of disperse systems

Table XXII—Additional Studies on Wetting and Contact Angle Measurement

Reference	Topic
826	A light interference measurement technique for determining small contact angles between liquids and solids
827	Relation between the wettability of a paraffin surface by an aqueous solution of sodium stearate and the adsorption of sodium stearate onto the solid paraffin surface
828	Use of three criteria to assess the wetting effect of similar anionic surface-active agents on cellulose
829	Description of wetting on a molecular basis by direct calculation of contact angles from intermolecular forces
830	Review of the determination of wettability by use of liquid contact angles
831	The mechanism of spreading of a drop on a smooth solid surface and the role of surface viscosity in the dynamics of this process

found large differences in micelle weight between di-(2-ethylhexyl)sodium sulfosuccinate and the other compounds in *n*-octane and suggested a significant role for the 2-ethyl side chain. The active participation of water in the organization of these micelles was suggested by significant changes in micellar weight well in excess of that accounted for by the added amount of water. The influence of different hydrocarbon solvents on micelle weight was also found to be quite significant. The effects of a series of nonionic surfactants on micellization of an anionic surfactant was studied as a function of mole ratio and polyoxyethylene chain length. Changes in the degree of association of the anionic surfactant brought about by its incorporation in the mixed micelles was also studied. The degree of ionic dissociation of ionic surfactant in mixed micelles increases as the proportion of a nonionic material increases and as the polyoxyethylene chain is lengthened. At low concentrations, specific conductances are smaller for mixed solutions than for anionic solutions alone, whereas at higher concentrations, mixtures have greater conductance. These results are explained by the degree of ionic dissociation and the mobility of the mixed micelles (833). Micellar weights were determined from mixtures of nonionic and anionic surfactants. The degree of association was less than that calculated, showing the existence of mixed micelles. The increase in micellar weight with rising temperature, characteristic of nonionics, is suppressed by adding anionic surfactants. The micellar weight and the degree of association increased in the presence of sodium chloride (834). Schott (835) noted a remarkable resemblance in the shape, compactness, degree of hydration, and intrinsic viscosity of solutions of globular proteins near their isoelectric point and of nonionic detergent micelles. The polarographic micelle point values of nonionic surfactants were determined by a polarographic maximum suppression method in the presence of electrolytes. These values did not compare well with the CMC's obtained by other methods, which were always higher. These differences were explained as due to the presence of ions which influence the water structure, causing a lowering of the CMC value (836). The decrease in the CMC caused by electrolytes was interpreted in terms of a salting-out mechanism, and evidence was offered in support of the contention that micelles of polyoxyethylated nonionic detergents have a weak positive charge. The effects of urea and formamide on CMC values indicate that hydrophobic bonding is lessened in their presence, with a resulting increase in the CMC (837). Sodium and potassium caprate, laurate, and myristate solutions, both below and above the CMC, were titrated with HCl. By simultaneous monitoring of hydrogen-ion and potassium-ion activity during the course of the titration of micellar laurate solutions, the authors were led to conclude that hydrogen ion competes with potassium ion at the negatively charged micelle–solution interface (838). Keymer (839) noted the unclear relationship that exists between CMC and molecular size or structure, pointing out that the CMC values of anionic substances decrease with an increasing ratio of hydrophilic to hydrophobic portions of the molecule, but that the CMC values of amphoteric, nonionic, and free acid molecules behave in a reverse manner. The author stated that as the aqueous solubility increases, the formation of micelles is reduced and the CMC increases, and if the solubility approaches infinity, no micelle formation is possible. Wan and Poon (840) studied the effect of salts on the surface interfacial tension and CMC of surfactants and noted that all the salts used produced shifts in the CMC to lower concentrations and reduced the surface interfacial tensions of air–surfactant solution and liquid paraffin–surfactant solution. No appreciable difference was observed when air was substituted for liquid paraffin as the upper phase, indicating that the hydrocarbon layer exerts no pressure effects. Shifts in the CMC were related to the valency of the gegenion, with a divalent gegenion producing a shift much greater than a monovalent gegenion. The CMC of cetomacrogol 1000 was practically unaffected by the addition of salt, and the extent of interfacial tension reduction was small with respect to salt concentration when compared with corresponding systems containing ionic surfactants.

Table XXIII provides additional references on micelle studies.

Adsorption Studies—The adsorption of cyanocobalamin on talc is remarkably repressed by polyvinylpyrrolidone (PVP); this phenomenon is due to the preferential adsorption of PVP by talc and not to any direct interaction between PVP and cyanocobalamin (874). Study of the sorption characteristics of cationic surface-active agents by a polyamide (nylon 6,6) showed that maximum sorption occurs in the region of the CMC of the surface-active agent. It was theorized that the hydrophobic moiety of benzalkonium chloride, a cation, interacts with the nonspecific sites in the hydrocarbon units of the polyamide (875). The surface behavior of aqueous dispersions of cholesterol was studied by microelectrophoresis and the adsorption of radiolabeled surface-active agents. Although bile salts were not greatly adsorbed on cholesterol, they did retard its crystal growth, apparently because their nuclear structure permits adsorption at those sites governing the rate of crystal growth but is too rigid to permit general adsorption at all sites and surfaces (876). The equation of state of an adsorbed film was used to derive both a more general equation of equilibrium and an analytical

Table XXIII—Additional Studies on Micelles

Reference	Topic
841	Hydrophobic and electrostatic interactions in ionic micelles, with particular reference to the problems of calculating the contribution of the monomer to the free energy
842	Determining the thermodynamics of micellization of some zwitterionic *N*-alkyl betaines using light-scattering techniques
843	Influence of structure, concentration, counterion concentration, pH, and temperature on the size and structure of bile salt micelles
844	Effect of temperature on the CMC of solutions of certain surface-active *N*-alkylpyridinium halides
845	Proposed model for treating the micelle of an ionic agent as a charged phase
846	Relationship between log CMC of certain acylcholines and the number of carbon atoms in the hydrocarbon chain
847	Effect of urea and amides on the micelle formation of anionic and cationic soaps
848	Micelle structure by fluorine magnetic resonance, with particular reference to the effect of organic additives on sodium 12,12,12-trifluorododecyl sulfate solutions
849	Employment of a fluorescein dye in a spectrophotometric determination of the CMC of some alkyldimethylbenzylammonium chorides, with varying results relative to surface tension measurements of the CMC
850	Claim for the amphiphilic nature of k-casein as the basis for its ability to stabilize micelles against aggregation
851	The reaction kinetics in certain micellar systems
852	The influence of hydrophobic hydration on the conductance and viscosity of *n*-alkylamine hydrobromides in water at 25° both above and below the CMC
853	Description of two types of micelle formation of ionically associated colloids in organic solvents in which the micelle core is either hydrocarbon or aqueous, depending on the solvents used
854	Solubilizing effect of binary systems of ionic surface-active agents, ascribed to the formation of mixed micelles with oleophilic properties different from those of the original components
855	The thermodynamics of micelle formation
856	Review of the interaction between nonionic surface-active agents and water, with particular emphasis on the phase behavior and the formation and thermodynamic properties of micellar solutions
857	Estimation of the degree of polydipersity of macromolecules in solution by comparing the weight average molecular weight value with the number average molecular weight value
858	The effect of sodium chloride on the micellar properties of anionic–nonionic detergents in aqueous solution
859	A light-scattering temperature-jump technique for assessing the kinetics of sodium lauryl sulfate micelle dissociation
860	Use of a stopped-flow conductance apparatus for measuring the rate of breakdown of micelles of anionic and cationic surface-active agents in solution
861	Dye solubilization and light-scattering methods for determining the CMC of sodium cholate
862	The influence of CMC on the detergent action of sodium dodecyl sulfate
863	The interaction between disperse dyes and surface-active agents below the CMC of the surfactant
864	Validity of an NMR method for the determination of the CMC of high molecular weight fatty acids and the lauryl ammonium salts of these acids in sulfuric acid and in carbon tetrachloride
865	The micellar properties of disodium monoalkyl phosphates in aqueous solutions, and the comparatively large aggregation numbers of these salts, reflecting the two dissociable groups characteristic of alkyl phosphate anions
866	The colloidal properties of mixed solutions of anionic and cationic surfactants: discrepancies between the molar concentrations obtained by the vapor pressure osmometer and the actual molar concentration, due to the formation of aggregates of several molecules at low concentration and the increase in degree of dissociation of the micelles at high concentration
867	Demonstration of an increase in the charge on the polyoxyethylene sulfate-type surfactant micelle with increasing oxyethylene content and a decrease in the degree of solubilization
868	The electrophoretic behavior of micelles of a polyether sulfate-type surfactant
869	Estimation of the micellar molecular weights of mixed surfactants using a gel filtration technique, with the observation of a linear relationship between log micellar weight and relative retention volumes of micelles at various ratios in the presence and absence of 0.1 *M* sodium chloride
870	Determination of the degree of ionic dissociation of mixed micelles in aqueous solutions of cationic and nonionic surfactants
871	The thermodynamics of micellar solutions: possible insight provided by examining the distribution ratios for the components of two equilibrium phases of certain systems of micellar solutions
872	The surface and micellar properties of long-chain nonionic surfactants
873	The aggregation of surface-active molecules to form micelles, as shown by a multiple equilibrium model which considers changes in the distribution of micelle aggregation numbers with concentration

expression for the heat of adsorption as a function of the amount adsorbed. The van der Waals equation was used to show that forces of molecular interaction on the surface of the adsorbent are generally repulsive and account for variation in the adsorption of heat with the amount adsorbed (877). Adsorption isotherms were obtained from the adsorption of methylene blue by carbon black, indicating that dye adsorption increases with increasing pH until the amount of dye adsorbed becomes constant between pH 7 and 9 (878). Based on simplified models of an adsorption system, equations were derived for estimating the role of various factors in adsorption. The relative surface activity of adsorbates which adsorb at a smooth adsorbent–liquid interface was estimated as a function of the state of distribution of molecules before adsorption, the structure of adsorption layers, the size and shape of adsorbate molecules, the orientation of adsorbate molecules in the adsorption layer, the interaction energy of adsorbate with solvent and adsorbent, and the interaction energy between adsorbate molecules (879). When large organic molecules diffuse through a multiphase matrix containing water, dispersed water-insoluble solvents, proteins, etc., they become partially immobilized by adsorption, the overall effect being a decrease in the apparent coefficient of diffusion. To differentiate the effects of sorption and free diffusion, a model was proposed which assumes a rapid, dynamic equilibrium between the diffusible and sorbed species. Fick's law is assumed to apply for the diffusing species, while the sorbed species is assumed to be immobile. Results show good agreement between the measured rate and that predicted by the model (880).

Additional references on adsorption studies are provided in Table XXIV.

Table XXIV—Additional Studies on Adsorption

Reference	Topic
881	Cation-dipole interactions in clay-organic complexes, showing that such interactions play an important role in the process of adsorption
882	The greater viscosity and higher structure of water when adsorbed onto kaolin than onto bentonite
883	History of formation and methods used to study the physical properties of natural adsorbents
884	Adsorption isotherms for dinonyl phthalate adsorbed from toluene solution by bentonite and kaolin
885	The *in vitro* resorption of sulfonamides from bentonite derivatives when the latter are incorporated into emulsion and fatty acid ointment-type bases
886	Employment of an IR method to determine the nature of water adsorbed on Wyoming bentonite
887	Interaction of water molecules with various montmorillonite surfaces
888	Adsorption of pigments from nonaqueous solutions
889	The binding of calcium and potassium ions to some polyuronides and monouronates
890	Comparison of the calculated and experimental adsorption isotherms of organic nonelectrolytes adsorbed from aqueous solution
891	Cyclic organic compounds that are adsorbed more strongly than other compounds by activated carbons
892	Employment of the Gibbs-Helmholtz equation to calculate the heat of wetting of charcoal by methanol
893	The effect of pH on the amount of phosphate ion adsorbed by fresh and aged boehmite, and the lack of such effect at very low phosphate-ion concentrations
894	Types of forces involved in particle interaction and particle–water interaction in clay–water systems
895	The cation exchange between the mobile metal cations of bentonite and some alkaloids, amino acids, sulfonamides, and quaternary ammonium and pyridinium salts
896	Adsorption isotherms of dodecyl sulfate and dodecyl amine acetate adsorbed from monazite–water systems
897	Review of crystal structure of amorphous and crystalline materials and the effect of free valences on surface adsorption
898	Reported on the reactions of phosphate with aluminum and Wyoming bentonite
899	Survey of current problems in the interpretation of data on adsorption from solution
900	The physicochemical and adsorption properties of D-cycloserine: adsorption by a strongly cross-linked sulfonated cationic resin
901	The adsorption of heavy metal cations by hectorite and its accompaniment by the removal from solution of silicic acid released by clay dissolution
902	The influence of adsorbed alkylammonium ions on the water sorption and swelling of sodium and calcium montmorillonite; decrease in the water uptake of the sodium salt, accompanied by extensive crystal swelling, with increase in the ratio of exchangeable alkyl ammonium to ammonium ions
903	Measurement of the electrophoretic mobilities of carbon black, titanium dioxide, ferric oxide, and bentonite particles in solutions of a series of sodium polyphosphates and metaphosphates
904	The static adsorption of a water-soluble polymer on natural sorbents
905	Ability of hydroxylated silica surfaces to carry two distinct types of surface hydroxyl sites
906	A multilayer theory for adsorption from solutions composed of molecules of different size
907	A parallel layer model for describing the thermodynamics of adsorption from polymer solutions
908	A phosphate-adsorption phenomenon in kaolin clays associated with exchangeable hydroxyl groups in the clay crystal
909	Adsorbed molecules which may either be localized or move freely along the adsorbing surface
910	Report on the interaction of clay–water systems as affected by hydrous aluminum oxide films
911	Classification of water vapor sorption isotherms of various solids with respect to the mechanism of water binding, chemical composition, and physical structure of the sorbents
912	The adsorption of carbon dioxide by alumina using IR and isotherm measurements
913	The acid character of montmorillonite as shown by titration curves in water and some nonaqueous solvents; the presence of aluminum ions at the edges of the clay crystal as an explanation of their weakly acidic character
914	A statistical theory of adsorption based on the reverse expansion method
915	Review of the progress of adsorption studies
916	Some of the essential features of adsorption isotherms of binary liquid solutions of low molecular weight nonelectrolytes at the liquid–vapor and solid–liquid interfaces
917	Correlation of the adsorption affinity of organic substances with their acid–base properties; the contribution of steric factors and molecular polarizability
918	Equation for the adsorption of two different adsorbates on the same adsorbent under different conditions
919	Use of the reactivity of magnesium- and calcium-saturated montmorillonite surfaces for studying the adsorption of organic amines and pyridines
920	An equilibrium theory of the kaolinite–water system at low moisture contents, with some remarks concerning adsorption hysteresis
921	The influence of a presorbed anionic surfactant on the sorption of a cationic surfactant by hair
922	The evaporation resistance and interaction of (polymethylvinyl ether/maleic anhydride) with plasticizers

Surface Area and Porosity Studies—Giles and Trivedi (923) described a rapid semimicro method for the determination of the specific surface of solids by dye adsorption. The method utilizes known volumes of solutions of rated concentrations, with which the solid is shaken and the adsorbed weight determined by analysis. From these data the adsorption isotherm is plotted, the level of the plateau representing the amount of dye in a complete monolayer on the surface. The authors have successfully used microporous silica, alumina, and graphite as solid adsorbents. The theory of multilayer adsorption on solid adsorbents was statistically and mechanically formulated by taking into account the lateral attractions between adsorbate models. The theory was generalized to a mobile adsorption on flat, homogeneous surfaces (924). Henson and Hunter (925) presented criteria for determining the best setting of relative pressures at which to conduct adsorption determinations so that a good estimation of the capacity and surface area of the monolayer can be obtained. Experiments were selected by maximizing a function of partial derivatives of equations at specific values of the parameters. *p*-Nitrophenol in water or in benzene solution and several dyes were used to measure the apparent specific surface of porous charcoals, silicas, and alumina by adsorption. The results reveal a relation between the apparent surface and pore size distribution (926). An apparatus was developed for B.E.T.-type adsorption measurements for surface area determinations. The apparatus is purported to expedite the measuring process and the evaluation of the resulting data (927). An air-permeability method compared favorably with the B.E.T. method for determining specific surface areas, owing to the smaller surface microporosity, but the calculated average particle diameters only

roughly coincided with those from microscopic measurements (928). Conductometric titration of clay suspensions with dodecylamine hydrochloride solutions was presented as a rapid method for the determination of surface area of clay particles suspended in aqueous media (929). A critical examination of the different methods proposed for the measurement of surface area of solids led to the development of a differential volumetric measurement technique (930).

Diffuse (Electrical) Double-Layer Studies—Jones (931) reported on the relation between surface charge density and the double-layer potential of soap films. With the aid of the Gouy-Chapman theory of double-layer potential, surface charge density, and electrolyte concentration in liquid films, it was shown to be more realistic for systems to behave as though characterized by constant surface charge density than by constant potential. Conway and Gordon (932) directed attention to some of the problems arising in the treatment of the double layer which can usefully be considered in light of similar or related problems regarding ionic solutions. They provided a table which compares the problems observed under conditions of ionic equilibrium with those observed in double-layer systems. Becher (933) published an excellent review on the theory of the electrical double layer, including a complete solution of the case of the diffuse double layer for an infinite flat plane. The effect of adsorption, ionic strength, and pH on the potential of the diffuse electric layer was described (934), along with an evaluation of the electrical double layer on silica in the presence of bivalent counterions such as magnesium, calcium, and barium (935). Electrophoretic measurements were made of micelles of dimethyldodecylamine oxide and betadodecylaminopropionic acid in 0.1 *M* sodium chloride solutions of varying pH. The electrical double layer around the micelle at different pH values was then constructed according to the Stern theory (936).

Foam Studies—The effect of electrolytes on the foam stability of aqueous solutions of nonionic surfactants was discussed (937). A study was made of the relation between the initial foam height, as measured by the Ross-Miles test, and such factors as concentration of the surfactant, CMC of the solute, surface tension of the solution, surface area of the foam, and the work involved in the production of the foam surface (938). Ranny (939) reported that optimum foam volume and stability were achieved with surfactants having long, straight carbon chains with the hydrophilic groups at one end. Shifting of the hydrophilic groups toward the middle of the chain decreased the stability of the foam.

General Studies on Colloids, Gels, and Sols—A silver iodide sol, when coagulated by aluminum sulfate in solutions acidified with sulfuric acid, showed an increase in the critical coagulation concentration with a decrease in the pH. This result, which was attributed to the formation of an $AlSO_4^+$ complex, indicated that the antagonistic effect observed when coagulation is carried out with pairs of electrolytes may be entirely due to counterion complexing (940). Napper (941) considered the stabilization of colloids by nonionic hydrophilic macromolecules to be steric. The stability of ion-stabilized colloids in the presence of surfactants was reported; according to this concept, the stability of the sol depends on the recession of the electrical double layer and the thickening of the adsorbed film of soap on the particles, a process which lowers the molecular forces between them (942). Dukhin and Stoilov (943) critically reviewed the three most frequently used methods for determining the permanent dipole moment of anisodiametric colloid particles. A method was reported for modifying the texture of aluminum phosphate gel by thermal treatment (944), and a description was given of a procedure for incorporating oils into transparent gels without the development of haze during storage (945). By studying the colloidal stability of silver iodide at levels far above the coagulation concentration, it was shown that sols do not restabilize at salt concentrations up to 3 *M*, even though a repulsive force can exist at such levels (946). Current views on the stability of colloidal solutions were discussed, along with approaches to stabilizing these systems (947).

Studies on General Properties of Surface-Active Agents—A comparison of HLB values according to two prevailing systems was made for two classes of nonionic surfactants, namely, the ethylene oxide adducts of *n*-dodecanol and of branched nonylphenol with increasing degrees of polyoxyethylation. The two systems were shown to differ fundamentally in that only one treats the HLB value as constitutive and additive. For both HLB systems, simple relationships were found between the HLB values of each class of surfactants and their critical micelle concentrations. These relationships have different forms for the two systems and, within the same system, different numerical values for the two classes of surfactants (948). Schott (949) compared the cloud points of 165 nonionic surfactants, based on their calculated HLB values. Increasing length of the polyoxyethylene moiety increased the HLB and cloud points. The equations for calculating the HLB, which had been derived from emulsification experiments, contained the weight-percentage of polyoxyethylene as the sole variable characterizing the surfactant. Therefore, the calculated HLB was not affected by the surfactant characteristics, which largely govern the values of cloud point, CMC, and interfacial tension. Additional HLB measurements would be needed to determine whether all experimental HLB values are really independent of the structure of the surfactant molecules, as proposed. The properties of sodium alkane (C_{13} to C_{19}) sulfonates were determined and shown to be highly dependent on their molecular weight (950). While studying the turbidity point of nonionic surfactants, it was noted that the length of the hydrophobic alkyl group influences the cloud point, contrary to the dehydration theory, which assumes clouding to be due to the hydrated ether groups of the surfactant (951). A change was observed in the physical and chemical properties of surface-active semicolloid solutions after magnetic field treatment. Concentration of surfactant above the CMC, by destroying micelles, caused an increase in the amount of the ionic form of the surfactant and, consequently, an increase in conductance and decrease in surface tension (952). Felmeister and Schaubman (953) reported on studies in which a monomolecular film of dipalmitoyl lecithin was spread on an aqueous phase into which a

Table XXV—Additional Studies on General Properties of Surface-Active Agents

Reference	Topic
957	The solubilization of a three-component system of liquid paraffin, water, and nonionic surfactant, showing that structure and number of ethylene oxide molecules affect the solubilizing power of the surfactant
958	Interaction between *p*-aminoazobenzene and anionic surfactants
959	The influence of *N*-methylacetamide and urea on the properties of surfactants in aqueous solutions
960	The effect of alkyl-chain structure on the physicochemical properties of sulfate-type and ether sulfate-type surfactants
961	The surfactant properties of hydroxylated sulfonated esters of various fatty acids, showing the generally superior properties of the unsaturated acids relative to the saturated fatty acids
962	The coalescence of a liquid drop at the liquid–liquid interface, and the effect of surface-active agents
963	The rate of formation of a monolayer on a drop of water from the vapor and dispersed phases of surface-active agents
964	The structure–activity relationships of nonionic and anionic surfactants
965	Biodegradability of alkyl benzene sulfonates and alkyl sulfates
966	Hydrolytic stability of ester-type nonionic surfactants; the near-constancy of log k between pH 4 and 6 and its proportionality to hydrogen-ion concentration or hydroxyl-ion concentration outside these pH limits
967	Criteria for surface-active agents which have emulsifying capacity
968	The concept of permeability number to define the permeation character of "intestinosolvent" coating materials
969	Synthesis and study of the properties of polyethylene glycol ethers of C_9 to C_{18} fatty alcohols
970	The composition and elasticity of thin-liquid films drawn from solutions containing sodium decanesulfonate and varying amounts of dodecanol pentaethyleneglycol ether
971	Review of the trends in types and uses of soaps
972	Basic values and typical properties of various surfactants and detergents

photosensitive phenothiazine drug was dissolved. The system was then exposed to UV radiation, and the resultant changes indicated that substitution in the 2-position of the phenothiazine nucleus is critical in the photosensitized interaction. In a similar study, the same authors proposed a relationship between the increase in surface activity induced by irradiating a drug and its *in vivo* photosensitizing properties (954). ζ-Potential measurements were made of plasma, bile, and solutions of albumin, calcium, and sodium chloride in order to evaluate their effect on the net surface charge of suspended particles (955). To test the validity of ζ-potential as a determining factor in the stability of colloidal systems, and the possibility that electrolytes might change the electrophoretic properties of colloid particles by their influence on ζ-potential and solution ionic strength, the electrophoretic mobility of suspensions of solid emulsion particles of paraffin with stearic acid, using petroleum spirit as a spreading solvent, was studied as a function of salt concentration. The electrophoretic mobilities were strongly influenced by the nature of the counterion, making it necessary to modify the equations expressing the effect of decrease of repulsion potential attributed to a hydration barrier (956).

Additional studies on general properties of surface-active agents are provided in Table XXV.

Crystallization—Lin and Lachman (973) reported that different crystal forms were obtained on dissolution and recrystallization of a new antihypertensive agent, as determined by X-ray diffraction, IR, and photomicrographs. A method was developed, based on dissolution rates, for estimating the ratio of crystalline drug to that dispersed at the molecular level within a carrier. Under appropriately chosen conditions in the two diverse systems, the dissolution rate of the drug was linearly related to its degree of crystallinity (974). Methods of preparation and characterization of two crystal forms of sulfathiazole, using differential scanning calorimetry and IR spectroscopy, were presented. The transition temperature depended on the rate of heating and the sample source. Interconversion of the crystal forms under different conditions, such as heating and suspension in water, was described. An assay procedure was devised, based on the area of the thermal transition peak of Form I, and results of analysis of synthetic mixtures of Forms I and II were given (975). To obtain basic data on crystallization of the molecular compound of aminopyrine and baribital from aqueous solution, the diagram of the ternary system aminopyrine–barbital–water was studied in the temperature range 0–98°. The molecular compound was best obtained by using an excess of aminopyrine and by crystallizing from concentrated solution at high temperature (976). Marshall and Nancollas (977) investigated the kinetics of crystal growth of dicalcium phosphate dihydrate and showed that, after a brief initial surge, the rate of growth of crystals follows a second-order rate, with respect to calcium and biphosphate concentration, over a wide range of calcium and phosphate concentration, suggesting a predominantly surface-reaction controlled process.

Similarly, the kinetics of calcium sulfate precipitation from aqueous supersaturated solutions containing gelatin or sodium carboxymethylcellulose were studied. The rate of precipitation was shown to depend upon the rate of conglomeration of the calcium sulfate colloidal particles present in the system. Gelatin and sodium carboxymethylcellulose concentration and pH all affect the kinetics. Above the isoelectric point, gelatin slows down precipitation, but below this point the precipitation is accelerated. The negatively charged carboxymethylcellulose stabilized the system and was more effective than gelatin in this regard (978). Phenobarbital can be freed of impurities, especially occluded mother liquor, by controlled crystallization (979). The aging of an aqueous suspension of amorphous aluminum hydroxide was followed in a simple dilatometer. Initially, an increase in volume was observed, and the simultaneous development of pseudoboehmite was revealed by X-ray diffraction. The subsequent formation of a trihydroxide was accompanied by a decrease in volume. Rheological measurements showed that the formation of pseudoboehmite through a condensation polymerization process was accompanied by gelation. The gel structure could eventually hinder the growth of pseudoboehmite particles, with a consequent discontinuity in the kinetics of the process (980).

Rheology—Rheological studies of triethanolamine–bentonite gels revealed their typical thixotropic characteristics (981). By postulating that thermodynamic transportation coefficients may be related to the friction that occurs in viscous flow, a relation between the viscosity and the intradiffusion coefficient was obtained for multicomponent systems (982). Several proposed mechanisms of thixotropic behavior of montmorillonite–water systems were evaluated and the effects of temperature, reshearing, concentration, and storage time on these systems were studied by NMR and rheological measurements. The specific parameters used were the change in line width of the NMR spectrum and the static yield values obtained from the rheograms. The results were in complete agreement with the theory that the colloidal particles, upon contact, adhere to form a spacious matrix resembling a house of cards (983).

Additional studies on rheology are provided in Table XXVI.

Table XXVI—Additional Studies on Rheology

Reference	Topic
984	Optimum method and suggested criteria for evaluating the thixotropy of macromolecular gels
985	Rheological characteristics and sedimentation rates of kaolinite suspensions
986	Use of ointments and pastes to determine static lower plastic-flow limits with the extensometer balance
987	Characteristics of kaolin suspensions, which are Newtonian at low concentrations, pseudoplastic at medium concentrations, and plastic at high concentrations, with thixotropy appearing at the yield point
988	Preparation of microemulsions of Spans (surface-active agents) and Tweens (polysorbates) in benzene and water and determination of their viscosities
989	Determination of the rheological properties of foam stabilizers with a canal viscometer which provides absolute values of surface shear viscosity and yield strength
990	Determination of the physicochemical properties of gels by rheological and thermal analysis
991	Comparison of the rheological properties of bentonite-based salves with petrolatum-based salves by means of a pendulum consistometer
992	Flow properties and hysteresis behavior of oily gelatinous preparations containing liquid paraffin, stearic acid, polyethylene glycols, petrolatum, stearyl alcohol, paraffin wax, and palmitic acid
993	The rheological behavior of kaolinitic clay in the presence of sodium salts of organic acids
994	The rheological characteristics of the kaolin–polyelectrolyte interaction
995	The influence of complex anions on the rheological properties of kaolinitic clay

PHARMACEUTICAL ASPECTS

Radiopharmaceuticals—Spencer *et al.* (996) demonstrated that, in man, aluminum phosphate gel reduces the absorption of radiostrontium by 85% and the absorption of radiocalcium by only 38%. Vertua (997) reviewed the theoretical concepts and applications of radioisotopes in pharmacology. Another article reviewed the compounds which protect against radiation and discussed possible mechanisms (998). Another described radioactive medicinal substances (999).

Antibiotics—In reviewing the chemical aspects of penicillin allergy, Schwartz (1000) discussed the biochemical basis of drug allergy and the antigenic determinants of penicillin allergy and penicillin metabolism. He concluded that more work should be directed toward defining degradation products, their rate of formation, and their ability to react with protein. Benzyl penicillin and 6-APA were shown to contain small but significant amounts of high molecular weight protein impurities attached to penicilloyl groups. These impurities stimulate formation of the antibodies with penicilloyl specificity that may be responsible for penicillin allergies (1001). The amphoteric penicillins, ampicillin and cyclacillin, possess properties similar to the alicyclacillinphatic amino acids. At a pH equal to the isoelectric point, they exist essentially as zwitterions, and in this form are most stable and least soluble in water. The aqueous solubility of ampicillin changes only slightly with a change in ionic strength, unless a nonpolar solvent is added. In water at 25° the carboxyl groups of all penicillins appear to have the same pK_1, while the amino groups of the amphoteric penicillins vary in the pK_2 values over a wide range, probably being influenced by the adjacent side-chain groups. A change in the dielectric constant affects the pK_1 more than the pK_2, while a change in temperature does the opposite (1002). Cyclacillin (WY-4508) was shown to have more selective *in vitro* activity than ampicillin against a variety of Gram-positive and Gram-negative organisms. Rapid absorption follows oral administration of this new antibiotic, with 44% renal excretion in 24 hr. (1003). Lincomycin-2-phosphate was inactive in a plate antibacterial assay using *Sarcina lutea*, although *in vivo* the phosphate ester is as active as the parent compound, lincomycin, in mice infected with *Staphylococcus aureus*. The ester gave slightly higher blood levels than the parent compound upon oral adminstration to dogs. In addition, the ester has a less bitter taste than the parent compound (1004). Compared with tetracycline, doxycycline has equal or better *in vitro* activity against a wide range of organisms. A greater lipid solubility and a greater degree of binding to serum protein was also noted for doxycycline (1005). The bactericidal activity of various deoxystreptamine antibiotics was tested against a large number of organisms *in vitro* and in mice. Good correlation was seen between the *in vivo* and *in vitro* activity (1006). Fifteen salts of erythromycin were prepared and their relative water solubilities and bitterness levels measured. The water solubilities were found to be related to the size of the alkyl group attached to the acid. The level of bitterness, however, was related not only to the size of the alkyl group but also to the stability of the salt, which was shown to be a function of the strength of the acid used to prepare it. The least bitter salt was the stearyl sulfate (1007). As shown by experiments using two antibiotics against *Escherichia coli* in the guinea pig, bacterial kinetics can be divided into a bacteriostatic phase, a rapid bactericidal phase, and a slow bactericidal phase. At high antibiotic levels the first phase slows, while the second phase intensifies. The same results were obtained *in vivo* and *in vitro* (1008). Cephalexin and cephaloglycine were tested for activity against a large number of pathogens *in vitro*. Both antibiotics were rapidly ab-

Table XXVII—Additional Studies on Antibiotics

Reference	Topic
1017	Relation between bacterial production of penicillinase and sensitivity to Penbritin (ampicillin)
1018	Emergence of *Pseudomonas aeruginosa* strains highly resistant to carbenicillin
1019	Greater effectiveness of colistin and polymyxin B than gentamicin against certain strains of *P. aeruginosa*
1020	Increase in resistance of *Bacillus subtilis* strains to oxytetracycline as the cause of its increased resistance to tetracycline, chlortetracycline, and penicillin
1021	Review of bacterial resistance to penicillins and cephalosporins
1022	Review of the physicochemical aspects of chelation and the role of chelation in antibiotic actions
1023	Review of the chemistry and production of antibiotics by several *Bacillus* and *Streptomyces* species
1024	Review of the use of polyelectrolytes as flocculants in fermentation broths of antibiotics, including mathematical equations for adsorption of flocculants and filtration of flocculated suspensions
1025	The mechanism of action of certain antibiotics in relation to protein synthesis
1026	Review of the use of chloramphenicol in ophthalmology
1027	Review of tyrothricin, gramicidin, bacitracin, polymyxin, colistin, and viomycin
1028	Review of the progress in antibiotics between 1945 and 1965
1029	Review of penicillins
1030	Suggested use of a blue dye to assure that a seed layer containing the test organism has been added to a base layer in microbiological assays by agar plate methods
1031	Investigation of the *in vivo* concentration and comparative *in vitro* sensitivity of some strains of staphylococci to dicloxacillin
1032	Report on the *in vitro* and *in vivo* activity of oxolinic acid, noting that its spectrum and primary activity against Gram-negative bacteria are similar to those of nalidixic acid
1033	The antituberculotic activity of tuberactin
1034	Correlation of the *in vitro* activity of gentamicin with that of other antibiotics
1035	Effect of chemical structure on polypeptide synthesis and miscoding activity of antibiotics
1036	Halomicin, a new micromonospora-produced antibiotic
1037	Limited activity of carbenicillin against resistant staphylococci and its special effectiveness against Gram-negative bacteria such as *Pseudomonas* and *Proteus* species
1038	Human pharmacodynamic studies with rifamycin and its role in interference with the bilirubin cycle
1039	Bacteriologic properties of rifamycin
1040	Antimicrobial activity and pharmcological behavior of cephaloglycine
1041	High *in vitro* antibacterial activity of furazolium chloride
1042	Antibacterial activities of a number of penicillin amide derivatives against penicillin-sensitive and penicillin-resistant organisms
1043	Comparative *in vivo* antibacterial activity of benzylpenicillin and penicillin dipeptides
1044	Review of the spectrum and activity of lincomycin
1045	Resistance of all *Clostridium perfringens* strains to therapeutic doses of various antibiotics
1046	Susceptibility of staphyloccci to new antimicrobial agents
1047	Comparative *in vitro* antibacterial activities of 7-chloro-7-deoxylincomycin, lincomycin, and erythromycin
1048	Lincomycin and clinimycin: comparative absorption, excretion, and antibacterial activity *in vitro;* the superior absorption properties of clinimycin
1049	Demonstration of synergy by competitive inhibition of β-lactamase in *P. aeruginosa*, using various combinations of benzylpenicillin, methicillin, and cloxacillin
1050	Therapeutic synergistic activity of ampicillin and cloxacillin, and the protective effect of cloxacillin on enzymic degradation of ampicillin by penicillinase
1051	Doxycycline, an antibiotic which resembles tetracycline in antibacterial spectrum but which is two to four times more potent *in vitro* and more stable to pH change
1052	Synthesis and *in vitro* fungistatic activity of some *N*-substituted amides and amine salts of sorbic acid

sorbed and excreted in the urine, with the absorption being delayed by food. Serum levels were shown to be higher when the agents were administered with probenecid (1009). The bactericidal action of chloramphenicol and streptomycin was tested on sensitive strains of *E. coli* and *S. aureus*. With a short contact time, chloramphenicol was completely inactive, but as the contact time increased so did its bactericidal activity. Streptomycin had a strong bactericidal action (1010). The plasma concentration curve for bamifylline after oral adminstration was similar to that obtained after i.v. administration of the same dose. The drug is rapidly excreted in the urine and follows two metabolic routes of degradation (1011). Koyama *et al.* (1012) described the configuration of viomycidine, as determined by X-ray diffraction. A review of various tetracyclines was published, including their absorption, excretion, distribution in the body, and daily dosage (1013). The apparent partition coefficients between *n*-octyl alcohol and aqueous buffers were determined for several tetracyclines. Using microscopic dissociation constants for tetracycline, the relative amounts of each microscopic ionic form of tetracycline theoretically present at each pH were calculated. The zwitterionic form, which was present in the highest concentration in the pH range from 4 to 7, appeared to be the most lipid-soluble form, its reduced polarity possibly resulting from an intramolecular type of ion-pair formation. The possible relationships between the biological activity of the various tetracycline analogs and their pH–octanol solubility profiles were discussed (1014). Carbenicillin-resistant variants obtained from each of eight strains of *Pseudomonas aeruginosa* were tested by growing inoculum on agar plates containing carbenicillin. The resistant variants resembled the parent strains in cultural appearance, pigment production, and virulence for mice (1015). The surface tension of 21 antibiotic compounds was correlated with their antibacterial activity *in vitro*. It was noted that the compounds with the lowest surface tension had the highest antibacterial activity (1016).

Additional studies on antibiotics are listed in Table XXVII.

BIOPHARMACEUTICS

A thorough review of biopharmaceutics was presented by Garrett and Araujo (1053). Also published during the year were reviews on drug–response evaluations, empirical equations for correlating the biological efficiency of organic compounds, and test models for

evaluating the chemotherapeutic effectiveness of drugs (1054–1056). Drug absorption, distribution, and excretion were reviewed, and, in particular, the metabolic fate of chlorpropamide, diphenylhydantoin, and hetacillin (1057–1061). The clinical effectiveness of hetacillin was shown to be due to its conversion to ampicillin (1062).

Reports were given describing the species differences in the metabolism of diazepam, apomorphine, sulfisomidine and sulfamethomidine, sulfadimethoxine, and phenacetylurea, and pharmacological response in general was discussed (1063–1071). Also studied were the effects of species differences on the binding of drugs to plasma protein (1072–1074). The effects of age and sex on drug metabolism were reported (1075–1077).

Effects of Physicochemical Properties—The various physical and chemical factors affecting drug absorption, availability, and therapeutic response in general were reviewed (1078–1083).

Two polymorphic forms of aspirin were prepared by Tawashi (1084) and shown to be thermodynamically different, based on their differential thermal analysis, thermogravimetric analysis, and dissolution rates. Form II, the most thermodynamically unstable, gave blood serum salicylate levels 70% higher than Form I for the same time period. The urinary excretion of ethylamphetamine and its metabolite, amphetamine, was studied in man after oral administration of the (+), (−), and (±) isomers of ethylamphetamine hydrochloride. The rate of excretion of these amines is dependent on the pH of the urine. At acid values, the (+) isomer is metabolized faster and to a greater extent than the (−) isomer, which is excreted mostly unchanged (1085). Similar results were shown for the influence of urinary pH on the rate of excretion of *l*-adamantanamine (1086). Partition coefficients in *n*-heptane–sodium hydroxide or HCl were determined for a series of amines and acids, and a linear relation was found between the chain length and the log of the partition coefficient. Alkyl chain length was linear with buccal absorption of certain amphetamines and fenfluramines when they were 1% nonionized. Similarly, there was a linear relation between the logs of the partition coefficients and buccal absorption of the amines and acids when these compounds were 1 and 10% nonionized. When the amines and the acids had similar partition coefficients, their buccal absorption was similar over a pH range of 4 to 9. *n*-Heptane was considered equivalent in solvent properties to the buccal lipid membrane for the compounds used in the test (1087).

The phenomenon of displacing one drug from a plasma-binding site with another drug continues to be of interest. Solomon (1088) advised that concurrent therapy with two compounds which bind to protein should always be undertaken with caution, since many drugs appear to compete for a common binding site. Data on the extent of binding of a drug to albumin and its rate of metabolism in man are of great value in predicting whether it will displace other compounds from binding sites on albumin. The effect of caffeine on the gastric absorption of nonabsorbable drugs such as sulfathiazole and *p*-aminobenzoic acid was studied in rabbits. While caffeine enhanced the gastric absorption of *p*-aminobenzoic acid, it had no effect on the rate of absorption of sulfathiazole, probably because of the negligible complex this compound forms with it at gastric pH (1089). Similar studies involving the competition between digitoxin and other drugs in their interaction with serum proteins were published (1090–1092).

The affinity of certain drugs for plasma protein and the resulting effect of this binding on drug absorption were extensively studied. Jusko and Levy (1093) indicated that the interaction between riboflavin and albumin is nonionic, but that electrostatic forces contribute appreciably to the binding of riboflavin-5-phosphate to albumin. Salicylates, when added to saliva, are bound to the saliva proteins to the extent of 35–50% after a contact time of 0.5–2 hr. at 37° (1094). The partitioning of bishydroxycoumarin from rat plasma to an organic solvent phase was found to decrease with increasing drug concentration to a minimum value and then to increase as the concentration was further increased. The same type of profile was observed in the partitioning of the drug from rat plasma to the liver, both *in vitro* and *in vivo*. These results demonstrate the unusual concentration dependence of the plasma protein binding of bishydroxycoumarin, the pronounced effect of the binding on the distribution of the drug, and the effect of the distribution on elimination (1095). The markedly greater affinity of digitoxin than digoxin for serum albumin is reflected in the higher plasma concentrations, lower rate of urinary excretion, and longer half-time of digitoxin when the compounds are administered to man (1096).

Additional studies describing the influence of physicochemical properties on drug absorption are provided in Table XXVIII.

Effects of Formulation—Schneller (1144), in describing the hazard of therapeutic nonequivalency of drug products, cited published examples whereby a given chemical entity showed different blood levels depending on the dosage formulation. He concluded that every manufacturer, before distributing any new or modified product, should be obligated to perform tests which are appropriate and sufficient to demonstrate the clinical safety and efficacy claimed for it. In the absence of such tests, it cannot be assumed that the product will prove clinically acceptable simply because an apparently identical product has already been marketed. Schamberg's (1145) review indicated that different drug formulations containing the same kinds and amounts of active ingredients may differ appreciably in their effect and cannot be considered therapeutically equivalent. In a similar vein, it was suggested that attempts be made to establish the therapeutic availability of dosage forms used in clinical trials and that outlined details of the formulations utilized be included in published reports of clinical comparisons of drugs (1146). Another review article described the importance of dissolution rates and the pitfalls of dissolution methods for chemical substances as well as drug products (1147). The solubilities and absorption rates of the active compounds in pharmaceuticals are known to be affected by the technological factors of manufacturing (1148). The fast, medium, and slow *in vitro* dissolution rates of three

Table XXVIII—Additional Studies of the Influence of Physicochemical Properties on Drug Absorption

Reference	Topic
1097	Direct pH dependence of benactyzine absorption and lack of pH dependence of procaine amide absorption from isolated rat ileum
1098	Charge density and superdelocalization: suggested relationship to partition coefficients and maximum biological response
1099	Extent of molecular interaction between carbazochrome or nitrotinamide and various other drugs; effect of the difference between the rate of absorption of the drug and that of the complexing drug on the absorption of the complex
1100	Enhancement in absorption of certain drugs by complex formation
1101	Investigation of the relationship between the excretion ratio (saliva/blood level) of various sulfa drugs and their binding rate with plasma protein
1102	The low level of carbenicillin and its failure to influence bactericidal activity
1103	Correlation between the absorption of barbituric acid derivatives from the small rat intestine and their binding to the mucosa
1104	Relationship between the lipid solubility, tissue binding, and metabolism of xanthine derivatives and their passage into the brain and the cerebrospinal fluid
1105	The unchanged activity of phenylbutazone in the presence of serum and the sharp decrease in serum activity produced by indomethacin and deoxycholic acid
1106	Significant reduction of coronary dilational properties of dipyrimidole by binding to human plasma
1107	Increase in albumin concentration of promazine by binding to bovine serum albumin
1108	Antibiotic binding to albumin, as reflected by decrease in activity in the presence of this protein
1109	Sex differences in binding of pentobarbital to plasma: the more extensive plasma binding capacity in the female than the male rat, despite similar fractions of drug bound in either sex
1110	Effect of structure and added electrolytes on the binding of unconjugated and conjugated bile salt anions to cholestyramine
1111	Appreciable binding of betamethasone, dexamethasone, and cortisol to cow, dog, and rat plasma protein
1112	Report on the binding capacity of serum protein for cardiac glycosides, especially pengitoxin
1113	Binding of various tricyclic antidepressants to human plasma, and the effects of other drugs thereon
1114	Possible mechanism for the loose binding of iron to protein: a molecular bridge susceptible to irreversible cleavage by EDTA–acetate buffer
1115	Optical methods of describing the interaction of phenylbutazone and its analog with human serum albumin
1116	Comprehensive table of number of sites and binding constants for complex formation between bovine serum albumin and aliphatic sulfates and sulfonates, aromatic sulfonates, naphtholates, and phenolates, generalized as to the relationship between ligand properties and free energy of binding
1117	Effect of pH on vitamin B_{12} binding capacity of the intrinsic factor
1118	Effect of plasma binding of radioactive iodine pharmaceuticals on their renal clearance
1119	The binding of salicylates to serum proteins
1120	Effect of salicylate concentration on the binding to bovine serum albumin at pH 7.4
1121	Binding of taurinophenetidine to rabbit serum protein *in vivo* and *in vitro*
1122	Possible inverse relationship between the number of albumin-bound molecules of salicylic acid and sulfanilamide and the molar concentration of the albumin
1123	Evidence to support the hypothesis that tryptamine and its relatives bind to nucleic acids mainly by intercalation, similar to the binding of LSD to DNA
1124	Inhibition of the proteolytic activity of trypsin by its binding to organic mercury compounds
1125	Suggested existence of a hydrogen bond of the type O—H···S in barium thiosulfate monohydrate and the importance of such a bond to the consideration of hydrogen bonding in biological systems
1126	Similarity of the *in vitro* transacetylation between aspirin and human albumin to that which occurs *in vivo*
1127	Linear relationship between the percent buccal absorption and alkyl chain length of a series of *p-n*-alkyl phenylacetic acids
1128	Increase in antibacterial activity of fluorophenols with increase in the number of substituent fluorine atoms
1129	Relation between structure and antimicrobial activity of aminosteroids
1130	Steric parameters used to describe the structure–activity relationships for certain monoamine oxidase inhibitors and antihistamines
1131, 1132	Structure–activity relationships of sulfonamide carbonic anhydrase inhibitors
1133	Quantification and prediction of the biological activity of *meta*- and *para*-substituted *N*-phenylsulfanilamides by microbialkinetics
1134	Multiple-parameter approaches to structure–activity relationships
1135	Homolytic constants that give a better structure–activity correlation for chloramphenicol derivatives than either the usual Hammett constant or polarizability constants
1136	The use of substituent constants and regression analysis in the study of structure–activity relationships
1137	Comparison of the parameters currently used in the study of structure–activity relationships
1138	Increase in anti-inflammatory activity of a number of carboxylic acid derivatives of phenothiazine by substitution of an acetic group on the nucleus, particularly at Position 2
1139	Suggested essential dependence of partition coefficient and biological activity of substituted benzene derivatives on molecular electronic conditions
1140	Contribution of the phytyl side chain of *dl*-α-tocopherol to its biological activity in rabbits and its enhancement by the presence of an intact 5-methyl group
1141	Review of the significance and limitations of various biological drug parameters used for studying structure–activity relationships
1142	Influence of α- and β-methylation of the ethylenic group in the procaine molecule on its physical and chemical properties
1143	Relationship between chemical structure and activity in a series of halosubstituted 4-quinazolones

sulfamethazine tablet formulations were correlated with the *in vivo* blood level data. A significant statistical difference existed for areas under the blood level curves and for maximum blood concentration of sulfamethazine when the fast-dissolving formulation was compared with the slow-dissolving formulation (1149). Using *in vitro* techniques, the penetration of ^{14}C-labeled fluocinolone acetonide and its acetate ester through human skin at 37° was examined with vehicle mixtures of isopropanol and isopropyl myristate or propylene glycol. Little penetration was found with either of the nonvolatile solvents. As the formulation was changed to include increasing amounts of a volatile component, however, the penetration was increased up to 8 to 10 times. Precipitation of steroid prevented greater increases (1150). Results were presented which showed that two oral dosage forms of nitrofurantoin, microcrystalline drug in a tablet and macrocrystalline drug in

Table XXIX—Additional Studies on the Effects of Formulation on Drug Availability

Reference	Topic
1158	Correlation between *in vitro* release of labeled dexamethasone from nonaqueous vehicles and its *in vivo* penetration
1159	Addition of antacids to aspirin tablets as a method of reducing injury to the gastrointestinal mucosa by shortening the time of contact without simultaneously increasing the area of contact with drug
1160	Prevention or significant reduction of aspirin-induced occult gastrointestinal blood loss by use of sufficiently buffered solutions
1161	Formulation factors affecting blood concentration of *p*-aminosalicylic acid
1162	Review of the adjuvant effects, particle size, and form of drug for optimum resorption
1163	Effect of vehicles on percutaneous absorption of fatty acid esters of pyridoxine: enzymatic hydrolysis during permeation through the skin as the rate-limiting process for percutaneous absorption of pyridoxine 3,4-dioctanoate
1164	Review of recent developments regarding the influence of pharmaceutical formulations on therapeutic effects
1165	Essentially equal availability of six generic and brand name formulations of isoniazid
1166	Superiority of nonionized to ionized species of drugs in absorption from degenerated intestinal mucosa, except those which participate in an ionic interaction with surfactants
1167	Unsuitability of the capsule dosage form of triamterene as an alternative to the tablet dosage form
1168	Intestinal absorption of heparin: facilitation by sulfated or sulfonated surfactants
1169	Rectal absorption of pharmaceutical amines: enhancement with sodium lauryl sulfate and saccharinate anions
1170	Increased absorption of salicylic acid–polysorbate solutions by the frog, due apparently to complexation and possibly to lowered surface tension
1171	Effect of nonionic surfactants on absorption of enduracidin from muscle
1172	Polysorbate 80-induced increase in the solubility and the *in vivo* absorption of an experimental compound, SKF 33134-A, in the rat: unsuitability of urinary excretion measurements for indicating the degree of absorption
1173	Sodium taurodeoxycholate and EDTA: different mechanisms of altering membrane structure and permeability in the rat, as shown by difference in transfer of salicylamide and salicylate across the everted small intestine
1174	Increase in permeability of the everted intestine to salicylate with increase in concentration of surfactant, sodium taurodeoxycholate
1175	Evidence demonstrating that the absorption of 4-aminoantipyrine is increased in the presence of sodium taurodeoxycholate and involves a passive process whether the bile salt is present or not
1176	Increase in salicylic acid resorption with increasing concentration of surfactant from various types of ointment bases
1177	Lack of relationship between the concentration and solubility of hydrocortisone acetate in liquid vehicles and its availability to human excised skin, as shown by the effect of nonionic surface-active agents on its release
1178	Inferiority of a premarketed formulation of chloramphenical (Amphicol) to chloramphenicol (Chloromycetin) in blood levels and urinary excretion
1179	Faster absorption of solutions of theophylline than equivalent amounts of the drug administered in capsules
1180	Liberation of active substances from soft gelatin capsules *in vitro* and *in vivo*
1181	Importance of drug particle size to biological activity
1182	The occlusion potential of various ointment vehicles on percutaneous absorption
1183	Absorption of drugs from various-type suppository bases
1184	Equivalent absorption of diazepam in capsule and tablet form
1185	Doubling the absorption of obidoxime from the rat intestine by use of 1% EDTA
1186	Factors affecting drug transfer in the presence of macromolecules: viscosity as the principal factor in transfer of sodium carboxymethylcellulose and hydroxypropylcellulose, except in the presence of mucin, when drug interaction and interfacial tension also appear to be involved
1187	Effect of antacids on the *in vitro* and *in vivo* absorption of ethionamide and prothionamide in various tablet and capsule dosage forms

a capsule, were both well absorbed. However, differences were observed in the urinary recoveries and in the urinary excretion patterns between these dosage forms, which suggested a slower rate of absorption for the macrocrystals than for the microcrystals (1151). The *in vivo* absorption and *in vitro* dissolution characteristics of a commercial suspension, a commercial tablet, and an experimental tablet formulation of salicylamide were compared. The absorption of this drug was shown to be dissolution rate-dependent, and the initial *in vitro* dissolution rate in 0.1 *N* HCl correlated well with the initial absorption rates of the test dosage forms in human subjects (1152). Studies were undertaken to define the effects of the emulsion components on the absorption of heparin, as measured by clearing factor activity, and to determine the optimum composition of the emulsion. Data suggested that heparin absorption is directly related to, and may vary with, the particle size and total surface area of the oil droplets, but that the relationships presented may be unique for the particular surfactant and oil chosen for study (1153). Low concentrations of polysorbate 80 in the water significantly increased the absorption- and exsorption-rate constants of 4-aminoantipyrine in goldfish. It was concluded that polysorbate 80 enhances the transfer of the drug by a direct effect on the biologic membranes and not by interacting with it (1154). In an attempt to develop an oral dosage form of aminoxafen which would produce prolonged, stable plasma levels of total drug, an arbitrary set of *in vitro* dissolution conditions were chosen which correlated well with *in vivo* absorption rates. A one-compartment open model was used to describe the system (1155). The enhanced absorption of dextromethorphan from trichloroacetate buffers appears to be due to the increased surface activity of the dextromethorphan rather than to ion-pair formation. However, thiopental was more strongly absorbed from trichloroacetate solution than from physiologic sodium chloride solution, apparently because of the preferential binding of serum protein with trichloroacetate rather than thiopental, thus leaving more unbound thiopental available for absorption. Dialysis experiments showed the binding of 55% of the thiopental to human albumin in the presence of physiologic phosphate buffer and only 22% in the presence of trichloroacetate solution (1156). The rate of dissolution of one investigational compound

Table XXX—Additional Studies on Absorption Control and Alteration

Reference	Topic
1193	Method for estimating the biologic half-life of tetracyclines from steady-state serum level data plotted semilogarithmically against time
1194	Review of drug interactions
1195	Mechanisms of drug interactions
1196	The comparative pharmacodynamic activity of single and divided doses of benzphetamine hydrochloride
1197	Enhancement in activity of orally administered reserpine–cholanic acid coprecipitates due to reduced particle size of reserpine in the coprecipitate
1198	Theories dealing with the mathematical interpretation of competitive actions of drugs on isolated tissues
1199	Method for estimating individual drug-dosage regimens
1200	Alternative approaches in the choice of experimental designs for estimating effective doses when there is some curvature in the dose–response relationship but a linear approximation is still used
1201, 1202	Review of drug interactions according to therapeutic activity
1203	Block of renal tubular secretion of sulfinpyrazone by probenecid and its lack of significant influence on the ability of sulfinpyrazone to increase urate excretion
1204	Inhibition by dicoumarol of the intestinal absorption of D-glucose and its enhancement of the absorption of L-arabinose
1205	Increased rate of conversion of diphenylhydantoin to *p*-hydroxylphenylhydantoin in the liver as a possible reason for the increased rate of disappearance of i.v. doses after pretreatment with phenobarbital
1206	Alteration in metabolism and distribution of methotrexate by neomycin and sulfathiazole so that excretion by the intestinal route is significantly enhanced
1207	Thyroxin-accelerated and insulin-delayed absorption of isoniazid from the gastrointestinal tract
1208	Effect on membrane of chymotrypsin permeability and binding to serum proteins in enhancing the absorption of penicillin G
1209	Chymotrypsin enhancement of tetracycline blood levels
1210	Heparin-induced increase in absorption of chlortetracycline
1211	Review of the biological reactions to drugs
1212	Reduction of the serum salicylate concentration of aspirin to 50% by administration of activated charcoal
1213	Relative *in vitro* absorption by activated charcoal of a wide variety of drugs found in the home
1214	Effect of drugs on the rate of disappearance of amphetamine in rats
1215	Effect of simultaneous administration of other pharmaceuticals on the competitive inhibition of biliary excretion of antibiotics and sulfonamides
1216	The dog as an experimental model for studying interaction of drugs with bishydroxycoumarin
1217	Retardation of wound healing by oral or topical administration of sodium salicylate, prednisone, or hydrocortisone and its reversal by local application of retinoic acid
1218	Influence of cholestyramine on thyroxine absorption
1219	Effect of caffeine on the absorption of salicylic acid derivatives from the small intestine of the rat
1220	Review of various factors in the transfer of drugs across the placenta
1221	Determination of plasma salicylate levels after administration of acetylsalicylic acid and a combination of acetylsalicylic acid with ascorbic acid, which greatly increases salicylate absorption
1222	Marked increase in renal excretion of the monomethylated tricyclic antidepressants as sole clinical result of changing the acidity of the urine
1223	Possible difference in metabolism or excretion of warfarin and vitamin K, as suggested by the marked individual variation in ability to antagonize the anticoagulant effect after simultaneous administration of both drugs
1224	Therapeutic importance of the ability of fatty acids and other drugs to interfere in the binding with albumin
1225	A mathematical treatment of two-point attachment between drug and receptor site
1226	Possible role of phenylbutazone in masking the influence of methandrostenolone on plasma levels of oxyphenbutazone by displacing the steroid from binding sites on plasma protein
1227	Salicylate-induced release of L-tryptophan from its binding sites on human serum protein
1228	Phenylbutazone displacement of sulphormethoxine from its protein binding site

from tablet and capsule formulations could not be related to its *in vivo* absorption in dogs. The rate of partitioning of the drug into organic solvents and its absorption in goldfish and through human buccal membrane depended on the pH of the solution. Absorption was shown to increase with a decrease in the degree of ionization. In man, however, the dissociation constant and the elimination rate of the drug are such that high blood levels are unlikely to occur after oral administration (1157).

Additional studies of the effects of formulation on drug availability are provided in Table XXIX.

Absorption Control and Alteration—The hypothesis that the formation of ion pairs and their transport across the lipid barrier are important mechanisms for drug absorption was examined, using a quaternary ammonium compound, isopropamide, as the cationic component and trichloroacetate as the anionic component of an ion pair. *In vitro*, ion pairing greatly increased organic solubility, while in mice, both the rate and the efficiency of oral absorption of isopropamide were increased when it was administered with an excess of trichloroacetate (1188). The extent of metabolism of the (−) isomer of mandelic acid is not significantly altered in the presence of sulfadiazine, sulfamethazine, or sulfamerazine, and this fact was utilized to calculate the ratio of the rate constants of the overall elimination of mandelic acid in the presence and absence of the sulfa drugs, as a measure of their inhibitory effects on its urinary excretion. It was concluded that the three sulfonamides probably share the same renal tubular transport system for their secretions in humans (1189). Chloramphenicol was shown to retard the biotransformation of tolbutamide, diphenylhydantoin, and dicoumarol in man, resulting in an increase in the half-life values of these compounds in the blood after its adminstration. A case of chloramphenicol-induced hypoglycemic collapse in a tolbutamide-treated patient was reported (1190). To design a dosage form, especially a sustained-release type, of amphetamine or other drugs which have an approximate 12-hr. half-life in blood and urine, it was recommended that blood studies be conducted to define the pharmacokinetic parameters necessary for calculating the initial and maintenance doses, and that excretion data be used mainly to confirm the half-life of amphetamine beyond the levels which are conveniently measurable in the blood. Blood data are more meaningful, since urine levels of amphetamines are highly sensitive to the urinary pH, re-

Table XXXI—Additional Studies on the Mechanism of Absorption

Reference	Topic
1240	Dependency of molecular penetration of spore wall and consequent toxicity on compatibility between geometry and charge distribution of the molecule and that around the periphery of the hole in the wall
1241	Concentration and dissociation gradient between the aqueous phases of a three-phase system as decisive factors in the absorption and rate of dissolution of drug
1242	Interfacial barriers in interphase transport: the retardation of the transport of diethylphthalate across the hexadecane–water interface by an adsorbed gelatin film
1243	Solubility diffusion as the most likely mechanism of water permeation through lipid bilayer membranes
1244	Suggested model for describing the nonmediated transfer of nonelectrolytes in terms of diffusion in homogeneous networks
1245	Review of the mechanisms of absorption, distribution, and elimination of drugs, with reference to methods of modifying these mechanisms by inducing changes in acid–base balance
1246	Evidence indicating that salicylates retard wound healing by inhibiting mucopolysaccharides synthesis
1247	Passive diffusion mechanism for absorption of dextromethorphan from the rat's stomach as a protonated species
1248	Confirmation of absorption of *S*-benzoylthiamine *O*-monophosphate into the blood after its dephosphorylation at the mucosal surface of the intestine
1249	Review of phospholipid cell-membrane models
1250	Data presented to support the hypothesis that benzylpenicillin is actively transported from the cerebrospinal fluid to the blood
1251	Review of the mechanisms by which cardiac glycosides are absorbed through the intestinal wall
1252	Rate of absorption of secobarbital in goldfish and the relationship between absorption-enhancing effect and surface tension (or concentration) and the type of surfactant used
1253	Three possible modes of interaction between membranes and surfactants incorporated into ointment bases: rupture of membrane, replacement of certain phospholipids present in the lipid micelles, and induction of configurational changes in the micelles
1254	Experimental results interpreted as an indication that permeability changes of nerve membranes are mediated by migration of hydrogen ions
1255	Suggested formation of a hydrogen-bonded complex between drug and acceptor group on the neural membrane as a mechanism in the action of local anesthetics

sulting in kidney reabsorption changes and a consequent wide variation in urinary excretion rates. While control of pH compensates for the variation, it is impractical for large-scale clinical studies (1191). The ability of methocarbamol to potentiate aspirin or morphine might be due to the competition between it and aspirin or morphine for glucuronide formation, with consequent enhancement in the aspirin or morphine blood levels (1192).

Additional studies on absorption control and alteration are listed in Table XXX.

Absorption Mechanism—A model was presented which can describe the overall transfer of a drug across biologic membranes in the presence of a complexing agent. This model was applied to the transfer of salicylamide across a cannulated everted rat intestine in the presence of caffeine. The intestinal transfer rate constant of the salicylamide–caffeine complex was found to be considerably lower than that of salicylamide but essentially the same as that of caffeine (1229). Some fundamentals of micelle formation and of solubilization of water-insoluble substances through micelles were reviewed. The accelerating effect of micellization on rate of solubilization and of transport of solubilizate through bulk liquid was considered. Transport across the membrane is accelerated whether or not micelles are effective within it (1230). Wagner (1231) presented equations to demonstrate the mechanism of gastrointestinal absorption, with special attention to the permeability coefficients for both ionized and nonionized species. The *in vitro* transfer of drugs from a buffered aqueous phase through a barrier consisting of a lipid liquid into another buffered aqueous phase was suggested as simulating the process involved in gastrointestinal absorption, *i.e.*, the partitioning of a drug between the gastrointestinal fluid and the lipoidal membrane and the plasma (1232). For studying the oil-water interface transport of drugs, a two-phase model was investigated. When the oil-water partition coefficient is large, the transport is aqueous diffusion-controlled and the first-order behavior is followed in the aqueous phase with time. Deviation from first-order behavior occurs when the partition coefficient is low, when the diffusion coefficient in the oil is low, when the diffusion coefficient in the aqueous phase is large, or when the thickness of the aqueous diffusion layer is small. These results may be useful in the design and interpretation of both *in vitro* and *in vivo* data on drug transport (1233). Similar investigations involving two-phase methods for investigation of the interphase transport of drugs were reported (1234, 1235). Wagner reviewed the transport of drugs through membranes and barriers other than the gastrointestinal tract, including buccal absorption as well as excretion by three different glands (1236). DMSO, in combination with sodium chloride, decreases skin electrical conductivity, probably by reducing skin resistance and facilitating the absorption of the electrolyte simultaneously with its own absorption (1237). With chlorpromazine, whatever the mechanism of absorption, the final therapeutic effect was shown to depend on the free radical form (1238). Using tritiated digoxin in rats, it was concluded that digoxin is absorbed by a passive nonsaturable transport process not dependent on metabolic energy (1239).

Additional references on the mechanism of absorption are provided in Table XXXI.

Kinetic Studies—Wagner (1256) reviewed certain aspects of pharmacokinetics and biopharmaceutics in relation to drug activity, considering such factors as route of administration, dose and dosage regimen, absorption, distribution, metabolism and excretion, effects of disease, and drug–drug interactions. The dose-dependent elimination of bishydroxycoumarin, known to occur in man and monkeys, can also be observed with warfarin when sufficiently high doses of the latter are administered. This effect is not seen clinically, perhaps, because the therapeutic dose range of warfarin is much lower than that of bishydroxycoumarin. The results suggest that the two coumarin anticoagulants are subject to the same major biotransformation pathways

Table XXXII—Additional Studies on Pharmacokinetics

Reference	Topic
1270	Characterization of the kinetics of salicyluric acid formation from salicylate by considering the formation process as the rate-limiting step in the excretion of salicyluric acid after salicylate administration
1271	Review of the relation between dosage forms, dosage regimens, and pharmacokinetics
1272	Description of a linear relationship between logarithm of warfarin concentration in the plasma at a given time and the pharmacologic effect at that time, and the decline in pharmacologic effect at a constant rate following cessation of therapy
1273	Calculation of the theoretical optimum dosage regimen for antituberculosis drugs
1274	Pharmacokinetics of large doses of penicillin
1275, 1276	Pharmacokinetics of two sulfonamides in children during the 1st year of life
1277	Pharmacokinetics of clindamycin
1278	Pharmacokinetics of streptokinase
1279	Pharmacokinetics of Fanasil (sulfaorthodimethoxine)
1280	Description of the kinetics of salicylic acid and the formation of gentisic acid, with the suggestion that the elimination of salicylic acid cannot be entirely described by first-order kinetics
1281	Toxicological, chemotherapeutic, and pharmacokinetic data for sulphormethoxine and other sulfonamides in animals and man
1282	The kinetics of 2-propanol and acetone in dogs and rats
1283	Postulation that the dose-dependent disposition kinetics of griseofulvin might be attributed to changes in the tissue distribution rather than to changes in the intrinsic metabolic activity
1284	Demonstration of the pharmacokinetics of 2-sulfanilamido-3-methoxypyrazine in children, including the elimination, intestinal absorption, distribution, and dosage
1285	Review of the pharmacokinetics of antibiotics in animals
1286	An equation for turnover time of goldfish as a function of concentration of ethanol, with a theoretical derivation based on a combination of occupation and rate-receptor theories
1287	Problems in data collection in analysis in human pharmacokinetics
1288	The value of the buccal absorption test for interpreting or predicting pharmacokinetic behavior of a drug such as imipramine and its metabolites
1289	Pharmacokinetics of peruvoside compared in man and dog
1290	Pharmacokinetics of ouabain, digitoxin, and peruvoside in the guinea pig
1291	Metabolism and pharmacokinetics of rifampicin in animals and humans
1292	Pharmacokinetics of kanamycin
1293	Kinetics of isoxazolylpenicillins
1294	Metabolism and pharmacokinetics of medazepam
1295	Review of pharmacokinetic principles
1296	Indications that computer analysis of pharmacokinetic data is a valuable and indispensable aid in the evaluation of experimental chemotherapy
1297	Some pharmacokinetic aspects of doxycycline metabolism in man
1298	A simple dilution analog computer for simulation of drug distribution processes: its uses in teaching and visualizing tandem first-order reactions, such as pharmacokinetic models
1299	Suggestion that linear models, used for compartmental analysis, can also be employed to study interactions between drugs and their receptors and to evaluate the kinetics of the pharmacologic response
1300	Employment of a digital computer for solution of pharmacological problems involving nonfirst-order models of drug metabolism
1301	Employment of a digital computer for statistical treatment of the data on a two-compartment model of the disappearance of ethoxybenzamide from plasma
1302	Use of apparent rate constants obtained by analog computer analysis of plasma and dialysate curves to compare a variety of compounds for their effect on the peritoneal dialysis of salicylate
1303	Description of dose-dependent effects in pharmacokinetics, indicating that studies should be done at more than one dose level, since neither humans nor animals have unlimited capacity to metabolize drugs

(1257). A model was presented which can be used to obtain the pharmacokinetic parameters of the two-compartment open system of drugs which are too poorly soluble or too irritating to be adminstered by rapid intravenous injection. Experimentally, the method involves administering the drug by a constant-rate intravenous infusion until the attainment of infusion equilibrium, and determining the plasma concentrations of drug in the postinfusion period. The approach was applied to literature data and resulted in the evaluation of the two-compartment pharmacokinetics of oxacillin (1258). The apparent volume of distribution at the steady state in a two-compartment open system cannot be used to relate the drug concentration in the plasma to the amount of drug in the body, except at the one point in time when the rate of change of the amount of drug in the peripheral compartment is zero. A new concept of apparent volume of distribution, introduced for the pharmacokinetic analysis of the three-compartment open system, was applied to the two-compartment open system (1259). A graphic method was described for estimating the absorption half-life from the time of the peak level following the extravascular administration of a drug. The method is useful for drug products having absorption rates five or more times faster than their elimination rates (1260). The pharmacokinetics of drug distribution was evaluated for two types of drug administration—*viz.*, constant-rate intravenous infusion and instantaneous intravenous injection. Both modes of administration eventually result in a constant tissue compartment–central compartment distribution ratio of drug. However, the distribution ratios are not equivalent at pseudodistribution equilibrium and at infusion equilibrium. Consequently, at equivalent plasma concentrations, more drug will be in the tissue compartment during pseudodistribution equilibrium than during infusion equilibrium, although the total amount which will enter the tissue compartment is independent of the mode of administration. These findings may have important implications for drug distribution studies and with respect to the relative effectiveness of continuous and intermittent drug administration (1261). The pharmacokinetic analysis of drug concentration in the plasma *versus* time data, achieved by use of multicompartment models, made it possible not only to examine the relationship between drug concentration in the plasma and the intensity of the pharmacologic effect, but also to assess the relationship between pharmacologic effects at the relative drug levels in other apparent compartments of the body (1262). A three-compartment open system was proposed to explain the influence of route of administration

on the area under the plasma concentration–time curve. Computer analysis of the model, using estimated pharmacokinetic parameters, provided a successful prediction of the relative area under the plasma concentration–time curves after oral and intravenous administration of aspirin in man. After intravenous administration, the proposed model yielded a curve which may be described adequately by a biexponential equation (1263). Gladtke (1264) determined the elimination half-life of phenylbutazone after intravenous administration in children to be 21 hr. After oral administration, 85% of the dose entered the blood within 8 hr. In patients with liver disease, the half-life of meprobamate in the blood was shown to increase to 24.3 hr. from the 12.6 hr. observed in the normal patient. In drug addicts it was lowered to 4.5 hr. (1265). Benet and Ronfeld (1266) reviewed the use of different types of volume terms in pharmacokinetic equations. Amsel and Levy (1267), in a pharmacokinetic study of the simultaneous conjugation of benzoic and salicylic acids with glycine, found that in man the availability of glycine is rate-limited by the formation of hippuric acid but not of salicylic acid. Apparently the inhibitory effect of benzoic acid on the formation of salicylic acid is not due to competition for glycine but involves another phase in the biotransformation process. In a study describing the pharmacokinetics of sulfonamides in patients with cirrhosis of the liver, it was noted that the half-life of sulfamethoxypyridazine was not sufficiently different from the control, while the half-life of sulfadimethoxine was significantly diminished as a result of the increased binding of the drug by plasma proteins (1268). Data generated with a two-compartment open model were analyzed according to the one-compartment open model, in an attempt to use single-dose blood level data to predict blood levels after multiple doses (1269).

Additional studies on pharmacokinetics are listed in Table XXXII.

Drug Absorption—Using a model consisting of a thermostated upper and lower chamber fabricated from methyl methacrylate and having various membranes sandwiched between the chambers, Aguiar and Weiner (1304) showed the effect of varying the concentration of surfactants and of propylene glycol on the permeation of chloramphenicol through the barriers. The authors measured the activation energies for permeation and diffusion of this drug through a filter membrane saturated with peanut oil and also those for its permeation through hairless mice skins, at the same time obtaining an estimation of the partition coefficients. The law of corresponding areas was used to assess the percent absorption of a drug, by comparing the relative areas under the plasma concentration–time curves after oral and intravenous administration. If any metabolism occurred in the gut wall or liver, the areas under the curves would not be similar. This was verified using aspirin in dogs (1305). Chiou (1306) concluded that it is almost impossible to obtain an empty stomach in the rabbit by fasting the animal, since the fasting state markedly prolongs the stomach emptying time; thus the rabbit is not a useful animal in which to study drug absorption. A method was reported for studying *in situ* the gastrointestinal absorption of drugs from isolated gut segments of the anesthetized rat. Disappearance of the drugs from the lumen of the small intestine followed apparent first-order kinetics. However, the observed absorption rates were much faster than those normally observed in *in situ* intestinal preparations (1307). The effects of fasting on the intestinal absorption profiles of salicylic acid, barbital, haloperidol, and chlorpromazine were studied in anesthetized rats. The *in situ* technique employed in the

Table XXXIII—Additional Studies on Drug Absorption

Reference	Topic
1313	Review of percutaneous absorption of medicinal agents
1314	A new method for calculating ionophoretic permeability of the skin
1315	Decrease in sweating ability of the skin as cause of a decrease in blanching and presumably a decrease in percutaneous absorption of steroid
1316	Occurrence of percutaneous absorption of steroids and other large molecules *via* appendages and through the unbroken stratum corneum
1317	Relative magnitude of percutaneous absorption of various ^{14}C-labeled steroids as shown by measuring urinary excretion
1318	Review of the cutaneous penetration of dimethyl sulfoxide
1319	Effect of skin conditions on susceptibility of topical tolnaftate penetration
1320	Demonstration that an increase in the perfusion flow rate significantly increases the penetration rate of some compounds, suggesting that data obtained *in vitro* may be more meaningful when ideal flow rates are determined and validated with *in vivo* data
1321	Effect of essential oils on drug absorption
1322	Review of the mathematical treatments used to describe the various parameters involved in drug absorption
1323	Review of drug schedules and drug combinations as factors influencing absorption and efficacy
1324	Review of the relationship between receptor structure and pharmacological activity
1325	Comparability of doxycycline plasma concentrations achieved orally and after i.v. injection in man
1326	Intestinal absorption of six tritium-labeled digitalis glycosides
1327	Intestinal absorption of cardiac glycosides *in vitro* and *in vivo*
1328	Significantly higher serum and urine levels obtained with oxolinic acid when administered with food
1329	Absorption of pyrazinamide in man
1330	Correlation of the analgesic effect of aspirin with the blood concentration of salicylic acid, suggesting that aspirin probably exerts its effect through its hydrolytic product, salicylic acid
1331	Demonstration that isonicotinic acid derivatives are absorbed from the skeletal muscle of the rat, their absorption being proportional to the amounts remaining at the injection site and to both their molecular weights and partition coefficients
1332	Gastrointestinal absorption of 2-pyridine aldoxime methiodide and its derivatives
1333	Blood levels of 2-pyridine aldoxime methochloride and symptoms in humans after single and multiple oral doses
1334	Relative absorption of tetracycline and penicillin G after rectal and oral administration in aqueous solution
1335	Independence of the absorption of guanidine and the dose used for clinical control of hypertension
1336	Use of a quaternary ammonium dye to describe biochemical and morphological correlations of intestinal absorption
1337	Colonic absorption of thiamine
1338	Influence of blood flow on the absorption of drugs from the jejunum of the rat

study yielded absorption rate constants which were realistic and comparable to those observed following oral drug administration. Although apparent deviation in absorption patterns occurred when fasting periods were less than 20 hr., with longer periods the absorption rates were found to decrease significantly, the decrease being dependent on the duration of the fasting period. The unusual drug absorption patterns noted in these studies might be accounted for by one or more of the various physiological and/or biochemical changes which occur within an organism subjected to conditions of prolonged fasting (1308). When prolonged administration of salicylates in amounts comparable to those used in acute rheumatic fever was used, plasma salicylurate formation occurred at an essentially constant rate practically independent of the amount of salicylate in the body, thus demonstrating the capacity-limited formation of salicylurate during the prolonged administration of aspirin (1309). The decline in plasma concentration of dextroamphetamine was more rapid under controlled acidic conditions than under conditions of fluctuating urinary pH. The apparent rate of urinary excretion of amphetamine was proportional to its plasma concentration only under controlled acidic urinary conditions. Under acid conditions, amphetamine was cleared from blood more rapidly than could be accounted for by glomerular filtration, but when urinary pH fluctuated, its clearance could be accounted for by this route (1310). By using crystalline folic acid to study intestinal absorption in rats, it was noted that when increasing doses are introduced into the jejunum the percent of drug absorption decreases, suggesting an active transport mechanism. Absorption from the ileum remains constant with increasing dose, suggesting passive diffusion (1311). Comparative urinary excretion studies after the oral administration of 4′-chloro-2-ethylaminopropiophenone in a sustained-release form and in single or divided doses indicated that when kidney tubular reabsorption is minimized, the biological availability of the drug can be followed by examining the excretion of either the unchanged drug or the metabolites that quickly and directly form from the administered drug (1312).

Additional references on drug absorption are provided in Table XXXIII.

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