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Pharmaceutical Sciences—1972: Literature Review of Pharmaceutics I‡

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‡*Editor's note:* Part II of this article will appear in the August 1973 issue of the *Journal of Pharmaceutical Sciences.*

This review of the literature represents a comprehensive cross section of the research and development effort in various selected disciplines of pharmaceutical sciences. As in past years, the scope of this endeavor has been limited to a review of the area of pharmaceutics because annual reviews of the literature related to other areas of pharmaceutical sciences are published elsewhere. This is the 11th annual survey of the series (1–10). To compile it, numerous journals, periodicals, and selected sections of *Chemical Abstracts* were abstracted.

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

GENERAL PHARMACY

A comprehensive review of the biosynthesis, chemistry, stability, analytical methods, metabolism, and biology of the prostaglandins was presented by Oesterling *et al.* (11). Other reviews appearing over the past year in the general area of pharmacy concerned formula-

tion of aspirin (12), use of polymers for pharmaceutical applications (13), boron compounds of pharmaceutical interest (14), application of silicones in pharmacy (15), use of silicates in the pharmaceutical area (16), and pharmaceutical properties of dimethyl sulfoxide (17). Statistical data were presented on the results of quality control of raw materials in the Brazilian pharmaceutical industry between 1940 and 1968 (18). The extent of drug product recalls occurring over an 18-month period and the types of product quality defects and their significance were discussed (19). Examples for each type of product quality defect were cited. A review was presented on the chemical and physical incompatibilities in drug solutions, emulsions, suspensions, salves, and capsules and their effects within the biological system (20). As an example, streptomycin in combination with anionic compounds, such as sodium alginate, exhibited greater antimicrobial activity than that observed for the sulfate derivative.

Preservatives—In a study relating cetrimonium bromide (cetyltrimethylammonium bromide) concentrations with the ζ-potential of the bacterial cell wall, this agent completely inhibited the growth of *Streptococcus faecalis* at a concentration producing only a 10–30% decrease in the absolute value of the ζ-potential (21). These results seem to indicate that the primary site of attack of this compound is probably not the cell wall. During studies on the antimicrobial efficacy of 4-hydroxybenzoic acid esters, a direct relationship between the lipid–water partition coefficient and antimicrobial activity was indicated (22). Introduction of a hydroxy or oxo group into the alkyl ester chain increased water solubility, but it decreased antimicrobial activity. Likewise, it was shown in a study of a series of homologous aliphatic amines that inhibition increased with increasing alkyl chain length and the maximum was reached at C_{12}–C_{15} (23). The poor inhibitory effect of the longer chain molecules was thought due to micelle formation, with concomitant lowering of the solubility. In determining the antibacterial activity in a series of quaternary ammonium compounds, it was found that the length of the side chain was less determinant in the case of Gram-negative bacteria (24). This was attributed to the differences in the cell wall lipid concentration between Gram-negative and Gram-positive bacteria.

Pseudomonas aeruginosa cells grown in the presence of phenylethanol were more sensitive to the action of benzalkonium chloride, chlorhexidine, and phenylmercuric nitrate than cells grown in nutrient broth alone (25). This suggested the use of phenylethanol as a co-preservative when using these other agents. Bradshaw *et al.* (26) were able to predict the degree of inhibition of cetylpyridinium chloride in combination with a nonionic surfactant on microbial cells at higher concentrations. However, at lower concentrations of bactericide, other factors, such as changes in cell wall permeability, made this prediction less possible. It was also determined that polysorbate 80 antagonized the activity of fenticlor against exponential phase cultures of *Staphylococcus aureus*, *Proteus vulgaris*, and *Escherichia coli* (27). In the same study, it was demonstrated that phenylethanol enhanced activity against similar cultures.

The effects of glycerol and propylene glycol on microbiological contamination of some oil-in-water emulsion ointment bases were determined (28). While glycerol stimulated the growth of molds and yeasts with the simultaneous decrease of bacteria, propylene glycol gave microbial purity. However, in another study with preservation of oil-in-water emulsions, it was found that propylene glycol caused apparent partial antagonism of potassium sorbate in these systems (29). Sterilization of contaminating bacteria by solutions of phenylmercuric nitrate and thimerosal was delayed or prevented by addition of edetate (EDTA) or sodium thiosulfate, but metabisulfite reduced the sterilization times of both these agents at acid pH (30). The antibacterial activity of sodium metabisulfite appeared to be due to an interaction with bacterial DNA.

Methods for the rapid screening of preservatives for pharmaceutical and cosmetic preparations, based on instrumental monitoring of indexes of cell development that occur early in the growth cycle and that are susceptible to preservative agents, were reviewed (31). In another review, the relative sensitizing potentials of parabens, sorbic acid, phenolics, formaldehyde, mercurials, quaternary ammonium compounds, betaines, dimethoxane, and dihydroacidic acid were discussed because they are used in cosmetic emulsions and dermatological preparations (32). Combinations of benzalkonium chloride, chlorhexidine, phenylmercuric nitrate, chlorocresol, and chlorobutanol with phenylethanol were consistently effective in preserving ophthalmic solutions (33). Polymyxin and benzyl alcohol were also found to be suitable preservatives for ophthalmic drops (34). However, the use of an antibiotic as a preservative was regarded as unadvantageous.

The safety of intravenously administered benzyl alcohol and paraben preservatives was ascertained (35). The higher antibacterial activity of benzyl alcohol, shown in challenge tests, plus its comparable tolerances to parabens favor the use of benzyl alcohol as a preservative. A study was made of eight substituted phenolic preservative solutions in 2% polysorbate 80 (36). These results showed less sorption into polyethylene than from aqueous solutions, but the micellized systems were not adequately preserved. Several common preservatives that are absorbed by filter paper, rubber stoppers, and inorganic adjuvants or that react with organic macromolecular compounds were discussed (37). Preservatives preferred or considered not suitable for different pharmaceutical preparations were also listed.

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

Flavor, Aroma, and Color—Additions to the list of Generally Regarded As Safe (GRAS) substances made in 1970–1971 and their maximum use levels were tabulated (52). The concept of "toxicological insignificance" was explained, and data on total daily per capita intake of flavoring substances were presented. A review of the classification of the components of taste, methodology, choice of flavor, control, and stability of taste-masking drugs was presented (53). It was pointed out that flavoring of a drug includes two processes: the masking of the disagreeable taste and aromatization (54). Prescriptions for flavoring were given using sac-

Table I—Additional References on Preservatives

Reference	Topic
38	Evaluation of parabens for protection against fungal and bacterial contamination
39	Uses of preservatives based on esters of *p*-hydroxybenzoic acid
40	Physicochemical properties and antimicrobial efficacy of 4-hydroxybenzoic acid esters
41	Effects of pH on the multiplication of a pseudomonad in chlorhexidine and cetrimide
42	Influence of polyethylene glycol gels on the effectiveness of preservatives (ninpagin and Fenosept)
43	Studies demonstrating that the USP XVIII preservative test is adequate for the intended purpose
44	Discussion on adsorption of antiseptic substances by filtration membranes
45	Effects of antioxidants on the long-term utility of ethyl linoleate as a water-holding lipid for topical postburn treatment
46	Composition and antimicrobial properties of essential oils of pine
47	Effects of the addition of antioxidants on changes occurring in pine oil
48	Selection, control of activity, efficacy after inoculation, and determination of germicidal potency of preservatives for cosmetics
49	Choice, activity, and effectiveness levels of preservatives for cosmetics
50	Protection of cosmetics by synergistic mixtures of preservatives and bactericides
51	Fat-soluble preservatives for oil-in-water emulsions only effective with solvents that increase water solubility

charin, chocolate, vanilla, caramel, orange essence, and raisin juice in different combinations. The flavor chemist's greater reliance on the results of instrumental techniques, the faster development of new aromatics from laboratory curiosities to accepted standard items, and the increasing number of new materials and methods determine today's trend in flavors (55). Hofmann (56) reviewed and discussed the several theories explaining the relation between sweetness and chemical structure. A study of several stereoselectively sweet amino acids molecules led to a prediction of the presence and approximate location of a third structural feature, relative to the currently postulated A–H/B features in the glucophore (57). A relationship between the polarizability parameter and sweetness level in a series of substituted nitroanilines led to the hypothesis that this third binding site may be involved in dispersion bonding with an appropriate receptor feature.

An encyclopedic evaluation of the literature in the perfumery materials field was continued by Bedoukian (58) in his 28th annual review. It was pointed out that modern perfumery is no longer a question of merely adding a harmonious blend of materials in proper concentrations (59). It involves chemical interactions, research, packaging, testing, and fragrance selection, coupled with the application of perfumes to a wider range of products. It was urged that fragrance materials be examined in their use environment (60). Since it has been demonstrated that fragrance materials associate with protein, factors that influence efficacious perfumery of protein materials can be considered in a new way. Encapsulation of fragrance material was postulated as a means for overcoming difficult problems (61). A water-soluble capsule would protect the fragrance up to the time of use.

In studying odor sensations arising from the 1,2,4-triaxial arrangement of the substituents in a decalin ring system, it was determined that the position of an oxygen function within the triaxial system moves the odor sensation in the direction of different but distinct qualities (62). On the other hand, the surroundings of the center triggering the odor, as well as the chemical nature of the oxygen substituent, seemed to be of minor importance. In discussions concerning the relationships observed between odor and molecular structure, it was stated that small differences in structure can create changes in potency in some cases, changes in quality in others, and changes in both quality and potency in still others (63, 64).

Stability—The stability of neutral regular insulin was compared to conventional acid regular insulin (65). The increased stability of the former warrants its consideration as a pharmaceutical form of soluble regular insulin and as a replacement for the conventional acidic form. Seydel and Voigt (66, 67) conducted extensive studies on the stability of amino acid solutions. Stability results on individual amino acids and on combinations of amino acids alone and with various preservatives were reported. The stability of amino acids in aqueous solutions of casein hydrolysate stored at various temperatures was examined (68). Only glutamine and cysteine were rapidly degraded in this system. In a further study, these same workers determined that lyophilization significantly enhanced stability of the amino acids (69). Macromolecules such as bovine serum albumin and macrocyclon effectively enhanced the stability of aromatic nitrogen mustards, including chlorambucil, while not necessarily altering the antitumor activity of these compounds when given concurrently (70).

The causes of coloring of sulfonamide suspensions with prolonged action were investigated (71, 72). It was determined that with the proper use of antioxidants, adjustment of pH, and nitrogen flushing, coloring could be eliminated. In a study on the thermal degradation of sulfonylureas, results indicated that dissociation rather than solvolysis was the most likely mechanism by which sulfonylureas undergo breakdown in alcohols and water (73). Procaine hydrochloride was successfully stabilized by the addition of methylidene, glycerin, and propylene glycol (74). The mechanism postulated for protection was a pseudochelating action. It was shown that dipyrone degradation was not subject to pH in the 4.8–8.8 range and that the probable mechanism of degradation was oxidation (75). It was suggested that improved stability could be obtained by flushing the headspace with an inert atmosphere and by incorporating a suitable antioxidant.

A stabilized phenylephrine hydrochloride nasal drop formulation was described which contained methylparaben, propylparaben, and sodium bisulfite with a pH adjustment of 5–6 (76). The decomposition of aspirin (acetylsalicylic acid) and possibilities for its stabilization in a solid dosage form were discussed and reviewed (77). During an investigation of the decomposition of physostigmine salicylate during thermal sterilization, it was determined that the quantity of decomposition in ampuls depends on the quantity of oxygen present in the solution (78). The replacement of

Table II—Additional References on Stability

Reference	Topic
86	Hydrolysis of aspirin (acetylsalicylic acid) in a mixture of polyethylene glycol 4000 and water
87	Stability of tablets with an aspirin (acetylsalicylic acid) base in tropical environments and requirements of packaging
88	Stability of aminopyrine (aminophenazone) and allobarbital in a liquid Pabialgin preparation
89	Thermal decomposition of a mixture of aminopyrine (aminophenazone), allobarbital, and cycloadiphenine in cetyl phthalate
90	Heat stability of eight samples of anti-yellow fever vaccine from various countries
91	Determination of stability of ergotamine and ergometrine in ergot extract as injectable solutions
92	Effect of different ions on the stability of carbazochrome sodium sulfate
93	Decomposition of sorbitol in acid solution
94	Solid-state stability of anhydrous morphine hydrochloride
95	Stability of dihydrotriazine in solution and dihydrotriazine pamoate in aqueous suspension
96	Effects of surfactants on the degradation of 2α,3α-epithio-5α-androstan-17β-ol and related compounds
97	Stability of 2α,3α-epithio-5α-androstan-17β-yl 1-methoxycyclopentyl ether in tablets and capsules
98	Determination of storage conditions for 2% pilocarpine hydrochloride solutions by accelerated decomposition method
99	Stability of 5-bromo-2′-deoxyuridine in solid state and in solution at different pH values
100	Glucose stability in a concentrated plasma-replacing Ringer solution
101	Determination of stability of some benzodiazepines in pharmaceutical dosage forms
102	Effect of pH on the stability of aceclidine and oxylidine parenteral solutions
103	Incompatibilities of selected cardiovascular and psychotherapeutic agents in solutions containing sodium ethacrynate
104	Stability of amphetaminyls in aqueous suspension
105	Hydrolytic decomposition of trantelinium bromide
106	Stability of ephedrine hydrochloride solutions during steam sterilization
107	Determination of stability of seven types of insulin preparations
108	Alkaline hydrolysis of phenobarbital
109	Enzymic hydrolysis of pilocarpine
110	Instability of sulfathiazole with polyethylene glycol 600 gels
111	Compatibility of sodium lauryl sulfate with 119 various drugs
112	Incompatibility of ethacridine (Rivanol) with polyethylene glycols
113	Stability of aspirin (acetylsalicylic acid) in different suppository bases
114	Stability of aspirin (acetylsalicylic acid) in coated pills
115	Stabilization of aqueous drug forms during heat sterilization
116	Optical behavior of sucrose solutions in the inversion process
117	Method for reducing discoloration of glucose solution
118	Oxidative degradation of terbutaline in aqueous solution
119	Effects of UV radiation on drugs in hard gelatin capsules
120	Effects of UV rays on dyes used in cosmetic products
121	Evaluation of the quality of drugs from the view of their stability
122	Stabilization of buffered pilocarpine drops by freezing
123	Discussion of problems of stability of plasma substitutes
124	Stability of inclusion compounds of deoxycholic acid and β-cyclodextrins in dosage forms
125	Shelflife of some injection formulations
126	Stability predictions for pharmaceutical preparations by accelerated testing
127	Stabilization of various eyewash solutions
128	Determination of the stability of meperidine (pethidine) hydrochloride solutions in polyethylene containers
129	Stability of hexahydroadiphenine, ethionamide, and aminophylline in lyophilic suppository bases
130	General discussion of drug incompatibilities

oxygen with nitrogen decreased the decomposition threefold. Boric acid had no effect on oxidative changes of lanolin, while glycero-boric acid was very effective in this respect (79). The protective efficiency for the stabilization of oxygen-sensitive systems using gas permeation was determined by measuring the relative deaeration produced by this technique *versus* current methods for reducing dissolved oxygen concentrations in liquid systems (80). In terms of deaeration efficiency, gas permeators ranked second only to the addition of antioxidant materials in the drug system, but they did have the advantage of eliminating the addition of chemicals in the dosage form which might produce adverse reactions.

In a discussion of the advantages of preservation of medicinal solutions by freezing, emphasis was placed on the proper choice of adjuvants and construction of the containers used (81). A method was described for the rapid determination of color stability in tablet formulations (82). Data obtained in the phenometer in 24 hr., as well as results from exposure in a light cabinet for 28 days, facilitated the comparative evaluation. Rapid testing for the stability of BCG vaccine by accelerated heat testing was accomplished, along with rapid viability testing by assaying for the adenosine triphosphate content of the vaccine (83). The viability determined by adenosine triphosphate analysis correlated well with the viable count as determined by culturing. Stability programs for determining chemical and physical stability and the analytical implications were reviewed by Rehm (84). Other workers warned against too heavy a reliance on accelerated stability testing (85). As an example, they cited the case of 500-mg. ascorbic acid tablets that had strong color degradation apparent although they were chemically unchanged.

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

Stability Kinetics—Drug and drug system stability predictions based on kinetics of degradative reactions and Arrhenius-type relationships were reviewed by several authors. These included both isothermal and nonisothermal methods (131–135). However, one group of workers pointed out that stability based on accelerated temperature studies may lead to erroneous results because mechanisms of degradation may change at higher temperature (136). While using procaine, meperidine, homatropine, and scopolamine as examples, the hydrolytic behavior of esters in aqueous solutions was discussed (137). Such factors as the effects of pH, solvents, ionic strength, acid and base catalysis, and steric hindrance were included. Dexamethasone 21-phosphate in aqueous solution was shown to be susceptible to a reversible bisulfite addition, which was a

second-order reaction in which sulfite ion and monoanionic dexamethasone 21-phosphate were the major participants (138). The decomposition of aspirin in polyethylene glycols was shown to be a pseudo-first-order reaction (139). Different molecular weights of polyethylene glycol had no effect upon the reaction rate, which was demonstrated to be due to transesterification. In alkaline media the 2-, 3-, and 4-monohexanoates of lincomycin rapidly isomerized, each entering into facile equilibrium with the other two, accompanied by hydrolysis of each species to lincomycin. By using a digital computer and a nonlinear estimation program, Oesterling and Metzler (140) were able to estimate simultaneously the four isomerization rate constants and the three hydrolysis rate constants.

It was demonstrated that the methanesulfonic acid derivative of sulfisoxazole undergoes successively reversible hydrolysis in aqueous solution (141). The pH profiles of the logarithm of apparent hydrolysis and reverse reaction rates and those of equilibrium constants were obtained, and the effects of ionization of the derivatives and hydrolysates were explained by mathematical equations. The decomposition of a series of benzoic acid derivatives in the solid state was studied (142). It was found that for decomposition to take place below the melting point, the σ value must be less than -0.35. The decomposition then follows Bawn-type kinetics. C-21-Dideuteriohydrocortisone was shown to be more stable than hydrocortisone under oxidative conditions (143). A possible explanation for this enhanced stability was that the reaction path for these degradations involved a rate-determining enolization in the C-17-dihydroxyacetone side chain. The pharmaceutical stability of a solution of potassium canrenoate was shown to be a function of the solubility of the lactone canrenone at equilibrium and the pH-dependent thermodynamic equilibrium of the reversible lactonization and hydrolysis processes. Garrett and Hermann (144) predicted the minimum pH values for various mixed solvent solutions that would maintain unprecipitating potassium canrenoate solutions for desired injectable concentrations of the drug. The hydrolytic decomposition of intrazole obeyed first-order kinetics and was subject to both acid and base catalysis (145). The pH of maximum stability of this compound under buffer-free conditions was 3.20. The kinetics of hydrolysis of the carbamoyl group in salicylanilide *N*-methylcarbamate and 4-biphenylyl *N*-methylcarbamate showed that the reaction was first order with respect to both hydroxide ion and carbamate (146). At 37°, the hydroxide ion-catalyzed hydrolysis of the former to yield salicylanilide proceeded at a rate over 200 times that for the hydrolysis of the latter, which produced 4-biphenylol. During a study of the kinetics of dextrose degradation during autoclaving, the reaction was shown to exhibit an induction period with respect to 5-hydroxymethylfurfural production, which was due to the formation of an intermediate compound (147). A reaction mechanism was proposed that appeared consistent with experimental measurements.

In studies aimed at predicting shelflife stability of arabinosylcytosine in aqueous solutions, Notari *et al.* (148) determined that the loss of substrate in the pH 0–6 region was accompanied by formation of an intermediate which reacts further to yield arabinosyluracil. In alkaline solutions the loss of arabinosylcytosine was about 10 times more rapid than in acid and was most likely due to hydrolysis of the pyrimidine ring, since no arabinosyluracil UV absorption spectra were detected. Other workers (149) confirmed by UV spectrophotometry and TLC that cytosine and cytidine deaminate to uracil and uridine, respectively, at all pH values. These products slowly degrade further in strongly alkaline solutions. Differences in the intermediates formed in the degradation of chlorothiazide in alkaline medium and acidic medium were investigated, using a molecular orbital method to understand the hydrolysis mechanism (150). The hydrolysis pathway was explained by the electronegativity of the atoms involved in the postulated activated complex, 3-hydroxyhydrochlorothiazide. Depending upon the reaction conditions, two pathways of cleavage of butalbital were described (151): (*a*) through 1,6-ring opening to the malonuric acid, and (*b*) *via* 1,2-cleavage of the barbiturate producing the diamide. In following the hydrolysis of certain 5-aminodibenzo-[*a*,*d*]cycloheptanes, it was determined that degradation is characterized by cleavage of a carbon–nitrogen bond at the 5-position of the fused ring system (152). The process was shown to proceed possibly by a carbonium-ion intermediate or its equivalent. The hydrolytic rate of degradation of sodium sulfacetamide in aqueous solution was shown to be minimal at pH 8–8.5 (153). Hydrolysis of methyl hippurate under the influence of α-chymotrypsin and some aliphatic alcohols was investigated (154). Methanol, ethanol, *n*-propanol, *n*-butanol, and *n*-pentanol were found to inhibit the rate of hydrolysis.

Other papers related to the topic of stability kinetics are listed in Table III.

Table III—Additional References on Stability Kinetics

Reference	Topic
155	Review of kinetic approaches and limitations
156	Computer technique for calculating the expiration date of drugs based on kinetic data
157	Use of an analog computer in drug-stability studies
158	Kinetics of the oxidation of dopamine
159	Decomposition kinetics of methallibure
160	Kinetics of hydrolytic decomposition of isoindoline-nitrourea
161	Degradation of 2α,3α-epithio-5-androstan-17β-yl 1-methoxycyclopentyl ether in aqueous dioxane solutions
162	Influence of a 6-methyl substituent on the degradative rates of cytosine nucleosides
163	Decomposition rates of 6-aminopenicillanic acid adsorbed on KU-2 ion-exchange resin
164	Kinetics of degradation and stabilization of the parabens
165	Kinetic investigation of the hydrolytic decomposition of *N*-butylscopolammonium bromide
166	Alkaline hydrolysis of xylamide
167	Kinetics of hydrolysis of chloramphenicol succinate
168	Hydrolytic decomposition of oxyphenonium bromide

Antibiotic Stability—In comparing the relative stabilities of hetacillin and ampicillin solutions, Schwartz and Hayton (169) found rates of degradation inconsistent with what should be expected. An explanation of this inconsistency was offered by adopting a model reaction scheme that incorporated the concentration

Table IV—Additional References on Antibiotic Stability

Reference	Topic
184	Comparative stabilities of ampicillin and hetacillin in aqueous solution
185	Stability of ampicillin in aqueous solution
186	Stabilization of penicillin against penicillinase
187	Physicochemical properties and stability of sulfocillin
188	Effect of Cu (II)–glycine chelates on the degradation of penicillin in mildly acid solutions
189	Stability of 6-aminopenicillanic acid in solutions of low and average concentrations
190	Solid-state stability of pirazocillin
191	Modes of degradation of potassium phenoxymethyl penicillin
192	Stability of tetracycline and tetracycline–urea complex in petrolatum ointment bases
193	Stability of nystatin

Table V—Additional References on Vitamin Stability

Reference	Topic
205	Stability of vitamins A and D in multivitamin preparations
206	Comparative studies on the stability of vitamin D_2 in different ointment bases
207	Effect of cupric ion on the thermal decomposition of thiamine
208	Possibilities of stabilizing a vitamin F concentrate for cosmetic purposes
209	Mathematical model for predicting stability of ascorbic acid in food products
210	Effects of surfactants on the aerobic oxidation of ascorbic acid

dependence of both the ampicillin degradation and the hetacillin–ampicillin equilibrium. Ionic strength up to 0.5 did not affect the chemical stability of potassium penicillin G unless one of the ions contributing to ionic strength was also catalytic (170). A study to elucidate, by *in vitro* kinetic analysis, the role of cupric [Cu (II)] ions through complexation with an amino acid was undertaken (171). A mechanism was postulated that involved the rapid formation of a ternary penicillin–Cu (II)–glycine complex followed by a rate-limiting hydroxyl-ion attack. It was demonstrated that the nature of the penicillin side chain, particularly the stereospecificity, played a significant role in the stability of penicillin toward β-lactamase (172). In another study, the rate constants for the penicillinase hydrolysis of a series of phenoxymethyl penicillins substituted on the benzene ring by methyl, ethyl, chloro, bromo, formyl, nitro, or cyano were correlated with the Hammett σ-constants (173).

In studying the compatibility and stability of disodium carbenicillin in combination with other drugs and large volume parenteral solutions, Zost and Yanchick (174) reported this antibiotic to be degraded rapidly when mixed with a combination of multiple B vitamins and vitamin C (ascorbic acid). The decomposition rates of a series of semisynthetic penicillins were measured in aqueous solutions at pH 4–9 (175). Methicillin was the most labile, ampicillin and oxacillin were of intermediate stability, and cloxacillin was the most stable. Chemical evaluation of the degradation of solid tetracycline dodecylsulfamate at various temperatures indicated a pseudo-first-order reaction (176). Predictions of shelflife using Arrhenius mathematics indicated a probable shelflife of 2600 days at 25°. These results were confirmed by actual data.

In studies dealing with the stability of antibiotics in frozen systems, Larsen (177, 178) demonstrated that the rate of degradation of these drugs is dependent on buffers, absolute temperature, antibiotic concentration, and rate of freezing. Other workers reported that sodium cephalothin and cephaloridine may be stabilized for short periods by freezing (179). Hamycin was shown to exhibit its maximum stability in aqueous solutions at pH 8 (180). The influence of honey on the stability of monomycin, neomycin, streptomycin, tetracycline, oxytetracycline, and chlortetracycline was reported (181). The microbiologically determined stability of dermostatin in 12 selected ointment bases at 37° was investigated, and maximum stability was exhibited in anhydrous bases as compared with those containing water (182). The stabilities of penicillin G, tetracycline, neomycin, and chloramphenicol were determined in bentonite glycerogels (183). Additions of sorbitan monopalmitate, polysorbate 80, sorbitan monolaurate, and sodium lauryl sulfate had drastic effects on reducing degradation rates.

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

Vitamin Stability—The effects of metal complexing agents on the stability of injectable ascorbic acid solutions were investigated (194). The optimum concentration of these agents on the stability of the drug depended on the amount of heavy metal ions in the solution. The pH–log rate profile of the rate of disappearance of ascorbic acid from an aqueous solution under aerobic conditions was determined at 67° in the pH 3.52–7.22 range and exhibited a maximum near the pKa of ascorbic acid (195). Other workers (196) reported that maximum stability of ascorbic acid solutions could be achieved by the addition of sodium thiosulfate and edetate (ETDA) after passing carbon dioxide through the solution. Microencapsulation of ascorbic acid increased its stability during storage both in the powder form and as tablets (197). Best results were achieved with cetyl alcohol as the coating agent, and the process was carried out by fluidization. An investigation of the stability of vitamin A palmitate in selected ointment bases indicated that lanolin accelerated the decomposition of this vitamin (198). The synergistic effect of the antioxidants butylated hydroxytoluene and butylated hydroxyanisole was demonstrated on the stability of vitamin A acetate in soybean oil (199). An extensive review on the oxidation of vitamin A was also presented (200).

The effects of common additives on the stability of injectable solutions of vitamin B_1 were evaluated (201). The most important factor for solution stability was shown to be the quality of the thiamine hydrochloride used. The stability of supersaturated solutions of thiamine chloride and thiamine bromide at 7 and 20° depended on the degree of supercooling (202). The addition of ethanol affected the rate of crystallization at nucleation centers, resulting from its influence on surface tension and activation energy. The stability of

multivitamin granules containing thiamine disulfide, sodium riboflavin 5′-phosphate, pyridoxine hydrochloride, niacinamide, cyanocobalamin, and calcium pantothenate was studied using accelerated tests (203). Granulation with ethanol and 5% polyvinylpyrrolidone was the recommended method of manufacture. The stability of pyridoxal 5-phosphate was determined in the presence of its degradation products and other substances with which it is commonly associated (204). It was found that the only additives increasing the degradation rate were riboflavin and cyanocobalamin.

Additional references on vitamin stability are listed in Table V.

PHARMACEUTICAL TECHNOLOGY

Recent advances in the pharmaceutical industry as they relate to pharmaceutical technology were reviewed by several authors (211–213). Use of computers in electronic data processing in the pharmaceutical technology areas was also reviewed (214, 215). The historical background, basic principles, and applications of lyophilization to pharmaceuticals were discussed (216). As an alternative to freeze drying for removal of ethanol from plasma proteins, vacuum distillation was offered (217). Both capital and operating costs were less than for freeze drying. Cookson and Morgan (218) compared the various methods for deionized water bed sterilization and recommended 0.25% formaldehyde solution, primarily because of the lower price as compared to other available agents. The various factors affecting antacid efficiency, including micromeritic properties, method of preparation, and effect of dosage form were reported (219–221). The suspension was considered the best dosage form since it has reasonable neutralizing capacity, the fastest rate for acid neutralization, and the longest sustained action within the desirable pH range. The influence of setting temperature on the organization of gelatin gels was studied (222). The gel structure and its behavior depend mainly on the first formed bonds, and a setting at a few degrees below the melting temperature promotes high rigidities. The physical and chemical properties of pharmaceutical gelatin were reviewed, with emphasis on alkaline or acid treatment and source of raw material (223). The principles and uses of microencapsulation of drugs was reviewed by Bakan and Sloan (224). Ultrasonic cleaning was reviewed from both a technological viewpoint (225) and as it can be used in the pharmaceutical industry (226).

Additional references on pharmaceutical technology are listed in Table VI.

Parenterals—Jennings (244) pointed out some problem areas in the manufacturing and administration of parenterals, including the need of a total concept of sterility, the potential hazard of particulate matter, the addition of other drugs to large-volume parenterals prior to their administration, and packaging designs for large-volume parenterals. Modes of administration, solubility, stability, and incompatibility with other drugs and their adverse effects were tabulated for 19 commonly used antibiotics including the tetracycline and penicillin derivatives (245). Procedures for the manufacture of parenteral suspensions were reviewed,

Table VI—Additional References on Pharmaceutical Technology

Reference	Topic
227	Discussion of general aspects of drug quality
228	Description of a method for optimization of sulfadimezine production
229	Sterile and ultrapure water in pharmaceutical processes—the Super-Q system
230	Use of metal stearates in pharmaceuticals and cosmetics
231	Preparation and characteristics of microcapsules containing asparaginase
232	Factors influencing microencapsulation of a waxy solid by complex coacervation
233	Complex coacervation in gelatin mixtures at temperatures below the gel melting point
234	Examples for the use of microencapsulated materials
235	Dehydration of oleandomycin phosphate by spray drying of its aqueous solutions
236	Survey of bacterial contamination in noninjectable dosage forms
237	Applications of membrane technology
238	Variations in theophylline, ephedrine hydrochloride, and phenobarbital tablets from different manufacturers
239	Influence of moisture content of the fibrous support of a nasal inhaler on the concentration of drug in the air stream
240	Review of production and control methods used for various dosage forms
241	Review of process instructions and mechanical processing techniques for the production of pharmaceuticals
242	Survival rates of microbial organisms in BPC preparations
243	Swelling of gelatin as a function of pH

with emphasis on the characteristics inherent to this dosage form not shared with other pharmaceutical suspensions (246). Perrin *et al.* (247) proposed that highly protein-bound excipients, which compete with drugs for binding sites, be added to lower the dose of drugs necessary to produce a given pharmacological response and, hence, to lower the toxicity and cost of parenteral dosage forms. Polyethylene glycol, when used as a solvent for intravenous injections of water-soluble agents, showed a relatively low toxicity (248). This solubilizing agent did not induce hemoglobinurea as was observed with glycerol, dimethyl sulfoxide, or dimethylformamide when used as solvents. The technology involved in preparing fluorocarbon emulsions as blood substitutes was reported (249). Five formulations of fat emulsions used in parenteral nutrition were reviewed as to their use in clinical medicine, absorption, and adverse effects (250). Riebe and Oesterling (251) outlined the procedures involved in the successful development of an injectable form of clindamycin. Problems encountered in the formulation of clindamycin 2-phosphate as a suitable parenteral dosage form were described.

Particulate matter in parenteral glass containers was significantly reduced by washing with either hydrofluoric acid or ammonium bifluoride solution (252). This method of washing also improved the chemical resistance of Type I glass containers to a degree equivalent to that of a good sulfur dioxide treatment. Minute crystals occurring in solutions packaged in multiple-dose vials and sealed with butyl stoppers were shown, by electron probe microanalysis, to be complexes containing zinc and calcium (253). These metal ions were believed to have originated as surface contaminants of the butyl stopper, and a procedure for washing the

stoppers to remove this contamination was described. Methods for testing of silicone coatings on ampuls and vials for injectable solutions were reported (254). Ampuls treated with a 1.5 or 2% aqueous silicone emulsion showed fewer defects of coating than those treated with a 0.5 or 1% emulsion. Hall (255) elucidated the potential problem areas in the manufacture of single-dose ophthalmic products. These included the chemicals used, the packaging materials, the water used, personnel, plant facilities, and control procedures. Use of methylcellulose and hydroxyethyl cellulose, polyvinylpyrrolidone, benzalkonium chloride, cetrimide, and thimerosal were evaluated for use in contact lens solutions (256). Tabulated data were presented to facilitate the selection of suitable combinations of these chemicals with respect to viscosity, film-forming properties, hydration, stability of solutions, and protection against microbial contamination. Ophthalmic solutions prepared with 2% aqueous polyvinyl alcohol were shown to be superior to solutions prepared with water alone (257). No side effects of polyvinyl alcohol were noticed when these solutions were administered to 30 patients with corneal lesions.

Reconstituted antibiotic intravenous products prepared by a number of companies were surveyed for foreign particulate matter (258). The results indicated a variation among companies as to the amount of particulate matter found in their products. Other workers noted that asbestos was found in approximately one-third of the samples from two sets of 17 widely used parenteral drugs (259). McGinn (260) reported that much of the nonviable particulate matter found in parenteral solutions packaged in glass vials originated from the packing material used in shipping the empty vials. He suggested that using a type of plastic film wrapping for these empty containers would reduce appreciably the rejects due to this source of particulate matter. However, all parameters involved in the manufacturing process of injectable fluids were investigated and shown to play an important role in contamination by particles (261). Summaries of the activities of a committee appointed by the Pharmaceutical Manufacturers Association (PMA) to explore the methodology for determination of particulate matter in large-volume parenterals was reported (262). A comparison of results obtained from visual inspection, Coulter counter measurements, microscopic examination, and counting of particles collected on membrane filters was made to evaluate the visual method commonly used to control the cleanliness of parenteral solutions (263). It was concluded that visual inspection data obtained during the manufacturing process must be controlled by the laboratory afterward.

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

Table VII—Additional References on Parenterals

Reference	Topic
264	Conditions for the acid hydrolysis of casein which ensure the production of preparations for parenteral use
265	Parenteral and oral formulations of marijuana constituents
266	pH of drugs for parenteral use
267	pH measurements of sterilized sodium bicarbonate solutions
268	Method for the preparation of injectable cannabis extracts
269	Preparation of a solution of apomorphine hydrochloride for parenteral use
270	Review of infusion solution production
271	Preparation of fructose, sorbitol, and sodium bicarbonate parenteral infusions
272	Review of vehicles and adjuvants for the preparation of injectable solutions of steroid hormones
273	Experimental preparation of freeze-dried urea for injection
274	Physicochemical examination of glucose injection
275	Review of properties of various contact lens solutions
276	Advantages of utilization of dextrans as excipients for viscous collyria
277	Polymers used in ocular wetting agents
278	Review of colloidal injectable plasma substitutes
279	Determination of freezing-point lowering, sodium chloride equivalents, and isotonic concentrations of some drugs in aqueous solution
280	Dimethylpolysiloxane compared to sesame oil as a vehicle for progesterone injection
281	Evaluation of laminar air flow for the preparation of intravenous admixtures
282	Review of the contamination of parenteral solutions by foreign particles
283	Identification of the leached ingredients from rubber closures

Sterility—Boucher (284) reviewed the various physical and chemical methods of sterilization. He concluded that synergistic sterilization, the use of combinations of chemical and physical methods, is on its way to making a profound impact not only in the pharmaceutical field but also in chemical, food, and decontamination industries. The current status of biological indicators was discussed, and plans for future studies were outlined (285). One investigator (286) reported significant differences found among five commercial biological indicators with regard to bacterial count and performance as measured by survival and kill in 10 autoclaves at 121°. He called for further work in the improvement and standardization of these indicators.

The use of cellulase in membrane sterility testing of solutions containing carboxymethylcellulose was discussed (287). An empirical filtration rate test was developed for determining cellulase activity. A group of compounds which rapidly inactivate certain antibiotics and thus facilitate sterility testing of the antibiotic solution was reported (288). The factors necessary to consider in establishing a successful ethylene oxide sterilization cycle were discussed (289). As an example, these factors were applied in the sterilization of a production lot of plastic disposable syringes in paper wrappers. Two compounds, 2-chloroethanol (290) and chloroacetaldehyde (291), which have been associated with residual ethylene oxide in sterilized material were subjected to biological testing. Ethylene oxide sterilization was shown to have no effect on the microbiological activity of streptomycin sulfate, dihydrostreptomycin sulfate, neomycin sulfate, and paromomycin sulfate (292). A slight increase in the color of streptomycin sulfate and dihydrostreptomycin sulfate was noted.

Relative humidities of at least 50% were essential for the sterilization of spore-contaminated materials using formaldehyde (293). The history and an extensive review of the use of radiation methods for the sterilization of drugs were presented (294). Also reviewed was

the method of sterilization of air and gases used in the pharmaceutical industry (295). A survey was conducted by the Food and Drug Administration to obtain a profile of the microbial load in all antimicrobial ophthalmic ointments manufactured in the United States (296). Of the 82 batches of ointments from 27 manufacturers that were tested, 16 showed contamination. Pyrogen-free solutions of 5% glucose were obtained by sterilizing at 121–124° for only 12 min. (297). Unsterilized glucose solutions were shown to be pyrogenic by injection of 10-ml. portions into rabbits, resulting in temperature rises of 0.7–1.3°. The Limulus test method for pyrogen testing was compared with the USP XVIII pyrogen test on a variety of commercial parenteral preparations (298, 299). The correlation was excellent, providing proper allowance was made for the greater sensitivity of the Limulus method.

Other papers relating to sterility are listed in Table VIII.

Table VIII—Additional References on Sterility

Reference	Topic
300	Sterilization and disinfection and processes for their control
301	Common misconceptions relating to ethylene oxide and steam sterilization
302	Review of cautions to be observed in use of ethylene oxide
303	Changes in fatty vehicles during thermal sterilization
304	Sterilization of plastic medical equipment
305	Sterilization of an acrylic resin prothesis by hydrogen peroxide
306	Disinfection and sterilization of pharmaceutical and medical plastics
307	Method for determining the effectiveness of filter materials for sterilizing air
308	Effect of energy-rich radiation on analgesics—Part I
309	Effect of energy-rich radiation on analgesics—Part II
310	Effect of cobalt-60 γ-irradiation on tetracycline

Tablets and Capsules—Cooper and Rees (311) presented an excellent review of the literature from 1969 to 1971, including all phases of tableting research and technology. A comprehensive review article covering the various factors affecting tablet disintegration was presented by Lowenthal (312). Several other areas dealing with the general topic of tableting technology were reviewed (313–315). The other numerous publications dealing with pharmaceutical technology of tablets and capsules have been subdivided into the following classifications to facilitate a search of the literature: comminution, mixing, granulation, and drying; powder characteristics; compression; effect of excipients; and tablet coating. For a thorough review, consideration of the entire section is advised since there is an obvious overlap in the subject matter of the subclassifications.

Comminution, Mixing, Granulation, and Drying—Size reduction of drug compounds by a method involving phase conversion was reviewed (316). The rate of decrease of the mean molecular weight and molecular weight distribution of polyvinylpyrrolidone powders as affected by ball milling in nitrogen, air, and oxygen was investigated (317). The influence of the ball milling atmosphere on the probability of the polyvinylpyrrolidone molecule breakdown in a unit time and the molecular size distribution of the polymers formed by the breakdown in a unit time were discussed. The problems involved in mixing and mixing mechanisms of particulate systems were reviewed (318, 319). Mixing properties of barium sulfate, lactose, spray-dried lactose, magnesium oxide, and basic magnesium carbonate were investigated (320). The effects of the specific volume of the powders, time of mixing, and type of mixing equipment used were studied. Mixing of potato starch and sodium bicarbonate under a very high dilution ratio (2500–100,000) was studied using a radioactive tracer technique (321). The results of this study demonstrated that the state of fully random mixing does not depend on the particle-size characteristics of the diluent. However, other workers using radioactive tracer techniques determined that mixing efficiency was very dependent on the particle size of the diluent (322, 323). The dependence of the degree of mixing and the time of mixing on the speed of rotation and quantity of powder to be mixed in solid–solid mixing was investigated for industrial applications (324). To obtain the same results with scale-up of the mixing equipment, consideration must be given not only to the geometric and dynamic similarities but also to the ratio between size of sample and size of batch in both pilot and largescale equipment.

Calcium phosphate requires more granulating fluid to produce a cohesive mass during wet granulation than other tablet diluents, such as lactose or starch (325). It was postulated that the intraparticulate porosity is such in calcium phosphate that at low moisture contents the liquid becomes located within the particles, thus preventing the formation of pendular liquid bridges between adjacent particles. Lactose granules were prepared by massing and screening, using water as a binder, and the effects of initial particle size, size distribution, and binder concentration on the physical properties of the granules were studied (326). Increasing the mean initial particle size decreased the amount of binder necessary to form granules and also decreased their strength, porosity, flow, and packing at equivalent moisture contents; narrowing the size distribution increased granule porosity but decreased strength even further. Granulations made by the spheronization method showed an improved granulation flow rate and narrow particle-size distribution as compared to a conventionally processed wet granulation (327). Other testing of this same method indicated that plate rotational speed was of great importance in establishing the geometric form of final granules but that dwell time did not have an appreciable effect (328).

The optimum parameters for granulation on laboratory scale and pilot plant equipment were investigated for a fluidized-bed spray granulation process (329). An increase in the amount of binding agent increased mechanical strength and decreased wear loss, while an increase in flow rate of fluidizing air and a decrease in feeding rate of the granulating fluid resulted in a particle-size decrease. Davies and Gloor (330) reported that the physical properties of fluidized-bed granulations were strongly influenced by the binder and the binder concentration. An increase in the binder concentration increased the adhesiveness, yielding less friable granules of a greater average size. Other workers obtained fundamental information on the relationship between

the amount of a binder and several characteristics indicating granulating state and properties of the granules formed (331).

A mixture formed by heating rosin and glycerol was found to be a satisfactory anhydrous binder for the granulation of tablet preparations (332). The surfaces of granules formed by the spray drying of aqueous slurries of salicylic acid and sodium salicylate with both gum arabic and polyvinylpyrrolidone were found to contain no holes or craters as compared to slurries spray dried with other binders such as gelatin, polyvinyl alcohol, carboxymethylcellulose, methylcellulose, tragacanth, and sodium alginate (333, 334). Sodium warfarin tablets prepared by a wet granulation method were unsatisfactory as to content uniformity due to the migration of the drug substance during the drying period (335). By using a TLC method, additives were selected which demonstrated inhibition of the migration of the drug substance. The use of ultrasonics for drying pharmaceutical granulations was discussed (336). It was reported that drying time was approximately one-sixtieth that of rack drying (337).

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

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

Reference	Topic
338	Diffusion and mixing of solid particles in a tube mixer
339	Parameters involved in mixing pharmaceuticals and other fine powders
340	Mixing and grinding processes during the preparation of pharmaceutical powders using a mortar
341	Agglomeration by spray drying
342	General methodology of fluid-bed granulation and spray drying
343	Effect of granule size on the physical properties of tablets
344	Review of tablet manufacture without granulation
345	Determination of the forms of moisture bonding in tablet granulations
346	Review of principles of nodular granulation, spray coating, and coating
347	Effect of moisture and heat on the decomposition of aspirin (acetylsalicylic acid) during granulation
348	Physical characteristics of tablets prepared by dry and wet granulation
349	Effect of the movement of the suspending medium during drying in a fluidized bed

Powder Characteristics—Reviews of the physical–chemical methods of characterizing powder surfaces were presented (350, 351). Both Hiestand (352) and Pilpel (353) discussed various methods for obtaining meaningful physical data for cohesive pharmaceutical powders. The problem of solid dosage forms containing small amounts of active ingredients was treated statistically (354). Equations which included particle-size distribution were derived for the calculation of theoretical coefficients of variation of drug content for solid dosage forms. Particle size of materials had very little influence on compressed tablet properties with substances having weak particle-to-particle bonding, but it had rather considerable influence with particles having strong interactions (355).

A simple test to determine the proportion of micronized drug that can be used to prepare satisfactory mixes for tableting was reported (356). The test consisted of measuring the angle of repose of a micronized powder–coarse particle mixture as a function of the concentration of micronized material. Particle densities, packing changes, and sieving properties of five commercially available samples of magnesium stearate were investigated (357). The significance of sample variation in relation to pharmaceutical processing was discussed. Description and evaluation of various testing methods for determining powder flow and powder cohesiveness were the subjects of several papers (358–360). Results of a study investigating mechanical properties of dry powders over a range of temperatures resulted in a postulation that, under the influence of pressure, melting can occur at the points of contact between particles at temperatures below their conventional melting points (361). This hypothesis accounts for the formation of solid bonds which contribute to the strength and hardness of pharmaceutical tablets. The role of moisture in compaction of particulate material was studied (362). It was determined that moisture decreases the compact strength by reducing the strength of interparticulate bonds. The effect of moisture on tensile strength of bulk solids was determined (363, 364). At a constant state of packing, the tensile strength was shown to increase as moisture content rose. This was attributed to an increase in number and dimension of liquid pendular bonds.

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

Compression—In a series of papers reporting studies of compression of powder-like materials, Bessho *et al.* (392–394) discussed, on a theoretical basis, stress distribution, density distribution, and energy involved. The ability to convert the load at which a tablet fails in tension under diametrical compression into a tensile strength was extended to deep concave tablets (395). It was demonstrated that sucrose tablets with an upper beveled edge capped at high applied forces unlike those tablets prepared with a flat upper face (396). This was thought due to high radial forces in the beveled top at the end of the compression cycle resulting in breakdown of interparticulate bonds formed during compression. Newton and Rowley (397) suggested that compaction force or pressure does not completely characterize the formation of a tablet. They offered the concept of force–time measurements as a possible solution. An instrumented punch and dye set was used to determine the force–displacement curve during compression of sodium chloride, boric acid, asagran, vitamin yeast powder mix, ibuprofen granulation, and acetaminophen (paracetamol) granulation (398). Although all of the materials behaved elastically following compaction, only sodium chloride was approximately linearly elastic.

A system designed to simulate the double-acting compression effect of rotary tableting presses was described (399). The double-acting compression was achieved by a controlled downward movement of the dye at a slower rate than the simultaneous downward movement of the upper punch. A 16-station high speed rotary tableting machine was fitted with pressure rolls containing piezoelectric transducers in the axles (400). The compaction force exerted at each tablet compression event produced an electrical pulse which could be fed to

Table X—Additional References on Powder Characteristics

Reference	Topic
365	Review of effects of water content of powders
366	Adhesion forces causing agglomeration of solid particles
367	Factors affecting the parameters of the flow rate equation
368	Effect of granule characteristics as related to weight variation of strip packages filled on automatic equipment
369	Cohesion of particulate solids
370	Theoretical calculations of tortuosity in a sedimentation bed
371	Significance of the form and dispersion composition of aspirin (acetylsalicylic acid) crystals in the tableting process
372	Effects of particle size, shape, and moisture content on the tensile properties of procaine penicillin powders
373	Specific surface area as a pharmaceutical control test for micronized drugs
374	Comparative study of four methods of granulometric analysis
375	Evaluation of powder surface properties by an adsorption method
376	Compactability of dispersed powders
377	Improvement of the flow properties of a chloramphenicol powder by the addition of Aerosil
378	Effects of surface tension on the tensile strength of beds of moist bulk solids
379	Compacting phenomenon of powders in the course of mixing with calcium stearate
380	Influence of particle size on the cohesion of particulate solids
381	Contribution of charge to powder particle adhesion
382	Random packing of equal and unequal spheres in two and three dimensions
383	Review of powder shear
384	Influence of particle size and tablet shape on the separation of sparingly soluble drugs from a hydrophobic matrix
385	Effect of the granulometric composition of powders on their volume weights and flow
386	Photometric process for particle-size analysis by microscopic examination
387	Electron-microscopic investigation of powders
388	Experimental studies of structural, mechanical, and thermophysical characteristics of some drug granules
389	Structural and mechanical properties of pharmaceutical molding powders
390	Flow properties of granules and powders
391	Dependence of capsule filling on the characteristics of powders

an integrated-circuit pulse-discriminating unit. An extensive review by Cavaco (401) was presented on the various aspects of tablet production by direct compaction and included physical factors influencing the cohesion of solid particles, their behavior during compression, improvement of the agglomeration by solid adjuvants, and the final characteristics of tablets. Reviews on the compression of powders (402) and the physical phenomena in tablet compression were also presented (403).

Other articles concerning compression are listed in Table XI.

Effect of Excipients—The effect of various starches such as corn, potato, rice, arrowroot, and a compressible starch on the rate of dissolution of salicylic acid tablets was investigated (415). In all instances, the dissolution of the drug was fastest from tablets containing compressible starch, whereas the rank order of the dissolution times of the other starch formulations depended on the dissolution test method used. In a

Table XI—Additional References on Compression

Reference	Topic
404	Prediction of tableting troubles such as capping and sticking
405	Theoretical consideration of several compression-state equations of powder-like materials
406	Factors affecting crushing properties of tablets
407	Effect of humidity and compression force on the retention of eucalyptol in tablets
408	Thermal processes during tableting
409	Discussion of the three stages of tablet compression
410	Pressure-process diagrams using a piezoelectric measuring method
411	Development of a formulation with the aid of force–displacement measurements
412	Compression behavior of phenacetin granulations
413	Porosity of tablets as related to compression pressure
414	Properties of tablets produced on an automatically controlled rotary press

study to determine the effect of intra- and extragranular maize starch on the disintegration of compressed tablets, intragranular starch resulted in the recovery of finer particles than when extragranular starch was used, but the disintegration time was longer with intragranular starch (416). Lowenthal (417) determined that starch grains were deformed by pressure and did not regain their original shape nor swell significantly when moistened. He concluded that the regaining of the shape of starch grains is apparently not the mechanism of action as a tablet disintegrant.

The effect of compression force on tablets containing sodium carboxymethylcellulose of two different molecular weights was measured (418). The lower molecular weight material resulted in tablets having larger specific surface area. An investigation of their disintegration properties showed that both cation-exchange resin and alginic acid were more efficient than calcium sodium alginate, sodium carboxymethylcellulose, and starch (corn) (419). Other studies determined that calcium sodium alginate compared favorably with alginic acid and starch when evaluated as tablet disintegrants (420). By using additives such as ethylcellulose, glyceryl monostearate, and sorbitol, it was possible to regulate the absorption levels for achieving a therapeutic effect with sulfosalicylic acid–polyvinyl chloride tablets (421). Tablets containing microencapsulated ferrous fumarate demonstrated that microencapsulation increased the dissolution of iron in gastric juice and reduced local irritation by preventing contact between the salt crystals and the gastric mucosa (422). Javaid and Cadwallader (423) studied 11 different compounds representing various classes of buffering agents with respect to their effect on dissolution of aspirin from tablet formulations. In general, carbon dioxide-producing agents such as sodium bicarbonate, magnesium carbonate, and calcium carbonate gave more rapid dissolution than the readily water-soluble buffering agents.

Magnesium stearate and sodium stearyl fumarate were compared as tablet lubricants in an antacid formulation and judged by punch force, distintegration time, and *in vitro* availability (424). By the three testing parameters used, sodium stearyl fumarate was superior. In another study, the pressure remaining immediately after compression was used as a measure of the lubrica-

Table XII—Additional References on Effects of Excipients

Reference	Topic
430	Mechanism of action of tablet disintegrants
431	Interpretation of the mechanism of disintegration
432	Incompatibilities of starch
433	Influence of starch, alginic acid, and Carbopol on the dissolution rate of aspirin tablets
434	Effect of binders and disintegrating agents on calcium monohydrogen phosphate-based tablets
435	Effect of incorporation of water-insoluble substances on delaying disintegration time
436	Effect of magnesium stearate and polytetrafluoroethylene as lubricants in direct compression of aspirin
437	Effect of adjuvants on the release of slightly soluble drugs from a hydrophobic tablet matrix
438	Factors involved in the formulation of soluble aspirin tablets
439	Formulation of aspirin tablets
440	Properties of powdered celluloses in tablet production
441	Ethylcellulose as a binder in meprobamate tablets
442	Tablet properties as a function of different binders
443	Determination of hydrogen bonds in tablet formation
444	Determination of the direct compressibility of phenothiazine derivatives
445	Characteristics of magnesium aluminosilicate under compression
446	Testing of directly compressible tablet bases
447	Evaluation of excipients for direct compression
448	Cellulose-type additives for direct compression
449	Excipients for tablet manufacture
450	Release of drugs from hard gelatin capsules

ting effect (425). By this measurement, both lubricants were shown to be equal. It was reported that magnesium lauryl sulfate possessed the lubricating properties of magnesium stearate but not its waterproofing liability (426). Factors affecting the direct compression of tablets using microcrystalline cellulose were reviewed (427). Twenty-four formulations of placebo tablets made from eight excipients for direct compression and three disintegrants were evaluated under various conditions of relative humidity (428). The data were evaluated statistically so that the formulations could be given a relative ranking on the basis of maximum hardness, minimum change in disintegration time, minimum moisture uptake, and minimum change in volume. Jones (429) reviewed the growing evidence indicating that formulation of the capsule fill is the rate-determining step in disintegration and dissolution.

References to additional literature on effect of excipients are listed in Table XII.

Tablet Coating—Several different films cast from solutions of ethylcellulose or polyamide resin were plasticized with varying concentrations of cetyl (hexadecyl) alcohol or butyl (tributyl) citrate (451). The permeability coefficient of ethylcellulose films was substantially greater than that of films consisting of polyamide resin, and it was also noted that the permeability coefficient was dependent upon the plasticizer used as well as its concentration. Two formulations were developed using polyvinylpyrrolidone for film coating of tablets by the pan-coating method (452). The addition of ethylcellulose and shellac eliminated the tackiness sometimes associated with polyvinylpyrrolidone due to the hygroscopicity of the film formed but did not alter disintegration or dissolution rates of the tablets. An apparatus for placing a film coat on individual tablets for film evaluation was described (453). Talc and

Table XIII—Additional References on Tablet Coating

Reference	Topic
455	Coating of pills and lozenges with polyethylene glycol and acrylate polymers
456	Film formers as coatings for solid, single-dose pharmaceuticals
457	Surface quality of film coatings
458	Acrylic resin film-coated tablets prepared by controlled spraying
459	Possibilities and problems in the automation of sugar-coated pill production
460	Description of tablet-coating processes
461	Small-scale enteric coating of hard gelatin capsules
462	Formulation of enterosoluble gelatin capsules
463	Characteristics of acidproof gelatin capsules
464	Treatment of capsules for gastric resistance

magnesium stearate were evaluated as adjuvants in enteric-coated tablets (454). Incorporation of talc was more satisfactory in providing favorable enteric coatings and served to preserve or augment the hardness of the tablets.

Additional references on tablet coating are listed in Table XIII.

Suspensions—Thickening agents for formulation of suspensions, emulsions, and gels of pharmaceutical interest were reviewed (465). Hiestand (466) developed the probable mechanism for the control of floc structure by polymeric materials from the theory of polymer stabilization of disperse systems. Although quantitative predictions were difficult to make, the curdled look after flocculation suggested that inadequate polymeric material was present and, therefore, the average coordination number was too high. On the other hand, settling to produce a very thick, noncaking sediment was probably due to excessive protection by suspending agents. Several agents were investigated for their stabilizing properties on griseofulvin suspensions (467). Among polyvinyl alcohol, polyvinylpyrrolidone, polysorbate 80, sodium carboxymethylcellulose, dry milk, and kaolin, polyvinyl alcohol was superior.

A graphical method was described for determining the effects of concentration and particle size on the sedimentation of suspensions; this method was based on traditional formulas describing the motion of particles in a liquid under the action of gravity (468). In the determination of yield values of hectorite gels, advantages of the falling sphere method over the cone-plate viscometer were discussed (469). Studies on the effects of particle charge of barium sulfate preparations indicated that charge alone contributes little to stability and cannot explain adherence of barium sulfate to mucosal linings (470). A microscopic electrophoretic method was used to study dilute aqueous barium sulfate suspensions (471). The isoelectric point for barium sulfate was reported at pH 4.2, and the ζ-potential varied from 140 mv. at pH 1 to -120 mv. at pH 10. The problem of pH measurements in suspensions was investigated (472). In the suspensions studied, the Wiegner–Pallmann suspension effect played a role which, however, was not identical with the pH-disturbing effect due to anomalous diffusion potentials.

Two types of mechanisms of particle adhesion to glass containers were found (473) by examining the adhesion

Table XIV—Additional References on Suspensions

Reference	Topic
476	Formulation and evaluation of two sulfamethazine (sulfadimidine) suspensions
477	Flow behavior of clay–water suspensions
478	Flocculation of Veegum suspensions by electrolytes
479	Evaluation of barium sulfate suspension formulations
480	Stabilization of suspensions by surfactants
481	Evaluation of the degree of dispersion of drug substances
482	Formation and properties of association colloids
483	Review of pharmaceutical suspensions

of chloramphenicol treated with benzalkonium chloride: (*a*) simple adhesion without mutual affinity or interaction and (*b*) adhesion with affinity. The ζ-potential of chloramphenicol crystals and glass powder was determined, and its influence on the adhesion and adsorption was discussed. In similar studies, but using prednisone, Runkel and Palagyi (474) determined that maximum adsorption of particles to glass containers occurred at a concentration of benzalkonium chloride that was just sufficient to neutralize the inherent negative charge of the prednisone particles. When the average particle diameter of the prednisone was increased to 50 μ, adsorption was negligible and drainage characteristics were excellent. A review of the physical and chemical characteristics of suspensions, including free energy of particles, humectation, flotation, crystal growth, sedimentation, rheology, and flocculation, as well as their pharmaceutical formulation, was presented (475).

Additional references on the subject of suspensions are listed in Table XIV.

Emulsions—Several reviews on the effects of processing and manufacturing procedures on the physical properties of emulsions were presented (484–486). The methods used in the evaluation of the physical properties and stability of emulsions were also reviewed (487, 488). Sherman (489) stated that accelerated aging tests at high and low temperatures and under centrifuge conditions are not suitable for predicting stability of emulsions. He reported that the measurement of the electrophoretic mobility better relates to the stability of oil-in-water emulsions at room temperature and at 40°. The effect of ultrasonic power on a mineral oil–surfactant–water emulsion system was reported (490). An optimum amount of energy was required to produce the best emulsion, but the effects of the hydrophilic–lipophilic balance (HLB) and surfactant parameters appeared to be more important in the emulsions studied. The time dependence of the droplet size distribution and the phase-inversion occurrence times were determined as functions of volume ratios, emulsifier concentration, and impeller speed for mixing water and carbon tetrachloride containing polysorbate 60 in a baffled, stirred tank (491). Phase inversion, which was very sensitive to emulsifier concentration, occurred even during stirring and the final specific interfacial area was independent of the emulsifier concentration.

An emulsion formulation suitable for freeze drying and reconstitution was described (492). Mannitol, urea, and glycine were used as supportive agents. In studying emulsifying agents, it was demonstrated that the critical

Table XV—Additional References on Emulsions

Reference	Topic
503	Factors affecting the formation of emulsions
504	Definition and theory of emulsions
505	Emulsifiers in cosmetic preparations
506	Water-in-oil cosmetic emulsions
507	Critical HLB and ternary diagrams of various oil phases of emulsions
508	Influence of HLB values of surfactants on drug release from emulsified systems
509	HLB for emulsifiers
510	Theory of linear HLB and its application
511	Determination of the HLB of anacardium gum
512	Theory and technology of submicron emulsions and their cosmetic applications
513	Review of the use of semisynthetic viscosity-increasing agents for emulsion preparations
514	Determination of the emulsifying properties of monoethyl polyoxyethylene esters of fatty acids
515	Copolymers of propylene and ethylene oxides as emulsifiers for organic liquids in water
516	Phase equilibrium of microemulsions, hydrotropic solutions, and emulsions
517	Role of mixed emulsifiers in emulsion stability
518	Stabilization of concentrated oil-in-water emulsions with aqueous solutions of proteins and surface-active polymers
519	Water-in-oil emulsion ointment bases with coupled emulsifiers
520	Emulsifying capacity of sodium lauryl sulfate
521	Emulsions of hydrophilic colloids in the presence of buffers
522	Physicochemical studies of the mutual breaking of emulsions
523	Wetting and emulsifying power of nonyl phenol polyglycol ethers
524	Application of the cohesive energy ratio concept to anionic emulsifiers
525	Differences in ultracentrifugal stability of various oil-in-water emulsions
526	Effect of initial concentration of emulsifying agents on stability of oil-in-water emulsions
527	Methods of production of binary emulsions
528	Properties, formation, and uses of binary emulsions
529	Influence of temperature-induced phase transitions on fat emulsions
530	Emulsion preparation by ultrasound
531	Preparation of pharmaceutical emulsions by electrical discharge

HLB numbers increased approximately linearly with the decrease of the logarithm of the oil phase dielectric constant (493). Pharmaceutical and chemical problems involved in the choice of an emulsifier for cosmetic formulations including anionic, amphoteric, cationic, and nonionic surfactants were discussed (494). Mathematical expressions for the HLB, minimum volume of emulsifier for oil-in-water and water-in-oil emulsions, and stability of the emulsions were developed. It was suggested that the optimum stability of oil-in-water emulsions stabilized by 1:1 molar ratios of sorbitan esters (Spans) and polysorbates (Tweens) is due to association between the emulsifier molecules adsorbed at the oil–water interface (495). The various analytical procedures for determining HLB values of emulsifiers do not account for interaction between emulsifiers and the aqueous and oil phases. It was, therefore, suggested that phase-inversion temperature determinations may provide more meaningful values (496), and a programmed viscometric technique was described for determining phase-inversion temperatures (497). With surfactant mixtures of polyoxyethylene ethers of fatty alcohols (Brij 92 and Brij 96), the phase-inversion temperature

was found to rise in approximately linear fashion as the HLB increased toward the optimum value.

The stability of mineral oil (Nujol) emulsions emulsified with sodium lauryl sulfate could be increased by adding lauryl alcohol (498). Speculation attributed the increase in stability to adsorption of lauryl alcohol at the interface not occupied by adsorbed sodium lauryl sulfate. Other workers concluded that combinations of emulsifying agents, as opposed to single emulsifying agents, produce more stable emulsions (499). The structure of oil-in-water emulsions stabilized by binary surfactant mixtures was represented schematically according to the oriented wedge theory (500). The stability of oil-in-water emulsions of paraffinic oils stabilized by sodium lauryl sulfate and sodium cetyl sulfate was shown to increase with increasing chain length of the paraffin (501). It was suggested that long-chain paraffin molecules are strongly held at the interface by association with alkyl sulfate molecules, thus increasing the coherence of the interfacial film. Starch treated with 4–5% glycerol monostearate formed a stable cream emulsion and was shown to be an effective emulsifier for cosmetic creams with a high water content (502).

Other references pertinent to emulsions are listed in Table XV.

Ointments and Creams—Particle dispersion as measured by the electron microscope was determined for salicylic acid in white petrolatum and polyethylene ointment bases and for a base of calcium soap and mineral oil (532). The rheological properties, as well as the consistency of the polyethylene base, were optimal and gave the best release of medication. The pharmacology, physical chemistry, and clinical actions of polyethylene glycol-based ointments containing hydrocortisone, antibiotics, iodine, potassium iodide, boric acid, sulfur, and coal tar were reviewed (533). Other reviews stressed the importance of selecting the correct vehicle for assuring greatest effectiveness of a drug applied to the skin (534, 535). Release of citric acid from ointments prepared with petrolatum or hardened soybean oil was enhanced by the addition of 1–7.5% egg lecithin (536). Phosphatidylcholine was considered to be the essential factor responsible for this effect. Ointment bases containing surfactants gave better release of salicylic acid, chloramphenicol, and tetracycline than bases without them (537). The HLB values of the surfactant incorporated into the ointment base influenced the release pattern, but the variation did not fit any general pattern and differed for different bases and drugs. When comparing hydrophilic and hydrophobic bases, it was shown that sulfathiazole and potassium iodide revealed higher release coefficients from hydrophilic bases (538).

The effect of some physicochemical properties of palmseed oil on the liberation of drugs from the vehicle was investigated, and it was found that release was more rapid and greater from palmseed oil of higher iodine numbers and also from bases that were mixtures of small-chain fatty acids (539). The release of citric acid was determined *in vitro* from ointment bases composed of white petrolatum and various natural oils and fats (540). Accelerated release was observed solely after addition of palmseed oil, and the rate of release was directly proportional to the content of palmseed oil in the base. Twelve protective creams containing silicone oil were evaluated by conductometric determination of diffusion rates for sulfuric acid and sodium hydroxide (541). The higher the diffusion rate, the lower was the protective capacity of the preparation. The technology for an anti-inflammatory ointment base for gums and oral mucosa was described (542). The penetration of crystalline particles of cosmetic and pharmaceutical formulations into the horny layer of human skin was evaluated by microscopic evaluation of stripped films of the stratum corneum in polarized light (543). Penetration was judged to be dependent on particle shape and solubility in the constituents of the horny skin layer rather than on particle size. A greater diffusion of methylene blue was obtained from an ambiphilic emulsion ointment on an agar base than from either lipophilic or hydrophilic emulsions, indicating the superior drug dispersal qualities of the ambiphilic systems (544).

Barry and Grace (545) investigated the rheological parameters operative during application of topical preparations to the skin. The information derived was used to develop a method for instrumentally determining rheological conditions in routine industrial control procedures and a spreadability screening test for application during innovative work prior to field trials. A review was presented on the use of creams in pharmaceuticals and cosmetics with examples of formulations and industrial manufacturing techniques (546). Polli *et al.* (547) described a laboratory investigation conducted to evaluate the use of conventional sterilizing techniques during manufacture of sterile topical dosage forms. Methods determined suitable for the sterilization

Table XVI—Additional References on Ointments and Creams

Reference	Topic
548	Rheological properties and composition of petrolatum
549	Use of an aliphatic sulfonate type of emulsifier as an ointment component
550	Technology and study of drug forms with dimexide
551	Rheological testing of several emollient creams
552	Effect of temperature on the consistency of hydrocarbon ointments
553	Effect of composition on consistency and bleeding of hydrocarbon salves
554	Properties and uses of sodium alginate for ointments
555	Excipients in preparations for dermatological use
556	Water absorption number of ointment bases
557	Technological and pharmaceutical characterization of dermatological preparations
558	Polyethylene glycols as bases for preparing salicylic acid ointments
559	Formulation and preparation of transparent dispersions of lanolin in liquid and gel forms
560	Dispersing capacity of dimethyl sulfoxide during preparation of white mercury and zinc ointments
561	Effects of triglycerides of saturated and unsaturated fatty acids on the liberation of active substances from hydrocarbon ointment bases
562	Review of various types of ointment bases
563	Liberation of active substances from eye ointments
564	Determination of the diffusion and distribution coefficients of active materials in salves
565	Stability testing of concentrated intermediates of suspension-type ophthalmic ointments
566	Methods for testing externally applied pharmaceuticals

of active ingredients, excipients, vehicles, and packaging materials were reported.

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

Suppositories—For lipophilic bases, the homogeneity of suspensions of active agents in the bases, the rheological behavior at 37–40°, the viscosity at 40°, and the thixotropic index could be used as criteria for determining the suitability of these bases for use in suppositories (567). The index of emulsionability, the maximum percentage of water that a suppository mass may contain as a stable emulsion, was determined by the uniformity of color given to the mass by Sudan II (568). Good emulsifying power was correlated with higher dehydration tendencies. The addition of sorbitan esters (Spans) or sorbitan ester–polysorbate (Span–Tween) mixtures to suppositories containing aminopyrine (amidopyrine) decreased their disintegration time and thus accelerated the release of the active ingredient (569). Approximately twice as much sodium iodide was absorbed in rats from rectal suppositories prepared with polyethylene glycol, Witepsol S, or Witepsol E as from those prepared with cocoa butter (570). Absorption was measured by ^{131}I activity in the thyroid.

Addition of monoglycerides to suppository bases did not improve the passage of drugs through a membrane (571). As the amount of monoglycerides in the base increased, the amount of liberated drug decreased. Triglycerides gave the opposite effect. In studies on Shay butter, it was determined that the addition of 20% hard paraffin or 15% white beeswax was necessary for use in suppositories (572). Gelatin and methylcellulose used in 2 and 0.75% concentrations, respectively, were more suitable than 1% sodium alginate, 2% polyvinylpyrrolidone, or 4% yeast in the manufacture of suppositories by freeze drying (573). The choice of active ingredients present in the suppositories and their concentrations strongly affected the lyophilization properties of the base compounds. Therefore, the appropriate base must be chosen to correspond with the desired active ingredient.

Additional references on suppositories can be found in Table XVII.

Aerosols—Several aspects of aerosols were reviewed, including the development of pharmaceutical aerosols (580), the pharmaceutical uses of aerosols (581), aerosol drug therapy (582), solvent propellants (583), and technical problems of powder aerosols and aerosol propellants (584). The series of events, including product development, leading to the marketing of a new aerosol product was traced through the eyes of a cosmetic chemist (585). Sciarra *et al.* (586) investigated the possible formulation of various epinephrine salts such as malate, maleate, and fumarate for inclusion in aerosol dosage forms. The results of solubility studies of these salts in propellants indicated that the formulation of epinephrine salts as an aerosol dosage form must be accomplished through use of a cosolvent or by formulating a dispersed system. A stable aqueous suspension of a mixture of thymol, peppermint oil, and eucalyptus oil was described for application as an aerosol (587). The use of nitrogen at 6 atmospheres as the propellant gave aerosol particles of 40–50 μ in diameter. The particle-size distributions of four hair-spray formulations were measured as a function of the propellant composition (588). The mass median diameters of the sprays were found to decrease with increasing pressure of the aerosol.

A method was described for determining comparatively the proportion of the emitted dose of an aerosol formulation that penetrated a system of wet-lined tubes and arrived at a filter (589). Clinical work with bronchodilators showed that this method permitted comparisons between different formulations of the same dose of the same drug. By using a conifuge, measurements were made of the particle-size distribution of aerosols generated by three types of nebulizers intended for therapeutic use (590). After converting the size distribution to a mass distribution, the deposition of different fractions in the human respiratory tract could be predicted. The critical variables that control the movement of aerosol particles were found to be the size and density of the individual particles, their initial velocity, and the velocity of the surrounding air (591). These may be adjusted, within limits, to promote the desired deposition of the particles or to prevent an unwanted deposition.

Timed Release—A listing of recognized types of timed-release dosage forms included: barrier coating, imbedding in a slowly eroding matrix, imbedding in a plastic matrix, repeat action through layering in tablets, mixture with ion-exchange resins, imbedding in a hydrophilic matrix, epoxy resin beads, soft gelatin retard capsules, and drug complexing (592). Methods of prolonging the action of antibiotics and some other drugs by altering molecular structure so as to decrease solubility and by using coatings or capsules to delay absorption were discussed and evaluated (593). Hollister (594) suggested that although oral timed-release medications delay or slow absorption of drugs, the advantages are often slight or, at times, disadvantageous. The oral antidiabetic buformin (butylbiguanide), which has a normal half-life of approximately 2 hr., was formulated in a timed-release form for which serum concentration remained almost constant for approximately 7 hr. (595). Timed-release tablets of the insoluble matrix type containing 15 mg. phenylpropanolamine hydrochloride (norephedrine chloride) and an antihistaminic were evaluated (596). *In vivo* and *in vitro* drug release showed good agreement with all tablets except one formulation in which the *in vitro* dissolution rate depended on the pH of the dissolution medium.

Table XVII—Additional References on Suppositories

Reference	Topic
574	Review of rectal drug forms and their properties
575	Compatibility of chloral hydrate with lipophilic suppository bases
576	Mechanical and rheoviscometric parameters of oleaginous suppository bases
577	Composition of fat bases for suppositories
578	Possibility of using thyrocalcitonin in suppositories
579	Proposal for the modification of the formulation of iodochlorhydroxyquin suppositories of the Hungarian National Formulary

Surface areas and transverse surfaces of fracture from timed-release tablets manufactured by the imbedding principle were investigated (597). Pressure-dependent differences in the texture of tablets influenced the drug release rate. Granulations for tablets with prolonged action were prepared containing lauric, palmitic, and stearic acid as adjuvants, applied by coating (598). The release rate *in vitro* decreased with the increasing molecular weight of the acids. A method for preparing timed-release calcium chloride tablets in which this ingredient was suspended in a melt of cetyl alcohol, hydrogenated cottonseed oil, and stearic acid was described (599). The release rate of sodium salicylate from timed-release tablets was measured as a function of the amount of magnesium stearate in the tablet (600). Large amounts of this agent blocked the release of the active substance, while too small amounts caused a rapid disintegration of the tablets. The possible use of biodegradable polymers impregnated with the drug for timed-release preparations was discussed in terms of diffusion and permeability theories (601).

Intravenous administration of sodium barbiturates formulated in a soybean oil emulsion showed prolonged-action effects (602). It was postulated that this effect was caused by the oil droplet acting as a depot, releasing the drug to blood and brain capillaries by direct contact, and, therefore, serving as a bridge between the circulation system and the blood–brain barrier. A parenteral suspension of microspheroids consisting of microcrystals of drug surrounded by a totally enclosing semipermeable protective shell was suggested as a prolonged-action intravenous dosage form (603). Release of drugs from the circulating microspheroids markedly prolonged the apparent biological half-life of the drug quinacrine hydrochloride. The alginic acid salt of pilocarpine, when administered as an ophthalmic disk in the cul-de-sac of the eye, provided a significantly greater miotic response than was obtained from pilocarpine solutions (604). This observation suggested that the use of solid ophthalmic dosages in the treatment of glaucoma may be more effective and require less frequent drug administration to produce a prolonged physiological effect.

Additional references in the area of timed release are listed in Table XVIII.

Table XVIII—Additional References on Timed Release

Reference	Topic
605	Different methods of producing long-acting oral pharmaceuticals
606	Review of design and formulation of pharmaceuticals with sustained action
607	Review of formulation materials for gradual-release dosage forms
608	Testing methods for sustained-release preparations
609	Description of a slow-release aspirin preparation
610	Release of active substances from enteric-coated gelatin capsules
611	Method for testing ulcerogenic effect and *in vivo* release of potassium iodide from slow-release tablets
612	Preparation in pharmacies of tablets with prolonged action
613	A mathematical model for optimization of spansule production
614	Controlled dosage of testosterone through silicone rubber

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

Microbiological Contamination of Cosmetics—Although contamination by Gram-negative organisms, particularly those of the pseudomonas group, is still a problem, the cosmetic industry continues to show a concerted effort to improve the quality of its products (615). Three years ago, 61 of 250 samples examined were contaminated; last year, only eight of 223 examined were reported contaminated. A review of the microbiological control of nonsterile products and raw materials was presented (616). A listing of essential oils, *e.g.*, orange and thyme oils, active against *Bacterium coli*, *Bacterium typhi*, *Corynebacterium diphtheriae*, *S. aureus*, *Streptococcus pyogenes*, and meningococcus was given (617), and other therapeutic properties of these oils were presented.

The inhibitory effect of ethanol and propylene glycol against three strains of *P. aeruginosa* was investigated in the presence and absence of 0.1% potassium sorbate (618). Results suggested that ethanol concentrations of 5% or more may exert a preservative action and that 10% propylene glycol is also suitable. The effect was augmented by addition of potassium sorbate at pH 6–7. Bruch (619) enumerated the common contaminating organisms present in nonsterile products and listed those that are most dangerous to certain types of products. The organisms of clinical significance in pharmaceutical and cosmetic preparations are "free living" types of Gram-negative bacilli and belong to the klebsiella, enterobacter, serratia, pseudomonas, and flavobacterium groups (620). Many of them have a remarkable ability to survive and even to multiply in the presence of commonly used disinfectant and bacteriostatic agents. The potential hazard to consumers from use of eye-area cosmetics contaminated with *P. aeruginosa* was evaluated (621). Experimental results suggested that corneal destruction resulted from the organism's elaboration of a collagenolytic enzyme, which may be activated *in vivo* during the infective process. A full discussion of the importance of monitoring the chemical and microbiological quality of the water used in cosmetics was presented (622).

Aspects of Formulation and Technology of Cosmetics—In suntan preparations containing a commonly used screening agent, oil-based vehicles gave better sunburn protection to human skin than oil-in-water emulsion vehicles (623). However, it was also reported that oil-in-water emulsions were superior in promoting tanning. Data were presented to indicate that substantive proteins, protein hydrolysates, may be useful moisturizing agents in skin-care products (624). Polyamino acids may have an immediate effect on the skin and/or hair, but polypeptides must be changed by enzymatic and acylatic processes to form polyamino acids (625). These processes of change often failed or were delayed, especially with unhealthy skin or hair, but polyamino acids always produced the desired results. Stratum

corneum, in the form of excised callus, was immersed in distilled water, organic solvents, and aqueous solutions of detergents, humectants, and soaps for different lengths of time (626). Weight increases were compared in an effort to determine the factors influencing the water content of skin and the conservation of this water. Although the chemical pyrrolidonecarboxylic acid has been known for many years, only recently was it reported that pyrrolidonecarboxylic acid, especially in salt form, was a naturally occurring moisturizing agent in the skin (627).

Idson (628) reviewed the factors that caused skin to retain or lose moisture, such as relative humidity, hygroscopic materials normally present in the skin, and water-binding mechanisms in the stratum corneum. In a discussion on humectants *versus* moisturizers, humectants were defined as components of cosmetic products that prevent water or moisture loss from the preparation and moisturizers as active additives which restore moisture to the stratum corneum (629).

Titanium dioxide was colored to increase its applicability in cosmetic preparations by reducing a synthetic vat dye to its leuco base followed by the addition of sufficient powdered titanium dioxide at 80° under carbon dioxide (630). Electron microscopy and X-ray analysis showed that a thin, well-adhering layer of the dye coated the particles. Tests to determine the safety of cosmetic products for infants were described. It was concluded that more attention should be paid to developing products best suited for the skin of particular age groups (631). Bell (632) predicted that, due to improvements in enzyme technology, the addition of these agents to cosmetic formulations will open a new field in the near future. Squalene was cited as a natural cosmetic raw material which could be incorporated into preparations to act as an emollient, humectant, and lubricant (633). The interrelations between moisture regulators and lipids of the dermal surface were discussed, and widely used test methods were described (634). Several formulas for modern cosmetic preparations using moisturizing factors were given.

Common ingredients used in emollient preparations and their contribution to emolliency, elegance, *etc.*, were reviewed (635). Properties of white mineral oils and their application to cosmetic preparations, differences between paraffinic and naphthenic oils, and the requirements of official compendia for these oils were discussed (636). The physical and chemical properties of various grades of white mineral oil used in cosmetic formulations were compared (637). Systems for thickening liquids using Carbopol and no alkali were described (638). The use of Carbopol as a thickening agent depended on having polyethoxy or polyhydroxy liquids present, in which case the thickening is based on hydrogen bonding. Courtney (639) presented an interesting review on the history, formulation, structure, and future of gels in cosmetics and toiletry products. Experimental results suggested that water affects the mechanical properties of single fibers of hair, and these in turn strongly influence the set-holding characteristics of hair tresses (640). The binding of water appeared to be a site binding process; *i.e.*, interactions occurred in stoichiometric ratios between the water molecules and the various hydrophilic groups of the protein (carboxylic, amino, and peptide groups) and were governed by the mass action law.

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

Reference	Topic
641	Origin and development of the science and technology of cosmetics
642	Review of ointments and transparent microemulsion gels
643	Review of formulations for modern hair shampoos
644	Factors influencing the formulation of suncreams
645	Review of light protection of skin
646	Discussion and definition of moisturizers
647	Behavior of moisturizers *in vitro* and *in vivo*
648	Petroleum derivatives as moisturizers
649	Review of the properties and possible use of montmorillonite in cosmetic and pharmaceutical preparations
650	Review of the role of fats and oils in cosmetics
651	Listing and possible use of biologically active compounds in cosmetics
652	Application of water-soluble resins to cosmetics
653	Summary of the uses and activities of substances commonly used in cosmetics
654	Review of alkyl sulfoacetates for cosmetic use
655	Review of cosmetic and toilet preparation research since 1968
656	Review of detergent use in cosmetics
657	Review of detergent use in cosmetics
658	Properties and use of cationic compounds in cosmetics
659	Review of biologically active substances as additives in cosmetic preparations
660	Cosmetic powder formulations and considerations in selecting a perfuming agent
661	Camelia oil and its use in cosmetics
662	Use of volatile hydrocarbons for cosmetics
663	Physicochemical properties of isopropyl myristate and palmitate and their use in cosmetic formulations
664	Review of new raw materials for cosmetic and perfume manufacturing introduced during 1971–1972
665	Use of emulsions and their behavior on the skin
666	Description of an irritation study for a feminine hygiene spray

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

Packaging—The factors that should be taken into consideration when designing a "childproof" package were discussed (667). The mechanism, functioning, filling, performance, precision and constancy of dosage, compatibility with valve and solution, safety, and application of metering valves were described and discussed (668). The uses of polyethylene, polyvinyl chloride, polystyrene, and blends of these plastics and the effects of processing on their suitability for packaging of cosmetic emulsions were outlined (669). Evaluation methods for plastics that are to be in contact with medicinal preparations were described (670, 671). It was stressed that approval of a formulation is only valid for the product–plastic combination (672). Polypropylene containers were shown to be satisfactory for storing aqueous solutions containing common phenolic preservatives (673). Sorbic acid solutions in the same containers deteriorated rapidly. In evaluating disposable rubber closures for bulk irrigating solutions, it was ascertained that the amount of total extractives from the closures was influenced by the total mass of the closure as well as its surface area (674). Based on the UV absorption decrease of aqueous solutions in the presence of various plastics, the effect on the stability of local

Table XX—Additional References on Packaging

Reference	Topic
683	Teratogenicity of phthalate esters in rats
684	Review of plastics for packaging applications
685	Some improvements in packaging materials, methods, and machines
686	In-use contamination of intravenous solutions in flexible plastic containers
687	Protection of pharmaceutical solutions from catalytic effects of light by amber glass
688	Stability of sodium bicarbonate injection stored in polypropylene syringes
689	Problems involved with the development of a large-volume radiopaque diagnostic agent
690	Use of surface-treated Parasolvex glass for pharmaceutical solutions
691	Effects of water at 121° on pharmaceutical glass
692	Review of unit packaging of tablets and capsules
693	Description of eight methods for detecting poorly sealed pharmaceutical packages
694	Federal regulations regarding packaging of nitroglycerin tablets at the retail level
695	Description of a new "childproof" aerosol actuator
696	Description of a safety vent in aerosol cans which relieves pressure and prevents explosions
697	Codispensing valve system for dispensing striped aerosol foams

anesthetics in the presence of polyamides 6 and 12 and high pressure polyethylene of low crystallinity was determined (675). Polypropylene, polyvinyl chloride, polystyrene, and polycarbonate had no influence.

The biological activity and toxicity of stabilized amyl nitrate were not affected by long storage when cellular polyurethane vial closures were used (676). Effervescent granules were stored in various containers for 6 months and evaluated for carbon dioxide loss (677). Aluminum foil (2 mm.) provided the best protection for this type of product. Guidelines were presented covering the selection of syringes in process controls and procedures for prepackaging parenteral drug products in hospital pharmacies (678). The shattering of sterile vacuum-sealed fluid bottles during removal of the cap was reported (679). Apparently this can occur when the cap is removed quickly with the bottle in an inverted or partially inverted position due to a "water hammer" effect. Instructions were presented to the practicing pharmacist for the packaging of nitroglycerin tablets for preventing loss of potency during storage (680). The use of varnished aluminum tubes for packaging of ophthalmic ointments partly resolved the problem of metallic particles (681). The manufacturing process of these tubes for ointments was reviewed briefly, and the different methods used in testing were described. Leakage tests, currently in general use, for flame-sealed ampuls were demonstrated to be inadequate for determining whether passages to the outside exist in finished ampuls (682). Those containing these passageways may or may not pass existing leakage tests, depending upon the severity of the test.

Table XX contains additional references in the area of packaging.

Equipment—A European cylindrical shredder was described, and its performance was evaluated for wet and dry granulations (698). It was shown to be comparable to the Fitzpatrick mill for normally wet granulations but superior when the material was overly wetted.

Table XXI—Additional References on Equipment

Reference	Topic
707	Comparison of Erweka and Stokes hardness testers
708	Homogenizers and double-cone blenders
709	Review of fluidized-bed granulating techniques
710	Comparison of fluid-bed and hot-air drying
711	Description of a wet sieving method using *p*-hexane as the liquid dispersant
712	Cake thickness and deposition rate in plate-and-frame filter presses

The principle of sieving pharmaceutical materials by gyratory vibration was reviewed and compared with the efficiency of standard vibratory methods (699). For powder mixtures containing low concentrations of active materials, the Erweka planetary mixer, with a fixed vat, was shown to be superior to the Erweka cubical mixer in the rapidity with which homogeneity was obtained (700). The speed of dispersion of the active principle throughout the excipient was greater in the cubical mixer, but the latter was unable to reduce the agglomeration of particles. Methods for testing the friability, disintegration time, and dissolution behavior of tablets using the E-70 apparatus were reviewed, and the details of testing, the prescribed limits of disintegration times, and the performance of the test were emphasized (701).

Shah (702) reviewed the nondrying applications of spray drying including stabilization, blending, use for reaction mixtures, timed-release formulations, and waste disposal with the production of useful by-products. The design of a continuous manufacturing process for an oil-in-water cosmetic cream was described (703). In arriving at a final process design and selection of equipment, emphasis was placed upon the determination of the basic chemistry responsible for the stability and characteristic consistency of the product and the determination of the relative importance of process and ingredient variations. The fundamental microbiological aspects of modern cleaning and sterilizing equipment were discussed (704). Beard (705) discussed the variables such as speed, changeover time, and product shape and how these considerations govern the choice of tablet-counting equipment. A prototype irradiation module was built and successfully tested (706). This unit could be adapted to packaging lines for the sterilization of packages and materials prior to filling at normal line speeds.

Additional references on equipment can be found in Table XXI.

PHYSICAL PHARMACY

Methods of preparation of three polymorphs, two solvates, and an amorphous modification of sulfameter (sulphamethoxydiazine) were described (713). The interconversion of these forms under various conditions of heating, suspension in water, and grinding, as well as dissolution behavior, was studied. Thermal analysis of sulfanilamide polymorphs indicated that the α-, β-, and δ-forms are transformed to the γ-form prior to melting (714). The phase-transition temperatures and heats of transition was as follows: α-form, 108°, 358 cal./

mole; β-form, 131–141°, 347 cal./mole; and δ-form, 108°, 386 cal./mole. Shefter *et al.* (715) used X-ray crystallographic methods to determine the structures of sulfadimethoxine, sulfadoxine, and sulfisoxazole. The molecules had similar conformations about their sulfonamide linkage but had markedly different orientations of their respective heterocyclic rings relative to the sulfanilamide portion of the molecule. In a study of polymorphism in sulfonamides, it was postulated that electron-withdrawing and electron-donating groups at the *N'*-position influenced the strength of the hydrogen bonds that form and, hence, the tendency of these compounds to exhibit more than one crystalline form (716). In some cases, however, minor alterations in structure resulted in disproportionate changes in the compactness of the crystal lattice, and this fact made it difficult to develop broad generalizations applicable to large groups of compounds.

The controversy over polymorphism in aspirin continued. Schwartzman (717) attributed apparent polymorphism to different crystal habits caused by different solvents used for crystallization, and dissimilar melting points to poor transfer of heat caused by the larger crystal size or to possible crystal defects. Other workers attributed the apparent polymorphism to salicylic acid impurities present in the aspirin samples tested (718). On the other hand, Borka (719) presented evidence for the existence of two polymorphic forms of aspirin. Solution phase transformation of the metastable Form II into the stable Form I was cited as further evidence for the existence of Form II.

The properties of liquid crystals were studied by spectroscopic or electromagnetic methods such as X-ray, IR, UV, NMR, double-refraction, and dielectric constant (720). The expansion coefficient and surface tension were also measured to obtain thermodynamic information. Phase transitions in mixtures of mesomorphic cholesteryl esters were studied by visual thermal microscopy (721). Binary mixtures of saturated cholesteryl esters showed transitions from the solid phase to the mesomorphic phase at temperatures that were depressed well below the phase-transition temperatures of either pure compound. The phase-transition temperatures in the solid, liquid crystal, and isotropic liquid states of four cholesteryl esters were determined by polarization microscopy, differential thermal analysis, and measurement of the dielectric constant and dielectric loss (722). Data on transition temperatures obtained from these various methods were generally in good agreement with each other and were found to be useful for mesophase identification.

Dissolution rates of drugs in solid dispersions in polyethylene glycol 4000 were investigated, but no differences in dissolution rates were shown in drugs that were not soluble in polyethylene glycol 4000 (723). In cases where drugs were soluble in polyethylene glycol 4000, an increase in dissolution rate was noted. Surpuriya and Higuchi (724) studied the kinetics of cholesterol and desmosterol transfer from aqueous sodium lauryl sulfate solutions and from sodium taurocholate–lecithin solutions into hexadecane and vice versa by means of the multiparticulate dispersion technique. The results were discussed in terms of an interface-controlled mechanism being operative, involving solute–micelle complex or free solute in the rate-determining step.

The diffusion of ephedrine, sulfathiazole, chloramphenicol, acetaminophen (paracetemol), isoniazid, and amphetamine in solutions of polysorbate 40, polysorbate 80, and polyethylene glycol 1000 monocetyl ether (Cetomacrogol 1000) was studied (725). With the exception of isoniazid, the observed diffusion coefficients, corrected for resistance to flow, depended upon the surfactant used and both the drug and surfactant concentrations. An extensive investigation of the kinetic and thermodynamic aspects of the transfer of sulfonamides through immiscible phases was reported (726). Included was a postulated activated complex for the interphase transfer of these compounds. A linear relationship with unit slope was found between the logarithm of the intrinsic partition coefficient of *p*-alkyl pyridines and the logarithm of the extraction constants of the corresponding ion-pairs of the protonated base chlorides, as determined in chloroform–water and octanol–water systems (727). Because of methylene increments occurring distantly from the polar portion of the molecule, their influence upon the oil–water partition coefficient would be expected to be the same for the free base and ion-pair. Yalkowsky *et al.* (728) suggested that change in crystal structure as a function of chain length in alkyl *p*-aminobenzoates is somewhat analogous to micelle formation within a homologous series. The lower members of a surfactant series exist only as monomers whose properties are primarily determined by the polar group; but as the chain length is increased, the increasing amphiphilic character provides for orientation of the molecules into a particular structure, the micelle. Further increases in chain length serve to increase the stability of these structures relative to the monomeric state.

By using diffuse reflectance spectroscopy, the interaction between dextroamphetamine sulfate and spray-dried lactose and dextrose in solid–solid mixtures was studied (729). Two new absorption maxima were observed in the reflectance spectra of heated samples and were attributed to the chemisorption of the amine molecules on the surface of the sugars. In preformulation studies of a lyophilized product, melting-point–composition diagrams were constructed and percent melt values at room temperature were calculated (730). Final product physical appearance correlated well with calculated percent melt as ascertained by controlled lyophilizations. The characteristic differences between one gel and another were reviewed and traced to the variations of framework flexibility, number and nature of cross-links, attractions and repulsions between framework elements, and interactions with solvents (731). Theoretical calculations based on the Debye–Hückel theory indicated that for weak monoprotic bases that do not involve a hydroxyl group, a stoichiometric pKa determined at any ionic strength would be no different from the thermodynamic pKa (732). The pKa's of two local anesthetic amines determined at several ionic concentrations supported this theory. Terada (733) described a method for determining true partition coefficients for amphoteric acids by determining the

Table XXII—Additional References on Physical Pharmacy

Reference	Topic
737	Use of differential thermal analysis in pharmaceutical technology for prediction of stability
738	Significance of polymorphism in drug technology
739	Kinetics of polymorphic transformation of sulfathiazole Form I
740	Kinetics of interconversion of sulfameter (sulfamethoxydiazine) crystal forms
741	Determination of valinomycin crystal structure by direct methods
742	Polymorphism of mafenide (homosulfamine) by thermal analysis and IR analysis
743	Determination of polymorphic forms of chloramphenicol palmitate by IR spectrophotometry
744	Review of aspirin polymorphism
745	Preparation of aspirin (acetylsalicylic acid) studied by an image identification method
746	Effect of temperature on the physical nature of phenobarbital (phenobarbitone) produced by acid–base precipitation
747	Physicochemical properties of lyophilized aluminum hydroxide
748	Thermophysical characteristics of drugs and granular materials
749	Physicochemical properties and application to pharmaceutical science of silicate powder
750	Two new methods for the spectral determination of microdissociation constants
751	Dissociation constants and activity coefficients of Carbopols by potentiometric titration
752	Demonstration of an interfacial contact resistance during the diffusion of water in gelatin gels
753	Surface tension of polymer liquids interpreted by the hole theory
754	Calculation of electronic structure of some drugs by the Pople method
755	Molecular estimates of molar attraction constants
756	Physicochemical properties of erythromycin estolate
757	Physicochemical properties of halothane
758	Physicochemical properties of levarterenol bitartrate
759	Physicochemical properties of meperidine hydrochloride
760	Physicochemical properties of meprobamate
761	Physicochemical properties of nortriptyline hydrochloride
762	Physicochemical properties of propoxyphene hydrochloride
763	Physicochemical properties of sodium cephalothin
764	Physicochemical properties of sodium secobarbital
765	Physicochemical properties of triamcinolone
766	Physicochemical properties of triamcinolone acetonide
767	Physicochemical properties of triamcinolone diacetate
768	Physicochemical properties of vinblastine sulfate
769	Physicochemical properties of vincristine sulfate

apparent partition coefficients as a function of pH. The values obtained for *p*-aminobenzoic acid, sulfonamide, and sulfameter (sulfamonomethoxine) agreed well with the results of others.

One of the most potentially successful approaches to drug design is the attempt to place correlations between changes in molecular structure with changes in biological activity on a quantitative and predictive level (734). While qualitative efforts were made in this area by chemists and pharmacologists for over 100 years, more recent progress illustrates the potential of regression analysis, molecular orbital calculations, and parameterization using various physicochemical measurements. A review was presented dealing with basic areas of molecular orbital theory important in interpreting drug activity (735). Peradejordi *et al.* (736) investigated the relations existing between electronic structure and base strength of benzacridines and their amino derivatives using semi-empirical molecular orbital calculations. Their results indicated that the energy to protonate a nitrogen derivative of a conjugated hydrocarbon may be divided into the terms ΔE_ρ and ΔE_π for changes in localized and delocalized energies, respectively, an energy for solvation, and a term for steric hindrance to protonation.

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

Dissolution—Dissolution times of some commercially available tablets of sulfamethizole were measured using four different methods, but no correlations of predictive value were obtained between dissolution and absorption parameters (770). The stationary-basket method discriminated best between formulations and was the most useful for quality control purposes. A new approach was described for increasing the dissolution rate of relatively insoluble powders (771). It was based on the concept of increasing the surface available for contact with dissolution media and was accomplished by equilibration of the drug in an organic solvent on an insoluble excipient with an extensive surface area (*e.g.*, fumed silicon dioxide). An increased rate of release from these minuscular drug delivery systems was observed in all instances, and it was suggested that a decrease in particle size was a major factor in improving the dissolution rates (772).

To minimize effects of differences in particle-surface areas which occurred from experiment to experiment and during each individual experiment, Higuchi *et al.* (773) employed a "concentration jump" technique during the determination of dissolution rates in solvents containing complexing agents. The results demonstrated the importance of the magnitudes of both the diffusion coefficient of the complexing component in the solvent and of the stability constant of the complex on dissolution kinetics. *In vitro* studies on the dissolution rate of cholesterol monohydrate crystals in micellar bile acid solutions showed that the addition of lecithin decreased the dissolution rate, even though lecithin increased the equilibrium solubility of cholesterol in these systems (774). The reduction in rates caused by lecithin was attributed to a large crystal–solution interfacial barrier.

The total solubility of benzoic acid in aqueous solutions of polysorbate 80 was shown to increase linearly as the concentration of the surfactant was increased (775). Since the concentration of polysorbate 80 was increased with a limited increase in viscosity of the micellar solution, the dissolution of benzoic acid was increased to a maximum rate, but further increases in the concentration of polysorbate 80 decreased the dissolution medium. Utilizing *in vitro* studies, Tawashi and Piccolo (776) demonstrated that very low concentrations of FD&C Blue No. 1 significantly reduced the dissolution rate of sulfathiazole crystals in 0.04 *M* sodium cholate solutions. These results were confirmed by *in vivo* absorption studies in man. The intrinsic dissolution rates of the monohydrochloride, dihydrochloride, and disulfate salts of an experimental antihypertensive were studied (777). Although there were significant differences in the dissolution rates of these salts, comparative hypotensive activity in anesthetized dogs showed that the three salts did not differ from each other.

Although the dissolution rate of powdered aspirin (acetylsalicylic acid) is inversely proportional to crystal size, the opposite was found true in tablets (778). This was shown to be due to the agglomeration of the fine particles, but this effect could be hindered by appropriate adjuvants. Under stirred and sink conditions, the dissolution of benzoic acid in aqueous solutions of polysorbate 80 was shown to occur in accord with the diffusion layer model (779). The micellar diffusion coefficient was decreased as the quantity of solubilized species in solution was increased, presumably due to changes in the size and weight of the solubilized species. Particles dissolving in a dissolution medium initially decrease in linear dimension while the number of particles remains unaltered. However, at a particular point in time, the smallest particle disappears and, from that point on, the number of particles decreases (780). These phenomena were simulated on a digital computer, and the agglomerate dissolution pattern under sink conditions was shown to follow a cube-root law.

The effect of low concentrations of an *n*-alkyl polyoxyethylene surfactant on the dissolution of hydrocortisone was investigated (781). It was shown that the plot of the dissolution rate constant *versus* the surfactant concentration exhibited a pronounced maxima at the region of the critical micelle concentration (CMC). Rates of dissolution of salicylic acid were determined at constant pH in the absence of buffer salts by using a pH-stat (782). The dissolution rate increased with increasing pH up to a maximum of pH 4. Wadke and Reier (783) described a method whereby transition temperatures and other thermodynamic parameters associated with the transitions of chloramphenicol palmitate form B, anhydrous ampicillin, and theophylline to chloramphenicol palmitate form A, ampicillin trihydrate, and theophylline monohydrate, respectively, were determined from intrinsic dissolution rates. In a series of papers, Kildsig and coworkers (784–787) investigated some parameters involved in the dissolution mechanism including concentration gradients, surface tension of solids, solid–liquid interface energies, and effective interfacial concentrations. The release of a mixture of two acidic drugs (benzoic and salicylic acids) and a mixture of two amphoteric drugs (sulfadiazine and sulfapyridine) from an inert matrix into different buffers was investigated using the physical model approach (788–790). Equations were derived describing the diffusional behavior and interactions of the various species under different conditions. The *in vitro* release of four progesterone-type steroids from a silicone polymer was studied by Roseman (791) and was found to be dependent upon the molecular structure of the steroid. Since the diffusion coefficients of the steroids were of the same magnitude, the diversity in release patterns was mainly attributed to the difference in the polymer solubilities of the steroids.

A flow visualization technique was used to compare flow patterns in several kinds of dissolution apparatus in wide use (792). The technique readily revealed the undesirable characteristics and provided a rational basis for judging an empirically developed dissolution apparatus. The shape of the dissolution flask, which is not clearly defined in USP XVIII and NF XIII, can significantly affect dissolution patterns (793). Formulators should be aware that these differences exist, and it was recommended that there be more definitive specifications for the dissolution vessel in the compendia. Tingstad *et al.* (794) described a modified, continuous flow column-type dissolution apparatus using commercially available components. Specific advantages of the flow method, especially for sublingual tablets, were cited. Dissolution studies were carried out on commercially available dosage forms of 300-mg. lithium carbonate tablets and capsules (795). Log-probability analysis of the data showed significant differences in the dissolution of the two dosage forms. The usefulness of a

Table XXIII—Additional References on Dissolution

Reference	Topic
798	Review of dissolution kinetics
799	Energy changes during the dissolution process
800	Kinetics of the dissolution process
801	Dissolution rates of poorly soluble solids in mixed organic solvents
802	Prediction of dissolution rates of slightly water-soluble powders from simple mathematical relationships
803	Influence of crystal structure on dissolution rate
804	Dissolution kinetics and thermodynamic parameters of polymorphs of an experimental antihypertensive
805	Dissolution behavior of polymorphic, pseudopolymorphic, and amorphous phases of drugs
806	Mathematical description of dissolution of a series of crystalline and amorphous drugs
807	Enhancement of dissolution rate by β-cyclodextrin inclusion
808	Dissolution rate of a monolayer of 1-monolaurin at constant area
809	*In vitro* release of active components from tablets
810	Review of factors affecting dissolution rate of oral dosage forms
811	*In vitro* dissolution rate of phenytoin in relation to particle size and specific surface area
812	Rate studies on the dissolution and degradation of phenoxymethyl penicillin at different pH values
813	Dissolution of alkyl vinyl ether–maleic anhydride copolymers and their ester derivatives
814	*In vitro* release of an amine salt by a water-soluble polyelectrolyte
815	Linearization of dissolution rate curves by the Weibull distribution
816	Influence of formulation factors and processing variables on the dissolution rate of hydrochlorothiazide tablets
817	*In vitro–in vivo* studies on commercially available nitrofurantoin tablets
818	Dissolution time of aspirin tablets as a function of the surface area
819	Critical comparison of different methods for the determination of dissolution rate
820	Review of methods for *in vitro* dissolution rates of tablets
821	Critical evaluation of the USP XVIII dissolution test for tablets
822	Technical problems of the USP–NF dissolution test
823	Review of dissolution tests, with some practical examples
824	Proposal for an *in vitro* release rate as a standard requirement for oral dosage forms
825	Modification and evaluation of a continuous flow apparatus for dissolution of tablets
826	Dissolution rate studies of some calcium phosphates using the rotating-disk method
827	Comparative study of the advantages of the modified apparatus of Warburg-type WA 0110 for control of common enteric-coated and timed-release tablets
828	Method for the study of timed-release films
829	*In vitro* dissolution of drugs from suspension ointments
830	Comparison of ointment bases by measuring *in vitro* dissolution (release) of drugs

rotating compartmentalized disk for dissolution rate determinations was demonstrated by the ease with which it discriminated between experimental capsule formulations and commercially available chlordiazepoxide hydrochloride capsules (796). An automatic multiple-channel apparatus for dissolution rate studies under sink conditions was developed, and an economical and reliable system for transmitting the experimental data to a remote computer was described (797).

Table XXIII lists additional references on dissolution.

Solubility–Solubilization Phenomena—Both Mukerjee (831) and Nelson (832) presented interesting discussions on the theoretical aspects of applying the Kelvin equation to the solubility of solids. Both refuted the concept that the effect of particle size on solubility is due to entropy changes alone. Methyl and propyl gallates were solubilized in aqueous solutions of surfactants which were polyoxyethylene ethers of cetyl alcohol, but ethyl gallate could not be solubilized in the same manner because it formed a gel-like product with the surfactants (833). The amount of the gel-like product formed was proportional to surfactant concentration and was greater when a larger number of polyoxyethylene ether units was present in the surfactant molecule. Solubility studies showed that testosterone was solubilized by glycocholate below the apparent binary CMC, although the solubilizing capacity was quite low (834). The complex association between testosterone and glycocholate suggested mixed micelle formation. Solubilities of phenobarbital, salicylic acid, and caffeine in a mixture of 12 kinds of solubilizing agents and water were measured, and the relationship between solubility and dielectric constant was examined (835). In a solvent system of water and solubilizing agents containing only a hydrophilic group, a plot of dielectric constant *versus* the logarithm of solubility, expressed as molar fraction, gave a straight line; for solubilizing solvents containing both hydrophobic and hydrophilic groups, the same plot gave one flexion in the straight line, indicating that these solubilizing agents undergo association at a specific concentration.

The solubilities of sulfadiazine, sulfisomidine, and sulfadimethoxine in several normal alcohols were determined over a limited temperature range (836). The entropy of solution was used for interpreting the results, which showed that in most cases the entropy quantity increased with decreasing solubility for any particular solute. To understand better the solubility behavior of nonelectrolytes in binary polar solvents, an equation for predicting solubility was presented and appeared to be applicable to many systems (837). Kramer and Flynn (838) examined the solubilities of two polysubstituted 1,3-dioxolanes, containing a 4-(2′-piperidyl) substituent, as a function of pH, temperature, and solvent composition. Mathematical equations describing the total solubility at any arbitrary pH in terms of the independent solubilities of the hydrochloride and free base species and the dissociation constants of the salt were derived and fitted to the data with good results. The method of sample preparation markedly influenced the rate of dissolution and attainment of supersaturated states of cholesterol in lecithin–bile salt systems (839).

Table XXIV—Additional References on Solubility–Solubilization Phenomena

Reference	Topic
840	Review of solubilization by surfactants
841	Review of solubilization by surfactants
842	Review of solubilization of soap by surface-active agents
843	Solubility parameter theory for mixed solvent systems
844	Mechanism of cosolubilization
845	Interaction of papaverine hydrochloride and sodium lauryl sulfate
846	Solubilization of steroid hormones
847	Maximization of the water solubility of vitamin D_3
848	Solubilization of griseofulvin as a function of low temperature and different nonionic surface-active agents
849	Solubility and solubilization studies on 3,4,4′-trichlorobenzenesulfonanilide (Reseptyl)

The equilibrium solubility of cholesterol studied as a function of its physical state in a model bile system was almost half that of the previously accepted values. The authors suggested that slow attainment of the equilibrium state may have acted to bias previous studies.

Other papers of interest in the area of solubility–solubilization phenomena can be found in Table XXIV.

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