JOURNAL OF **Pharmaceutical Sciences**

July 1967 volume 56, number 7

Review Article

Pharmaceutical Sciences—1966

A Literature Review

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THIS SURVEY of the literature is the fifth compilation to be published in *J. Pharm. Sci.* (1–4). It represents a comprehensive cross-section of the research and development efforts in the various disciplines of the pharmaceutical sciences. Numerous periodicals and selected sections of *Chemical Abstracts* were selectively abstracted. Two changes have been made from the 1965 literature review. The *Pharmacognosy* section has been discontinued and sections on *Sustained Release* and *Cosmetics* have been created. In order to maintain continuity with the previous pharmaceutical sciences reviews of *J. Pharm. Sci.*, their general format was retained.

GENERAL PHARMACY

A series of papers presented an exhaustive review of the problems associated with the production and marketing of new drugs (5, 6). Another survey outlined the application of a broad knowledge of physical and chemical properties of materials in the formulation of new drugs into suitable dosage forms (7). A systematic

approach to the development of a product formula, using the development of a gelled alcoholic formulation as an example, was described (8). The problems involved in the construction, design, and equipment of a new drug plant were reviewed (9). Meyers described in detail the information which might be supplied to obtain approval for marketing a new drug (10). He also commented on good record keeping as essential to maintaining high standards of quality control (11). Another review article, containing 54 references, was concerned with the application of statistical methodology in quality control functions of the pharmaceutical industry (12). The need for good quality control and how it can be achieved was stressed (13). A discussion of the need for good record keeping during the manufacturing and prepackaging of drugs was also published (14).

Excellent review articles on over-the-counter (O-T-C) antacids, O-T-C antiacne aids, O-T-C laxatives, cough depressants, nasal decongestants, antihistamines and other allergy aids, sleep aids and other O-T-C sedatives, and dry skin and chapping aids appeared in *J. Am. Pharm. Assoc.* (15–22). A survey on dimethylsulfoxide also appeared in the literature (23).

Preservatives—Garrett suggested a basic model for the quantification of preservative action which considered the thermodynamic activity of the biologically effective concentration of the preservative in the aqueous phase (24). Instructions and tabulated data, with general rules and exceptions for testing and preservation of medicinals, were published (25). Methods for the evaluation of preservative systems in proprietary products were discussed (26). The factors affecting the binding of phenol derivatives to *Micrococcus lysodeikticus* cells were evaluated (27). Another study was concerned with the stability of chlorobutanol in aqueous solutions (28). Another paper assessed the importance of the lack of moisture to prevent the growth of microorganisms in soap (29). The results of tests on 41 different preservatives in polypeptide containing cosmetic formulations were described (30). In a study designed to examine the effects of preservatives on the aging characteristics of acacia solutions, the unpreserved control solution showed the most pronounced reduction in pH and viscosity (31).

Paruta and Sheth determined the solubilities of methyl, ethyl, propyl, butyl, and benzylparabens in syrup vehicles of varying concentration (32). The effect of surfactants on activity of phenolic-type germicides and preservatives was reviewed (33). The addition of surfactants to 1,3-dichloro-5,5-dimethylhydantoin increased its solubility but did not impair its bactericidal activity as tested on staphylococcus (34). The interaction between methyl *p*-hydroxybenzoate and polysorbate 80[1] has been determined using a molecular sieve technique (35). The use of the Coulter counter to detect the inactivation of preservatives by polysorbate 80 was demonstrated (36). In another study benzoic acid was shown to interact with glycol ethers in water and in aqueous polysorbate 80 solutions (37).

Flavor, Aroma, and Color—Wesley discussed the possibility of using flavor combinations called nondescript flavors instead of individual flavors to get the desired taste for products (38). Several useful tips were presented toward the achievement of good taste and mouthfeel in a vehicle as well as high resistance to cap-locking (39). The solubilization of essential oils by surfactants was the subject of two papers (40, 41). A complete review of sweetening agents was presented (42). One paper showed a direct dependence of relative sweetness on hydrophobic bonding (43). In another paper the use of malic acid in place of citric acid in hard candy was discussed (44). The mechanism of chemical excitation of taste and olfactory receptors was shown to depend upon adsorption of the stimulus molecules to the receptor surfaces (45). The present state of the stereochemical theory of odor was described (46). Some 400 essential oils and pure perfumes were examined for suitability to scent aerosol products (47).

Bhatia, Sokoloski, and Bhatia studied dye–polyethylene glycol 6000 interactions in film-coating solutions and their effect on color uniformity (48). Carotenoids were successfully incorporated into sugar-coated tablets as color agents (49). In another paper the fading of colors was attributed to reduction or oxidation of the dyes; the actual mechanism was not determined (50). In two publications concerned with the influence of ultraviolet absorbers on the color stability of certified dyes, one paper showed the ultraviolet absorbers have little value as color stabilizers for tablet coating, whereas the other publication showed the ultraviolet absorbers can be used to protect certified colors against fading by incorporating the absorbers into the product or into the coating of the package (51, 52). A modified Godlove's equation was adapted to the color changes of various pharmaceutical preparations (53).

Adjuvants—The effect of humidity and temperature on the cohesion of wheat starch,

[1] Marketed as Tween 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

cornstarch, potato starch, acacia, tragacanth, alginic acid, lactose, dextrose, and sucrose powders was determined by Shotton and Harb (54). Anhydrous lactose was found to possess excellent tableting properties and could be run directly on a high-speed tablet machine (55). The montmorillonites were studied for their use as disintegrants, binders, and lubricants in the manufacture of compressed tablets (56). Experimental data indicated that inositol, due to its nonhygroscopic nature, chemical inertness, nontoxicity, physical stability, superior mouthfeel, and texture, could be beneficially employed as the base for the formulation of chewable tablets (57). Other researchers reported on the use of mannitol as the preferred excipient for chewable tablets (58). Microcrystalline cellulose has been recommended as an extremely valuable tableting agent (59). Based on the results of compression effects, physical properties, stability, and drug availability, amylose was shown to have the characteristics desired of the ideal direct compression tablet binder (60). The utilization of sodium carboxymethylcellulose in the preparation of tablets has been proposed (61). Other investigators announced the use of haluasite, a clay mineral of the kaolinite group, as a useful tablet ingredient (62).

The application of silicones to cosmetic and pharmaceutical preparations was the object of publications by Leberl and Dias (63, 64). The relative effects of tortuosity, electrostatic attraction, and increased viscosity of water on the self-diffusion rates of cations in bentonite–water systems were described (65). Karaya gum and ghatti gum were found to be good emulsifying agents at all pH's (66). Corn oil was found to be less stable to oxidation than olive oil in the formulation of topical preparations (67). Malucidin, a protein obtained from brewer's yeast, has been recommended for cosmetic use in the formulation of skin and hair products (68).

Stability—A paper by Parrott discussed the stability of pharmaceuticals, covering parameters such as biological contamination, container, light, age, temperature, moisture, and oxidation (69). Those properties of emulsions, suspensions, and solids which are amenable to measurement and which can be used as parameters for establishing and predicting deterioration of finished consumer products were considered (70, 71). Another report examined seven of the most important chemical reactions taking place during the storage of drugs. Examples of each kind of reaction were given; the kinetics and parameters of these reactions were discussed and counteracting agents were suggested (72). An apparatus for accelerated temperature cycling was disclosed (73). A comparison of short-time storage tests at higher temperatures with the usual commercial storage time period has been made (74). An outline of recommendations regarding methods for accelerated testing of the stability of pharmaceutical preparations has been presented (75). Refractometry was used as a tool to measure the stability of solutions of pharmaceutical preparations (76).

Several investigators studied the hydrolysis of acetylsalicylic acid in the presence of accompanying substances in powder mixtures. Decomposition was shown to be dependent on the pH of the powder mixture (77–79). Brown *et al.* enhanced the stability of pilocarpine hydrochloride solutions by adding methylcellulose (80). The degradation of sodium bisulfite in dextrose solutions was followed (81). Ergotamine injections were stabilized by the addition of ethylenediaminetetraacetic acid and thiourea (82). Heat sterilization (100° for 15 min.) did not affect solutions of lobeline which were acidified to pH 2.8–4.0 by the addition of hydrochloric acid or sodium bisulfite (83).

Doppert and Staverman investigated the kinetics of the retrogradation of amylose in aqueous solutions of pH 4.0, 9.2, and 11.9 (84). In another study the degradation of pectin by γ-radiation under various moisture conditions was reported (85). The autooxidation of fats and oils was shown to be a chain reaction catalyzed by traces of metals or enzymes from bacteria or fungi (86). The results of stability tests of several medium-chain and liquid long-chain triglycerides have been correlated with the results of peroxide number determinations after storage (87). The effect of antioxidants on the stability of hydrated and anhydrous ointment bases was tested (88). Phenylbutazone stability in suppositories was shown to be dependent on the vehicle employed (89). The stability of chloramine-T in acidified aqueous solutions was recorded (90). Matsuoka *et al.* reported that α-chymotrypsin in aqueous solution is stabilized by the addition of glyceryl acetate (91). Standards have been suggested for shipping thermolabile drugs and biologicals (92). The use of tartaric acid as an efficient synergist for antioxidant action in cosmetic products was reported (93).

Stability Kinetics—A detailed analysis was presented on the use of the first-order rate equation with data which only approximates first-order kinetics (94). Pincock and Kiovsky published on the kinetics of reactions in frozen solutions (95). Some of the methods currently

available for studying chemical reactions in the time range 1 to 10^{-10} sec. were considered in another publication (96). A review, with 134 references, covered the subject of acid-catalyzed hydrolysis of glycosides (97).

The rates of hydrolysis of chlorobutanol were found to be reduced by surface-active agents but not by polyethylene glycols (98). Other workers investigated the rates of alkaline hydrolysis of ethyl benzoates in water and in aqueous dimethylsulfoxides (99, 100). The optimum pH for the stability of injection solutions of tetracaine HCl (dicaine), bencaine, and procaine was reported as 3.8, 2.7, 4.4, respectively (101). A difference in rate of degradation of phenobarbital and pentobarbital in alkaline solution was shown (102). The hydroxyl ion-catalyzed hydrolysis of glyceryl esters in aqueous medium in pharmaceutical systems was investigated (103).

Wadke and Guttman showed that the unionized species were much more susceptible to hydrolysis than the ionized form while investigating the hydrolytic behavior of 9-methylisoalloxazine (104, 105). The heats of activation for the reaction of nonionized isoniazid and isoniazid-anion were found to be approximately 11 and 5.6 Kcal./mole, respectively (106). The order of reactions, rate constants, and half-life periods for the hydrolysis of acetylsalicylic acid occurring in aqueous solution in the presence of the salts of phenobarbital,[2] codeine, caffeine, sodium benzoate, magnesium oxide, calcium oxide, calcium carbonate, and calcium gluconate were studied (107). The kinetics of hydrolysis of colchicine and some related tropolone methyl ethers were announced (108). The decomposition of idoxuridine was shown to be first order and maximum stability in solution was obtained at pH's below 7.0 (109). A series of publications on phenothiazine derivatives appeared in the literature (110–114): the rate of photooxidation of propericiazine and its sulfoxide increased with increasing amounts of oxygen and lowering pH; acetylpromazine and its sulfoxide showed less photodegradation than thioproperazine and its sulfoxide; the mechanism of the photodegradation of 10-(2-dialkylaminopropyl)phenothiazines was found to be dependent on the amount of air present; the 10-alkylaminoalkyl side chain was observed to influence photodegradation.

Herd, Eberson, and Higuchi investigated the mechanisms and the relative rates of alkaline hydrolysis of succinanil and methyl-substituted succinanils (115). The anionic forms of polycarboxylic acids, such as succinic and citric acids, were shown to interact reversibly and rapidly with glutaric anhydride in aqueous solution at room temperature to produce species which undergo subsequent hydrolysis (116). The same researchers also studied the irreversible interaction of acetic anhydride with di- and tricarboxylic acids in aqueous solution (117). The kinetics of the reaction of reserpine with nitrous acid were published (118). The acid demineralization kinetics of enamel were reported in an attempt to explore further a recently developed mathematical model in which it was assumed that hydroxyapatite is the thermodynamically governing phase in the mineralization of enamel (119). One paper considered the kinetics and transformations of cycloheximide as a function of pH and temperature (120). The decomposition of meperidine hydrochloride was found to be first order with respect to hydronium-ion concentration and ester concentration (121). Optimum stability for *N,N*-dimethyleneoxide-bis-(pyridinium-4-aldoxime)-dichloride in aqueous solution was reported at pH 3 (122). General equations were derived which related the half-life of tr methylene-bis-(4-formylpyridinium bromide)-dioxime in aqueous solutions to pH and temperature (123).

Antibiotic Stability—Belen'kii *et al.* announced that water, acids, increased temperature, and ultraviolet irradiation inactivate sodium nystatin. They reported that both the photo- and thermoinactivations of nystatin were prevented by the addition of the antioxidant, propyl gallate (124). The kinetics of the stability of oxacillin in aqueous solution were researched over the pH range of 1.44–10.93 (125). Data were collected showing aqueous solutions of methicillin to be most stable at pH 7.44 (126). Streptomycin sulfate, neomycin sulfate, and tetracycline hydrochloride were suspended in a dry mixture of tragacanth and sucrose; after addition of water the suspensions lost 7, 3, and 36%, respectively, of their antibiotic activities when stored for 10 days at room temperature in daylight (127). The stabilization of penicillin G solutions by sodium edetate was demonstrated (128).

Garrett *et al.* quantified and predicted the biological activities of chloramphenicol analogs through the use of microbial kinetics (129). The best viomycin stability in aqueous solution was disclosed to be in the range of pH 3.0 to 4.0 (130). Gramicidin was shown to be hydrolyzed by a *Bacillus subtilis* proteinase at the peptide linkage between L-valine and L-ornithine; the resulting peptide had no antibacterial activity (131). Stability studies of neomycin and penicillin in ointments were presented (132).

[2] Marketed as Luminal by Winthrop Laboratories, New York, N. Y.

Vitamin Stability—The stability of vitamins in pharmaceutical preparations was the subject of several publications. The stability of vitamins A, B, B_2, B_6, ascorbic acid, vitamin D_2, and niacinamide in oral liquid formulations was followed as a function of sucrose, glycerol, and water concentrations (133). The changes of vitamin contents and pH values of liquid medicines during storage in ampuls were also announced (134). Gurevich *et al.* employed Na_2SO_3 to stabilize ascorbic acid in a compound injection solution (135). The effect of liver extract on the stability of vitamins A, B_1, and ascorbic acid when present alone or in multivitamin formulations was determined in a syrup–glycerol–water vehicle (136). Over 100 samples of vitamin preparations were checked for vitamin content after storage for 1–16 years under various climatic conditions (137).

Carstensen *et al.* illustrated moisture stress studies, using vitamin A to exemplify this point (138). The effect of various suppository bases on the stability of a synthetic vitamin A palmitate and of a natural vitamin concentrate was investigated with and without the addition of antioxidants (139). Disodium edetate was found to be the most suitable autooxidation inhibitor for ascorbic acid (140). In comparison with KCNS, edetic acid (Idranal III) was shown to be a more effective inhibitor of oxidation of ascorbic acid in aqueous solutions, at room and at elevated temperatures, as well as in solutions containing copper, iron, or zinc ion (141). All salts studied, except sodium chloride, were shown to have a deleterious effect on the stability of ascorbic acid (142). The stability of dehydroascorbate was observed to be best at a pH of 2.4, the half-life being greater than 1000 min. at 20° (143). Second-order reaction kinetics were shown for the oxidation of ascorbic acid by various quinones using a polarographic technique (144). Stability tests on 12 ascorbic acid formulations at 80°, 60°, and 55° showed the failure of Arrhenius' law in a heterogeneous solid system (145).

Attention continues to be focused on thiamine stability. Two different groups of researchers studied the stability of thiamine solutions in the presence of dipyrone (Sulpyrin) (146–148). Data were presented which showed thiamine nitrate to be more stable than thiamine hydrochloride in a mixture containing vitamin B complex (149). The effects of γ-radiation on vitamin B_6 stability were probed (150). The effects of initial riboflavin concentration, hydrogen-ion concentration, and ionic strength on the light fading of riboflavin solutions were recorded (151).

PHARMACEUTICAL TECHNOLOGY

A discussion of controls on tablets (hardness, disintegration, and drug accuracy), injections (foreign particles and closure), and ointments appeared in the literature (152). Fluidization and its applications in pharmaceutical technology were covered in a two-part review. The first part covered the medical aspects, whereas the second part covered practical applications (153, 154). Ridgway and Segovia elaborated on fluidization and gas suspension techniques in pharmaceutical manufacturing, tablet coating, and granulating (155). Tablet coating by the air suspension technique was commented on by other researchers (156). Punch and die control was the subject of a publication which outlined a program to ensure the protection from defects of punches and dies (157).

Sterility—The use of a biological-chemical indicator for ethylene oxide sterilization of disposable medical and pharmaceutical materials was reported by Brewer and Arnsberger. The indicator system affords an immediate visible indication of gas penetration into the materials during the sterilization cycle and also serves as a biological control (158). Oils, such as liquid petrolatum and castor oil, were safely sterilized by using 0.1% ethylene oxide (159). A review of the properties of ethylene oxide and results of sterilizing tests with filter cartons, membrane filters, and vegetable parchment were summarized (160). Gelatin, when exposed to ionizing radiation, was shown to undergo molecular weight changes through free radical mechanisms involving scission, crosslinking, and weak bond formation (161). A review, with 66 references, was tabulated on the effects of radioactive irradiation on pharmaceutical preparations (162). Sterilization by electrohydraulic treatment was demonstrated by applying this technique to suspensions of *Escherichia coli*, spores of *Bacillus subtilis* var. niger, *Saccharomyces cerevisiae*, and bacteriophage T-2 (163). Methods for the preparation of sterile ophthalmic solutions were discussed in detail (164). Experimental data, collected from various laboratories, were published on the sterility tests of penicillin (165). Membrane filtration procedures for antibiotic sterility testing were offered as an improved approach for determining the sterility of antibiotics (166).

Parenterals—A review of the solubilizing agents used in parenterals appeared in the literature (167). Zoellner and Vastagh demonstrated that *m*-xylidine is a contaminant which causes discoloration of injectable solutions of lidocaine (168). Information on sodium chloride equiv-

alents, cryoscopic properties, and hemolytic effects of certain medicinals in aqueous solution was compiled (169). A discussion on the extemporaneous compounding of intravenous additives was presented (170). A survey of the literature pertaining to problems of incompatibilities and instabilities of parenteral solutions with admixtures was tabulated (171). Mixtures of potassium penicillin G–tetracycline hydrochloride, and potassium penicillin G–chlortetracycline hydrochloride in 5% dextrose were investigated for physicochemical incompatibilities (172). An incompatibility chart of 61 frequently used intravenous additive combinations was published (173).

Tablets and Capsules—Tanaka, Matsushita, and Utsumi ascertained that the disintegration time of calcium *p*-aminosalicylate increased with time due to formation of the hexahydrate which was detected by calorimetric measurements (174). Many manuscripts appeared on the subject of tablet disintegration. In a study on the mechanism of action of starch as a tablet disintegrant, pH was shown to have little effect on swelling, whereas salts were shown to affect swelling (175). In another publication the concentration of water-soluble medicament did not significantly change the disintegration time of tablets (176). Temperature of liquid and tablet compressional force was reported to directly affect the wetting of powder and disintegration time (177). In a study on the mechanism of the action of starch as a disintegrating agent in aspirin tablets, the authors concluded that the primary mechanism appeared to be a swelling action; capillarity *per se* did not appear to have a disintegrating effect (178). Tablets disintegrated 2 to 10 times faster when polysorbate 80 was added to the tablet formulation (179). A comparison was made of the influence of various chemicals on the disintegration time and on the crumbling rate of compressed tablets of acetylsalicylic acid at various stages of storage (180). The disintegration of tablets was studied by changing the ratio of aluminum hydroxide gel and diluent, such as potato starch, lactose, and cornstarch (181). Two methods were developed for testing the swelling capacity of tablet disintegrants (182).

A preliminary report on experiments carried out to find optimum tableting pressures, based on crystallographic consideration for potato starch, lactose, ascorbic acid, phenacetin, phenobarbital, and aminopyrine (amidazophen) appeared in the literature (183). The compression of mixtures of lactose and starch with different binding agents was studied using the dry granulation technique (184). A review of the physical phenomena which occur during the compression of tablets was published (185). An Instron physical testing instrument was adapted to permit its utilization in the evaluation of the compressing characteristics of drug particles and granules (186). In a two-part series, the physical properties of particles prepared by five different granulation methods and factors involved in the sieving of pharmaceutical granules were analyzed (187, 188). A method of measuring the fluidity of semifluid powders was described and used to investigate the role of various silica-type glidants in the direct compression of microcrystalline cellulose and a spray-dried lactose–microcrystalline cellulose blend on two different tablet presses (189). The influence of the addition of lubricants upon the flow rate of granulates was studied by measuring the flow velocity in an apparatus based on the device of Paksy and Sabjan. All lubricants delayed flow, especially polyethylene glycol 4000 and the stearates (190). The rate of flow of varying ratios of four sieve size fractions of rock salt through the hopper of a rotary press was represented by a second degree polynomial equation. No correlation was found between the tangent of the angle of repose and flow rate (191). Gold *et al.* studied the effect of glidants on flow rate and angle of repose (192). An article concerned with the influence of particle size of a glyceryl tri-ester lubricating agent on the physical properties of compressed tablets was presented (193). Tablet binders were evaluated by means of adhesion tension determinations (194). Spray-dried flour was evaluated against spray-dried lactose as a suitable carrying agent for direct compression formulas in tableting (195). Two new physical forms of lactose, spray dried and agglomerated, were used in the direct compression of tableted formulations (196).

Daragan suggested that the rate of dissolution of ethylcellulose films could be increased by including polysorbate 80 or citric acid in the composition of the film (197). A new method of coating tablets, using the revolving coating pan, was published. The coating materials were applied in suspensions or solutions as a spray from a centrifugal disk atomizer (198). A new dosage form, tablets of coated aspirin microspherules, was developed (199). The influence of particle size distribution, particle shape, apparent bulk density, moisture content, additives, and punch shape on the directly compressible characteristics of potassium chloride was investigated (200). Gastric-soluble films were applied to tablets by the dry-pressing method and by the spraying method (201). A three-part series on

medicated candies described the method of manufacture, the problems peculiar to medicated candies with hard sugar bases, stability, and the control aspects (202–204).

Sustained Release—A review dealing with the development and biokinetics of oral sustained-release medications was published (205). A two-part publication discussed the various patents obtained for prolonged-action dosage forms (206, 207). The quantitation of procedures and quantitative studies involving the release of sulfanilamide, caffeine, and potassium acid phthalate from polyethylene matrix disks into aqueous media were presented (208, 209). The mechanism of drug release from tablets made from mixtures of drug and polyvinyl chloride particles was investigated (210). One author pointed out that the development of oral sustained-release dosage forms is predicated on sound physical, chemical, and pharmacological properties of drugs and their bases (211). Another investigation dealt with the result of a mathematical and an analog computer analysis of the kinetic relationships governing the rate of release of drugs from sustained-release dosage forms (212).

A new method of preparing a sustained-action dosage form was developed. This entailed the tableting of film coated granules with subsequent recovery of the intact granules on disintegration of the tablet (213). The formulation and evaluation of a sustained-action compressed tablet with a plastic matrix composed of a vinyl acetate–vinyl chloride copolymer, zein, and gypsum were described (214). A sustained-release tablet preparation containing microcrystalline potassium chloride in a fatty base was developed which was free from any local irritant effect (215). Sucrose distearate, sucrose monostearate, and cellulose acetate phthalate were used for the preparation of prolonged-release granules and pills of sulfisoxazole (216). Draper and Becker observed a direct relationship between *in vitro* drug release rate and average theoretical surface area of sulfaethylthiadiazole–wax[3] particles, but did not observe this relationship for sulfaethylthiadiazole–beeswax particles (217). Spray-dried formulations of sulfaethylthiadiazole for prolonged-release medication were prepared by using shellac, cellulose acetate phthalate, a synthetic wax-like ester,[3] hydrogenated castor oil,[4] aluminum monostearate, and glyceryl monostearate as the dissolution-retarding materials (218). An article appeared which discussed the rationale for sustained-release aspirin (219). Factors affecting the release of a water-soluble drug from a compressed hydrophilic matrix were investigated (220). The influence of the concentration and particle size of the active substance and of polyethylene matrix on the speed of release of the active substance from a delayed-release tablet was published (221).

Suspensions—Nakagaki and Kitamura used an integrating sphere turbidimeter to study particle size distribution of silica suspensions (222). A review on pharmaceutical suspensions was presented which covered types of suspensions, particle size determination, and dependence of stability on factors such as viscosity and agglomeration (223). The effect of ultrasonic vibration on the deformation processes and stability of water dispersions of montmorillonites was investigated (224). The stabilization of clay suspensions during ultrasonic treatment and the effect of electrolytes were presented (225). Ultrasonic waves, at a frequency of 100 Kc., were found to cause a significant reduction in the particle size of polyethylene spheres only if surfactants were present (226). Using an aqueous sulfamerazine suspension, experiments showed good correlation which tested the validity of an accelerated procedure for determining settling volumes, following both centrifugation and storage under ambient conditions (227). A novel method was suggested for accelerating the physical changes in suspensions (228).

Nakanishi published three articles on the viscosity and sedimentation of the dispersed systems of barium sulfate in methylcellulose and carboxymethylcellulose (229–231). The use of high molecular weight compounds such as methylcellulose, sodium carboxymethylcellulose, and polysorbate 60[5] in the production of sulfamethazine (sulfadimezine) and sulfanilamide (streptocide) suspensions was suggested (232). Formulas were given which modified the unpleasant taste of calcium and phosphorus salts (233, 234). The influence of the disperse medium on the stability of an aqueous suspension of propyliodone was studied (235).

Emulsions—A review, with 18 references, on the theory of emulsion stability appeared in the literature (236). Another review covered tests for determining emulsion types, emulsion viscosity, and emulsion stability as influenced by emulsifying agents, particle size, temperature, viscosity, density, and types of emulsion (237). It was pointed out that the key to "leveling" in aqueous emulsion systems is that the product must wet both the substrate and its own drying

[3] Glyco Wax, Glyco Chemicals, Inc., New York, N. Y.
[4] Castorwax, Baker Castor Oil Co., Bayonne, N. J.
[5] Marketed as Tween 60 by Atlas Chemical Industries, Inc., Wilmington, Del.

film (238). Emulsion stability was considered with regard to inversion and HLB balance (239). The electrical conductivity of emulsions was used as a tool for testing and production control of emulsions (240). The effect of the shape of dispersed particles on the dielectric constant of emulsions with a low content of the dispersed phase was studied (241). One manuscript indicated that inversion of emulsions from water-in-oil to oil-in-water is a characteristic of the oil and appears to be most directly related to the viscosity of the oil (242). The relation between the solvent power and the hydrophile–lipophile balance of the emulsifier was determined (243).

In a study dealing with phase interfaces, Ford and Furmidge concluded that a strong interfacial film should be formed which prevents the coalescence of water droplets while permitting the coalescence of oil droplets (244). Flocculation of oil droplets in dilute emulsions was shown to depend upon concentration of oil droplets, the size distribution of the primary droplets, and the amount of salt present (245). The nature and influence of the attractive and repulsive forces which occur during emulsion film formation were discussed (246). Aggregation behavior was observed when an emulsion was diluted in saline containing cetrimide below the micelle concentration (247). The mechanism of emulsion stabilization with reference to yield value and surfactant chain length was outlined (248). New calculations showed that larger amounts of energy are required to overcome the viscous forces and secure emulsification than have been assumed hitherto (249). The effects of aging and surfactant concentration on the rheology and droplet size distribution of a nonaqueous emulsion were presented (250). Interfacial viscosities were studied by means of a viscous traction interfacial viscometer (251). The flocculation and coalescence of emulsion droplets of the normal and inverse types, studied simultaneously, confirmed that the attainment of a stable coalesced emulsion always requires the same amount of any given surfactant, the optimal concentration being independent of the size of the electrostatic energy barrier and the oil medium (252). The factors affecting stability in nonaqueous emulsions were presented (253).

Fox and Shangraw described an automated reciprocating capillary emulsator which duplicates the low-pressure homogenization principle of the interconnected glass syringe method used to prepare repository water/oil emulsions (254). These same authors showed that inorganic electrolytes at concentrations as low as 0.01 *M* increased apparent viscosity, retarded sedimentation, and had a marked stabilizing influence (255). Emulsions made with an ultrasonic emulsifier were reported to be superior to those made with the standard homogenizer (256). New emulsions were developed in which filter and screen light-protective substances were incorporated (257). The relative viscosities of water-in-oil type emulsions were shown to be a function of volume fractions of the dispersoid and also of the sorbitan monostearate[6] concentration (258). Systems having low interfacial viscosities were shown to give relatively stable emulsions (259). A comparison was made of results obtained on a typical pharmaceutical emulsion using optical and electron microscopes, and the Coulter counter for determining emulsion particle size (260). The emulsifying properties of sodium β-boswellate were investigated and shown to be quite good (261).

Ointments and Creams—Whitworth and Becker published on the effects of solubility factors on the diffusion of sulfacetamide and sulfathiazole from ointment bases (262). A "dialysis cell" method was developed for comparatively measuring the release of salicylic acid from various ointment bases (263). The rate of diffusion of procaine from an ointment base and several water-in-oil emulsions was shown to be inversely proportional to the amount of sodium lauryl sulfate present (264). Adsorption was shown to be responsible for a decrease of drug release from ointments (265). The diffusion of sulfanilamide from ointments was less when sulfanilamide was solubilized in the surfactants as compared to when the surfactant was incorporated into the ointment base (266). The diffusion of both salicylic acid and sodium salicylate from hydrophobic bases was shown to be very slow (267). A new apparatus, a rake bladed stirrer which keeps the ointment in constant circulation during an experiment, has been described and used in *in vitro* experiments (268). The rate of chlortetracycline and chloral hydrate release from ointment bases containing bentonic gel was studied (269).

Kutscher *et al.* applied sheets of polyvinyl alcohol coated with gentian violet to oral mucosal tissue and noted dye absorption in 5–55 min. indicating the usefulness of the vehicle as a base for drugs (270). Other investigators used solutions of ethylcellulose and sodium carboxymethylcellulose containing antibiotics as bactericidal film-forming liquids in treating cuts and small skin wounds (271). A rheological investigation of various ointments was described to

[6] Marketed as Span 60 by Atlas Chemical Industries, Inc., Wilmington, Del.

facilitate the selection of the most convenient base for medicinal ointments (272). An easy procedure was developed for the sterilization of ointments (273). Anhydrous ointment vehicles containing palm oil were best stabilized by using butylhydroxytoluene and butylhydroxyanisole, whereas hydrated ointment vehicles containing palm oil were best stabilized by using gallates (274). Polymethylphenylsiloxane liquid has been investigated as a component for ointment bases (275). The hydrophilic capacity of official polyethylene glycol ointment was increased 48% by the addition of 0.5% of dry unneutralized carboxypolymethylene compound (276). Various topical preparations for application to lips to reduce chapping were evaluated (277).

Suppositories—The absorption of streptomycin and chloramphenicol was increased slightly when sodium lauryl sulfate was incorporated in the fatty suppository base (278). Rectal absorption studies of various sulfonamides from aqueous polyethylene solutions in rabbits showed the ionized drugs to be better absorbed than the nonionized drugs, and the sodium salts of sulfonamides to be more effective than their free form (279). The adsorption of a brand of purified siliceous earth[7] in a cocoa butter suppository base was the same as that in a brand name glycol ester suppository base (280). The influence of various commonly used viscosity-inducing modifiers of suppository bases was determined *in vitro* using antipyrine (phenazone) and aminopyrine (aminophenazone) (281). An apparatus was described which can be employed for the control of the physical properties of suppositories made with fatty bases or with water-soluble or water-dispersible bases (282). Upon partial hydrogenation, some liquid vegetable oils assumed consistencies which made it possible to use these reacted oils as vehicles for rectal suppositories (283).

Aerosols—All types of pharmaceutical aerosols were discussed in detail in a review article by Marshall (284). New developments in aqueous foams, and their many interesting applications in cosmetics, were considered (285). In a two-part series, the properties of aqueous alcohol aerosol foams and how they apply to products were discussed, along with the effects of additives and how they may affect the foaming properties of these aerosols (286, 287). The changes in size distribution of an initially homogeneous aerosol were studied as the aerosol coagulated and deposited on the walls of a closed chamber (288). One author demonstrated that molecular complexes formed in aerosol emulsion systems increased emulsion and foam stability and decreased foam drainage (289). The use of the Rotovisco rotational viscometer was described in evaluating the rheological properties of pressurized foams (290). The microbiological testing of aerosol preparations was conducted using *Chaetomium globosum* under conditions that were applicable to the natural growth habits of the organism (291).

The development of water washable spray-on bandages was discussed (292). A new aerosol antiperspirant was considered along with safety data and formulation suggestions (293). A review on germicidal preparations in the form of aerosols along with the qualitative compositions of various air fresheners and surgical antiseptic aerosols was published (294). Chemical specialties foamed with water-dispersed colloidal alumina were studied (295). Hardness, clarity, and gloss retention of leading commercial hair sprays were evaluated to determine formulating goals in preparing aerosol hair sprays (296). Formulation and activity of water-based aerosols containing pyrethrum was the subject of still another manuscript (297).

Cosmetics—deNavarre predicted the development of more treatment cosmetics, some only for prescription sale (298). The physical and chemical properties of branch-chain hydrocarbons, fatty acids, alcohols and esters, both of synthetic and natural origin, which have found increasingly growing application in bases of creams and other cosmetics, were reviewed (299). "Some New Keys to Cosmetic Chemistry 1965" was the title of a review article which contained 278 references (300). One author's experience led to the publication of a manuscript entitled "Cosmetics for Use Under Tropical Conditions" (301). Another review article on cosmetics and toilet preparations contained 47 references (302). A discussion of lipids and their derivatives and other fats and waxes commonly used in cosmetology and dermatology was reported (303).

Rees analyzed the various properties of a good shampoo and also described the numerous types of modern shampoo formulations, including liquid, lotion, cream, powder, and jelly shampoos (304). Appearance, performance during use, and effect on hair after use were the three major criteria for evaluation of shampoos in the opinion of a team of investigators (305). The type of surface-active agents used in modern shampoos was commented on in detail (306). Quaternary ammonium salts were used in hair treatment preparations (307). Another publication presented the various hair dressing formulas for

[7] Trademarked as Aerosil by Degussa, Frankfurt on Main, Germany.

men and the requirements for each type (308). The use of oxidation dyes in hair coloring preparations was surveyed (309). Progress has been made with the formulation of stable, clear, emulsion systems, particularly hairdressing gels (310). The emulsifying, wetting, and foam properties of quaternary ammonium compounds, as applies to their use in hair treatment preparations, were reviewed (311). Protein based detergents were suggested for application in shampoos (312).

Goldrick discussed the need of vitamins for topical application and also gave several typical formulas (313). Water standards were suggested for use in the manufacture of cosmetic preparations (314). Aspects of microbiology, with reference to antimicrobial agents, in cosmetic products were presented (315). The problems relating to the proof of efficacy of antiperspirants and deodorants were examined (316). The significance in the choice of an appropriate vehicle for antiperspirants and deodorants was explored in detail (317). New techniques contributing to the laboratory evaluation of chemical, physical, and chemical/physical combination sunscreen products were presented (318). The nature and type of dermatological testing were discussed with special reference to different categories of cosmetics (319).

Schlossman categorized the types of skin cleaning preparations and gave sample formulations of each (320). The properties of cationic surface-active agents were reviewed and their suitability for use as emusifiers in cosmetics was discussed (321). The various surface-active agents used in bubble bath formulas were disclosed (322). The clear gel system was examined and typical formulas were outlined (323, 324).

Packaging—Lees discussed the use of plastics for packaging (325). A package development checklist was presented along with an explanation on how it is to be used (326). Reports of the committee developing test procedures for the determination of the safety of plastics in pharmaceutical and medinical uses were given (327). A very searching test for the suitability of plastics for cosmetic packaging was suggested (328). Published data were used to establish the superiority of foamed plastics over other pharmaceutical packaging materials. Among the foamed plastics, polystyrene foam was rated best on the basis of its mechanical, heat insulating, water-repellent, and aging properties (329).

The feasibility of using ultrahigh frequency power to accelerate freeze-drying was demonstrated and the facilities were described (330). The engineering aspects of ultrahigh frequency dielectric heating to accelerate freeze-drying was outlined (331). A method for determining the bacterial permeability of plastic films was announced (332). The permeability of plastics was shown to cause problems in the packaging of pharmaceuticals (333). The permeability of various solvents through polyethylene was expressed by an equation (334). The designing of machines for the packaging of sterile pharmaceuticals was described (335).

EQUIPMENT

A recording powder flowmeter consisting of a hopper, a strain gauge, and a recorder presented a new approach to the measurement of powder flow (336). Cohn *et al.* employed an IBM 1620 computer to evaluate data obtained from a compactor optimized to prepare a basic granulation to which other drugs could be added and directly compressed into tablets (337). In another paper the surface areas of powders were determined by flow microcalorimetry (338). A laboratory glass spray drier made from borosilicate glass was described (339). The design, critical components, method, and costs of spray driers were presented (340).

One mixer was described which utilized compressed air to mix solids rapidly, while another was described to blend or agglomerate solids by atomizing liquid into air-suspended solids (341). Nash and Haeger stressed the importance of zeta potential in the development of stable pharmaceutical suspensions (342). Some basic theories about the use of instrumentation in cosmetic color control with emphasis on practical application were reviewed by one author, while another elaborated on an instrument that measured color objectively (343, 344). A new machine for unit dose packaging of tablets and capsules was also described (345). In addition, the automatic packaging of individual ointment-impregnated gauze bandages was a subject for discussion (346).

PHYSICAL PHARMACY

Biles studied the distribution of quaternary ammonium salts between chloroform and water (347). It was also shown that pH affected the distribution of certain medicinal preparations between chloroform and water (348). The kinetics of reactions involved in penicillin allergy revealed that the aminolysis of penicillins by glycine is general base catalyzed (349). A number of antacids were granulated by dry, wet, and spray methods and compared for specific surface area, angle of contact, porosity, and acid-neutralizing capacity (350). An interesting paper concerned with the kinetics of swelling of dextran

gels in water was published (351). The diffusion of water vapor through a hydrophilic polymer film was determined using a multifilm technique (352).

Mark *et al.* studied the oxygen permeability of amylomaize starch films over a wide range of relative humidity (353). The permeation, sorption, and diffusion of water in ethylcellulose were also investigated (354). Freezing point curves were published for the system dimethylsulfoxide–water (355). Phase relationships were presented for a system containing isoelectric gelatin, ethanol, and water (356). A study of membrane characterization by measurement of transient osmotic pressures was reported (357). A review article concerned with the physical aspects of drug action appeared in the literature (358).

Solubility—Bates *et al.* published several papers concerned with the solubilizing properties of bile salt solutions on glutethimide, griseofulvin, and hexestrol as a function of temperature, bile salt concentration, and inorganic electrolyte (359–361). The solubility of 21 steroids in water at 25° was determined and compared to previously reported data (362). The dissolution rates of powdered preparations of sulfonamides and benzoic acid derivatives were studied, and the data were found to be in good agreement with the Noyes-Nernst equation concerning transport controlled dissolutions (363–365). The solubility of sulfonamides in phosphate–citrate buffer systems appeared in the literature (366). Sulfanilamide solubility increased with an increase in concentration and chain length of nonionic solubilizers and temperature (367). Another study presented data giving methods of solubilizing difficultly soluble materials by way of intermediates (368).

Paruta *et al.* investigated the solubility of xanthines, antipyrine, and succinic acid as a function of dielectric constant in several solvent systems (369–372). The dissolution rate and solubility behavior of 3-(1-methyl-2-pyrrolidinyl)-indole as a function of pH have been evaluated (373). In another study data were presented showing the effect of complex formation on dissolution kinetics (374). Benzoic acid was solubilized by polyoxyethylene compounds (375). Another article explored the mechanism of solubilization of water-insoluble substances with sodium benzoate derivatives (376). In addition, spectroscopic examination revealed that benzoic acid was solubilized by nonionic surfactants (377). The rate of crystal growth and dissolution rate of cholesterol crystals in aqueous media were probed (378).

The hydrophilic–lipophilic balance concept was utilized effectively to solubilize a wide variety of perfumery materials (379). Nonionic surfactants have been widely used to effect solution of a number of pharmaceuticals (380, 381). Antibiotics such as erythromycin and chlortetracycline have been the subject of papers in which their solubility and stability have been investigated (382, 383). Goldberg *et al.* presented a series of papers which demonstrated that dissolution rates and gastrointestinal absorption of drugs could be increased by preparing solid solutions and eutectic mixtures (384–386). A new method of solid state dispersion for increasing dissolution rates was described (387). Dissolution rate data appeared for drugs in powder form, granules, and tablets (388).

Slightly soluble acidic drugs were solubilized by using mixtures of alcohol and water (389). It was reported that the rate of rehydration of lyophilized serum globulin can be influenced by temperature, dilution, and the addition of sodium chloride, glucose, or sucrose (390). The solubility of acetanilide and several derivatives was determined in aqueous sucrose solutions (391). Anderson and Morgan showed that the solubilization of hexachlorophene had some effect on its antibacterial activity (392). Another study pointed out that supersaturated micelles form during solubilization (393). Poly-*n*-vinyl-5-methyl-2-oxazolidinone was found to solubilize several barbituric acid derivatives (394).

Complexation—In a study of the interaction of weak organic acids and phenols it was indicated that the drug–plastic interactions were due to hydrogen bonding of the agents to the polyamide, but that secondary valence forces of the Van der Waal's type play a predominate role in the binding mechanism for the more hydrophobic molecules (395). Several papers were concerned with the complexation tendencies of various antibiotics in the presence of metal ions and bovine serum albumin (396–399). Lach and Bornstein reported on solid–solid interactions by diffuse reflectance studies (400, 401). A potential mechanism for aspirin allergy due to an interaction with amines has been mentioned (402). Metal complexes of *d*-glucosamine and its derivatives with copper were found to be stable (403). The interaction of phenothiazine drugs with riboflavine and xanthine dyes was the subject of two papers (404, 405). It was pointed out that pK values, molecular weight, and the number of hydrophilic groups of organic ions are important in dye–drug salt interactions (406). The binding tendencies of cationic dyes to nucleic acids and other biological polyanions were investigated (407); also the nature of bonding in dye aggregates was reported (408).

Connors and Mollica analyzed comparative

studies of complex formation and found that different experimental approaches may not always yield the same numerical result and that comparative studies with several techniques may yield valuable information concerning the natures of the complexes (409). Viscosity measurements were used to study the interaction of benzoic acid derivatives and cationic surfactants (410). It was also reported that imidazole derivatives are useful as chelating agents (411, 412). The general nature of the interaction of phenol and certain macromolecules was investigated utilizing equilibrium dialysis techniques (413, 414).

The solubility product principle and phase rule diagrams were used to demonstrate interactions involving sulfanilamide and sulfathiazole (415). Data were also published which pointed out that β-cyclodextrin and sodium deoxycholate interact with many pharmaceutical agents in aqueous solution (416). Static dialysis techniques were utilized in studying the transfer of drug molecules from the micellar phase (417–419). The mechanism of solubilization of water-insoluble substances in aqueous sodium benzoate solutions has been determined (420, 421). The degree of binding of 8-hydroxyquinoline sulfate to polysorbate 80 was shown to be a function of the concentration of the nonionic surface-active agent (422). The interaction of aqueous polyethylene glycol solutions with iodine was investigated (423). The interaction of several local anesthetic drugs and sodium polyethylenesulfonate was evaluated by membrane dialysis measurements (424). The binding tendencies of methyl orange with proteins were also observed in a similar manner (425). Metal ions were shown to form complexes with ascorbic acid (426); molybdenum-thiol complexes were used as models for molybdenum bound in enzymes (427).

Beckett and Choulis investigated molecular interactions of stereoisomers in the solid state (428). Differential thermal analysis, infrared, and X-ray analysis were employed to evaluate the interactions between ionized surfactants and long chain polar compounds (429). The chelation of sugars and polyols with iron was exhibited most strongly by those compounds that contained a dihydroxyacetone structure in their molecule (430). Hydrophilic gel beads were utilized to form insoluble biologically active compounds (431). The metal chelating tendencies of glyoxylic acid have been investigated (432). The interaction of cationic drugs with polyacrylic acid was studied by phase separation as a function of temperature, polymer, and drug concentration. Separation temperature varied with polymer added, drug concentration, basic structure of drug, and valence of drug cation (433).

Surface Phenomena—A review article, containing 146 references, was concerned with particle–particle interactions (434). Another review commented on the study of the texture of porous solids (435). Micelle formation and other typical phenomena of surface-active substances were the subject of still another review (436). The scope of methods for estimating surface areas of solids from results of adsorption from solution has been described (437). A computer program was set up to reduce the calculations in surface area determinations and to provide an estimate of accuracy and reliability of a set of experimental data (438). The difference between flocculation and coagulation was discussed in detail by Ecanow *et al.* (439). The various methods of determining the surface tension of solids and their shortcomings have been described (440).

The drop volume method was used to study the surface activity of several phenothiazines at the air–solution interface (441). It was also pointed out that the presence of organic cations inhibited surface activity at this interface (442). Solid adsorbents such as kaolin, talc, and activated charcoal were shown to adsorb phenothiazine derivatives (443). Horikoshi and Hata published several papers concerned with a physicochemical study on water contained in solid medicaments (444–446). The neutralization rate, crystal structure, and crystal growth rate of dried aluminum hydroxide gel were shown to be affected by aqueous environment (447, 448). The sedimentation and aggregation of aluminum hydroxide and aluminum oxide particles were explored (449). It was also pointed out that the volume of aluminum hydroxide gels changes when it crystallizes (450).

A new method, comparing the flux magnitudes corresponding to different conditions of gas flow through porous media, has been proposed for the determination of surface areas of powders (451). Adsorption studies were conducted on a number of steroid powders (452). An investigation of the flow rate of loosely packed magnesium hydroxide has shown that the general equation developed by Jones and Pilpel can be applied to single as well as multicomponent mixtures in a wide size range (453). The sorption and desorption data for methylene blue on kaolinite fit the Langmuir equation (454). Brunauer published a review article which discussed the surface behavior of solids (455). Spray-dried clays were evaluated *versus* oven-dried clays and found to vary somewhat in their physical characteristics (456).

The influence of lanolin derivatives on the physical aspects of dispersions was discussed by Conrad *et al.* with particular reference to pigment wetting (457–459). By using the Levich model for the effect of surfactants, a quantitative conclusion was drawn concerning the hydrodynamics of a laminar liquid film in the presence of surfactant, when their distribution on the surface depends on the rate of the adsorption and desorption processes (460). Surface-active agents were shown to have a marked influence on the electrokinetic potential of some sulfonamides in aqueous syrup suspensions (461). In another study the general criteria for the stability of lyophobic sols was established and found valid for any potential of the colloid particles in the critical state (462). From the general criteria of the stability of disperse systems, complete curves were calculated which characterized the coagulating effect of mixtures of various electrolytes for potentials of colloid particles (463). Using a hydrosol of titanium dioxide stabilized by sodium oleate, it was shown that, when the stabilizer content in the dispersion medium is close to the micelle forming concentration, the disperse particles aggregate (464). A quantitative theory was presented which describes the kinetics of coagulation of colloidal systems containing more than one dispersed species (465).

The adsorption of three quaternary ammonium salts has been measured at the oil–water interface (466). In another investigation the electrophoretic mobilities, the rates of agglomeration, and the rates of flow through sedimented particles were studied for a model suspension consisting of spherical particles (467). Nash elaborated on structural vehicles for stabilized suspensions along with physical stability test methods and special factors in producing good parenteral suspensions (468). A detailed study has been made on the destabilization of dilute clay suspensions with a cationic polymer under controlled conditions of pH, ionic strength, initial clay concentration, and intensity and duration of agitation (469). A simple and inexpensive *in vitro* test was utilized to evaluate the defoaming activity of a silicone defoamer in tablet combination with a number of commonly used antacid materials (470). The equilibrium adsorption of kanamycin A by cationic exchange resins was explored (471). The adsorptive mechanism of a palm oil–water emulsion stabilized by a mixture of casein and gelatin was elucidated by combining surface tension studies of the oil–water interface with electrophoresis studies (472). The kinetics of particle adhesion for glass beads in liquid media containing surfactants were investigated (473).

Crystallization—The crystallization of petrolatum waxes was the subject of a review article (474). Morawetz observed that the reactivity of organic crystals is sometimes different from reactions that take place in the liquid state (475). The water solubility of chlortetracycline hydrochloride varied with the change in crystal structure of the compound (476). It was also observed that the biological properties of erythromycin polymorphs were similar, but the melting points and the water of hydration were different (477). The effect of polymorphism on the solubility of pharmaceuticals was shown (478).

Rheology—A visco-coagulograph was developed which records continuously the structure formation in liquids (479). Neuwald and Scheel did a rheological study on new cream bases as a function of temperature, while Boylan presented a rheological study on 13 pharmaceutical semisolids (480–482). A method was described for the continuous monitoring of solutions of stirred reaction media (483). The problems encountered in determining the viscosity of shampoos were discussed (484). The parallel plate plastometer was modified for the measurement of Newtonian and non-Newtonian fluids (485). The rheological behavior of granular material was investigated by another investigator (486). Another paper described the various methods of characterizing the thixotropic properties of an oil-in-water lotion (487). Extrusion type cells have been developed for measuring and recording rheological properties of gels (488).

In another study a modified Brookfield viscometer was used to evaluate dispersions of lipophilic suspending agents (489). Powell *et al.* studied the effects of high shear processing and thermal exposure on the molecular weight and the solution viscosity of selected polymers and found that the viscosity degradation followed a first-order reaction rate with the viscosity half-life for the higher molecular weight grade polymer being considerably less than that of the lower molecular weight grade polymer (490). It was also shown that the limiting shear stress and torque under which a gelatin solution can retain its structure are a function of concentration, time, and temperature (491). The various techniques used for assessing the rheological properties of toiletry and cosmetic products were considered (492). A rheological evaluation of pressurized pharmaceutical foams was presented (493).

PHARMACOCHEMICAL ASPECTS

This section of the review considers many of the papers on polymers, antibiotics, and radio-

isotopes which might be of interest to the pharmaceutical scientist. It is not intended to encompass the vast area of pharmaceutical chemistry concerned with synthesis, structure activity studies, reaction mechanisms, analysis, *etc.* These related disciplines are reviewed annually in other publications and are, therefore, omitted from this report.

Polymers—Carpenter presented a review article, containing 135 references, in which irreversible, reversible, macromolecular, and association colloids were reviewed (494). Recent theory and developments relating to the formation and modification of synthetic polymeric films in relation to the pharmaceutical uses of such films in dosage form development have been discussed (495). Several polymeric materials, currently used in the plastics industry, were evaluated for their use in pharmaceutical film coatings (496). Five commercially available polymers were considered for the preparation of enteric compression coatings utilizing a unique polymer incorporation method which was part of the granulating process (497). In another investigation cellulose acetophthalate was examined as an enteric tablet coating (498). Surfactant polymeric materials have been used to prepare prolonged action insulin preparations (499). Film forming macromolecules have been utilized as protective coatings for skin wounds and for antiseptic sprays and balms (500, 501). The water vapor transmission properties of free polymer films were explored (502). In addition, the water vapor transmission of applied polymer films on tablets was found to be a function of polymer coat formulation, film coat thickness, and nature of the tablet matrix (503).

Antibiotics—Schumacher presented a review, containing 27 references, on the chemistry, microbiology, pharmacology, and the therapeutic application of cephalosporin antibiotics (504). Another paper reviewed both broad spectrum and narrow range antibiotics for activity against Gram-positive or Gram-negative organisms (505). A complete discussion of the newer semisynthetic penicillin derivatives was given (506). The properties of some of the new antibiotics, spinamycin, leucomycin A_1, ericamycin, xanthocidin, and cineromycins A and B were disclosed (507–511). The kinetics and mechanisms of action of chloramphenicol and tetracycline on the generation rates of *E. coli* were investigated (512). Another paper discussed the compatibility of some pharmaceutical preparations with antibiotics (513).

The binding tendencies of sulfonamide drugs to serum protein have been the subject of several papers (514–517). A number of papers appeared in the literature concerning the protein binding of antibiotics, especially the penicillins (518–525). Several papers contained data on blood serum levels of penicillin and some semisynthetic penicillins (526–529). A comparison of tetracycline concentrations, following oral and intravenous administration, indicated that intravenous administration gave superior therapeutic response (530).

Radioisotopes—Wagner and Emmons reviewed the characteristics of an ideal radiopharmaceutical (531). The problems characteristic of radioactive pharmaceuticals have been outlined (532). A biochemical view of radiopharmaceutical developments indicated that to date more attention has been paid to the physical characteristics of the isotopes incorporated into radiopharmaceuticals than to the biochemical aspects of their use (533). Another author pointed out the value of computer analysis of kinetic biological parameters (534).

BIOPHARMACEUTICS

The area of biopharmaceutics considers research efforts directed toward studying the influence of pharmaceutical formulations on the biological activity of drugs. Numerous review articles appear in the literature. An article, containing 67 references, was published on the noncompetitive mechanism governing the action of medicinal drugs (535). Another review discussed pharmaceuticals which modified the activities of gastric enzymes (536). Beckett reviewed the problem of drug distribution and metabolism (537). In addition, another review article discussed the aspects of clinical trials of new drugs and the difficulties of evaluating them for one species from the results obtained in another species (538). Pharmacokinetics were reviewed and discussed (539). The induction of drug-metabolizing enzymes in liver microsomes was the subject of another review article containing 83 references (540). The application of statistics and biometry in the comprehension of drug action was noted (541).

Methods were described which utilize the analog computer as a laboratory aid in the preparation of drug formulations with improved therapeutic efficacy (542). A mathematical and theoretical interpretation of drug distribution and dosage, involving complex pharmacokinetic models and the analog computer, was presented (543). The analog computer was used to help clarify the distribution processes of *d*-tubocurarine in experimental animals (544). Protein binding tendencies of some azo dyes, thyroxine, diphenylhydantoin, and pentaerythritol have

been the subjects of several papers (545–547). The biphasic elimination of noscapine was published (548). Human bioassay techniques have been used for determining the availability of vitamins from preparations resistant to *in vitro* disintegration (549). Data concerned with the modification of drug responses by hydrolytic enzymes were recorded (550).

Effects of Physicochemical Properties—The urinary excretion kinetics of methylamphetamine in man were studied by Beckett and Rowland (551). In a similar study, it was shown that the rate of excretion of methylephedrine and its metabolite, ephedrine, fluctuated with a change in urinary pH (552). Several papers reported data on some basic *in vitro* and *in vivo* studies with six different sulfa drugs (553, 554). The transport of volatile fatty acids across rumen epithelium was altered by concentration gradient, pH, and metabolism (555). It was demonstrated that cholestryamine resin interacted with commonly used, orally administered drugs in both *in vivo* and *in vitro* systems (556). The relation between the physicochemical and pharmacological properties of iron and chromdoitin sulfate colloid for intravenous injection was studied (557).

Effects of Formulation—Lammers reviewed the ways in which a drug can interact with an inactive substance to produce a potentiation or a lessening of the effect of the drug (558). Another review article commented on the effect of drug formulations on the absorption rate (559). Percutaneous absorption of lipid substances and their effect on skin surface was the subject of another review (560). The relationship between the *in vitro* dissolution kinetics and the *in vitro* intestinal absorption characteristics of tablet preparations of coumarin revealed that the composition of the dissolution medium had a significant quantitative and qualitative effect on dissolution kinetics (561). It was also pointed out that the absorption of a number of alcohols and barbiturates was affected by the concentration of nonionic surfactant (562). Static dialysis studies indicated that it was possible to anticipate the amount of drug absorbed in the small intestinal tract containing polysorbate 80 solution (563). Drug release from water-in-oil emulsion systems, containing tensides of a sorbitan[8] series, was investigated (564, 565). Another study further substantiated that drugs are absorbed from micellar solutions (566). It was also shown that a relationship existed between the concentration of polysorbate 80 and the rate of absorption of salicylamide from the small intestine of the rat (567).

A comparative investigation on the rectal absorption of aminophylline and theophylline from various medicated preparations was carried out in man by Neuwald and Ackad (568). The rectal absorption of sulfonamides from oily solutions seemed to take different paths: that of absorption through the rectal membrane after being liberated into the excretion fluid and that of absorption directly from the fatty oil through the rectal membrane (569). Surfactants were found to enhance the release and absorption of barbiturates from suppository bases in most cases; however, binding of the drug was suspected in some bases (570). The rectal absorption of aminopyrine and isopropylantipyrine was carried out in rabbits from an improved hydrophilic ointment base (571). Inert suppository ingredients sometimes have an adverse effect on the rectal absorption coefficient of drugs; this was apparent when antipyrine (phenazone) was evaluated (572).

Several papers were published on the action of proteolytic enzymes on the serum concentrations of the tetracyclines (573–575). Other investigators evaluated the feasibility of using an enzyme–substrate system as a mechanism for controlling the rate of drug release from a dosage form (576, 577). When ethinylestradiol was introduced directly into the small intestine of the rat as an oily solution, it was absorbed more slowly than when administered as an aqueous suspension (578). An antidiarrheal preparation containing attapulgite and citrus pectin was studied for its potential effect on the absorption of promazine from the human gastrointestinal tract (579). The inverted sac technique was used by Aguiar and Fifelski to investigate the effect of pH on the *in vitro* absorption of flufenamic acid. The study revealed that the passage of this drug through the gut membrane was by passive diffusion (580). An evaluation of the blood level duration properties of procaine benzylpenicillin in oil with aluminum monostearate was carried out (581).

Micronized medroxyprogesterone acetate displayed more metabolite in 8 hr. than a nonmicronized preparation, indicating improved absorption with smaller particles (582). Rosen *et al.* reported on the absorption and excretion of radioactively tagged dextroamphetamine sulfate from a sustained-release form. The data suggested that the sustained-release dosage form is a reliable way to administer the drug (583). The absorption, distribution, and excretion of iron following oral administration in the presence

[8] Marketed as the various Spans by Atlas Chemical Industries, Inc., Wilmington, Del.

of various ligands was the subject of another communication (584). Plasma and urinary excretion levels of 5-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyridine were measured after application of various ointments and solutions to the skin of rats or rabbits (585). Flame photometry was used to determine the activity of ointments (586). The topical absorption of various polypeptides in the presence of dimethylsulfoxide has been evaluated (587). Wagner *et al.* pointed out that the rates of absorption of indoxole after oral administration varied with the nature of the dosage form (588). A study evaluating the effect of polyethylene glycol 4000 on the absorption of several barbiturates has also been reported (589).

Absorption Control—A review on the absorption and biochemistry of vitamin B_{12} was published (590). Holt demonstrated that competitive inhibition of intestinal bile salts in the rat was apparent (591). It was also further substantiated that iron was transported across membranes, using a loop of gut with an artificial circulation (592). The release rate characteristics of sulfaethylthiadiazole from various wax formulations were revealed (593).

Absorption Mechanism—Palva discussed the drug-induced malabsorption of vitamin B_{12}, pointing out that *p*-aminosalicylic acid interfered with certain metabolic processes mediated by folic acid (594, 595). An investigation of the prolongation of the therapeutic effect of penicillin by polymeric preparations indicated that the mobility and the rate of elimination of the polymer molecules from the body were responsible for the delayed effect (596). In a similar study polyvinylpyrrolidone was shown to prolong the activity of tetracycline (597). Other authors studied the effect of cations on the transport of sulfonamides through the small intestine of rats and found that absorption of sulfisoxazole was reduced when potassium ion was substituted for sodium ion (598). Ascorbic acid was shown to increase the absorption of iron (599), while allopurinol had no effect on the absorption of iron (600). It was reported that the topical application of dimethylsulfoxide enhanced the topical absorption of phenylbutazone; however, when the dimethylsulfoxide was administered subcutaneously there was no effect (601).

Kinetic Studies—The kinetics of the metabolism, absorption, and decomposition of drugs were reviewed in a paper citing 14 references (602). Another article discussed the pharmacokinetics of various tetracyclines (603). Nelson presented data showing the application of results of pharmacokinetic estimations and their significance (604). A theoretical study of drug action was outlined and the concept was tested with hormones of the neurohypophysis and their analogs (605). Kinetic interpretation was used as a tool to explain pharmacological response (606). A pharmacokinetic model involving first-order processes for drug release, absorption and elimination, for sustained-release preparations, has been described (607). Several papers surveyed the distribution, absorption, and excretion of sulfonamides (608–611).

Gibaldi and Kanig studied the effect of body position and pH on the gastrointestinal absorption of salicylate and creatinine in man (612). The pharmacodynamic behavior of the salicylates has been the subject of several papers (613–617). Tritiated digoxin was used to determine the distribution and excretion of this material in experimental animals (618). Using plasma salicylate levels, the rates of drug absorption and elimination from the blood were determined for salicylic acid and sodium salicylate administered in four different suppository bases (619). In studying protein binding tendencies of sulfonamides it was observed that there was a deviation from first-order kinetics, characterized by a diminishing steepness of the slope of the time–concentration curve (620). The analysis of expired air was shown to offer several advantages over the analysis of blood and urine samples (621).

A kinetic model to explain the elimination of bromsulfophthalein using the Michaelis-Menten expressions has been proposed by Winkler (622). In another study, urinary excretion data were utilized to evaluate some oral prolonged-release forms of dextroamphetamine in man (623). The first apparent demonstration of competitive inhibition of drug metabolism in man was reported (624). The elimination constants and biological half-lives of thiamine were determined for a series of thiamine derivatives (625). Radioactive tracer techniques were used to follow the absorption and excretion of hydroxycyanocobalamin, benzoylthiamine disulfide, and a hypoglycemic metabolite of glycodiazine (626–628). A complete pharmacodynamic evaluation of a sustained-release aspirin product was published (629). The absorption, excretion, and metabolism of nalidixic acid and hydroxynalidixic acid was the subject of two papers (630, 631). The use of kinetic models to study antibiotic absorption, metabolism, and excretion has been proposed (632).

Drug Absorption—Munies described a method for investigating *in vivo* percutaneous absorption based on the determination of methyl ethyl ketone in expired air following topical

application (633). In another paper the absorption, excretion, and elimination of chlorphenesin carbamate in the dog were discussed (634). A large volume liquid scintillation detector was used to determine the rates of excretion, absorption, and intercompartmental clearance in ambulatory dogs (635). A similar study was carried out with cyanocobalamin (636). Radiotracer techniques were used to follow the absorption of furosemide and thimerosal (637, 638). The problems associated with sensitivity and cross sensitivity to drugs were pointed out (639). The absorption, duration of circulation, and elimination of sodium sulfapyridazine by different routes of administration have been evaluated (640). It was reported that the absorption of a vitamin A–casein complex was more efficient than absorption of vitamin A (641).

Levy and Jusko pointed out that the enhanced absorption of riboflavin in the presence of food appeared to be due to the decrease in intestinal transit rate causing the vitamin to remain at absorption sites longer (642). The absorption, distribution, and elimination of a long-acting vitamin B_{12} preparation have been studied (643); and the absorption and excretion of 5-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyridine were determined when it was administered by different routes (644, 645). It has been shown that sulfaphenazole appears in the saliva after intravenous administration (646). Data were presented for the absorption of betamethasone from the gastrointestinal tract in dogs (647). Another publication presented data concerned with the effect of physical activity on the absorption rates of procaine penicillin G implants (648). Another investigator carried out research on the absorption and activity of griseofulvin and some derivatives in rabbits (649). Sweetening agents were also the subject of absorption and excretion studies in humans, rats, and rabbits (650).

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[9] *Index Medicus* abbreviations were used for journals not listed in *Chemical Abstracts*.

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