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Review Article

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A Literature Review of Pharmaceutics

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CONTENTS

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THIS REVIEW of the literature represents a comprehensive cross-section of the research and development efforts in various selected disciplines of the pharmaceutical sciences. It is the sixth survey in this series (1–5). Numerous periodicals and selected sections of *Chemical Abstracts* were abstracted. The *Pharmacognosy* section has been discontinued. In order to maintain continuity with the previous pharmaceutical sciences reviews of the *Journal of Pharmaceutical Sciences*, their general format was retained.

GENERAL PHARMACY

Solmssen discussed pharmaceutical research with respect to the synthesis and testing of new drugs (6). Another survey reviewed the federal, state, and foreign drug regulations regarding stability testing and formulation research (7). Comments on the empirical and the rational method for the development of new drugs were the subject of another review (8). The similarities and differences of the pharmacopeial

standards and specifications for bulk drugs and solid oral dosage forms were discussed (9). The location pattern of the pharmaceutical industry was outlined by Smith *et al.* (10). Another paper pointed out methods of stimulating creative output in small laboratory groups (11). The teaspoonful dosage was critically evaluated. The authors pointed out that there was a great deal of variation with this type of dosing (12). Schwartz elaborated on the serious problem of penicillin allergy (13).

Excellent review articles on gastrointestinal enzymes, over-the-counter (O-T-C) depilatories, O-T-C antiobesity drugs, O-T-C anthelminthics, O-T-C burn and sunburn remedies, O-T-C poison ivy and poison oak remedies, O-T-C external analgesics, O-T-C psoriasis and eczema remedies, O-T-C deodorants and antiperspirants, O-T-C internal analgesics, O-T-C hemorrhoidal preparations, and O-T-C preparations for disorders of the scalp appeared in the *Journal of the American Pharmaceutical Association* (14–27).

Preservatives—Bean discussed the use of preservatives to protect pharmaceuticals from contamination (28). Another study was concerned with the preservation of pharmaceutical and cosmetic preparations against microbial spoilage (29). Chemical preservation of ointments and creams in cosmetics and pharmaceuticals was the subject of another paper (30). In addition, the physical, chemical, microbiological, and toxicological properties of several new preservatives were reviewed and their application in dermatologic and cosmetic preparations was demonstrated (31). The interaction of nonionic surfactants with preservatives was shown to be responsible for partial inactivation of the preservative (32). Vitez utilized sodium hyposulfite to eliminate the bacteriostatic effect of various chemical preservatives during sterility testing (33). Several derivatives of β-naphthol were found to have antimicrobial properties in very low concentrations against both bacteria and fungi (34).

Flavor, Color, and Aroma—A concise history of the development regarding the use of color additives in foods, drugs, and cosmetics was presented (35). Another review was concerned with dyes commonly used in foods, pharmaceuticals, and cosmetics (36). Raff reviewed the concept of color as a psychological-physical phenomenon and gave examples illustrating this viewpoint (37). An account was also given of the fundamental mechanisms which occur when coloring matter absorbs light (38). Another paper considered the limitations of conventional color measurements from the point of view of applicability to routine storage testing (39). The suitability of some natural dyes for coloring sugar-coated tablets was investigated (40).

Bedoukian discussed the progress in the use of perfumery materials (41). Another review concerned itself with the updating of flavoring materials currently in use (42). The influences of the methods of perfuming and the requirements of the perfume for various types of preparations were considered (43).

Adjuvants—The effect of water, surfactants, and binders on the adhesion of solid particles was studied by a centrifugation method (44). Mendes evaluated a number of selected new materials as binders for tablets (45). The application of bentonite in the technology of tablet preparation was the subject of a paper (46). The role of various adjuvants in the mechanism of tablet disintegration was the subject of a review (47). Dextran was investigated as a binding agent (48). Kaplan studied the effect of varying the ratio of isopropanol–water granulating solution on various tablet parameters. He found that the ratio affected the hardness, thickness, and disintegration of tablets (49). The role of starch in the mechanism of tablet disintegration was elucidated (50). Another group studied holocellulose and technical cellulose as substances that support the disintegration of tablets (51). The change in flow properties of sodium bicarbonate in the presence of small amounts of magnesium stearate was observed (52). It was also pointed out that surface-active quaternary ammonium and pyridinium compounds are adsorbed on colloidal silicic acid to different degrees depending upon the concentration (53).

Polyvinyl alcohol was found to be a useful ingredient in vehicles for ophthalmic solutions (54). Parker investigated the effect of solution additives upon the stability of intravenous fluids (55). The concepts of ophthalmic compounding were also the subject of another paper (56). A review and discussion of the use of parenteral water-in-oil emulsions as adjuvants administered with allergens in the treatment of seasonal allergy appeared in the literature (57). The effect of various solvents on the stability of reserpine was described (58).

Stability—Tingstad discussed the various aspects that should be considered in the design of stability studies in product development (59). Another review article by Garrett elaborated on the stability of drug solutions (60). A

review of the chemical and physical properties of epinephrine as related to its use in glaucoma was published (61). Microdiffusional analysis was successfully applied to the stability of drugs in the solid state (62). Stability of reconstituted drugs and intravenous fluids received some attention in several articles (63, 64). Therapeutic incompatibilities caused by drug interactions were reviewed (65).

The chemical mechanism that explains the accelerated hydrolysis demonstrated by aspirin in combination with an alkaline stearate in a solid dosage form was elucidated by employing a suspension technique (66). Undissolved sulfadimidine removed benzoic acid from solution in sulfadimidine mixtures (67). The stability of sulfacetamide ophthalmic drops was discussed (68). The degradation of aspirin in commercial products containing acetaminophen was found to be accompanied by the formation of diacetyl-*p*-aminophenol or *p*-acetoxyacetanilid (69). In another article Pellerin discussed the value of analytical methods which indicate the degree of purity and the effect of the latter on the stability of pharmaceutical preparations (70). A colorimetric method was outlined for studying the stability of certified dyes (71). The comparative hydrolytic rates of *N*-substituted 6-aminothiouracils were obtained in acidic and alkaline media (72). Pearl-shaped granules were found to be the most stable form of vitamin A (73).

The relative stability of penicillin salts was similar at pH 1.5–4.5 (74). Another study gained some insight about the reactions possible in aqueous pharmaceutical systems of amines buffered with di- and polycarboxylic acids (75). The change in color of aqueous solutions of sodium sulfathiazole was related to decomposition (76). The autoxidation of sodium salicylate solutions was followed by polarographic methods (77). The stability of the amide group of glutamine derivatives in aqueous solution was determined (78). Another group studied the effect of pH, temperature, nature of the stabilizers, and conditions on the stability of pyridoxine (79). The effect of gamma radiation on the stability of several drugs packaged in glass and plastic containers was the subject of another investigation (80). The acid-catalyzed anaerobic degradation of isoniazid was elucidated (81). Acetylcysteine was susceptible to oxidation during nebulization (82). Rubber closures containing substances that are relatively inert should be used for insulin preparations (83). Racemization of drugs sometimes attributes to stability problems (84). Cod liver oil stability was examined using an accelerated aging test for evaluation (85). The stability of dextran during prolonged storage was investigated (86). The oxidation reactions involving white lotion, paraffin, and linoleic acid indicated that peroxides were the degradation products (87–89). Stability studies were also carried out with novobiocin, tartar emetic, alcoholic solutions of iodine, methoclopramide, belladonna alkaloids in antacid tablets, ethionamide, and sulfonamides (90–96). Barry and Shotton checked the influence of 1-hexadecanol on the acid-catalyzed hydrolysis of sodium dodecyl sulfate (97). Another group followed the reaction between boric acid and *p*-aminosalicylates by thermal and conductivity measurements (98). Benzoyl peroxide stability in pharmaceuticals was determined (99). An improved theoretical calculation of the stability ratio for colloidal systems was proposed (100). A simple method was also described for testing light absorption of various glass, plastic films, and other wrappings (101).

Stability Kinetics—Connors and Favilla described a method for kinetic studies of reactions in which the concentration of one reactant was held essentially constant by the addition of that reactant throughout the course of the reaction (102). The general concept of chemical kinetics in relation to the study of drug stability was reviewed (103). In another study on stability kinetics, Seydel demonstrated the application of reaction kinetics in predicting stability of drugs and derived rate equations related to drug degradation (104). Several papers appeared which discussed the stability of some cardenolide preparations (105–107). The hydrolysis of solubilized aspirin in solution buffered from pH 1.7 was studied at 37° (108). Another group presented data on the hydrolysis of aspirin in aqueous solutions of polysorbate 80 (109). In an excellent review article Garrett discussed the rate–pH profile in solvolytic degradations (110). An improved iodometric technique was used to investigate the kinetics of the reversible reaction between methionine and iodine (111). The ultraviolet light-catalyzed reaction of chlorpromazine under anaerobic conditions appeared to be different from the reaction under aerobic conditions (112). Several papers appeared on the stability of *N,N'*-di-[α(1-naphthyl)-propionyloxy-2-ethyl]piperazine (113, 114). A mechanism for the hydrolytic deamination of cytosine arabinoside in aqueous buffer was proposed (115). The degradation kinetics of 6-aminopenicillanic acid was the subject of another paper (116). Hurwitz established the mechanism for the

degradation reaction of *N*-chlorosuccinimide in aqueous solution (117). The mechanism of the base-catalyzed hydrolytic reactions of isoalloxazine was proposed (118) while Guttman and Platek were investigating the hydrolytic behavior of the same compounds. Kinetic data indicate both ionized and unionized species underwent specific base-catalyzed reactions but at different rates (119). Reactions involving cyclic acid anhydrides in aqueous solution were studied in an effort to understand biological mechanisms and in predicting pathways by which drug mixtures may undergo decomposition (120).

A method was described to determine the chemical stability of labeled fluocinolone acetonide incorporated into pharmaceutical preparations (121). The kinetics for the decomposition of chlorophenyl-benzylpiperazine derivatives was considered in another study (122). The hydrolysis of solubilized esters and amides was the subject of several papers (123, 124). The kinetics of solvolysis of various sydnones was investigated spectrophotometrically as a function of HCl and NaOH concentrations, pH, and temperature by Garrett and Mehta (125).

5-Methyl-3(2*H*)-furanone was formed from the acid-catalyzed solvolysis of 2-deoxy-D-ribose (126). The effect of certain additives on the hydrolysis of phenobarbital was shown (127). Methylparaben hydrolysis was also the subject of another paper (128). Fractional factorial experiments were used to evaluate related liquid formulations (129). A kinetic study of the reaction between dehydroacetic acid and primary amines in various solvents was investigated (130). The kinetics of degradation of chlorothiazide in acidic and alkaline solution was also reported (131, 132). The decomposition of morphine was followed as a function of temperature and pH (133).

Antibiotic Stability—Schwartz and Pflug described the mechanism of hydrolysis of penicillins catalyzed by catechol using benzylpenicillin and methicillin as model compounds (134). Potassium penicillin G was found to be incompatible with *p*-hydroxybenzoate. The authors isolated and identified the products of the reaction (135). Another group determined and eliminated the cause of the yellow discoloration in penicillin after sterilization (136). It was also shown that magnesium ions overcome the activity of novobiocin by forming a complex with the antibiotic (137). The stability of tetracycline hydrochloride in the presence of pyridine compounds, magnesium salts, and aliphatic and aromatic hydroxyacids was the subject of several papers (138, 139). Nystatin exhibited excellent stability on prolonged storage when kept under phosphorus pentoxide (140). Monciu *et al.* studied the interaction of chlortetracycline[1] with various components and related this effect to the duration of activity (141).

Vitamin Stability—The color stability of ascorbic acid tablets containing eight commonly used lubricants and glidants was studied by light reflectance (142). The stability of ascorbic acid tablets prepared by three different methods was evaluated (143). The discoloration of ascorbic acid tablets under prolonged storage was traced to ingredients commonly used in tablet formulations (144). Phytic acid derivatives have been used successfully to stabilize ascorbic acid (145). Sodium ascorbate solutions maintained satisfactory potency in the presence of sodium sulfite and carbon dioxide; however, on prolonged storage oxidation due to the presence of trace metals was observed (146). Another study dealt with the behavior of ascorbic acid solutions subjected to ultrasonic treatment (147). The rate of ascorbic acid decomposition under aerobic and anaerobic conditions was reported (148). Quantitative changes in L-ascorbic acid occurred in aqueous solution (149). The *in vitro* evaluation of the interaction of vitamins was discussed (150). Another group examined the photodegradation and stabilization of vitamin K_1 (151).

Ophthalmic solutions containing vitamins neutralized with bicarbonate were not irritating and were relatively stable (152). Multivitamin tablets containing vitamin A, D_2, and B_{12} coated with a gelatin–sugar coating showed better stability in artificial gastric juice (153). The factors affecting the stability of polyvitamin hydrosols were reviewed (154). Another group studied the stability of thiamine salts and calcium pantothenate in various vitamin B complex preparations (155). It was also pointed out that vitamin A preparations were more stable when vitamin A was converted to anhydrovitamin A (156).

PHARMACEUTICAL TECHNOLOGY

Knoechel *et al.* designed an instrumented rotary tablet machine and showed its applicability in pharmaceutical research and development and in production (157, 158). The spray pan method of coating tablets was described. It involved applying coating materials in solution or suspension as a spray from a centrifugal disk atomizer (159). Another group developed a small coating machine for enteric coating small

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

batches of tablets (160). An apparatus for studying the disintegration of tablet coatings was designed (161).

The pharmaceutical application of internal reflectance spectroscopy and UV spectroscopy was the subject of several papers (162, 163). An excellent review containing 60 references on spray drying and its application in pharmaceutical systems appeared in the literature (164). The use of differential scanning calorimetry and its application in pharmacy was commented on with reference to the detection of polymorphism and purity (165). The B.E.T. method for determining specific surface area was described in detail (166). Campiglio reviewed the apparatus and techniques for microfiltration and microcrystallization (167). Ultrasonic treatment of alumina gel did not alter its adsorption heat (168).

Parenterals—Several papers were published dealing with the danger and control of particulate matter in parenteral solutions. They pointed out methods of estimating the number of particles in injectable solutions and the danger involved when an excess of particles are present (169–171). Extemporaneous mixing of parenterals often presents problems (172, 173). They often show some type of incompatibility (174). A change in pH may be an important factor contributing to the problem (175).

The sorption, leaching, tensile, and other properties of a series of butadiene–acrylonitrile rubbers from the medium high acrylonitrile group were evaluated to determine the suitability of this type of closure for multiple-dose vials (176). Anschel discussed the requirements for suitable solvents and solubilizers for use in injectable preparations (177). The separation of microcrystals in injectables containing calcium gluconate was investigated (178). Parenteral solutions were found to develop precipitates after storage for 2 years indicating that hydrolysis can occur even in supposedly stabilized preparations (179).

Parenteral solutions of papaverine were stabilized by the addition of disodiumethylenediamine tetraacetate (180). Another investigation dealt with the stability of epinephrine[2] in parenteral form (181). Parenteral solutions of certain fat-soluble vitamins were also the subject of another paper (182). A comparison of the efficacy of several glass filters commonly used to filter parenterals appeared in the literature (183). The interaction of various types of rubber with medicament was reviewed (184).

[2] Adrenalin, Parke Davis & Co., Detroit, Mich.

Sterility—The dynamics of air sterilization was presented by Dorman (185). Another excellent review article was prepared describing sterilization with ethylene oxide in medicine and pharmacy (186). A new aseptic processing unit for sterile products was introduced (187). Filters for removing pyrogens and bacteria from pharmaceutical injection solutions were evaluated (188). Anderson studied the hydrolysis of sulfacetamide solutions at sterilization temperatures (189). The effect of preservatives on the heat sterilization of sesame oil was the subject of another paper (190). The causes and prevention of pH change in glucose solutions during sterilization were investigated (191).

Tablets and Capsules—The *in vitro* evaluation of physiological availability of compressed tablets was the subject of a review (192). The compression characteristics of some pharmaceutical materials were investigated (193). Hardness and disintegration time of tablets as a function of compression force were studied. The results indicated that there was no relationship between hardness and disintegration time in water (194). The effect of moisture on the behavior of sodium chloride under compression was investigated by measurement of compaction and ejection forces (195). Another investigation was concerned with the various changes of compression by pressure measurements (196). Abdel Khalek *et al.* elaborated on the effect of humidity on mechanical strength weights and disintegration rates of tablets (197). A quantitative evaluation of the dissolution rates of active ingredients from tablets was discussed. The authors checked filler binder, lubricant, disintegrating agent, and hardness on the dissolution rate of sodium salicylate from tablet bases (198).

A new technique was described for the observation of the stresses involved during a compaction operation (199). Hanus studied the thermodynamic and resistivity effects involved in the compression of solids (200). Graphic illustrations of the effects of air temperature, air velocity, and layer thickness on the drying process appeared in the literature (201). Meanwhile, the effect of particle size on the strength of sodium chloride tablets was measured. The results show that there was no simple relationship between crushing strength and particle size over the range of particle size studied (202). The disintegration of tablets containing triamterene was classified according to the type of dispersion obtained (203). High molecular weight film-forming compounds were used by Daragan for coating tablets (204). The determination of

certain parameters of free-flowing pharmaceutical products was carried out (205). It was proposed that the uniformity of weight test may sometimes replace individual chemical assay when the percent of active ingredient is high (206). Tablet coatings were the subject of another investigation (207).

Williams and Shields discussed the segregation of granules in a vibrated bed (208). Another group measured the drying rates of beds of magnesium carbonate powder wetted with various liquids (209). The shape of the core of a tablet was found to have some effect on its ease of sugar coating (210). A bowl granulation process was described for the granulation of lactose (211). Tablets were also prepared containing chemically incompatible materials (212). Various pill bases were evaluated to improve the technology of pill making (213). Dissolution studies were carried out for commercial brands of phenylbutazone and phenindione tablets (214, 215).

Suspensions—Various theories of dispersion were critically presented. Dispersions take place in two stages, *i.e.*, the wettability of the substance by the medium and the stability which is inversely related to the number of particles flocculating per unit time (216). A review containing 34 references classified disperse systems and described their general physical properties (217). A detailed study was made of 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 (218). The stability of white lotion was increased by using zinc oxide with a high sedimentation volume and by machine dispersal of the solids (219). In another paper the theoretical principles involved in the preparation of a physically stable suspension were discussed, and some examples of successful application of these principles in pharmaceuticals were given (221). Smith discussed the physical properties of suspensions (222). Crystal growth in aqueous suspensions was the subject of a detailed study (223). A reduced form of the particle-size distribution function, designated "self preserving," satisfied the Smoluchowski equation of coagulation by Brownian movement (224). The viscosities of dilute solutions of carboxymethylcellulose and methylcellulose influenced the sedimentation rate of barium sulfate particles (225, 226). The structural and filtration properties of kaolin and kaolin clay dispersions were shown to be affected by surfactants and electrolytes (227). A relationship describing the structural strength of disperse systems was derived (228).

Several articles discussing the preparation and stability of barium sulfate suspensions appeared in the literature (229, 230). A study of the translation and rotation of rigid spheres, rods, and disks, as well as the deformation of fluid drops in pulsatile and oscillatory flow was conducted (231). A graphical method was utilized to compute sedimentation coefficients (232). Zeta potential measurements can be obtained with an electrically driven pendulum with viscous damping (233). The properties and applications of several different gel systems were elaborated on in a number of papers (234–237). Lanolin derivatives were utilized to disperse various pigments in aqueous media (238). A polymeric preparation, K-4, stabilized suspensions of natural and monocationic forms of clays (239). Mueller and Schneider studied the wettability of granular material and the wetting action of surfactant solutions (240).

The Gibbs equation for the adsorption of surface-active monovalent and polyvalent ions in the presence and absence of neutral salt was extended (241). In another publication Samyn and Jung investigated the negative thixotropy in flocculated clay systems (242). Micelle formation, micelle size, and critical micelle concentration in the presence of dissolved macromolecules were thoroughly investigated (243–245). Another study was conducted to determine the formation and structure of sediments in pharmaceutical systems (246). The acceleration of sedimentation of fine solid suspensions was also examined (247). α-Dialkyl-β-aminopropionic acid was found most useful in the modification of flow properties of lipophilic vehicles (248). The technology of the production of microcrystalline suspensions was also investigated (249). The stability of dispersions of alumina and aluminum hydroxide was affected by various chain length alcohols and water (250). Light transmission measurements on suspensions were made by Hepplestone and Lewis (251).

Emulsions—A review containing 30 references dealt with emulsification and the selection of nonionic surfactants (252). Several papers also appeared which discussed the theory of emulsification, characteristics of the emulsifier, and finally the selection of the emulsifier (253, 254). The more important principles and some fundamental aspects of disperse systems were presented (255). Another review concentrated on the factors which determine the choice of emulsifying methods, the phase volume ratio,

and the emulsifiers (256). Two excellent papers appeared on emulsification. The authors stated that the HLB value and the rheological properties of the interfacial films were important factors affecting emulsion stability (257, 258). Jass stressed the importance of controlling the process variables to insure emulsion stability (259). Smoluchowski's equations were used to determine the kinetics of the rapid coagulation of emulsions (260). Negative interfacial tension in mixed films of soaps and long chain alcohols results from a large depression between the aqueous and oil phase with its adsorbed alcohol monolayers (261).

A thermodynamic study of emulsions showed that the mechanism of action of the emulsifier was twofold and involved surface phenomena and solution stability (262). Centrifugation was used to evaluate the stability of emulsions (263). The influence of pH on the stability of emulsions formulated with hydrophilic colloids was considered (264). Rimlinger elaborated on the influence of containers, chemical variation of emulsion constituents, and the power of the third solvent in preparing stable emulsion systems (265, 266). It was pointed out that oil-in-water emulsions can be obtained when the emulsifier–water ratio is such that the emulsifier is in micellar solution (267). A mechanism for the action of specific electrolytes on emulsion systems containing certain nonionic polyoxyethylene ethers as emulsifying agents was postulated (268). Electrolyte solutions did not affect the creaming of fat emulsions. The variation in creaming was attributed to the differences in composition or purity of the phosphatide emulsifiers and to the differences in properties of the respective oils (269). In another study Mizutani investigated the relation between phase inversion temperature, cloud point, and HLB values for emulsions prepared from nonionic emulsifiers (270). Pepsin was utilized as an emulsifier to prepare a stable system (271). The stability of an emulsion is increased by using a stabilizer with a high free energy of adsorption and as low a compressibility as possible in the monolayer (272). Particle-size changes were monitored in determining the stability of oil-in-water emulsions (273). A new method of studying the particle-size distribution of mechanically prepared hydrocarbon-in-water emulsions was presented (274). The effect of mixing of oils and of nonionic surfactants on the phase inversion temperatures of emulsions was considered (275). Another study involved spontaneous emulsification caused by the lowering of interfacial tension (276). The interfacial surface effects in a homogeneous multicomponent liquid mixture were measured (277). The possibility of the appearance of a synergism in the decrease of interphase tension was examined by mixtures of surfactants differing only in the structure of the polar groups (278). An effective method for measuring the emulsifying properties of surfactants was presented (279). Low-pressure capillary homogenization was used to prepare emulsions. The stability of the resultant emulsion was followed (280). The formation of microemulsions can be affected by different hydrocarbons (281). Cavitation mills produced more homogeneous creams than did colloid mills, however, after prolonged storage the creams produced by the cavitation mills showed poorer stability (282). Peroxides were found to affect the rate of emulsification of mercury in anhydrous lanolin (283). The charge on the disperse phase particles influenced the stability of some water-in-oil type emulsions (284). Admixing oils was shown to control the activity of phenols in oil-in-water dispersions during storage at different temperatures (285). The distribution of benzoic acid in some emulsified systems revealed that its fungistatic activity was dependent upon the amount of free acid in the aqueous phase (286). Conductivity measurements were used to follow the creaming rate of aggregate systems (287). The emulsifying properties of several surfactants were evaluated (288). A new polysaccharide gum was announced as a potential emulsifier for pharmaceutical systems (289). Gum arabic and tragacanth were determined to be the most satisfactory agents for maintaining the stability of paraffin oil emulsions (290). The method of preparation had an effect on the initial size distribution of oil-in-water emulsions (291).

Ointments and Creams—Schlossman discussed various hand creams and lotions and listed typical formulas (292). Several new water-washable bases and their properties were described (293). Oil-soluble lanolins were used in the preparation of typical creams (294, 295). Several papers were published describing typical ointment bases useful for various externally applied medicinals (296–299). Lukas described a new synthesis of ointments with fatty acid lead salts (300). Formulas for chloramphenicol ointment were also described (301).

The evaluation of the chemical stability of ointment bases was determined by the method of accelerated aging (302). Polymyxin B sulfate was found to be most stable in an ointment base containing methylcellulose and polyethylene glycol[3] (303). Antioxidants were effective in

[3] Carbowax, Union Carbide Corp., New York, N. Y.

preventing the breakdown of ointment bases hydrated with rose water (304). A synergistic behavior was observed when ointments were prepared by incorporating β-naphthol, iodochlorhydroxyquin[4] and undecylenic acid into water-soluble bases (305).

The rheological behavior of various ointments of the suspension type was investigated (306). Penetration measurements using a rotating viscometer slightly modified by the addition of penetrators permitted the determination of consistency of ointments (307). Whitworth and Becker studied the release of soluble sulfonamides from ointment bases through a membrane for a 6-hr. period (308). In a similar study the liberation of active substances from ointment bases was followed by dialysis (309).

Suppositories—The methods used in a physical study of suppositories were described in detail (310). Several papers were written on the compounding of colored suppositories (311, 312). Plaxco *et al.* studied the effect of some nonionic surfactants on the rate of release of drugs from suppositories. Their data indicate that the HLB value of the surfactants had an influence on the rate of release of the drug (313). Several substances were evaluated as possible viscosity increasing agents for the suppository base lasupol-G (314). The use of 1,3-butylene glycol as a glycerol substitute in suppositories was investigated (315). It was also pointed out that amidopyrine was unstable in the presence of certain agents in suppository bases (316). The formulation and evaluation of new rectal dosage forms including a study of microcrystalline cellulose–carboxymethylcellulose gels as suspension vehicles were reported by Wakling (317).

Aerosols—A discussion of the theory of foaming, foaming properties of nonionic surfactants, and of foam stabilizers and foam inhibitors was published (318). Nonionic aerosol foams were studied with respect to emulsion stability, bubble size, foam stability, stiffness, and drainage as various fatty alcohols or acids were added (319). Silicone antifoams are often used to decrease the tendency for foaming (320). Kuebler commented on the dosage accuracy in aerosol preparations. He stated that the filling of aerosol preparations entails some dosage variation which increases as the container size decreases, however, the variations are within limits (321). An outline of the available literature on aerosols was presented (322). The development and application of aerosols in pharmacy were reviewed in several articles (323, 324). The quality control requirements for aerosols were outlined (325). Several authors discussed the significance and determination of particle size for oral inhalation aerosols (326, 327). Sciarra wrote a review article concerning the particle size of topical aerosols (328).

Several additional papers were published which described the measurement of aerosol particles by light scattering and by acoustical measurements, respectively (329, 330). In another paper a series of electrolytes were dispersed from solutions with a modified Dautrebande-type aerosol generator (331). The modification of an aerosol generator resulted in the preparation of sodium chloride aerosols of narrow particle-size distribution (332). The particle-size distribution of an aerosol continually reinforced by the introduction of particles and undergoing Brownian coagulation was calculated by integrating the equation of Smoluchowski modified to include a feed term (333). The effect of a weak electric charge on the rate of coagulation was studied using dioctyl phthalate (334). Several additional papers discussed propellant blends and perfumes commonly used in aerosols (335–337). Richman studied pressurized foams with emphasis on rheological evaluation (338). An experimental method for measuring the drop size distribution in liquid sprays was presented (339).

Sustained Release—A review was presented describing the means of prolonging medicinal action of various drugs and the various factors involved (340). Recent achievements in the field of pharmaceutical preparations with prolonged action were the subject of a survey containing 300 references (341). Another survey appeared which emphasized the importance of timed-release preparations (342). Drug latency, durability, metabolic activation, and water solubility were reviewed with respect to sustained-release dosage forms (343). Stuart offered a table of variable-release dosage forms and of the principles of the timed-release dosage forms (344).

Several papers appeared elaborating on the use of microencapsulation of pharmaceuticals (345, 346). An attempt was made to develop a parenteral form of an antibiotic by coacervation (347). Luzzi and Gerraughty commented upon the effect of additives on the controlled release from microcapsules (348, 349).

A modified half-change method was suggested to maintain proper enzyme levels during a prolonged-action test (350). Coated granules have been investigated in the preparation of phar-

[4] Trademarked as Vioform, Ciba Pharmaceutical Co., Summit, N. J.

maceuticals with prolonged action (351). Sustained-action thiamine tablets were prepared. The author studied the *in vivo* and *in vitro* release patterns (352). Ion-exchange resin adsorbates of aspirin were prepared and evaluated for sustained action (353). A carboxyvinyl polymer[5] was found to affect the dissolution rate of a tablet. It was concluded that this agent could be used successfully to prepare sustained-action tablets (354). The effect of surfactant concentration on the release rate of sulfaethylthiadiazole from synthetic wax particles prepared by aqueous dispersion was studied (355). Long-action compressed tablet formulation was prepared from a plastic matrix. Both *in vitro* and *in vivo* tests were carried out on the finished forms (356). Newly developed coating laquers made from acrylic resins were also used to prepare depot medicinal dosage forms (357). Another paper appeared which described the preparation and effectiveness of long-acting diethylstilbestrol injections for veterinary use (358).

Cosmetics—Moxey published a survey dealing with perfumery and cosmetic material (359). Another review dealt with the structure of emulsions, emulsifiers, and their use in the cosmetic industry (360). The application of silicones in cosmetic preparations was the subject of another article (361). It contained formulas for a number of preparations. A paper dealing with the use of modern surfactants in the manufacture of cosmetics appeared in the literature (362). Bergwein reviewed hair creams, commenting on their history and development in the various forms (363). Several interesting articles appeared relating the role of glycerin in modern cosmetic products (364, 365). Another author discussed the use of glyceryl esters in cosmetic emulsions (366). Fatty acid esters of xylitol were experimented with as possible ingredients in the preparation of cosmetics (367). Schmolka elaborated on the application of pluronic polyols in the cosmetic industry. He pointed out that these agents may aid the cosmetic chemist in improving current formulations and developing new products (368).

Diisopropyl adipate was evaluated as an ingredient for cosmetic formulations (369). New types of pearl pigments have been developed for cosmetics which previously were not practical because of natural limitations (370). Cosmetic grade propoxylated ethers were discussed and formulations were suggested to illustrate their application (371). The use of polymer microspheres as raw materials for cosmetics and toiletries was suggested (372). Cotta *et al.* described some important points relative to the production and control of tissue protein and their use in cosmetics (373). The importance and the influence of grain size in pigments used in cosmetic preparations was the subject of another paper (374). The synthesis of two new groups of alcohol-soluble aluminum compounds was described. Their antiperspirant activity was also measured (375). Because of unique properties of silicones it was pointed out that a variety of performance characteristics can be built into cosmetic formulations (376). Other papers listed several new active substances that were useful for the care of the skin (377, 378). It was also found that the application of a lipid film containing dewaxed lanolin was of value both in maintaining hydration and in serving as a potential lip barrier (379). A synthetic copy of the natural moisturizing factor present in human skin was formulated based on amino acid analysis (380). Several papers were presented dealing with the evaluation of sun screen agents (381–383). The background and practical application of gel formation in nonionic systems in relation to cosmetic preparations were discussed (384). Fatty acid chain length had some effect on the physical properties of cosmetic emulsions (385).

Packaging—Beal *et al.* described a comprehensive study on pharmaceuticals stored in plastic containers (386). Another study pointed out that direct measurements of light transmission of plastics is affected by diffusion and is not a trustworthy test of suitability for packaging (387). An excellent review on the structure problems of silicates and glass as a construction material, on its resistance to heat change, and on the physical and chemical properties of pharmaceutical containers was published (388). The quality requirements of the pharmaceutical industry for flasks and ampuls were outlined (389). The research and development of safety closures was the subject of another paper (390). Rehm conducted the testing of water resistance of container glass (391). Autian presented a review of the interaction between medicaments and plastics (392). Several papers discussed the problem of permeability of various components through polyethylene and polypropylene containers (393–395). Corrosion problems in aerosol packaging were reviewed (396). High polymer plastics with their flexibility, shock resistance, and other helpful aspects lend themselves well for developing interesting packages for cosmetics (397).

EQUIPMENT

Several papers were published concerning the

[5] Carbopol 934, B. F. Goodrich Co., Cleveland, Ohio.

use of vibration mills (398–400). The performance of several industrial mixers was compared using segregating materials (401). An excellent review article on the application of ultrasonics in pharmacy was written by Skauen (402). Unit-dose packaging was the subject of another article (403). The use of new automated techniques for the pharmaceutical industry has been reported (404). Several typical spray driers were described and their application to pharmaceutical systems was discussed (405). Another paper described the mechanical bottling of oral solutions under protective gas (406). A review, containing 175 references, concerned with automatic adjustments of the meniscus, the dosing adapters for pipets, special devices, the sources of error, and calibration of the dosing adapters was published (407). The construction and use of laminar flow rooms were described by Soltis (408). Another article appeared which described equipment utilized in high speed film coating of tablets (409).

PHYSICAL PHARMACY

The various aspects concerned with dissolution and diffusion studies have produced a number of interesting papers. A new method of studying the diffusion of liquids through gels has been noted (410). Nixon *et al.* have determined the concentration effect on diffusion coefficient (411). In another study, based on the first principles of diffusion, the authors derived appropriate equations to predict the transport of solubilized systems (412). The effect of high surfactant concentration on the kinetics of dissolution, the importance of sink conditions, and the simultaneous determination of dissolution and partitioning rates *in vitro* have been demonstrated (413–415). In regard to the solid dosage form, Singh *et al.* described the release rates from the inert matrices in cases where there existed noninteracting drug mixtures, as well as mutually interacting drug mixtures (416, 417). Formulation effects on the tablet dissolution pattern were also investigated (418, 419). An apparatus for determining the drug release from tablets has been described (420). The dissolution phenomenon has also been reported in somewhat of a different but definitely pertinent interest, *i.e.*, the dissolution of phosphate kidney stones by citrate buffer (421). In addition to dissolution rate studies, the deaggregation behavior is likewise relevant. Aguiar *et al.* have developed equations and demonstrated such rates quantitatively (422). The association of dissolution to insoluble compounds immediately directs itself to the effect of particle size. In fact, it was suggested that the use of an appropriate particle-size terminology be used in pharmacy (423). A review of particle size and surface area and critical evaluation of measurement methods were discussed (424). The following methods for determining particle size were described: photosedimentometer, ultramicroscope, permeability, sedimentation balance, X-ray, turbidimetry, and light scattering (425–434). Other results indicate significant influence of a polar nature of the solution on cluster formation when hindered setting was used for determining particle size (435). A study on the dispersion of clay for particle size determination was made (436). Relative to this, studies on particle reduction to μ size, the effect of grinding on precipitated magnesium hydroxide, and a new technique for fractionating powders were performed (437–439). A comparative study of commercial griseofulvin with reference to official standards was also investigated (440).

Solubility—Solubility determinations of the following systems were reported: the solubility of antibiotics in 26 solvents, purines, pyrimidines, and their nucleosides in urea and sucrose solutions, vinbarbital in ethanol–water systems, sodium bicarbonate in glycerol, and some aminoalkylphenothiazine tranquilizers and related compounds in water (441–445).

The increase of aspirin–water solubility was accomplished through the interaction with urea (446). The effect of urea on the solubilities of benzoic acid and the effect of salicylic acid on the dissolution of some polymers was also determined (447, 448). The solubility relations and solubilization by nonionic surfactants were noted in a number of cases such as, the ascorbic acid–water–polysorbate 80 system, lecithin in antibiotic preparations, benzocaine and homatropine, testosterone, hydrocarbons, hormonal steroids, and chloramphenicol (449–455). Several papers described the increased yields of essential oils when nonionics were utilized in the extraction process (456–458). A review with 167 references outlined the solubilization of drug compounds by polysorbates[6] (460). A study was also conducted on the solubilization of water from its vapor pressure over nonionic and ionic surfactant solutions in various nonpolar solvents (461). Kuettel described saturated and supersaturated systems prepared by solubilization (462). The effect of the cation on solubilization by oil-soluble surfactants and solubilization of polymers in aqueous cationic surfactant solution has been noted (463, 464). The use of some synthetic

[6] Tweens, Atlas Chemical Co., Wilmington, Del.

surface-active substances as well as the solution of sulfonamides with polyglycols was reported (465, 466). Bjaastad and Hall have investigated the value measure of relative solvent polarity in micellar solubilization (467). The solubilization and rate of dissolution of drugs in the presence of physiologic concentrations of lysolecithin were determined (468).

Complexation—Patel presented data to show that antimicrobial activity of several preservatives is primarily a function of the free or unbound preservative (469). A series of papers elaborated on the interaction between drugs and macromolecules (470–472). The calculation and determination of stability and dissociation constants have been reported (473–475). The stability of metal complexes of salicylic acid derivatives and caffeine with various benzoic acids has been evaluated (476, 477). Seventeen drugs were tested against seven ion-exchange resins and activated charcoal for binding capacity *in vitro* (478). Diffuse reflectance studies of solid–solid interactions of drugs were made and in the case of dye–adjuvant chemisorption, the results indicate that a metallic or polyfunctional adsorbent molecule is necessary (479). Evidence of the following complex formations has also been noted: epinephrine with boric acid in aqueous solutions, benzoquinone solutions with indole derivatives, adrenochrome–adrenolutin, weak organic acids and phenols with nylon-6, anionic detergents with cellulose, and starch with organic substances (480–485). The effect of neutral salts in gelatin–gum arabic complexes was also determined (486). A report on the hydrogen acceptor properties of griseofulvin and related compounds, in order that its physical behavior would allow a more rational approach to the formulation of dosage forms, was also reported (487). Interactions of penicillin with deoxycholic acid polymer-like structures have been shown (488). Soluble copper chelates were suggested for addition to injectable solutions such as iron saccharate (489). Also appearing in the literature, was a paper which describes complex formation in aerosol emulsions and foams (490). The use of complexes as antacid preparations has been evaluated for a new aluminum hydroxide complex as well as metal complexes of tris(hydroxymethyl)aminomethane (491, 492). NMR spectroscopy has been used to study molecular interactions and mobility at liquid–liquid interfaces (493).

Surface Phenomena—Aspects of surface-active agents in pharmacy, in which their classification and properties are given, were described (494). A review contained historical, chemical, and biological aspects of surfactants (495). Discussions were also given for the modern theory of fluid surface tension, physical basis of wetting, and some aspects of classical surface thermodynamics (496–498). The properties and chemistry of silicones and clay material have been reported (499, 500). Descriptions of nonionic and anionic surfactants have been noted (501, 502). Another paper contained data on the bactericidal properties of straight-chained alkyltrimethylammonium bromides in a simple emulsion system (503). A paper by Beckett *et al.* contained data on surface-active betaines (504). A review on the use and analysis of sucrose fatty acid esters also appeared in the literature (505). The structure and rheology of sodium dodecyl sulfate–cetyl alcohol–water can be found in a series of papers (506–508). Several other papers have noted micellar properties of sodium dioctyl sulfate (509–511). A study using monooctyldecyl phosphate included data which showed the surface viscosity of the monolayer increased linearly with time and this rate increased as the pH was lowered (512). Studies of the surface viscosity of monomolecular films of *n*-chain alcohols were also conducted (513). Other aspects of surface-active agents which have been reported included monolayers formed by mixtures of anionic and cationic surfactants, surface excess in solutions of surface-active agents, and the effect of composition on the critical surface tension of polyvinyl butyral (514–516). Another report included the physiochemical properties of monoglyceride sulfonate–water systems near the critical micelle concentration (517). Definitions of kinetics and kinematic surface tension on the physiochemical surface characteristics of moving surfactant solutions were given (518). Electrocapillary curves for the interfaces between aqueous solutions of inorganic electrolytes and oils containing detergents were published (519). A number of papers have considered the following aspects of the micellar state: the relationship with cloud point, influence of temperature, the effect of tracer dyes on the size distribution and transport properties, density, hydration, shape and charge, and the ionic dependence of micelle number (520–524). The determination of critical micelle concentration of cationic surfactants has been made through the use of alizarine red S (525). The osmotic coefficient and equivalence conductance of aqueous solutions of medical amine salts were used to determine aggregating properties (526). Quantitative measurements of the interfacial free energy of black lipid membranes

separating two aqueous solutions were made (527). A number of papers have included various facets in the measurement of surface tensions of surfactant solutions including methods (528–533). Ho and Higuchi used the RIDL multichannel particle counter and size analyzer to develop a method for studying the kinetics of aggregation of denatured proteins (534). Another paper described the use of flow ultramicroscopy in particle-size analysis (535). The kinetics of monolayer desorption at constant surface pressure was analyzed (536). Fluorine magnetic resonance was used to investigate micelle structure while the sedimentation equilibrium method was used to determine micelle molecular weight (537–538).

A geometric model of floc formation using Smoluchowski's rate equation for perikinetic flocculation was developed (539). The colloidal–chemical properties of nonionic surfactants is included in another paper (540). A number of papers included discussions on colloid stability (541–546). Another author presented the effects of low concentrations of electrolytes upon electrophoretic mobility of aqueous colloidal suspensions (547). The description of the double-layer structure of colloidal electrolytes was also made (548). Temperature effect on micellar state of surface-active semicolloids in aqueous solutions has been noted (549). Also presented in the literature was a paper which contains the description of liquid–solids separation with particle growth (550). Papers specifically directed to pharmacy included data on the application of surface-active agents to pharmaceutical preparations, the effect of griseofulvin upon lipid films at the air–water interface, and the work on the formation of micelles in topical anesthetics (551-553).

A general equation for adsorption isotherm was derived and the factors involved in adsorption at the solid–liquid interface were described (554, 555). A method and determination of surface areas of solids has been described in separate papers (556, 557). Investigations of adsorption have included that of the effect of aprotic solvents on phenol alumina, the adsorption of alkaloid salts on silica gel, and the adsorption of mixtures of organic substances from aqueous solutions by activated charcoal (558–560).

The homogeneity of powder mixtures and the segregation kinetics of particulate solids were discussed (561, 562). The aggregation of particles during the grinding process and a report on the development of cohesion in granular materials during comminution were noted (563, 564). The effect of the particle size of granulated drugs on free-flowing properties can be found in another paper (565).

Crystallization—A study was conducted on the mechanism of crystallization of hydrocortisone by ultrasonic irradiation (566, 567). Several authors presented data on the development of optimal crystal shape of basic pharmaceutical materials. This included the influence of solvents and solvent mixtures on crystal shape (568). The conversion of six cholesterol esters from crystalline solid to the isotropic liquid during heating and cooling was studied (569). It was also found that the rate of crystallization depended upon the concentration of starting materials in studies of the crystalline aluminosilicates (570).

Separate studies on sulfathiazole and methylprednisolone described heats of transition and fusion and crystal growth and dissolution rate of the two polymorphic forms of both compounds (571–573). The polymorphic forms of chloramphenicol palmitate and stearate were examined by IR spectrophotometry (574). The polymorphic forms of cortisone acetate and sulfamethoxydiazine were also reported (575, 576). The phase transformation of theophylline hydrate to an anhydrous form was measured at a variety of temperatures using X-ray powder diffractometry (577).

Rheology—The viscosity of some suspensions was studied in which an equation was derived for the effective viscosity of low concentration emulsions containing surfactants (578). It was also stated that the measured viscosity of a suspension depends upon the diameter of the tube of the capillary viscometer used in determining it (579). A Ferrante-Shirley cone and plate viscometer was used to estimate the spreading characteristics of pharmaceutical semisolids (580). An evaluation of the rheological properties of monodisperse latex systems flow curves of thickened latexes was made (581). The structure and rheology of dispersed and flocculated colloidal systems was reviewed (582). Another study described the rheology of surfactant solutions by a novel viscometer based on the principle of harmonic damped oscillations (583). The mathematical criteria of the thixotropy of starch gels were reported (584). Other studies included the viscosity of phospholipid solutions and the development of a standard gel for interlab comparison (585, 586). The Stormer viscometer in the measurement of certain pharmaceutical systems was evaluated (587). Studies reported on clays include: thixotropy and rheopexy of

clay suspensions, negative thixotropy, colloidal and surface properties, sedimentary volumes, structure formation in hydrothermal conditions, and rheological properties (588–594). Another worker determined the sorption and exchange capacity of cations in clay materials (595). The rheology of some oil-in-water emulsions and the rheological changes in emulsions on aging have been reported (596–598).

The following agents have been evaluated as to rheological properties: methylcellulose hydrogels, ternary system of sodium carboxymethylcellulose–glycerol–water, surfactants, sugars in pectin solutions, and the effect of cations on γ-carrageenan (599–605). Another report contained a description of the five general stages in the formation of ionotropic gels (606). The rheological and stabilizing properties of some soaps of naphthenic acid were also investigated (607).

The application of rheology in pharmaceutical cosmetic practice with plastic gels was described in a survey on the main principles of rheology (608). A study on the rheology of a thixotropic lotion and the rheological characteristics of emulsion ointment bases appeared in the literature (609, 610). A paper describing the alteration in flow properties of light mineral oil with an organic derivative of a special montmorillonite[7] was also noted (611).

PHARMACOCHEMICAL ASPECTS

Antibiotics—A review included the new derivatives of semisynthetic penicillin and their clinical applications (612). The pharmaceutics of the semisynthetic penicillins, the compatibilities, and the incompatibilities with other compounds, were presented (613). Gibaldi and Schwartz have determined, from literature data, the kinetics of absorption and elimination in the dog of a new penicillin derivative, penamecillin (614). New antibiotic preparations and other biologically active agents of natural origin have been reported (615). The biochemical mechanism of action of antibacterial antibiotics has been reviewed and the physical-chemical properties of novobiocin were discussed (616, 617). Several authors investigated the hygroscopic properties, thermostability, and solubility of oleandomycin salts (618).

Radiopharmaceuticals—Radiopharmaceuticals were reviewed quite extensively (619). The development, preparation, and application of nuclear pharmaceuticals were described (620). The problems of radiochemical purity, analytical methods, label stability, isotope effects, tissue residues, and clinical studies were considered in a review article (621). Equations were derived without steady-state assumptions for inactivation of enzymes in dilute aqueous solution by ionizing radiation (622).

BIOPHARMACEUTICS

This area appears to be commanding progressively more interest and it probably is the single most investigated area in pharmacy. Interesting work but perhaps least pertinent is that dealing with molecular aspects of drug–receptor interactions as noted in these papers (623–626). An interesting review was presented on alicyclic amines showing relations between structure and pharmacologic activity (627). Others worth noting include the material basis of drug activity and the concepts of the mode of action of drugs in which specific absorption is suggested as a basis of biological activity (628–631).

Studies related to biological systems included the determination of acetylsalicylic acid and salicylic acid in plasma (632). The behavior of erythrocytes in various solvent systems has been investigated (633, 634). Also reported were the excretion levels in the saliva of dogs in which the excretion levels in saliva paralleled the blood levels for salicylate, pentobarbital, and sulfanilamide (635). It was also noted that saliva added to meals significantly retarded gastric emptying while a review pointed out that gastrin was the most potent stimulator of gastric digestive processes (636, 637). Included in the literature was a report that blood plasma was a Newtonian fluid over a wide range of shear rates to cover any likely situation in a living animal (638). Drug accumulation and the storage of drugs have been treated in separate papers (639, 640).

Numerous papers have dealt with a wide range of drug-binding phenomena. These include antibiotic–metal ion interactions, complex formation of tetracyclines with different components of blood serum, protein-binding of local anesthetics, binding of cortisol, binding of phenothiazine derivatives, and sulfonamide binding by serum albumin (641–646). Others included studies of norchlorcyclizine and norcyclizine and the thiazole moiety of thiamine (647, 648). The correlation of serum binding of penicillins with partition coefficients and studies of the binding of phenoxazone compounds were reported (649–651). The competition phenomena in binding of drugs to albumin were discussed (652). A review contained the agents which affect enzyme activity and another the enzymatic degradation

[7] Marketed as Bentone 38, National Lead Co., Brooklyn, N. Y.

of drugs in the organism (653, 654). In another paper, the effect of proteolytic enzymes on tetracycline absorption was studied (655). In separate studies, the *in vivo* degradation of penicilloic and penilloic acid and the hydrolysis of acetylsalicylic acid in human blood were discussed (656, 657).

Studies in which the routes of administration were compared included the comparison of oral and parenteral calcium administration, the difference between parenteral and rectal administration of thiamphenicol, and the rate of equipotent oral and intravenous doses of propranolol and H56/28 (658–660). Species comparisons were also made in which the binding of salicylate to plasma proteins in different species, the comparative metabolism of griseofulvin-^{14}C in the rat and rabbit, and the species difference in duration of action of cardiac glycosides were studied (661–663). The dose dependence of drug plasma level decline in dogs was investigated, and the statistical analysis of log-dose response bioassay experiments were described (664, 665).

Effects of Physiochemical Properties—Evidence of there being a definite pKa which a sulfonamide must possess in order to exhibit maximum activity was discounted (666). In another paper, it was noted that the carbonate derivative is the prodrug of trichlorethanol (667). In a study of pharmaceutical potentiation of drugs, it was reported that the long-chain alkyl derivatives of *para*-aminosalicylic acid were characterized by sustained release and maintenance of high levels in body fluids for long periods (668). In another study, the complex of salicylic acid with caffeine appeared to affect the absorption of this drug in the rat stomach (669). Other authors compared the sulfate and *para*-chlorophenoxyacetate of DL-amphetamine (670). The enteric absorption of formosulfathiazole and phthaloylsulfathiazole was also investigated (671).

Effects of Formulation—An interesting paper on the effect of adjuvants in the manufacture of pharmaceutical preparations was reported. It was noted that the release of antibacterial active drugs from aerosil, white clay, and talc was dependent on the structural relation between the drug and adjuvant (672). The review by Higuchi described the diffusional models useful in biopharmaceutics drug release rate processes (673). Using a new estimation method for release of drugs from dosage forms, an estimate was made of the actual sulfamethylthiadiazole release from the tablet in the gut (674).

Other authors compared the activity, fate, and absorption of chloramphenicol in different suspensions, while Aguiar *et al.* studied the effect of polymorphism on the availability of chloramphenicol from the chloramphenical palmitate, on the degree and velocity of hydrolysis, and the extent of resorption (675–677). The crystalline phases of fluprednisolone were reported in which a comparison of the physical properties and biological activities was made (678).

The action of tetracyline hydrochloride, oxytetracycline, and monomycin was prolonged through the use of polyvinylpyrrolidone aqueous solution (679). A description of the ability of certain additives to influence the absorption of salicylic acid from solutions was given (680). In another report, *in vivo* tests revealed a slight delay in absorption of a sulfa from a topical suppository base (681). A review of the biochemical and physiological mechanisms underlying fat-emulsion preparations also was written (682). A sensitive analytical method was described for the effect of formulation in phenmetrazine levels in man (683). Polymeric pharmaceutical coating materials as enteric coating *in vivo* were evaluated and the intestinal absorption of quinine from enteric-coated tablets was determined (684, 685). A report contained a method for studying the *in vivo* disintegration of orally administered pharmaceuticals (686). In studies of griseofulvin, in which the dissolution rate and absorption in man were compared, a good correlation was seen (687). Paul *et al.* related the effect of varying the crystal size of orally administered nitrofurantoin on absorption in the rat and man and emesis in dogs (688).

Absorption Control—A number of examples have been reported in which the absorption of a compound is altered by the presence of another. One study showed the effect of EDTA on intestinal absorption of sodium *p*-aminohippurate (689). Nikethamide[8] was found to produce a marked decrease in the blood levels of chloramphenicol, and methimazole was found to decrease the absorption of iron in rats (690, 691). Similar studies included the effect of certain nonsteroid antirheumatic drugs on the active amino acid transport across the small intestine and the effect of phenobarbital and glutethimide on the biological half-life of warfarin (692, 693). It was also reported that acetylsalicylic acid reduced the excretory rates of sodium, chloride, calcium, and magnesium ions by about 50% (694). Another author considered the retention and distribution of vitamin B_{12} activity and requirement for B_{12} following parenteral adminis-

[8] Coramine, Ciba Pharmaceutical Co., Summit, N. J.

tration of hydroxycobalamin (695). Uropepsin excretion and the effect of antacid materials, the effect of chelating agents on the excretion of metals, and the effect of probenecid on riboflavin absorption and excretion was also reported (696–698).

Serum levels of vitamin A and β-carotene in patients with and without dermal diseases were determined (699). In another paper, the excretion of trancyclomine sulfate was increased from 1 to 8% after acidification of the urine (700). Levy noted the effect of bed rest on the distribution and elimination of drugs (701).

Absorption Mechanism—A review by Weiner described the mechanisms of drug absorption and excretion (702). The theory of the molecular transport phenomena through thin membranes can be found in another paper (703). A diffusional model for transport rate studies across membranes was proposed by Stehle and Higuchi while another group related drug transport to its solubility parameters (704, 705). Studies utilizing the isolated rabbit mesentery and the urinary bladder of the rabbit have also been reported (706, 707). Electrochemical properties of membranes and anion-exchange resins with inorganic groups of different structure have been noted (708). Several papers included the transfer of compounds across the intestine. Among the compounds studied were L-selenomethionine, basic amino acids, quaternary ammonium ions, and leucomycin (709–712). An interesting paper describes the mechanisms of water transport through nonaqueous liquid membranes (713).

Kinetic Studies—A review on pharmacokinetics was prepared (714). Wagner and Metzler described the estimation of rate constants for absorption and elimination from blood concentration data (715). Equations for excretion rates and renal clearances of exogenous substances not actively reabsorbed have also been derived (716). It was also reported that blood level data and urinary excretion data may lead falsely to the conclusion of zero-order kinetics (717). Martin appraised some aspects concerning the interpretation of drug urinary excretion data (718). Another paper related kinetic considerations to the accrual and elimination of drug metabolites (719).

Pharmacokinetic studies were reported separately on the following compounds: salicylamide, paracetamol, pentobarbital, and ioglycamate (720–723). The digital computer was used to describe the kinetics of the distribution of estradiol-^{3}H (724). Kinetic constants for mixed inhibitors of cholinesterase were evaluated (725). Several authors reported on the effect of repeated oral dosage of nalidixic acid, while others derived a formula for calculating effective levels after repeated doses of hyoscyamine (726, 727). Subcutaneous absorption kinetics were also reported in which benzyl alcohol was studied (728).

Drug Absorption—Krueger-Thiemer and Hansen reported on the solution of pharmacological problems by computers, and a new computer program to determine biological constants was written by others (729–731). A report was also noted on the formal theory of drug-dosage regimens in which the desired plateau effect was not reached if the product of the rate constant for absorption and the dosage interval was low (732). Perrin described the mathematics of the three-phase *in vitro* model and the *in vitro* model for soluble drug absorption (733, 734). Another paper provided a method of estimating relative absorption of a drug in a series of clinical studies in which blood levels were measured after single and/or multiple doses (735). O'Reilly discussed the biological factors in dosage design in which drug absorption was related to membrane transport mechanisms (736, 737). The absorption profiles of drugs were reported (738). In another paper the buccal absorption of basic drugs was applied as an *in vivo* model of passive drug transfer through lipid membranes (739). Reports on the absorption, excretion, and metabolism of the following compounds were made: dextroamphetamine, barbiturate, riboflavin-5′-phosphate, methyl anthranilate, pentaerythritol tetranitrate, methyridine, haloperidol, propranolol, 5-methyl pyrazote-3-carboxylic acid, alloferin, fenfluramine, dimethylsulfoxide, pilocarpine, and lidocaine (740–752). A review of drug and chemical metabolism outlines the fate and distribution of drugs (753).

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

Keyphrases

Pharmaceutics—1967 literature review
General pharmacy
Pharmaceutical technology
Equipment—pharmaceutical
Physical pharmacy
Pharmaceutical aspects—antibiotics, radiopharmaceuticals
Biopharmaceutics

Research Articles

Studies on the Mechanism of the Mannich Reaction

By W. LEWIS NOBLES* and N. D. POTTI

A study of the Mannich reaction has been carried out in which the importance of the nature of the amine component has been noted; with unsymmetrical bisamines, based on limited studies to date, the stronger base of the two amines involved in such a moiety appears to be always incorporated into the final Mannich product. Also, the importance of steric factors in the mechanism of the reaction has been noted.

FOR MORE THAN 60 years the Mannich reaction has been studied by several groups of workers, especially in the field of medicinal chemistry, primarily because of its synthetic utility and the favorable pharmacological properties of the Mannich bases and their derivatives. The mechanism of this reaction has been the subject of considerable discussion (1–13). Yet, thus far, no single mechanism which will account for all the experimental facts has been suggested.

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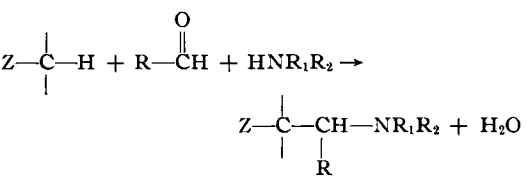
The reaction in its most generalized form may be represented as follows:



Several investigators (2, 5, 7, 14, 15) have indicated the possibility of considering a methylenebisamine as the most probable intermediate under normal reactions. A quasi-six-membered hydrogen-bonded transition state has been offered, in the case of the Mannich reaction with phenols as a plausible mechanism for the selective