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Pharmaceutical Sciences—1968 A Literature Review of Pharmaceutics

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CONTENTS

This review of the literature represents a comprehensive cross section of the research and development efforts in various selected disciplines of the pharmaceutical sciences. It is the seventh survey in this series (1–6). Numerous periodicals and selected sections of *Chemical Abstracts* were abstracted. In order to maintain continuity with the previous pharmaceutical science reviews of *J. Pharm. Sci.*, their general format was retained.

GENERAL PHARMACY

A series of review articles on the current aspects of pharmaceutics discusses a wide number of topics including preservatives, tablets, suspensions, ophthalmic solutions, stability effects of crystal characteristics, and packaging technology (7–9). Many papers were published in which the preparation of dosage forms of specific compounds was noted. Discrepancies in luminal preparations, preparations containing trypsin and chymotrypsin, ammonium glycyrrhizate and sodium glycyrrhetinate, terpin hydrate, barbituric acid deriva-

tives, oral anticoagulants, analgesics, antiseptics and disinfectants, as well as the preparation and processing of colloidal sulfur, were included in these (10–19). Several papers relating to eye drops have been published. Included among these were articles on the generalities of ophthalmic preparations, present requirements for the quality of eye drops, and eye drops as a ready medicinal form (20–23). The formulation of ophthalmic solutions, osmosis, osmotic pressure and reverse osmosis, and a method for computing isotonic concentrations have been reviewed (24–26). Specific preparations of eye drops were noted in which the preparations contained lachesine and boric acid, antibiotics, merthiolate, and pilocarpine (27–30). The effectiveness of preservatives in eye drops was also studied (31). Christensen and Garup describe a new multiple-dose container for eye drops (32).

Several papers covered the purification and large-scale production of tetanus toxin (33–35). A method was described for the preparation and purification of heparin (36). The use of the funda filter and a review of continuous filtration in the pharmaceutical industry was reported (37, 38). Also noted was the review dealing with the development of X-ray opaque media and a discussion of diagnostic preparations (39, 40). The progress in ion exchange since 1964 was surveyed (41).

Comprehensive and interesting reviews of various OTC preparations were published. These included diarrhea remedies, hair preparations, ophthalmic products, topical oral antiseptics and mouthwashes, medications for menstrual problems, oral hygiene aids, vitamins, and astringents (42–49). Factors in the evaluation of antacids and the use of spray drying in antacid production were studied (50, 51).

Informative articles appeared in which the commonplace occurrence of poisons and a discussion of glue sniffing were reported (52, 53).

In an article on the use of the unit dose system in a private hospital, the advantages and disadvantages are discussed (54).

Preservatives—A report appeared in the literature in which the preservatives used in injections, eye drops, syrups, decoctions, and ointments were tabulated with solubility data (55). A determination of possible sources of contamination was made, and tentative bacteriological specifications were established for oral liquid products (56). A series of papers considered the microbial content in nonsterile pharmaceuticals such as tablets and the raw materials (57–60). The evaluation of the literature on the effectiveness of antibacterial agents used as preservatives in ophthalmic solutions, and the principles and substances used to stabilize therapeutic agents were reviewed (61, 62). A broad-spectrum preservative (Phenonip) and antimicrobially active adjuvants were discussed (63, 64). Jungermann published a critical review of the use of bacteriostats in soaps as well as screening techniques for these agents (65). Also studied was the mode of action of phenolic and ampholytic disinfectants as well as a series reviewing certain theoretical aspects of disinfectant testing (66–69). Lachman reviewed the instability of antimicrobial preservatives due to effects of pH, binding, and interaction of the preservative with the active component and the container (70). In another paper, the author discussed the behavior of various antimicrobials in nonionic systems and showed that only the materials in the aqueous phase possess an antimicrobial effect (71). It was also shown that aqueous solutions of boric acid did not exhibit any inhibitory action against several common organisms in a study of its antimicrobial activity and stability (72).

Flavor, Aroma, and Color—An article by Cowley states that flavors which are compatible with the ingredients and color association remain prime factors in selecting flavors (73). A very interesting paper on taste receptor proteins appeared (74). In studying taste stimuli the author described the formation of weak complexes between sugars and bovine taste bud papillae, which do not appear to be enzymatic in nature.

Adjuvants—A group of authors reported on the use of carboxymethyl starch as an adjuvant in pharmaceutical preparations (75). Reviewed also was the use of polyethylene glycols in suppositories, ointments, tablets, and liquid preparations (76). Papers by Chalmers included the description of the nature of starch, its chemical properties, and the types of starch available (77, 78). The properties, manufacture and use of dimethylsulfoxide in pharmaceutical preparations was reported (79). The components of colocynths and castor oil were characterized in separate studies (80, 81). Closely chemically related dyes showing a different toxicological behavior were also discussed (82). Other interesting reports included those describing the influence of macromolecular adjuvants on the dialysis of some drugs, and the mechanism and quantitative course of cationic drug absorption on colloidal silicic acid (83, 84).

Stability—Several reviews dealt with the general problem of stability in pharmaceuticals and drug products and discussed the effects of light, humidity, temperature, and oxygen (85–89). Zoglio *et al.*, described studies from which stability predictions from a single experiment can be made while Wuensch presented the advantages and disadvantages of using temperature coefficients, stability charts, and the application of the Arrhenius equation (90, 91). The stability of various injection solutions containing novocaine, phenylbutazone, reserpine, procainamide, and atropine sulfate was studied (92–96). Similarly, studies were conducted on liquid pharmaceutical preparations of ascorbic acid, refamide, insulin, imidazoline derivatives, and glutathione (97–101). Details of stability studies of sweet spirit of nitre, nux vomica tincture, noradrenaline, and a series of concentrated solutions of 20 drugs used in prescriptions also appeared in the literature (102–105).

In a paper on equilibrium phenomena in solid dosage forms, aspects of the mechanics of drug decay in solid dosage forms are given (106). A number of papers were presented which discussed the stability of aspirin tablets. Included among these were studies on the effect of lubricants such as the stearates and stearic acid, the effect of humidity, and the significance of salicylic acid sublimation in the stability testing of aspirin-containing solids (107–112). Other stability studies also were performed and reported on tablets, among which the stability of ferrous salts in tablets was discussed (113–115). The absorbed energy radiation was calculated in a

study of stability and radiochemical purity of some radiopharmaceuticals (116).

Numerous papers dealt with the incompatibilities possible in pharmaceutical preparations. In a paper by Huyck, the compatibility of several present mixtures of prescription specialties was given (117). Featured in two papers was the effect of impurities on the stability of sodium-*p*-aminosalicylate (118, 119). The influence of surfactants and cyclodextrins on ester hydrolysis was reported (120, 121). A number of papers dealt with specific incompatibilities. Among these were polyoxyethylene mixtures with aminophenone, and dimethylpolysiloxane with menadione (122–128). Ozaki and Inoue mixed glumin (glutamic acid 5-amide) with 109 possible drug combinations and found no incompatibilities (129). Studies on copper-catalyzed oxidation of ascorbic acid, influence of sodium bisulfate in sucrose inversion, and the effect of peroxide containing oils on the stability of dihydrotachysterol were also reported (130–132). A series of papers discussed the stability of thiamine and its related compounds while another described the mode of interaction between theophylline and ethylenediamine in aqueous solution (133–137).

The literature also contained reports of studies directed toward stabilization through the use of other agents. The addition of 0.1% sodium edetate to sulfacetamide sodium solution was found to prevent discoloration, as did the use of sodium bisulfate or the filling of ampuls under nitrogen for other sulfonamides in aqueous solution (138, 139). The effectiveness of some surface-active substances on the stability of oleum pini pumilionis was also measured, and another paper noted that the inhibition of surface decomposition of lysozyme was brought about by the addition of nonionic surfactants with a polyethylene glycol or polyglycerol as a hydrophilic moiety (140, 141). A paper by Lachman contained a discussion of antioxidants and chelating agents as stabilizers in liquid dosage forms (142). Specific antioxidants also reported were borate and a new inhibitor of auto-oxidation in ether, 1-phenyl-3-pyrazolidone (143, 144). The stability of an iodophor was evaluated with and without an antirust agent (145).

Transformations which occur with various organic structures upon exposure to visible and UV light were reviewed (146). Photochemical reactions were reported on *N*-substituted imines, perfluoroazomethane, flavine mononucleotide, and menadione (147–152). Reported also were the mechanism of formation of acetaldehyde and butanediol in radiolysis of ethanol, and changes due to IR radiation applied in pharmaceutical techniques (153, 154). Ultrasonic waves were shown to affect the stability of aqueous solutions toward hydrolysis as well as the degradation of polymers (155–157).

Stability studies on specific compounds were innumerable. Among the compounds studied were salicylic acid-morpholine complex, cycloserine, pangamic acid, levorin, furterene, sulpyrine, methylparaben, chlorhexidine, benzothiadiazines, nitrate esters, nitrofurazone and furaltadone, diosgenin, amidopyrine, and sorbic acid (158–173). The effect of the cation on the thermal stability of stearic acid salts was noted, while another study considered the physicochemical properties and stability of cytidine diphosphate choline (174, 175). Bowles found that prednisolone in an organic vehicle, used in dentistry, was quite stable in comparison to literature values of its thermal stability in aqueous preparations (176). A review with 12 references outlined the stability of some local anesthetics and methods for their determination in the presence of their decomposition products (177). Stability studies were also conducted on alpha-mercapto and alpha-alkoxy-acetic acids and their ethyl esters, corticosteroids, homatropine, allopurinol, papaverine hydrochloride, and sweetened choline salicylate solutions (178–183). Wichtl discussed the stability of vegetable drugs and methods for their stabilization, while Oza reported on the theory of decomposition of hyponitrites (184, 185). Reports on the stability of 2-hydroxyiminomethyl-1-methyl pyridinium, peracetic acid, and lobeline were also published (186–188). Guttman presented work on the heterogeneous catalysis of aspirin degradation in chloroformic solution and its relationship to the determination of salicylic acid in buffered aspirin products (189). Paulssen *et al.*, characterized racemic alpha- and beta-hydroxysuccinanilic acids (190). Reported were acid-catalyzed hydrolysis of methoxysufandamidodiazines and the effect of sodium dodecylsulfate on 1-hexadecanol (191, 192). The implication of the study of acetic anhydride in malic, tartaric, and succinic acid buffers in pharmaceutical formulations is discussed in another report (193). The mechanism of solvolysis of liberin and 5-haluridines and related nucleosides is discussed in separate papers (194, 195).

Stability Kinetics—A review of applied kinetics containing 420 references covering books, reviews, experimental investigations, and theories of kinetics published during 1966 and 1967 has been published (196). Another paper discussed cases where classical kinetics give false results as a result of test conditions used in accelerated work (197). Separate papers considered the use of nonisothermal kinetic methods (198–200). Also published were the kinetics of hydrolysis in strong acid media and the effect of buffers on the kinetics of glucose decomposition (201, 202). Other kinetic studies included the hydrolysis of meperidine hydrochloride, the degradation of chlorthiazide in acid solution, and the degradation and stabilization of the parabens (203–206). In a study on the alpha-chymotrypsin hydrolysis of some carbonate esters, the kinetics was found to be described by the Michaelis-Menten equation (207). Another report consisted of a kinetic study of consecutive second-order reactions involving ester cleavages with hydrobromic acid (208). Also reported were the kinetics of hydrolysis of 5-trifluoromethyl-2′deoxyuridine and the kinetics and mechanism of the decarboxylation of anthranilic acid (209, 210). Additional kinetics studies included the following compounds: echothiophate iodide, glutethimide, thiobarbiturates, and ergot alkaloids (211–214). The kinetics of proton exchange in radicals derived from simple alcohols was also studied (215). A kinetic study of the decomposition of strophanthidin cardenolides in drugs and their metabolism in animals was presented (216).

Antibiotic Stability—A study was made on the influence of physical agents on pharmaceutical preparations containing antibiotics in which tablets containing

novobiocin were used (217). In another study, eight antibiotics were used in an investigation of the effect of several organic and inorganic compounds used as adsorbing, suspending, and solubilizing agents (218). A number of papers dealt with the penicillins. These included the aminolysis of benzylpenicillin by aliphatic diamines, the catalytic effect of buffers on the degradation of phenoxymethylpenicillin, the stability of aqueous penicillins, and the effect of freezing on the stability of sodium methicillins (219–223). The stability, absorption, and excretion of hetacillin were reported (224). Kinget and Schwartz discussed model catalysts which stimulate penicillinase (225). Pyrrocyclin-*N* stability was studied in aqueous solutions, and changes in antibacterial activity and the changes caused by compounding with other parmaceuticals were reported (226, 227). Other studies involving tetracyclines included the effect of temperature on chlortetracycline activity in aqueous solutions and the tetracycline-bismuth incompatibility in pharmaceutical preparations (228, 229). Reports on cephalosporins covered such topics as biological stability and microbial degradation (230–232). The effect of carboxyl ion-exchange resins on kinetics of streptomycin was also determined (233). Dosage forms containing antibiotics such as terramycin eye drops and cephalosporin C and penicillin ointments were noted (234, 235). Comparison of the microbiological and colorimetric methods of assay in which good agreement was found, was the subject of a paper by Gallelli (236).

Vitamin Stability—A number of interesting papers on the chemistry of vitamin B_{12} covered such topics as *cis* and *trans* effects, complexes, and potential reduction (237–240). In a paper on the stability of cyanocobalamin in film-coated tablets, the effects of the various solvents commonly used in film coating were discussed (241). A method was described for determining vitamin D_3 in the presence of its decomposition products using injection solution preparations, whereas the stability of the same vitamin in a syrup was analyzed by another author (242, 243). Included among the studies reported on ascorbic acid were degradation under aerobic conditions at various temperatures and pH, degradation in heavy water, and the influence of the flavonoid fraction of *Rosa cinnamomea* fruit on its stability (244–246). Another paper evaluated the stability of ascorbic acid in oral formulations in which the vehicles and additives were varied (247). Zoni and Lazzeretti developed an improved multivitamin drop preparation based on accelerated storage tests which showed that addition of polyvinylpyrrolidone in an aqueous base gave satisfactory chemical stability and prevented the development of unpleasant odors (248). Other vitamin stability studies reported included those of vitamin K, thiamine, and a new series of sterically hindered esters of vitamin A (249–251). Also noted was the base-catalyzed hydrolysis of flavins (252).

PHARMACEUTICAL TECHNOLOGY

Interesting papers by Fowler describe engineering aspects of fluid flow, heat transfer, evaporation, mass transfer, bioengineering, and a review of recent literature regarding pharmaceutical engineering (253, 254). Also reported were pharmaceutical technological studies with enzymes (255–257). Appearing in the literature were reports on the improvement in the quality of vitamin A concentrates as well as improvements in the technology for processing these concentrates (258, 259).

Parenterals—In a paper on injectable aqueous solutions, a number of aspects were examined ranging from materials used in the formation to record-keeping of the sale of the solutions (260). The influence of acidic or basic additives was used in the study on the prediction of pharmaceutical incompatibilities of parenteral medications (261). The migration of alkaline substances from glass of ampuls and the comparison of two methods for testing release of alkali by pharmaceutical glasses were also reported (262, 263). Madsen suggested the use of electronic counting devices (Coulter counter) as the accurate way of measuring particulate matter while Trasen described the use of millipore filters in handling contamination and cleaning of products (264, 265). A review of lyophilization and a study on the use of a lyophilization method for incompatible pharmaceuticals also were reported (266, 267). Isopropyl myristate and peanut oil were compared as vehicles for cutaneous and parenteral use (268). Aoki noted that the presence of glucose proved to be effective for alleviation of pain in injectable solutions of thiamine hydrochloride (269). A comparison of the isotonicity of sorbitol, sorbose, and galactose to glucose and sodium chloride was made (270). Lomolino found that the use of the antioxidant, sodium metabisulfite, accelerates decomposition of thiamine, and adrenalin, inactivates vitamin E and transforms procaine and prednisolone (271). The 2-naphthol derivatives were evaluated for use as preservatives in parenterals (272). Another study considered the use of ultrasound for the preparation of fat emulsions for intravenous administration, and preliminary clinical investigation showed that the emulsions can be safely administered to humans (273). Propylene glycol was recommended over water for the preparation of a 5% chloramphenicol solution in a study of the action, stability, and use of such a preparation (274). Evaluation studies were conducted on a 4% gelatin solution containing 1% glycine to be used as a blood substitute (275). An amino acid infusion was tested chemically and physically and the sterilized and nonsterilized preparations were compared (276). Conductometric determinations were performed on injectable solutions of atropine sulfate, strychnine sulfate, and morphine hydrochloride (277). Included among the specific injection solutions reported were colorless solutions of sodium salicylate, concentrated sodium bicarbonate infusion solutions, and sodium indigotindisulfonate (278–280). Stability studies of injection solutions covered those containing amidopyrine, mesocaine and promethazine, aminocaproic acid, hydroxycobalamin, and procaine (281–284). Another study was carried out on suspensions of cortisone and hydrocortisone for parenteral administration (285). In a study of pyrogens in injections and their removal, the origin, chemical nature, and physicochemical properties of pyrogens as well as chemical and physical methods of removal were described (286).

Sterility—In a paper by Lange, the destruction of bacterial pyrogens by hot air at 200°, superheated saturated steam, ultrasonic waves, and beta and gamma

rays was discussed (287). Each of these methods has been individually treated in a number of reports. In the case of thermal sterilization, the aspects covered included changes in pH and drug decomposition, physical and physicochemical criteria in thermal treatment, corrosion during autoclave sterilization and, the survival of heat-resistant spores after thermal treatment (288–291). Three reviews were published on sterilization by ethylene oxide in which chemical and physical factors were considered (292–294). Also noted were reports on the applicability of ethylene oxide as a sterilizer, controls in this type of sterilization, and limiting factors in its use (295–297). The influence of various pretreatments on the destruction of *Bacillus subtilis* by ethylene oxide, and the effect of ethylene oxide sterilization on the activity of organ extracts were also studied (298, 299). Process systems for sterilizing filtration which utilized a membrane filtration system were described and an evaluation of this type of filter for sterile processing was made (300, 301). Other authors evaluated membrane filters as a technique for testing bactericidal activity (302, 303). The synergistic effects of sonochemical sterilization and ethylene oxide were also investigated (303). The value of chemical sterilization was also discussed (304, 305). A review of radioactive rays in the pharmaceutical industry covered the application of gamma rays in sterilization and a brief description of the irradiation apparatus (306). The use of radiation sterilization for medical devices and supplies and its effect on the sterilizated surgical sutures, and disposable syringes and needles (307–309). The literature also contained articles on the sensitivity of stored melon fruit fungi to gamma radiation and the effects of irradiation on pectin methyl esterases of some fruits and vegetables (310, 311). A detailed discussion of the proper use of biological indicators in sterilization was published (312). Noted also was the behavior of D-sorbitol, paraffins, and fatty oils when subjected to heat sterilization (313, 314). Brown evaluated the survival of *Pseudomonas aerugenosa* in fluorescein solution (315).

Tablets and Capsules—Several reviews appeared in the literature which covered current technical and therapeutic aspects of the manufacture of compressed tablets and the art and science of tablet coating (316–318). Recent trends in tablet manufacture and multilayer tablet production were also topics mentioned (319, 320).

Studies on powder flow and particle size commanded much attention. A number of papers considered such aspects of powders as cohesion, adhesion, contact angles, free surface energies, and electrification phenomena (321–326). Hiestand described an apparatus and procedure for measuring static friction coefficient in his paper on the measurements of friction in simple powder beds (327). Other powder-flow studies covered factors affecting the flow of lactose granules, and the use of the recording powder flowmeter for the evaluation of uniformity of flow (328, 329). The mechanism of flow improvement was accomplished by the addition of fine particles to bulk solids and the use of silicones (330, 331). Another paper found in the literature pertinent to pharmacy described the building of free-flow properties into detergents (332). A review article on particle size research described the methods of analysis and compared these (333). In another paper on the practical problems in particle size and surface area measurements, the use of ultrasonic vibration and freeze drying was suggested to improve dispersion of particles (334). Particle-size effects on packing, fluidity, and strength of powders were also reported (335–338). Measurement of particle-size distribution by air permeation, filtration, and sedimentation analysis was discussed in separate reports (339–341). Another paper described the use of gamma-ray absorption as a technique which enables localized measurements of total porosity, open porosity, and pore-size distribution of porous solids (342). A method was also given to differentiate between adsorbed water and water of crystallization of powdered solids (343).

The effect of granule-size crystal formation and granulometry of compressed particles on the properties of some tablet formulations was presented (344–346). Also a method was described for the measurement of granulometry and porosity of solids by X-ray scattering (347). Another author described a device for granulation and drying of pharmaceuticals for making tablets (348). The mixing of powders was also the topic of three reports which covered methods of describing, specifying, and testing mixtures, the degree of mixing and the dispersion of powders (349–351). Relative to this was a study on homogeneity of drug mixtures and dose accuracy of tablets (352). Also studied by several people were various aspects of the physics and thermodynamics of tablet compression (353–356). In a study on the use of pseudoliquefaction for preparing granulates, the mixing of initial ingredients was discussed (357).

A number of studies were conducted on the various inert ingredients used in tablet formulations. Using the parameters, hardness, friability, and disintegration time, several binders such as pregelatinized starch, cold water-soluble gum, and invert sugar were evaluated (358). Studies on various cellulose derivatives included the mode of action of sodium carboxymethyl cellulose and hollocellulose on disintegration rate, and the use of methylcellulose in nonaqueous solvents as a granulating agent for aspirin (359–362). Direct compression of tablets containing microcrystalline cellulose as well as some effects of humidity and heating in tableting properties of it were discussed (363, 364). FRC, a protein powder with uniform particle size, was shown to act as a good adsorbent for various substances in its application as a filler (365). A number of authors commented on the use of starch. Among the studies on starch were discussions on the mechanism of action, the concentration influence on disintegration, and the use of cassava and yam starches as disintegrants (366–370). The use of surface-active substances in the technology of tablet production and the effect of a nonionic surfactant[1] on the uniform distribution of tablet density were reported (371, 372). The papers on lubricants for tablets were an evaluation of some water-soluble ones, comparison of various lubricants on filling weight and repose angle, and their effect on tablet hardness (373–375). Another paper contained a discussion of the specific volume of tablet mixtures in which the

[1] Polysorbate 80.

Westman principle was used to evaluate lubrication (376).

Studies on tablets also were made in which the physical parameters of the finished tablet were noted. Among these were studies on the application of the correlation between weight and height of tablets in quality control and tensile strength of lactose tablets (377, 378).

An explanation of reaction mechanism of auxiliary materials in tablets was given in which the influence of pressure, binders, and lubricants was discussed (379). A paper on molecular interactions at solid surfaces also seemed applicable for reference to such interactions occurring in solid dosage forms (380). Also appearing in the literature were reports on the use of thin-layer and column chromatography and X-ray diffractometry for determination of substances in tablets (381, 382).

Ludwicki suggested some general requirements for the evaluation of granulates while Speiser discussed lozenge formation using pigment syrups (383, 384). The granulation of griseofulvin and a new approach to the fusion method for preparing granular effervescent products were also noted (385, 386).

With respect to tablet coating, three papers of a general nature reported the influence of certain factors, such as shape and mixing of coating on the coating of medicinal cores, the theoretical aspects of film coating, and the effect of moisture on the strength of tablet coatings (387–389). Reports on the manufacture of sugar-coated tablets contained discussions on the stability of decavitamin sugar-coated tablets and the binder in the coating liquid (390, 391). Two other papers gave descriptions of automatic coating apparatus (392, 393). A series of papers contained reports on synthetic polymers for tablet coating (394–397). Also published were reports on the use of some acrylic resin lacquers and rapid coating with poly (oxyethylene) glycols (398, 399). Cellulose acetate phthalate, anionic polyacrylate, and cellulose methophthalate were tested for use as coatings soluble in intestinal juice while cellulose acetate dibutylaminohydroxypropyl ether was evaluated as an acid soluble coating (400–403). Also discussed were monomolecular film properties of protective and enteric film formers in which the effect of polymer side chain on surface pressure-area isotherms was given (404).

An evaluation of factors which affect the encapsulation of powders in hard gelatin capsules was made and the relation of particulate properties, capsule size, and operating rate of the filling equipment was also noted (405).

Suspensions—Interesting papers pertinent to suspensions discussed the role of water structure in disperse systems, theoretical model of floc structure, and a review of adhesion of liquids and wetting on solid surfaces of low energy (406–408). A new method for studying dispersed systems is discussed in another paper in which equations are derived for determining the solubility, rate of growth, and solution of particles in a polydispersed system (409). Studies on the structure and formation of suspensions were performed in which the kinetics were investigated, and the kinetics of dehydration of gels also was noted (410, 411). Another author studied the factors which determine the preparation and stability of suspensions and pointed out the problems of the determination of particle size by sieve analysis (412). The structural viscosity of oil suspensions as well as the relation between rheological data of oil suspensions and the data obtained from sensory evaluation tests were reported (413, 414). The flow properties of dispersed systems and the rheological properties of solid-liquid systems were the subjects of other studies (415–417). In the study of the dependence of plastic flow behavior of clay suspensions on surface properties, two theories of pseudoplastic behavior were compared (418). Evaluation of the thermal effect on some alumina gels and aluminum oxides and on the structural properties of heavy clay suspensions was made (419, 420). Two separate studies involved the relation between time of coagulation and electrolyte concentration (421, 422). A paper by Dennis describes the determination of diffusion coefficients of electrolytes in gels (423).

The application of the Verwey-Overbeek theory to the relative sediment volume of kaolin-water dispersions and the relation of total volume to total surface area for a suspension of particles undergoing growth were reported (424, 425). Other papers on sedimentation volume discussed a theoretical calculation, the sedimentation volume of coarse powders in organic liquids, and sedimentation volume of terephthalic suspensions, in which the nature and concentration of monovalent cations was also reported (426–428). The settling behavior of unflocculated suspensions at high concentrations and the effect of water "magnetic treatment" on aggregative stability of suspensions were discussed (429, 430).

In the study of flocculation mechanism, the mutual flocculation of particles of various sizes and charge neutralization and bridging were discussed (431, 432). Ho developed methods for a quantitative mechanistic study of certain areas in the formation, growth, flocculation, or coalescence behavior of particles in liquid systems (433). Studies of flocculation phenomena were made in which the experimental techniques included microelectrophoresis, the particle counter (Coulter counter), and standardized stability methods (434). The role of flocculant molecular weight and complex formation and the effect of magnetic field on the coagulation of suspensions were the topics of separate studies (435–437). Another author noted the effect of flocculants and peptizers on the physicochemical properties of saline-clay suspensions (438). Also discussed were the flocculation of clays and soils by organic compounds and the nature of calcium salts of carboxylic acids (439–441). Scott conducted an experimental study of continuous thickening of a flocculated silica slurry (442).

Electrical phenomena and properties of dispersed systems, and the relations among electrochemical properties, type of colloid, and adsorbed cations of soil and mineral colloidal suspensions were described (443–445). Similarly, studies were conducted on the electrophoretic behavior of alumina suspensions, electrokinetic properties of silicic acid suspensions, and the influence of particle size on electrokinetic potential of some sulfonamides in suspension syrups (446–448). In another report, a comparison was made of three methods of determining

electrokinetic potential in nonaqueous suspensions, *i.e.*, electrophoresis, electro-osmosis, and streaming potential (449).

Articles on the clay-water system included discussions of the dependence of plasticity on the dispersed phase concentration and a review of such systems (450, 451). Among the reports on bentonite, were discussions of mixed sorption of cations and anions on it and the peptizing ability of fractionation of it (452, 453). The hydrophilic-hydrophobic character of organomontmorillonites, the chemical and physicochemical properties of agar, and the viscometric behavior of sodium carboxymethylcellulose in aqueous sucrose solutions were evaluated (454–456). Also appearing in the literature were discussions of surface dissociation of clay minerals in aqueous medium, coagulation structure formation in hydrocarbon media, and the thixotropy of structural dispersions with low dispersed phase contents (457–459).

A number of papers described the effect of various compounds on the structural rheological properties, structure formation, physicochemical properties, and sedimentation of clay suspensions. The effects were brought about by compounds such as sodium salts of dibasic fatty acids, peat-alkaline reagent, calcium hydroxide, surfactants, and sodium triphosphate (460–463). The particle size and optical properties as well as the effect of various treatments on the optical properties of montmorillonite suspensions were reported (464, 465). Similarly, studies were conducted on the effect of magnesium sulfate on the strength of highly dispersed fine pore structures of magnesium hydroxide and magnesia, and the effect of soluble polymers on the structural and mechanical properties of concentrated bentonite suspensions (466, 467). The subject of a number of studies was the stability and stabilization of suspensions in which the compounds used were polysorbates, anion and cation-active surfactants, nonionic surfactants, potassium ions, and sodium dodecyl sulfate (468–473).

Other studies concentrated on the preparation and properties of specific suspensions such as stabilization of anthelmintic suspensions containing sodium arsenate, the preparation of calamine lotion with microcrystalline cellulose, and the micromeritic and rheological study of milk of magnesia (474–477). Using titanium dioxide, studies were performed on the preparation of finely dispersed suspensions with the aid of ultrasonic vibrations, and the relation between dispersability and treatment conditions was investigated (478, 479). Also investigated were the structure of aluminum hydroxide gel and the soluble gel transformation of aluminum hydroxide in the presence of dyes (480, 481). Interesting and relevant descriptions were given of a noncaking agent for urea,[2] and the preparation and evaluation of sodium suspensions (482, 483).

Among the techniques discussed in relation to suspensions were those using ultrasonics, a particle counter, X-ray, and NMR. In one study a method was discussed for the quantitative evaluation of the effect of ultrasonics on the dispersed composition of suspensions (484). Another study described the applicability of ultrasonic absorption measurements for concentration determination of ammonium sulfate suspensions (485). Matthews and Rhodes used the particle counter and a digital computer to evaluate the stability ratios in flocculating monodisperse systems (486). Also noted were the determinations of mobility and structure of bound water in clays from NMR spectra and the number concentration of poly-dispersed colloidal spheres by light scattering (487, 488). The sol-concentration effect was used by another author for the determination of the iso-electric point (489). Also found in the literature were papers on the use of X-ray diffraction in the quantitative analysis of suspensions (490, 491).

Emulsions—Review articles on basic emulsion theory, modern theories of colloid stability, the application of phase equilibrium diagrams in formulating solubilized and emulsified systems, requirements for formation and existence of water-in-oil emulsions, and the progress in oil-water-type emulsification technology were published (492–496). Other reports described the application of rheology in the development and manufacture of emulsions and the fundamental problems of emulsions (497, 498). In a paper by Ho and Higuchi, a theoretical study of preferential coalescence and aggregation of small particles in heterodispersed systems was carried out in order to give an explanation to the relatively narrow particle-size distribution observed in emulsions (499). Nonaqueous emulsions in which the polar phase was either glycerol, propylene glycol, or polyethylene glycol 400 were discussed (500).

In the paper on the flocculation stability of disperse systems, the flocculation process was characterized on model emulsion droplets by measuring the approach speed and equilibrium distance in order to describe mutual effects between drops (501). A review with 191 references described the principles of the stability of lyophobic colloidal dispersions in nonaqueous media (502). Another study revealed the electrochemical activity of concentrated emulsions stabilized by solid emulsifiers (503). Reports of the stabilization of triethanolamine soap emulsions and the stability of emulsions at high dilution were noted (504, 505). The influence of several high molecular weight polymers on the stability of a hexadecane-in-water emulsion was investigated (506, 507). Rehfeld investigated the effects of initial surfactant concentration and emulsification time upon particle size and distribution of benzene-in-water emulsion, while others studied the stabilizing effect of ionogenic surfactants in concentrated emulsions (508, 509). The role of interfacial tension in the preparation and stability of emulsions stabilized by hydrophilic colloids was also presented (510). Other papers on emulsions discussed studies on the properties of liquid films between emulsion droplets and the characteristics of a paraffin oil emulsion at the critical hydrophile-lipophile balance (HLB) (511, 512). Two separate articles dealt with the lyophilization of oil-in-water emulsions and discussed the use of supports (513, 514).

The literature also contained articles which reported the effect of mixing of oils, nonionic surfactants, and phase volume on the phase inversion temperature of emulsions (515, 516). The influence of hydroxyl value

[2] Uresoft.

and solubility of nonionic surfactants on HLB and the effect of initial surfactant locations on viscosity of emulsions were the subjects of other papers (517, 518). Results of work on the role of the medium in the process of formation of lyophobic colloidal particles are in contradiction to the theory of Volmer (519).

The determination of the effectiveness of an emulsifier and the use of the phase inversion temperature and HLB value for choosing an emulsifier were reported (520, 521). Empirical findings and theories for physical and chemical properties of solid-liquid dispersions were illustrated to aid appropriate applications of surfactants to dispersion systems (522). Middleton described a titration method for the determination of HLB in emulsifiers (523). The effect of variation of concentration of soap, the use of solid emulsifiers on the stability of emulsions, and the effect of emulsifier concentration on the rheological properties of emulsions were the topics of other papers (524–527).

Methods of measuring particle size in emulsions included spectroturbidimetry and use of a particle counter, while a parallel plate-type apparatus was used to measure the thermal conductivity of vegetable oil-in-water emulsions (528–530). Some workers evaluated the effect of temperature on the stability of a fat emulsion and on the dielectric properties of water-in-oil emulsions, while another reported on the rheological changes in emulsions on aging (531–533). A paper on the emulsifying properties of sodium beta-boswellate reported that it exerted a marked influence on the interfacial tension of water against air and liquid paraffins even in minute concentrations (534). A useful model which can be used for various oil-soluble drugs resulted from a study of oil-in-water emulsions containing mixed surface-active agents of the nonionic type (535). A simple method was also given for the preparation of a stable emulsion of benzyl benzoate (536).

Theoretical calculations on dosage variation as a result of mixing and sampling errors with possible application to suspensions and emulsions were described (537). Others investigated the effect of nonionic surfactants of the sorbitan series on the liberation of isoniazid from oil-in-water emulsions (538). Koizumi and Higuchi analyzed data on drug release from emulsions and reported good agreement between theory and experimental work (539, 540).

Ointments and Creams—A survey paper by Alexander described various hand cream formulations and the factors desired in such products, while a report by Kalish discussed water-washable creams and recent progress in this field (541, 542). Triglycerides, semihydrogenated milk fat, fatty acids, and fatty acid sucrose esters were mentioned as bases applicable to ointments (543–546). Ion-exchange resins were investigated as carriers for topical medication in a film-forming base (547). Among the auxiliary agents mentioned for use in ointments were microcrystalline cellulose and saccharose glycerides (548–550). In a study of corticosteroid ointments, the corticosteroid solubilities were determined in some alkyol amides while another study examined iodochlorhydroxyquin[3] and undecylenic acid in two new water-washable bases (551, 552).

[3] Vioform, Ciba Pharmaceutical Co., Summit, N. J.

Included in several papers on the rheology of ointments were a review of the gel structure, the effect of technological processing on the rheological properties, and a study on techniques adopted for testing ointment extrusion, penetration, and viscosity (553–555). A dielectric measuring test was used in which the dielectric constant as a function of water and emulsifier content was determined. This technique was shown to be more sensitive to changes in structure than microscopic methods (556). Investigations on the physicochemical properties of ointments and a concentric cylinder creep study of pharmaceutical semisolids were also reported (557, 558). As a result of a study on the automatic measurement of thermodynamic properties of organic compounds, the optimum moment for addition of active ingredients to polyethylene glycol base during the manufacture of ointments was determined (559). Studies of particle size in ophthalmic ointments in which the active ingredients used were chloramphenicol and boric acid were reported. Comminution by means of available equipment was found to be inadequate for the preparation of useful products according to the German standards (560). In another study of boric acid ointment, the results showed particle-size increase after a few days' storage (561). A detailed report, with 54 references, was published on the determination of pH for semisolid cosmetic and pharmaceutical products (562). The influence of surfactants on the absorption of water by white petrolatum was the subject of one paper while another compared the compatability of 20 nonionic surfactants in the finished products of 18 drugs (563, 564). Stability studies were conducted on ointments prepared with lard, triglycerides, and some which contained enzymes (565–567). Tar dispersions in lipophilic and hydrophilic bases prepared with emulsifiers[4] were shown to have better shelf life than those prepared with nonionic surfactants[5] (568).

Several reports dealt with the evaluation of antiseptics in ointment bases (569–571). The effect of topical vehicle composition on fluocinolone acetonide and its acetate ester and the effect of various liquids and vehicles in salicylic acid ointments were evaluated through *in vitro* release and diffusion changes (572–574). Among the effects studied when surfactants were added to ointments were the liberation of sodium salicylate from oil-in-water emulsion bases, the release of antibiotics from petrolatum base, and release velocity and structural rheological properties of an ointment base in which a nonionic surfactant was added to white petrolatum (575–577). Using a modified agar-plate analysis, it was found that DMSO either had no effect or inhibited the release of antiseptics from hydrophilic ointment and petrolatum (578).

Several interesting papers were published in which various aspects of the skin were discussed. One discussed the chemical composition of normal and acne skin lipids from humans and another reported a symposium on mechanical properties of skin, contact allergy, and the influence of vehicles on percutaneous penetration (579,

[4] Span 40, 60, and 80, Atlas Chemical Industries, Inc., Wilmington, Del.

[5] Tween 20, 40, 60, or 80, Atlas Chemical Industries, Inc., Wilmington, Del.

580). Others reported studies of the skin's ability to promote spreading and the contact angle of water on viable human skin (581, 582). Realistic methods for determining photosensitization potential of topical agents and topical toxicity and testing were reported (583, 584). The determination of percutaneous absorption and residual of a bactericide, using labeled drug, and a comparison of absorption between oil-in-water bases and water-in-oil bases were the subjects of other papers (585, 586). Discussions of new allantoin complexes and alginates as keratolytic agents in dermatological use were also presented (587, 588).

Suppositories—A review on rectal medicinal preparations covered the different dosage forms for these products (589). Also reviewed was the history of suppository compounds, and the preparation and properties of a new base derived from guerbert alcohols were reported (590). The physical, physicochemical, colloid-physical, and rheological properties and interactions of Witepsol-based suppositories were given in the report by Kata (591). The results of this study showed that the release rate from a suppository of this base containing aminophenazone and a dispersing agent (submicroscopic pyrogenic silica),[6] depended on the degree of dispersion of the drug. In another study, the addition of submicroscopic pyrogenic si ica to oily-type bases containing amidazophen inhibited the release while the addition of a nonionic surfactant accelerated it (592). The effect of nonionic surfactants, polyethylene glycol,[7] and wax concentration on the release rate of various drugs from suppositories also were noted (593, 594). The effect of the degree of trituration of therapeutic substances was demonstrated. For suppositories containing sodium chloride and calcium lactate, the release decreased when small particles were incorporated while the opposite proved true when the active ingredient was boric acid (595). Rather interesting was the fact that the administration of phenoxymethylpenicillin gave higher blood levels when the drug was given as suppository than when given orally (596). The literature also contains a short review of methods for melting point determination of suppositories and a paper which describes the melting and solidification of binary and ternary systems containing glycerol esters of fatty acids (597, 598).

Aerosols—Appearing in the literature were reviews and discussions of the theoretical basis and technology of aerosols, the microbiological considerations for pharmaceutical aerosols, and a general review of aerosol science (599–601). The paper by Parisse on formulation and component requirements for pharmaceutical aerosols emphasized that ingredients and packaging components for aerosols must be evaluated together (602). Factors such as particle size, pressure, valve and actuator orifices, surfactants, and delivery rates were evaluated for effectiveness of radiopaque aerosols (603). The selection of propellant mixtures, the use of chlorinated solvents, and the use of carbon dioxide as a propellant in aerosols were the topics of other publications (604–606). An investigation was also conducted on the possible solubility range in the manufacture of a three-component aerosol for homogeneous systems (607). Explosivity and flammability in pharmaceutical aerosols and the pressure and volume limits for perfume aerosols in glass containers were discussed (608, 609). A review paper by Harris dealt with types of filling equipment, sterilization techniques, types of containers, and the types of propellants for aerosols (610). Ways of solving problems related to leakers in aerosol cans was given in a paper on crimping aerosol bottles (611). Included in another report were general considerations regarding the filling of aerosols and components for food and pharmaceutical use (612). Methods for measuring the charge of aerosol particles, the theory of charging aerosol particles in an electric field, and ultramicroscopy of electrically charged aerosols were reported (613–615). Brock described photodiffusiophoresis, the new modes of aerosol particle motion (616).

A review with 43 references outlined the theory of formation, formulation, and methods of evaluation of foams (617). Foam stability in relation to the effect of sheer and in nonaqueous solutions of surfactants was presented (618–620). Other investigations dealt with the analytical characteristics of the stability of aqueous and organic foams, and a method of measuring foam by the Ehmeda friction apparatus (621, 622). Sanders evaluated complex formation in aerosol emulsions and foams (623). Foamability of senegin solutions was related to other physicochemical properties of the boundary layer such as surface tension, absorption, and surface viscosity (624). Among the compounds investigated for their antifoaming or foaming-regulating properties were polysiloxane and phosphates (625–627). In a study on the bubble-size analysis of high-consistency aerosol foams and its relationship to foam rheology, the effects of container emptying, propellant type, and time were examined (628, 629). Other studies included the interaction of dust particles with foam bubbles and the lifetime of aerosol particles (630, 631). Rather interesting and relevant was a study on the basic physiochemical characteristics of microbubbles (632). A statistical theory was given for predicting size distribution of aerosols in which countable pulses are generated by a high concentration of subcountable sized particles in the sensing volume of optical counters (633). Also published was a method for determining the dynamic shape coefficient and apparent density of solid nonspherical aggregated particles of aerosols with a solid dispersed phase (634). The determination of size distribution of aerosols was accomplished by such methods as light scattering and use of the particle counter in separate studies (635, 636).

Reports on specific aerosol preparations dealt with the warnings for human use of isoproterenol inhalation preparations, the preparation of radioactively labeled aerosols, and the stability of sodium benzylpenicillin and procaine penicillin in aerosol vehicles (637–639).

Sustained Release—In a review on the formulation of sustained release preparations, the polymorphic form of the drug, its water solubility, and the particle size are discussed as to their influence on the rate of absorption by the body (640). Rosen described the theoretical considerations in the design of sustained-release dosage

[6] Aerosil.
[7] Carbowax 1500.

forms and emphasized the screening of preliminary formulations, the establishment of *in vitro* specifications, and the evaluation of the formulations by clinical pharmacological tests (641).

Among the agents which were described for use in the preparation of sustained release products were acrylic resin coatings, hydrophilic gums, and amylsodium polyethylene (642–646). Delayed action of cationic drugs was brought about by the association with anionic detergents (647). Other studies described the variables involved in the use of inert matrices composed of wax, vinyl chloride-vinyl acetate copolymer, and amylsodium-polyethylene (648–651). The role of wetting on the rate of drug release from inert matrices was evaluated (652). Descriptions of the entrapment of cationic drugs by polymeric flocculation and the use of fat homologs were given as potential sustained release preparations (653, 654). Using gelatin encapsulation, others showed that urinary excretion patterns were much the same as those of sustained-release preparations (655). The effect of pH and electrolytes and the preparation and *in vitro* release of sulfamerazine in a gelatin coacervate were discussed in a series of papers (656–658). Also noted were the effects of selected variables on the microencapsulation of solids and a description of pharmaceutical dosage form produced by coacervation (659, 660).

Reports on prolonged release sulfaethylthiadiazole preparations covered such topics as the description of the preparation of spray-congealed products using various waxes, as well as the effect of surfactants and modifiers upon the release of drug from these preparations (661–666). Among the drugs which were studied in sustained release forms were aspirin, antibiotics, sulfonamides, theophylline, carbinoxamine, pyridoxine hydrochloride, and hormones (667–674). In the paper by Beckett, the effect of urine pH is discussed in relation to the evaluation of sustained release preparations of amines (675).

Cosmetics—Two separate articles dealt with the microbiological control of cosmetics; methods of testing preservative effectiveness and the types of preservatives used were discussed (676, 677). The article by Day reviewed skin care and the types of creams available (678). The use of water-soluble films, 1-3 butylene glycol, distilled lanolin alcohols, and silicones in cosmetic preparations were noted (679–684). Included among the discussions pertaining to perfumes was the ignition temperature of odorants, oxidation of perfumes, and a method of assessing odors by numbers (685–687). Other publications described the external application of curative earth and the use of hydrogen peroxide and vitamins in cosmetics (688–691). Various reports on hair preparations appeared in the literature. These included the effect of base components on properties of oxidation of hair dyes, recent development in synthesis of hair dyes, and new protein-based cosmetics for hair treatment (692–694). Other articles reported on modern technology of hair preparations, surfactant shampoos, and polymeric substances in hair spray film forming compositions (695–697). Among the papers on soaps was one describing the production of toilet soaps, possible problems, and their elimination (698). Components of soaps such as heavy metals and perfumes were the subjects of other papers (699–701). The aging phenomena of toilet soaps and the rapid determination of soap stability were also described (702, 703). Reports on modern methods for gellification of bubble baths and shampoos, a review of formulation problems, and manufacturing and packaging considerations of bath cubes also appeared in the literature (704, 705). Further studies included the use of UV absorbers in cosmetics and the selection of sun-screen agents and perfumes for cosmetics; a report supporting the general use of sun-screen chemicals in cosmetics was published (706–708). Donoel reviewed components and formulation of suntan preparations while Kalish reviewed antiseptic cosmetics (709, 710). Cosmetic beauty masks for deep physiological cleaning of skin were discussed and a review of Negro cosmetics was presented (711, 712).

Packaging—In the article on the pharmaceutical uses of plastics, the permeation and sorption of drugs in plastic containers is reviewed (713). Also published were articles giving a short classification of plastics and their properties and the design and operating principles of an apparatus capable of measuring the inherent static charge of packaging materials (714, 715). A series of papers by Autian reviewed drug packaging in plastics (716–719). The review article by Sacharow described a guide to unit-dose packaging (720). Compounds evaluated for use in packaging included segmented polyurethane, polystyrene, and aluminum foil (721–723). In a report on the stabilization of plastics for pharmaceutical application, various stabilizers which are used were reviewed (724). Matthews described tests to assure suitability of packaging for cosmetics (725). Toxicological studies were conducted on medicinal-grade plastics sterilized by ethylene oxide (726). Studies on the stability of phenol in injection flasks sealed with rubber, the storage effect on preservatives in glass and plastic bottles, and the loss of organomercurial preservatives from medicaments stored in glass ampuls and metal tubes were conducted (730–732). An interesting article describes the uncertainties of dropper dosage for critical administration of medications (733).

EQUIPMENT

The evaluation of tableting tool life records and the instrumentation of a rotary tablet machine were the subjects of two papers (734, 735). A miniature air-suspension coating apparatus was shown to be comparable, with respect to uniformity of coating, to the 15.24-cm. (6-in.) Wurster apparatus (736). A method for coating discrete solid particles and a diagram of the apparatus used was presented (737). Another report compared four comercially available "crushing strength" instruments used for compressed tablets (738). Systems useful in producing sterile, pyrogen-free water were described by Perrin (739). An apparatus for determining solution kinetics was also presented (740). A sampling device was developed which made available a sample of aerosol product that could be assayed directly in the chamber (741). Other interesting papers described the sterilization of freeze-drying equipment and the ma-

chinery used in packaging when plastic films are used (742, 743).

PHYSICAL PHARMACY

Many techniques for performing dissolution studies have been described in the literature. An apparatus in which 20 dissolution tests may be conducted simultaneously was evaluated (744). A continuous-flow apparatus has been employed in studying the dissolution character of solid dosage forms (745). The release rates of ^{14}C-labeled materials from solid dosage forms *in vitro* were studied using scintillation counting devices (746). The factors affecting influence of micellular solubilization and discrepancies between theory and experimental data for dissolution of solid drugs under stirred and static conditions were described (747, 748). Investigations were performed to determine the role of surface tension of gastric juice and the effect of physiological surfactants on the dissolution kinetics of drugs (749–751). The release pattern of salicylic acid and polyvinylpyrrolidone from compressed mixtures was found to fit the theoretical model for the dissolution of two noninteracting phases (752). Also reported was the release of drugs from matrixes of hydrophilic colloids as well as from wax and plastics (753–756).

The effects of various factors such as particle size and additives on the *in vitro* dissolution of solid dosage forms were discussed by several different authors (757–759). The importance of dissolution rate for predicting the absorption and physiological availability of drugs was reviewed in several interesting articles (760–762). Aguiar *et al.* reported the importance of physical and pharmaceutical factors on the release and availability of chloramphenicol from capsules obtained from different sources (763). Comparisons were also made between *in vitro* and *in vivo* availability of various drugs from enteric-coated tablets (764).

The dissolution of hydroxyapatite in the presence of acid and the effect of enzymes on the rate of kidney stone dissolution were other examples of the use of this technique (765, 766).

The field of particle-size measurements produced a number of interesting papers this past year. The use of the hindered settling technique was evaluated and compared to the results obtained by particle counter methods for freshly precipitated cupric carbonate (767). An instrumental method for the determination of particle size by dielectric measurements was described (768). Results obtained by this method for griseofulvin and phenothiazine agree well with these obtained by the Andreasen method. Described also were microphotographic methods and surface area measurements by low temperature nitrogen absorption (769, 770). A spectrophotometric method was employed in measuring the particle size of polyvinyl acetate emulsions (771).

The use of the spectropolarimeter in determining the acid dissociation constants of various betaine salts was reported (772). Other authors described the dissociation constants of various acids and bases in mixed solvents (773, 774). These studies indicated that acetone exhibits a differentiating effect on the base strength of a great many pharmaceutically important amines. Investigations into the thermodynamics of ion solvent interactions were also reported for several mixed solvent systems (775, 776). Conti *et al.* studied the influence of the solvent structure on ion-pair association of various alkylammonium salts (777). Also described were the effects of substitutents of quaternary ammonium salts on their partition coefficients between immiscible solvents (778).

Articles of interest of a miscellaneous nature, relating to the validity of melting points as measured by thermolysis curves, light-scattering analysis, and the application of molecular sieves were also published in the past year (779–781).

The use of reflectance spectroscopy in determining iron-adjuvant interactions was described by Bornstein *et al.* (782). The development of computer models and the use of the digital computer in evaluating monodisperse systems have been reported (783, 784).

Solubility—Two review articles very thoroughly covered the solubilization of various materials with different types of surfactants (785, 786). The effect of temperature upon the solubilization of benzoic acid by a series of nonionic surfactants has been observed (787). The effects of surfactants on the solubilization of dyes, sulfonamides, alkaloids, and benzoic acid were reported (788–792). Also described were the solubilization and stabilization of vitamins and certain oils by the use of various surfactants (793, 794). The effect of ions and the charge of the micelles on their solubilization properties have been determined (795–797). Micellular solubilization of hydrocarbons, phenyl salicylate, and testosterone has been described in a series of papers (798–802).

The physiochemical factors affecting the solubilization of pharmaceuticals were discussed in two interesting review articles (803, 804). The solubilities of compounds of pharmaceutical interest such as antipyrine, testosterone esters, benzoic acid, sulfadiazine, griseofulvin, and vinbarbital have been determined in aqueous as well as certain mixed solvent systems (805–810).

The effect of hydrotropic salt solutions and macromolecular agents on the solubility of various compounds of pharmaceutical interest has been studied (811, 812). The increased solubility of aminopteridines, essential oils, 3,4-benzopyrine, and other drugs as a result of the inclusion of various additives was the subject of several papers (813–816). Other notable papers in this field relate the effect of increased solubilization of hydrocarbons on the rheological properties of aqueous soap solutions and the effect of increased water solubility of nitrocellulose on the stability of its emulsion (817, 818). Saunders described the effects of ultrasonic vibrations on the properties of lecithin solutions (819).

Complexation—Shefter, by the use of X-ray diffraction, was able to elucidate the molecular structure of caffeine-5-chlorosalicylate complex (820). Other studies of possible complex formation utilized thermal, osmotic, polarographic, spectral, viscosity, and dialysis methods (821–829).

The nature of the interaction between parabens and selected sucrose esters, as well as between starches and certain pharmaceuticals has been studied (830, 831).

Also investigated were the complex behavior of barbiturates with adenine derivatives, thiamine with pyrazolone derivatives, and sodium fluorescein with polyvinylpyrrolidone (832–834). Nakano and Higuchi studied the effect of molecular conformation on the interaction of various organic species in water (835).

A series of prodrugs and esters of acetaminophen and salicylic acid were synthesized and shown to have different properties such as solubility, partition coefficients, and rates of hydrolysis which led to improved blood levels when ingested (836–839). The effect of chelate formation on the stability of various drugs in liquid dosage forms was the subject of several interesting articles (840–842). Also reported were the effect of chelates on acetylcholinesterase activity and the effect of complex formation with 8-chlorotheophylline on the kinetics of 3-carboxymethoxy-1-methylpyridine (843, 844).

X-ray diffraction was used to characterize the bindng of anesthetics to certain blood proteins (845). The interaction of 8-hydroxyquinoline, a preservative commonly used in Tuberculin P.P.D. solutions, has been shown with certain metallic impurities (846). Evidence was also presented describing the interactions of detergents and zwitterions with proteins (847, 848). Complex formation between ferric salts and sorbitol as well as other carbohydrates has been shown and characterized by the use of gel filtration techniques (849, 850). Others studied the mechanism and changes which occur following the interaction of aluminum hydroxide gels with various dyes (851).

Surface Phenomena—A thorough review of recent developments in the studies of surfaces has been given by Menter (852). The role of diffusion and the use of the Elovich equation in adsorption kinetics were described in separate papers (853, 854). Another report explained the long-range forces between chemisorbed atoms (855). A review concluded that use of the Moessbauer effect is one of the most effective methods of studying the physicochemical properties of solid surfaces (856). A method for evaluating the desorption kinetics of surface-active substances was published (857). The effect of the position of substituted benzenes on the free energy during absorption has been reported (858). Also investigated was the effect of ionic association on the decrease of free energy during the adsorption of colloidal electrolytes (859). The adsorption mechanism of gelatin-activated colloidal particles at the hydrosol-solid interface was described (860). The influence of temperature on the adsorption of kanamycin, dyes, and some organic acids was evaluated in a series of papers (861–863).

The structure of water adsorbed on kaolins, montmorillonites, and other solid surfaces has been described (864–867). The dielectric constant of water adsorbed on silica gel having different pore sizes was determined (868). The various factors affecting the adsorption of water on gelatin, aluminum oxide, and cation-substituted vermiculite were also noted (869–871).

The effect of chain length of a series of detergents on the critical micelle concentration and diffusion coefficient was the topic of a very interesting paper by Mukerjee (872). Several other papers have also been published which indicate the effect of hydrocarbon chain length on absorption at an oil/water interface (873, 874). The absorption characteristics of water-insoluble polymers at the aqueous air-interface were also investigated (875, 876).

The aspects of the surface properties and adsorptive characteristics of silica gels were the subject of a great many papers. The surface properties of silica gels were investigated by the use of IR spectroscopy as well as by nitrogen absorption methods (877–880). The adsorptive interactions of silica gels with water, alcohols, and methylsiloxanes were thoroughly examined (881–885).

The properties of kaolin and other natural clays were very extensively reviewed during the past year. The adsorption of various cations as well as the surface leaching of kaolinite has been studied (886–888). Other papers described the factors affecting the adsorption properties of bentonite, kaolin, and other natural clays (889–891). The effect of pH on the adsorption of methylene blue and atropine from aqueous solutions by kaolin was investigated by various workers (892–894). The basic concepts of charcoal adsorption and a review of the mechanism of carbon black adsorption have been presented (895–897). Aided by polarography other investigators determined the adsorption isotherms for a series of phenols on a specially purified lignite (898). It was also noted that the adsorption of various acids and alcohols from aqueous solutions on to charcoals was greater if the pH of the solution was maintained neutral (899). The adsorption of various dyes by sodium carboxymethylcellulose, starch, talc, and aluminum hydroxides has been evaluated by several workers (900–902). Samsonov *et al.* studied the kinetics of sorption of tetracycline by sulfonic acid resins (903). The ion-exchange rate of the tetracycline was controlled by the diffusion of the antibiotic and the diffusion coefficients related to the amount of crosslinking in the resins. The adsorption of water and alcohol on aluminum oxide was investigated using IR spectrophotometry (904). Adsorption isotherms of the Langmuir type were obtained for the adsorption of sodium lauryl sulfate and polyethylene glycol on the mercury electrode interface (905). The surface properties of apatite in electrolyte solutions and the mechanism of action of interfacially adsorbed agents on the demineralization rate of enamel were studied (906, 907).

An account has been given of the general theory of interfacial tension and its application to adsorption phenomena (908). Theoretical considerations of the attractive forces at solid-liquid interfaces and on surface stress received attention in a series of papers (909–911). The mass transfer through a liquid-liquid interface was investigated in an acetic acid–water–benzene system (912).

A review article discussed measurements of the surface tension and other surface properties of pure water and aqueous electrolyte solutions in the presence and absence of soluble and insoluble monolayers (913). A precise method for the rapid determination of small variations in surface tension of liquids was described (914). A series of papers reviewed the measurement of surface tension using modifications of the drop-weight method (915–922). Other articles described the use of automatic recording systems to measure the surface

viscosity, the use of radioactive sources to measure interfacial potential, and the determination of surface tension of hydrophobic bodies according to the size of the contact angle (923–925). Lane developed a multilayer model of a solid-regular solution interface (926). The adsorption, surface tension, and heats of wetting for the multilayer model were derived and methods for obtaining the model parameter from experimental data were suggested. The effect of surfactants on van der Waals' forces at a solid-liquid interface has been calculated (927).

The interfacial properties of surfactant, soap, and detergent films received attention in a series of interesting papers (928–936). Also reviewed were the theoretical considerations of the surface tension of binary liquid mixtures (937–939). The surface tension of liquid mixtures of DMSO and ethanol with water were obtained (940, 941).

The relation of the initial spreading pressure of a series of pure alcohols on water to the interfacial tension, work of adhesion and solubility was outlined (942). Also investigated were the surface tensions of aqueous procaine amide solutions, aqueous sodium chloride, and sucrose solutions and some phenoxyethanol and quinolyloxyacetic acid derivatives (943–945).

The theory of the measurements of surface viscosity was reviewed (946). The reaction between calcium ions and stearic acid at the air-water interface has been determined by the measurement of surface viscosity (947). The effect of surface viscosity was shown to influence the gravity collapse at flat surfaces to a greater extent than the viscosity of the other phases in three phase systems (948).

Many review articles on the history, applications, and properties of different types of surfactants appeared in the literature during the past year (949–963). Chun described the measurement of HLB balance of surface-active agents while Lowenthal developed an equation which describes the relationship between HLB number and molecular configuration of certain polyoxyethylene polyoxypropylene surfactants (964, 965).

The presence of hydroxyethylated surface-active agents has been determined by means of their tendency to react with potassium ferrocyanide (966). The physicochemical properties of surfactants in nonaqueous solutions as well as in aqueous solutions were reviewed (967–972). The relation between the state of solution of nonionic surfactants and their emulsifying action has been pointed out (973). Another report describes the hydrolysis of surfactants with acid and alkali (974). The interactions of cationic surfactants with those of a nonionic nature were shown to result in a lowered antiseptic activity, while those between anionic and cationic surfactants resulted in the formation of 1:1 complexes (975, 976). Also observed were reactions of surface-active agents with macromolecules (977, 978). Surfactant effects on precipitate formation in general and on the coprecipitation of potassium with barium sulfate were the subjects of two interesting papers (979, 980). The effect of cationic surfactants on the viscosity and turbidity of chondroitin sulfate solutions was investigated (981).

The effects of the binding of lecithin with cholesterol and with inorganic electrolytes at the oil-water interface have been studied by several workers (982, 983).

The thermodynamics and general reviews of micelle formation have been reviewed in several papers (984–988). The use of NMR for the measurement of critical micelle concentration was demonstrated (989, 990). The use of electrocapillary curves to determine the critical micelle concentration of nonionic surfactants was reported (991). The effect of temperature on the surface potential of surfactant micelles and on the critical micelle concentration of surfactant semicolloids received attention (992, 993). The effects of electrolytes on micellar properties such as viscosity, surface tension, and light scattering were outlined in several papers (994–1000). The micellar molecular weight and the electrical conductance of aqueous solutions of surface-active agents was determined for a series of sulfonates (1001). Light scattering and hydrodynamic measurements of certain nonionic surfactants led to conclusions that the smallest micelles are the most hydrated and that hydration decreases as micelle size increases (1002). The surface chemical and micellar properties of drugs as well as some sodium alkylbenzenesulfonates were reviewed (1003–1005). The effect of micelles on solubilization, in hydrolysis, and on the kinetics of the Cannizzaro reaction has been described in several reports (1006–1009).

Colloid chemistry and the stability of colloidal dispersions were the subjects of several review articles (1010, 1011). The application of small angle X-ray for the purpose of studying colloids and macromolecules has been demonstrated (1012). The behavior of ultrasmall particles and the surface activity of metastable colloid solutions were investigated (1013, 1014). The colloidal phenomena during the formation of precipitates and the coagulation of lyophobic colloids by surface-active agents received attention in several papers (1015, 1016). The colloidal properties of chlorohexidine and its interaction with some macromolecules as well as the interactions of soluble particles with macromolecules were described (1017, 1018). Ho and Higuchi discussed preferential aggregation and coalescence in heterodispersed systems (1019). Their findings may explain the relatively narrow particle-size distributions observed in certain emulsions and flocculated suspensions and the limited flocculation and coalescence behavior observed in certain instances. A computation method which simulates floc structure was used to calculate the shape and bulkiness of random flocs (1020). The orientation of colloidal particles in laser optical fields and its effect on light scattering has been evaluated (1021).

The mechanism of foam stabilization and inhibition was extensively reviewed (1022). An automatic method of determining foam has also been presented (1023). New equipment for the determination of the charge and particle size of electroaerosols was also described (1024).

The structure of the electrical double layer on porous surfaces was the topic of an interesting paper by Lyklema (1025). The effect of the zeta potential on coacervate soap micelles, particles in organic media, and lyophobic colloids has been investigated (1026–1028).

Reviews of the physics of thin films as well as general properties of films were published (1029, 1030). The

monolayer properties of a number of protein films were measured in the presence of different surfactants (1031, 1032). These studies noted the significance of these surfactants on the properties of the films and their possible biological importance. The effects of surface tension on film elasticity and on the contact angles between the film and the bulk liquid were shown (1033, 1034). The main forces affecting film stability was found from light-scattering determinations of the shape of free liquid films (1035). The use of a microviscometer cone for the determination of the thickness of surface layer of mineral oil was described (1036). The mechanism which this layer plays in lubrication is discussed in detail. Torosian and Lemberger investigated the properties and the interactions between lecithin and lipid substances in mixed monomolecular films (1037). The effect of polymer side chain on the surface properties of monomolecular films was also investigated (1038). The properties of monolayers of synthetic grisan derivatives were determined and correlated with the molecular orientation of these entities at the air-water interface (1039).

Several review articles dealing with wetting and wettability have been published during the past year (1040, 1041). Methods of characterizing the surface activity of solids were described (1042). The thermodynamics of wetting has been discussed in interesting articles (1043–1045). It was also noted that the wetting power of surfactants decreased with increasing temperature (1046). The wettability of some organic polymers was evaluated and determined by measuring contact angles and the rate of penetration into capillaries (1047, 1048). Other papers describe the wettability of gels and films of gelatin and of other surfaces (1049–1051).

The effect of capillary liquid on the force of adhesion between spherical solid particles was the subject of a series of papers by different authors (1052–1054). Adhesion problems were discussed with respect to contact angles and surface tension in an excellent review article (1055). An adsorption model for contact angle and spreading has been demonstrated which allows calculations of the contact angles and spreading coefficients from adsorption data (1056). The significance of contact angles and various methods of determining them was the topic of another review article by Gray (1057). The effect of temperature on the contact angle of the naphthalene-water-air system has been investigated by several workers (1058–1060). The wetting and adhesion processes of solids with a liquid under equilibrium and nonequilibrium conditions were analyzed assuming a negligible vapor pressure of the components (1061). The contact angles of soap films and of thin lipids was investigated, as was the wettability of various low energy surfaces, such as Teflon and paraffin with water (1062, 1063).

Crystallization—Palermo published an excellent review of crystallization and the crystallization processes (1064). IR spectroscopy was utilized in the determination of different polymorphic forms of drugs which are present in the *Japanese Pharmacopeia* (1065). Several papers have been published which described crystallization processes which occur in aqueous steroid suspensions (1066–1068). These papers describe in detail the effect of dissolution and agitation on the crystal growth of cortisone acetate from aqueous suspensions. The crystal growth in these suspensions was related to formation of a more stable crystal form which had less solubility than that observed with the unstable form. Agitation was also observed to accelerate the diffusion controlled process of dissolution and crystallization in these systems.

Poole and Bahal (1069) studied the dissolution and solubility of the anhydrous and trihydrate forms of ampicillin. The thermodynamic properties of these two forms of the antibiotic were evaluated and it was noted that the properties of the two forms were consistent with the observed differences in biological utilization of ampicillin in animals and humans. Difference in dissolution of two different aspirin polymorphs have also been pointed out (1070). The dissolution rate of these different polymorphs both as crystals and as tablets indicates that one form of aspirin dissolves 50% faster than the other.

Crystallization occurring in emulsion-type ointment bases was described by Barry (1071). DTA, X-ray diffraction, and microscopy were utilized to study the polymorphic crystal changes of glyceryl monostearate (1072). Materials which inhibit or modify fatty crystal formation from oils as well as those observed in cocoa butter-containing products were discussed in a very interesting review article (1073).

The polymorphism and crystal structure of thiolphthalidine, cephaloridine, and phenobarbital were investigated (1074–1076). Although not specifically related to pharmacy, studies were conducted to determine the rate of formation of calcium fluoride on hydroxyapatite in buffered fluoride solutions (1077).

Rheology—The use of computers to evaluate various rheological systems was discussed in two very interesting articles (1078, 1079). The effect of various emulsifier concentrations on the rheology of oil-water emulsions has been described (1080–1082). Also evaluated was the effect of viscosity on the dynamic surface tension of aqueous sucrose, *n*-heptanol systems, and the effect of solubilized hydrocarbon additives on the rheological properties of aqueous sodium cholate solutions (1083–1085). The determination of van der Waals' constant from the rheological properties of emulsions has been demonstrated (1086).

The rheology of disperse systems and concentrated suspensions was reviewed (1087–1089). These articles summarize the equations for non-Newtonian flow and thixotropy as well as describe possible interactions between particles and their effect on these systems.

The complete rheological curves for aqueous suspension of different clays were given (1090). These curves show plastic flow at low-shear stresses while at the higher stresses destruction occurred and viscosity decreased. The utilization of X-ray diffraction in the studies of pharmaceutical clays has been demonstrated (1091).

The viscoelastic properties and slip fraction of bentonite gels were investigated as was the exchange between potassium and sodium ions on bentonite (1092, 1093). The dependence of plastic-flow behavior of clay suspensions on the surface properties of the clay has been shown (1094). This paper describes the two current theories explaining pseudoplastic behavior. Also

demonstrated was the effect of surfactants, salts, and various other chemical impurities on the rheology of clay suspensions (1095–1099). The effect of alumina pretreatment on the rheological and technological properties of alumina suspensions was pointed out in other articles (1100, 1101).

The rheological properties of various gelatin gels were the topic of several interesting papers (1102, 1103). Discussed in greater detail was the effect of electrolytes on the rigidity of these gelatin systems (1104–1106). The effect of temperature on the structure and strength of certain gel systems was also investigated (1107, 1108). The properties of gels formed with various macromolecules such as cellulose gums, agar, 1-3 glucan, and ethylene glycol esters were described in other papers (1109–1112).

The properties and applications of aluminum stearate gels in oils were described (1113). The effect of time and temperature on the rheological stability of procaine penicillin G suspensions has been demonstrated by Boylan and Robison (1114). These studies indicated increases in viscosity and thixotropy formation after storage at 25 and 35° for 2 years while samples stored at 5° for similar periods remained unchanged. Another paper of pharmaceutical significance evaluates the influence of rosin, zinc acetate, and olive oil on the consistency of zinc oxide eugenol paste (1115). A viscosimeter (Brookfield Synchro-Lectric) was used to measure the rheological properties of aqueous submicroscopic pyrogenic silica dispersions (1116).

PHARMACEUTICAL ASPECTS

Antibiotics—Several excellent review articles on antibiotics, their properties, and spectrum of effectiveness were presented (1117–1119). The semisynthetic penicillins were subject to even greater scrutiny. Articles were published which related bacterial activity of these penicillins to chemical side-chain structure and their stability (1120–1124). The mechanism of action of penicillins on bacterial cell walls was also investigated (1125). The properties, activities, and uses of various antimycotic antibiotics were the subject of a review article (1126). Also discussed was the composition of nystatin and of various carboxamide derivatives of chloretetracycline hydrochloride[8] (1127, 1128). A unique technique utilizing a "pulsating" layer for drying tetracyclines was proposed and shown to be superior to normal oven-drying methods (1129). The effect of antibiotic binding to agar and its effect on the inhibition zone of various antibiotics was discussed in a very interesting paper (1130). The results obtained indicate that the binding of the antibiotics is fairly rapid and was reversed by the presence of salt.

Radiopharmaceuticals—A review of the basic concepts of tracer kinetics and the nomenclature to be used was presented by Brownell *et al.* (1131). The use of radioactive pharmaceuticals in medical diagnosis has also been reviewed (1132). The use of radioisotope analysis in determining *in vivo* hemolysis following intravenous injection was described (1133). Other uses of radioactive materials were in the determination of drug distribution and availability following administration (1134). Some examples of such studies were the measurement of distribution of radioactivity in mice following the oral administration of labeled orphenadrine, as well as the fate of labeled noscapine and dicarbethoxythiamine in mice (1135–1137).

[8] Aureomycin, Lederle Laboratories, Pearl River, N. Y.

BIOPHARMACEUTICS

The topic of biopharmaceutics was very ably reviewed by Higuchi *et al.* (1138). Another article outlines the mechanisms of action and interactions of drugs, covering the mechanism of absorption and actions at receptor sites, displacement, biotransformation, and alteration of excretion (1139). The use of the analog computer to predict the relationship between urinary pH and kidney reabsorption and excretion of drugs which are partially ionized at physiological pH's has been described in a series of papers (1140–1142).

A mathematical review of the equations pertaining to the compartmental analysis of drug kinetics was presented by Segre (1143). Other authors present the shortcomings of such a system and propose the use of a two-compartmental open-system model to lessen the error introduced into the usual absorption rate and elimination rate constants and on the volume of distribution (1144–1146). The development of a three-compartmental open-system model was proposed to explain the elimination kinetics of bishydroxycoumarin (1147). These compartments are defined as a plasma compartment, a rapidly accessible drug-metabolizing system compartment, and a more slowly accessible compartment.

The pharmacokinetics of bromsulphalein elimination were studied following intravenous injection (1148). Based on these studies a four-compartmental model was developed to fit the observed elimination rate.

The absorption, excretion, and tissue distribution were evaluated following the administration of pyrbenine and salicylates (1149, 1150). Other workers have investigated the absorption, distribution, and elimination of various antibiotics including penicillin G, oxacillin, kanamycin, and spectinomycin (1151–1154). Wagner has demonstrated the correlation of performance score with "tissue concentration" of lysergic acid diethylamide in human subjects (1155).

The effect of species, sex, and age differences on absorption, excretion, and activity of drugs has been well documented. Differences in absorption observed with different animal species following the administration of barbiturates, thiamine, and labeled serum albumen were discussed (1156–1158). Also noted were the effect of species differences on the metabolism and storage of various drugs (1159–1164). The effects of species and sex differences were even noted on the *in vitro* metabolism of digoxin by liver slices (1165). The question of the predictive value of animal tests in relation to drugs affecting the cardiovascular system in man was raised in a very interesting article (1166). The effect of genetic factors on the predictability of drug responses was the subject of a series of papers (1167–1170). Examples were given of the effects of genetic factors on

drug induced hemolysis, unusual sensitivity, and resistance and excretion rates. The effects of temperature and environmental conditions on the metabolism and excretion of ephedrine, cocaine, barbiturates, and curare have also been reported (1171, 1172). Sex differences were observed in the absorption of iron, demethylation of ethylmorphine, and the water excretion effects of certain diuretics (1173–1175). The effect of age differences and physical state on the pharmacokinetics of reserpine, nitrofurantoin, gentamycin, and digoxin was described (1176–1179).

Effect of Physicochemical Properties—The chemical and physical factors influencing the properties of drugs and their absorption from the intestinal tract were reviewed in a very interesting article (1180). The effect between chemical constitution, physicochemical properties, chemical reactivity, and local anesthetic activity of a series of benzocaine derivatives in rabbits was investigated (1181). It was observed that the activity of these compounds increased with decrease in water solubility and with increase in partition coefficient and surface activity. The basicity appeared to have no effect on the activity. The differences in aqueous solubility between the anhydrous and the trihydrate forms of ampicillin were reported to be responsible for the higher blood levels obtained upon administration of dosage forms prepared with anhydrous ampicillin (1182). Similar differences in absorption were noted from the various polymorphic forms of chloramphenicol palmitate (1183, 1184).

Effect of Formulation—Several excellent articles were presented by Wagner reviewing the effects of formulation on the availability and therapeutic activity of drugs (1185–1187). The influence of formulation upon the activity of chemotherapeutic agents as well as on the chemical stability was the topic of several other articles (1188, 1189). A general discussion covering proposed criteria for the performance of different drugs and formulations has been presented (1190). Also discussed in this paper was the use of *in vitro* models to establish the partitioning characteristics of the drugs and means of predicting excretion profiles based on buccal absorption tests. The effect of formulation on absorption and blood levels was noted for various commercial chloramphenicol products and compared to the *in vitro* results obtained with these same materials (1191). The influence of tablet *versus* capsule formulations of diuretics upon excretion was compared (1192). These authors indicate that administration in the tablet form gave much better and more rapid drug absorption than the identical formulation given in a hard gelatin capsule. The effect of formulation variations on the *in vitro* and *in vivo* availability of drugs such as griseofulvin, potassium chloride, tetracycline, and some radiopaque agents was evaluated in a series of papers (1193–1197).

The effect of the route of administration on the blood levels and length of activity has been reported for certain anticholinergic drugs (1198, 1199). Also described was the influence the method of administration had on the metabolism as well as the plasma fluoride levels of sheep (1200).

Fincher reviewed the effect of particle size on clinical aspects, drug absorption, and physical properties of drugs (1201). This effect was graphically shown by observing the dissolution and blood levels obtained following the administration of 4-acetamidophenyl 2,2,2, trichloroethyl carbonate (1202). These investigators noted that lower peaks and slower rates of decline of plasma levels were observed with the regular particle sized material than when the fine material was administered. The effect of pH on the action of some parasympathomimetic drugs was investigated (1203). It was apparent that only the protonated form of these tertiary parasympathomimetics had activity on the isolated guinea pig intestine.

The importance of pre-equilibrating drugs and adsorbents was studied using the absorption of promazine from the gastrointestinal tract (1204). It was noted that small amounts of attapulgite and charcoal did not affect drug absorption as long as the drug and adsorbent were not equilibrated prior to administration. The effect of pH upon the absorption of atropine from aqueous solution by kaolin has also been described (1205). The effect of different additives, chelating agents, and complex formation upon absorption of drugs was outlined in a series of papers (1206–1209).

The influence of ointment vehicles on skin absorption has been well documented (1210–1212). It was noted that organic solvents which are miscible with water and are capable of increasing the solubility of a water insoluble drug in the aqueous phase of the base will increase the penetration of the drug. The influence of dimethyl sulfoxide on percutaneous absorption of salicylates and picrates was shown (1213, 1214). The mechanism by which DMSO increased absorption was theorized to be due to the effect that this agent has on protein chain in the skin barrier causing it to undergo unfolding or expansion (1215). Also published were several review articles describing drug release from fatty matrixes and its influence on the rectal absorption of drugs (1216, 1217). The effect of nonionic surfactants on the rate of absorption of aminophylline from suppositories was also investigated (1218).

Absorption Control—Muenzel discussed the effect of auxiliary substances with respect to the absorption of drugs in oral, rectal, and parenteral applications (1219, 1220). A method for determining pPy, a measure of potentiating activity, was proposed (1221). This term, which is defined as the negative logarithm of the molar concentration of a potentiating drug which increases the response of a fractional dose of agonist to that of the initial submaximum dose, is useful in quantifying the potentiating or inhibiting effects of drugs.

The effect of pH on ethanol absorption and of a nonionic surfactant-secobarbital complexation on absorption of these drugs by goldfish was demonstrated by various workers (1222, 1223). Also examined was the effect of taurine and glucuronamide on aspirin absorption from the gastrointestinal tract (1224, 1225). It was also noted that the coadministration of salicylamide and sodium salicylate resulted in a pronounced decrease in the formation of glucuronides of these two drugs (1226). The effect of caffeine on the absorption of various analgesics was investigated (1227). The effect of caffeine was marked with the more easily absorbable drugs but very small for poorly absorbed

drugs, such as aspirin. The effect of food on the absorption of sulfonamides and proteolytic enzymes on the absorption of tetracyclines was also described (1228, 1229). Also investigated was the effect of bile salts on gastric emptying and intestinal transit time of rats (1230, 1231). Several drugs affecting intestinal lipid and labeled strontium absorption in rats have been noted (1232, 1233).

The effect of various surfactants on the rectal absorption of aspirin from fatty base-type suppositories was shown (1234). Methods were also described to evaluate detergent absorption and penetration of the skin (1235). These studies indicate that the superficial and lower layers of the skin of hands soaked in sodium lauryl sulfate solution had a greater affinity for cationic stain than nonsoaked hand skin.

No effect was noted due to the ingestion of some commonly used drugs on blood alcohol levels in dogs (1236). The effect of propylthiouracil on the transport of labeled thyroxine was also studied (1237). Gibaldi and Schwartz published an interesting paper in which they carried out a pharmacokinetic analysis of literature data of penicillin blood levels with and without probenecid (1238). Their findings indicate that although probenecid markedly diminishes tubular secretion of the pencillins it more significantly reduces the apparent volume of distribution of the drug. Also reported was the inhibitory effect of probenecid on the renal excretion of indomethacin (1239). The influence of various complexing agents, such as EDTA, citric acid, ascorbic acid, and nicotine hydroxamic acid, on the retention of iron in normal and anemic rats was the subject of a further paper in this field (1240). The effect of citrates on the excretion of citric and uric acid in the urine of normal persons and patients with uric acid calculi was also investigated (1241).

Absorption Mechanism—The dependence of drug action upon the lipophilic character of several hypnotics was discussed (1242, 1243). Data was presented in these studies which shows that the hypnotic activity of certain barbiturates depends almost entirely on their lipophilic character as defined by their octanol-water partition coefficients. The partition coefficients of acetylsalicylic and salicylic acids were examined in order to explain differences in their biological activity (1244). Lien and Hansch supplied data which indicate that the metabolism of drugs is markedly dependent on the lipophilic character of drugs (1245). The mechanism of action and potency of general anesthetics, especially as they relate to the structure of water and their solubility was reviewed (1246, 1247). Also investigated was the relation of activity to the lipid solubility of various other drugs (1248).

A review by Lemanowicz described the factors and possible mechanisms of gastrointestinal membrane transport (1249). The nature of membrane structure, methods of molecular transport through a barrier, and other factors were also discussed. The thermodynamics of transport phenomena was outlined in several papers (1250, 1251).

Also described was an improved method for determining the diffusion coefficient employing a silver membrane filter (1252). A mathematical model for studying the diffusion kinetics of drugs through membranes was proposed (1253). The kinetics of absorption at liquid-liquid interfaces and factors affecting these kinetics were described for several steroids (1254–1256).

The properties of lipid bilayers at water-water interfaces and the permeation of water through bilayer lipid membranes were outlined (1257, 1258). It was noted that the formation of more lipid-soluble complexes caused greater permeation through the lipoid barrier than the the uncomplexed drug (1259). The thermodynamics of bimolecular (black) lipid membranes and the effect of electrolytes on the properties of such membranes were the topics of several papers (1260, 1261). The rate of water transport was found to undergo significant changes at soap concentrations lower than the critical micelle concentrations (1262). It appears that the generation of colloidal structures from soap ions can apparently have significant effects on the dialysis transport rates. The effect of pressure and DMSO on permeation through semipermeable membranes was also investigated (1263, 1264). It was also observed that the penetration of chlorpromazine into a lecithin film was found to be dependent upon surface pressure, pH, and UV irradiation (1265). Garrett and Chemburkar evaluated the effect of temperature, pH, and solvents on the diffusion of drugs through silastic membranes in a series of excellent articles (1266–1268).

The transfer rate of ions across a membrane when the solutions on both sides are in dynamic equilibrium was shown with the use of labeled sodium chloride (1269). The transport of ions across lipid monolayers and membranes was investigated in a series of papers (1270–1274). The effect of drugs on the rate of persorption, the transport of solid undigested food particles through epithelial layers into the portal circulation, was studied (1275). The results indicated that the motor activity of the gastrointestinal tract was the most important factor in the persorption process. The effect of surfactants on peritoneal dialysis and passage of hydrocortisone across rat intestine was reviewed (1276, 1277). The intestinal absorption of cardiotonic steroids, lipoic acid, and some of its derivatives has also been observed (1278–1280). The effects of drugs on the bulk flow rate through mesenteric membranes of rabbits in the presence of a constant hydrostatic pressure were examined (1281). Also investigated were the absorption of fatty esters of pyridoxine and salicylamate-caffeine complex through everted intestinal sacs (1282, 1283). Sjoqvist in an interesting article discussed the effect of fat solubility and ionization on the transplacental passage of various drugs (1284).

A review of new developments and mathematical interpretations in the field of receptor-drug inhibitor binding was presented (1285). A novel method for studying protein binding of small molecules based on the rate of dialysis of these materials from the protein-containing compartment has been demonstrated (1286). Factors influencing protein binding of drugs and the effect of this binding on therapeutic activity were the subjects of several investigations (1287–1290). Factors affecting the binding of various drugs to albumin and ribonucleic acid have been determined (1291). It was noted that the affinity for binding increases if the hydro-

phobic character of the drugs were strengthened while any decrease in hydrophobic character by the introduction of amino or hydroxyl groups decreased the binding strength. The binding of penicillins to serum proteins and the correlation between lipid solubility and binding were very thoroughly reviewed in the literature during the past year (1292–1294). The clinical significance of protein binding of penicillins was discussed for oxacillin, nafcillin, cloxacillin, and ampicillin (1295). The effect of disease, dilution, and chemical structure of the binding of sulfonamides in human plasma was described (1296, 1297). The effect of metals on the binding of tetracycline analogs to proteins and amino acids as well as the implications of protein binding of tetracyclines has been pointed out (1298, 1299). Also described in the literature was the binding of actinomycin and related compounds to DNA and that of iodochlorhydroxyquinoline and glyceryl guaiacolate to serum proteins (1300–1302). Patel *et al.* have described the interaction of *p*-hydroxybenzoic acid esters to bovine serum albumin and have calculated the free energy, enthalpy, and entropy changes for these interactions (1303). The effect of pH on the binding of salicylate to human serum has also been reported (1304). The relation between binding of thiopental to plasma and its distribution into adipose tissue was the subject of a very interesting paper (1305). The effect of 8-chlorotheophylline and three aromatic acids on reducing the binding of 8-nitrotheophylline to bovine serum albumin was reported (1306). Factors affecting the interactions of digoxin with serum albumin have been investigated (1307). Also reported in the literature was the effect of histamine supply on the histamine binding capacity and the binding of chlorpromazine and similar drugs to heparin (1308, 1309).

Kinetic Studies—A series of very interesting articles was published describing the various aspects of pharmacokinetics (1310–1313). The mathematical treatment of excretion, volume of distribution as applied to drug elimination, and other parameters affecting drug availability and activity were discussed in these articles. The kinetic aspects, such as half lives, for absorption and elimination, as well as limiting solubilities, which should be considered in the simultaneous administration of drugs, have been pointed out in a very interesting article by Taraszka and Forist (1314). The kinetics of competitive absorption was derived by other authors (1315). A method was described for calculating the rate and degree of drug accumulation following multiple-fixed interval dosage schedules from the average plasma concentrations of the drug (1316). The kinetic considerations relating to the rise of drug precursors were investigated by other workers (1317). The kinetics of absorption, distribution, and excretion were obtained for a great many drugs including: ephedrine, imipramine, phenylbarbituric acid and fluphenazine, succinyl choline, thiopental, aspirin, acetyldigoxin, mefexamide, griseofulvin, cephalosporins, doxycycline, and coumarin (1318–1332).

The application and limitations of the principles of pharmacokinetics in the assessment of drug dosage and effectiveness for several antibiotics and corticosteroids were discussed (1333). A new mathematical treatment was proposed for the analysis of plasma clearance curves from 2-hr. experimental data (1334). Other papers in this related field have described the use of the overturn end point for the estimation of absorption and elimination kinetics in goldfish, as well as the effect of flow rate on the distribution kinetics of drugs from the perfusate to a perfused organ (1335, 1336). A new "consistent" model was proposed to explain the results observed for the iodine kinetics in man (1337).

Drug Absorption—The physiological prerequisites for drug absorption were reviewed in several papers (1338, 1339). The mechanisms of gastrointestinal absorption were discussed in a very interesting article which described passive and facilitated diffusion, active transport as well as other factors influencing absorption (1340). The use of the Thiry-Vella dog as a biologic model for the evaluation of drug absorption from the intestinal mucosa has been proposed (1341). The factors influencing the absorption of xenophymethyl penicillin[9] were discussed (1342). The effect of complex formation between antipyrine and salicylamide, salicylic acid, and nicotinamide on the absorption from the alimentary tract was pointed out (1343). It was also noted that the absorption of barbituric acid derivatives from the small intestine did not depend on the chemical structure and lipid solubility to the same extent as did gastric absorption (1344). The gastrointestinal absorption and the excretion were investigated for a number of drugs including methixene, fatty acid esters of pyridoxine, nalidixic acid, and an antibiotic[10] (1345–1349). Other authors have shown that egg shells compare favorably with precipitated calcium carbonate as a source of absorbed calcium (1350). The intestinal absorption of nitrofuran derivatives and intestinal antiseptics derived from 8-hydroxyquinolines were the subject of further investigations (1351, 1352). Comparisons between oral and intramuscular administration of chloramphenicol in horses have been determined (1353). Similar studies have been carried out to measure the effect of intravenously and orally administered and inhaled orciprenaline on the respiratory flow resistance of patients with diseases of the respiratory tract (1354).

A theoretical study of percutaneous absorption of various drugs was presented by Jato (1355). An *in vivo* method for evaluating the topical effectiveness of local anesthetics has been proposed (1356). Also described was the absorption of *p*-toluenediamine through human skin during hair dyeing (1357). A comparison of oral *versus* rectal administration utilizing DMSO-containing bases indicated that higher levels were obtained rectally with aminopyrine and isopropylantipyrine but not with salicylamide (1358).

The dynamics and biopharmaceutical considerations in subcutaneous and intramuscular drug administration were discussed in several interesting papers (1359, 1360). The mechanism of percutaneous absorption was investigated by measuring the absorption of sulfide from hydrosulfuric acid mud baths (1361). The electrochemical properties of certain drugs administered by means of iontophoresis were observed for various drugs (1362). Pharmacologic activity by this method was obtained for

[9] PenicillinV.
[10] Clinimycin.

chloramphenicol, tolazoline,[11] and prednisolone sodium succinate. The kinetics of buccal absorption of amphetamines and the salivary levels from neomycin and gramicidin chewing troches were also investigated (1363, 1364), Also evaluated was the absorption of arylamines from the urinary bladder of dogs (1365).

Factors influencing drug elimination in man were comprehensively reviewed. Several authors described the present concepts regarding the mechanisms of extrarenal excretion of drugs (1366, 1367). Wagner and Northam derived equations to estimate the lag time between the initiation of maintained constant input rate to the plasma compartment and the time when the asymptotic plasma concentrations and constant urinary excretion rate were reached (1368). The pharmacokinetic rates of excretion and acetylation of sulfonamides were reported in several articles (1369–1371). It was noted in these studies that the excretion of sulfonamides was markedly influenced by urinary pH; the more basic, the more rapid the sulfonamide excretion. The influence of urinary pH on the excretion of ephedrine and phenylephrine was also reported (1372, 1373). The excretion and metabolism of pheniramine, brompheniramine, amphetamine, phenobarbital, and metopimazine were the subject of various articles (1374–1379). Other drugs whose urinary excretion was investigated were phenformin, *p*-butoxyphenylacethydroxamic acid, anisotropine, and urea (1380–1384).

Koechel discussed the principles of metabolism and detoxification processes of commonly used drugs (1385). A similar review was published regarding the metabolism of drugs employed in anesthesia (1386). The metabolism of thiazesim, isoproterenol, and 2,3,5 triiodobenzoic acid were also investigated (1387–1390). The hydrolysis of aspirin due to esterases present in rat small intestines was investigated (1391). The hydrolysis of para-oxon and armine in human serum was also shown to be due to the presence of enzymes (1392). The degradation of α-tocopherol in man was reported (1393). The differences observed with ampicillin and phenoxymethyl penicillin levels were attributed to the differences in inactivation rates of these penicillins in the liver (1394). Ampicillin was noted to be inactivated only half as rapidly as phenoxymethyl penicillin in isolated rat livers. Bishydroxycoumarin was another drug whose metabolism in the liver was thoroughly investigated to explain the observed differences in dose dependency observed between humans and rats (1395). The effect of perfusion rate and distribution factors on drug elimination kinetics of a perfused organ system was also investigated (1396). The effect of intestinal microorganisms on drug metabolism in general and chloramphenicol metabolism specifically, has been thoroughly reviewed in several articles (1397, 1398).

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