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REVIEW ARTICLE

Tableting Research and Technology

JACK COOPER[A] and JOHN E. REES

Keyphrases ☐ Tableting research and technology—review ☐ Excipients, tablet formulation—review of active drug substance, diluents, binders, glidants, lubricants, disintegrants, colorants, coating materials, surfactants ☐ Processing of tablets—review of particle-size reduction, mixing, granulating, drying, compressing, coating ☐ Biopharmaceutics—general aspects, tablet timed release, dissolution rates, review ☐ Quality control, tablets—review of drug content, organoleptic properties, weight variation, disintegration test, mechanical strength, stability

CONTENTS

Essentially following an industrial research perspective, a review monograph by Cooper (1) attempted to bridge the gap between the fundamental principles involved in tablet research and development and the evolution of technological advances in the pharmaceutical industry through modern process research. The majority of studies on pharmaceutical materials, formulation, processing, quality standards, and biopharmaceutics selected and surveyed in the monograph covered the 5-year period from 1964 to 1968. An expansion of tablet research activity in university and industrial laboratories in terms of quantity as well as a modest elevation of quality at the technological level has prompted us to continue in this direction and review the international literature for the 1969–1971 period. In essence, it is hoped that these two reviews will provide a reasonable approximation of the current, overall state of the "art."

Useful introductory sections on various phases of tablet technology in chapters of a recent edition of a textbook include those on Tablets by King (2), Coating by Schroeter (3), and Prolonged-Action by Ballard and Nelson (4). In another book, probably the first com-

prehensive text directed toward industrial pharmacists and students of industrial pharmacy, chapters of importance are those on Drying by Lieberman and Rankell (5), Mixing by Rippie (6), Milling by Parrott (7), Compression by Shotton and Hersey (8), Coating by Ellis *et al.* (9), Biopharmaceutics by Gibaldi (10), Design and Evaluation of Tablets by Gunsel *et al.* (11), Sustained-Release Dosage Forms by Eriksen (12), and Pilot Plant Scale-Up Techniques by Michelson (13). A monograph by Martin (14) on the formulation of aspirin is notable for an extensive review of the biopharmaceutic aspects of the most frequently administered tablet in the world.

The latest revisions of the USP (15) and NF (16) describe new test methods and specifications important to the control of tablet quality. Of these, the dissolution rate test has stimulated the interest of research pharmacists to the greatest extent. The 1969 Addendum (p. 92) to the British Pharmacopoeia requires uncoated tablets to conform to a stated diameter except for slight differences due to normal punch and die wear. Burlinson (17) stated that: "this standardization in official compendia was an important step in resolving the problem of manufacturers supplying tablets of identical strength but differing diameters." Within the usual physiological requirements for swallowing tablets, it is difficult to see what this standard has to do with the quality of tablets. As will be shown later in this review, some investigators express the view that the drug–excipient ratio can be a significant biopharmaceutic parameter. The designation "slow tablets" was adopted in the 1971 Addendum to the British Pharmacopoeia 1968 (18) for the generic description of tablets formulated to prolong or delay the release of the medicament. This Addendum includes two monographs—Slow Lithium Carbonate Tablets and Slow Orphenadrine Citrate Tablets—for preparations of this type which include a solution rate test based on a modified BP disintegration apparatus.

FORMULATION

General Principles—Recognition of the risk that "inert" excipients in tablet compositions might lead to undesirable effects upon the stability or bioavailability of the drug has led formulators to exercise caution in the selection and inclusion of such additives. This selectivity requires a greater understanding of the inherent physical and chemical properties of excipients so that within the framework of processing necessities there will be no interference with the ultimate quality of the finished product.

Omitting colorants, flavors, and surfactants, Keller (19) selected a group of important tablet excipients and reviewed those physical, chemical, and biological characteristics which, in his view, should be required in specifications. He proposed that such information collected in a codex of excipients would be of value to formulators. Kornblum (20) discussed methods for preformulation screening of drugs and excipients that would facilitate optimal design of solid dosage forms. A key element in his program involves the use of solid-state and aqueous systems, but he warned that misleading predictions can result from solid-state studies conducted at abnormally high temperatures. Since the most common degradation mechanisms in solid systems depend upon the presence of liquid films, excipients such as surfactants that cause solubilization should be avoided in the presence of relatively unstable drugs. Other additives, such as buffering salts that might react with a drug to form soluble compounds, fall into the same category of potential accelerators of degradation.

From an analytical perspective, Ehrhardt and Sucker (21) devised simple and rapid methods for the identification of a number of excipients used in tablets and tablet coatings; Setnikar (22) reviewed a variety of formulation factors affecting the biological activity of drugs. Fonner *et al.* (23) generated a strong case for the use of optimization techniques in pharmaceutical research as a means of reducing development costs and of achieving optimal product or process design and quality assurance of final product. Structured as constrained optimization problems, these are then solved by the Lagrangian method of optimization. The pharmaceutical problem selected as an example involved the location of binder and disintegrant levels that served to optimize the physical properties and drug availability in a model tablet formulation. The drug chosen was phenylpropanolamine, and the primary parameters measured were tablet hardness, friability, volume, *in vitro* release rate, and urinary excretion rate in man. Practice with optimization techniques will at least serve to keep in sharp focus the complex interplay of materials and processes involved in tableting technology.

Active Drug Substances—Although considerable evidence exists that the physical properties of an active drug substance can exert significant influence upon processing and tablet quality, research activity along these lines during the period under review has been essentially limited to reports on dissolution rates and stability. These topics are covered in other sections of this report. Rieckmann (24) discussed some of the efforts made to relate therapeutic effect with the particle-size characteristics of such drugs as spironolactone, chloramphenicol, and nitrofurantoin in tablets and other dosage forms. He explained the fallacy of the oversimplified statements concerning micronization, rapid dissolution, and good absorption. After studying two forms of aspirin possessing different thermodynamic activity, Mitchell and Saville (25) concluded that the intrinsic dissolution rate may be a superior method of discriminating between mixtures of polymorphic drugs than are such analytical techniques as IR spectrophotometry or X-ray diffraction. This interpretation is only one element in a controversy related to the polymorphism of aspirin in which Tawashi (26), Summers *et al.* (27), and Mulley *et al.* (28) also participated.

Diluents—A somewhat cursory evaluation of a microcrystalline dextrose containing small quantities of higher molecular weight saccharides[1] as an excipient for tablets was reported by Bergman *et al.* (29). Some technological advantages of the free-flowing material as a diluent-binder were presented, but no measurements of compaction or ejection forces were undertaken and no

[1] Celutab, Penick and Ford Ltd., Cedar Rapids, Iowa.

studies were made to assess segregation tendencies—a major problem in the direct compression of many drug substances. Henderson and Bruno (30) compared the physical properties and direct compression characteristics of special lactose USP[2] and dextrose[1] with spray-dried lactose USP and anhydrous lactose USP. Special lactose USP represented a spray-dried form of lactose monohydrate processed in the form of white, free-flowing beads while the dextrose was processed in the form of aggregated, porous, crystalline beads. By using an instrumented rotary tablet press, compression and ejection forces were monitored and correlated with tablet hardness, friability, weight variation, and disintegration time. The results were interpreted by the authors as indicative of the superiority of the new diluents over the older lactose sugars. However, neither of the new materials was better in terms of physical stability of the tablets.

Manudhane *et al.* (31) investigated the properties of a special form of starch[3] for its potential as a diluent-binder in the direct compression of tablets. In spite of the free-flowing nature of this compressible starch, its fluidity was still not adequate for high speed compression of tablets. Additional lubricant was needed in the presence of as little as 5–10% of nonlubricated excipient such as spray-dried lactose. From the data presented, it is difficult to conclude that this material possesses particular advantages as a diluent-binder. Although better in this respect than starch USP, the latter may not be the best standard for comparison.

Recognizing that changes in crystal structure during spray drying could be responsible for the direct compression properties of spray-dried lactose, Fell and Newton (32) characterized several batches of this material. A polarimetric technique was used to distinguish between α- and β-lactose, while thermogravimetry was used to determine the proportion of α-lactose monohydrate. Three samples of commercial material contained only α-lactose monohydrate. By controlling the drying conditions in experimental production of spray-dried lactose, the proportion of each form could be varied. Another approach to the conversion of lactose and other materials to a directly compressible form by coating with microcrystalline cellulose was patented (33).

A claim for the use of calcium citrate as the major excipient in tablets has been allowed (34), as has been another that describes the formulation of a tablet which disintegrates so rapidly in even a small quantity of fluid that it can be administered rectally (35).

With respect to quantities of excipients handled in tablet processing, diluents probably represent the most important group and, consequently, must be considered in connection with bulk, solid handling properties. A factor of major importance, atmospheric relative humidity, was investigated by Eaves and Jones (36). They measured packing density and bed depth as variables influencing moisture uptake and, consequently, the tensile strength of a number of pharmaceutical materials.

[2] Beadlets, Foremost Dairies, Inc., San Francisco, Calif.
[3] Sta-Rx 1500 Starch, A. E. Staley Manufacturing Co., Decatur, Ill.

The physical properties of benzalkonium chloride are such that only an aqueous concentrate is commercially available. Seeking to develop a solid dosage form, Cadwallader and Quamar-Ul-Islam (37) selected urea as a diluent which, in combination with the germicide, could be tableted by direct compression. Based on IR spectral data, the authors deduced that the favorable tableting characteristics of the admixtures were due to adduct formation rather than to simple adsorption. Satisfactory tableting was very sensitive to compression pressure, and stability studies were run over too short a time for reaching firm conclusions. Accelerated stability studies were used by Ward *et al.* (38) to demonstrate the compatibility of mannitol with various classes of active drugs. Equilibrated samples of mannitol, lactose, dextrose, and sucrose in combination with oxytetracycline hydrochloride failed to demonstrate chemisorptive properties of the excipients. Tablet dissolution studies provided evidence for the necessity of investigating the effect of excipients upon drug release.

Although not experimenting directly with tablets, Hu *et al.* (39) investigated the interaction of isoniazid with magnesium oxide and lactose in the solid state by means of diffuse reflectance spectroscopy. This study represents an approach to preformulation research of particular significance to tableting technology. The application of this technique during the preliminary screening of potential interactions between drugs and excipients, or between excipients, can conceivably expedite this phase of product development. The authors were able to demonstrate both chemisorption and physical adsorption as interaction phenomena between isoniazid and magnesium oxide as well as to confirm the tendency of lactose to participate in the browning reaction.

In continuing studies with the diffuse reflectance technique, Lach and Bighley (40) tested solid–solid interactions of tetracycline, dicumarol (bishydroxycoumarin), and methantheline bromide with such excipients as magnesium trisilicate, tribasic calcium phosphate, and talc. At about the same time, McCallister *et al.* (41) reported similar studies of interactions as applied to metallic ion chelates of dicumarol (bishydroxycoumarin) and furosemide, but the biological significance of these interactions was suggested rather than demonstrated. The suggestions are rather strongly worded, as illustrated by the following sentences: "The importance of strong surface interactions pointed out here can not be overemphasized with respect to their effect on the therapeutic availability of furosemide. It is possible that these interactions could occur during the wet granulation process of tableting and in the compression of the tablet." It seems more reasonable to assume that there is very little that cannot be overemphasized by enthusiastic researchers.

Binders—The determination of the cohesiveness of powders is important in mixing, screening, and transporting materials in solids technology. It is even more important in providing the structural strength necessary in handling tablets and in the retention of their original geometric form. Pilpel (42) reviewed the fundamental principles involved in measuring the cohesiveness of powders. He described in detail a shear cell apparatus

for quantitative measurements and presented some data of pharmaceutical interest. In addition to a description of interparticulate forces, the author mentioned a few unsolved problems in powder technology.

Research on new cohesive agents as tablet excipients appears to be at a low point currently when judged by our search of the literature. Starch mucilage, 15%, and a copolymer of vinylpyrrolidone and vinyl acetate[4], 20%, in water–ethanol solution were investigated by Suren (43) as binders in a tablet formulation of amobarbital (amylobarbitone). Compression at different pressures was carried out on an instrumented eccentric press with digital readout. The tablets were then tested for hardness, weight variation, disintegration time, and dissolution rate. Those made with the copolymer binder were reported to be superior in rate of dissolution of the drug and in manufacturing properties.

Glidants—As emphasized by Cooper (1), the uniform flow of particulate mixtures from hoppers to feed frames to dies of tablet presses is an important processing requirement, amplified in urgency by recent regulatory implementation of unit dose specifications. In addition to papers dealing with glidants, this section also covers investigations involving the measurement of flow properties.

Factors involved in the flow of particulate materials from hoppers, including methods for avoiding nonmass flow conditions when mixtures have a tendency to segregate, were discussed by Miles (44). Since many pharmaceutical granulations fall into this category, the design of hoppers specific to individual products may not be an unrealistic objective in process optimization. Unfortunately, although considerable progress has been made with methods for designing a hopper for mass flow, no generalized equation has yet been derived for predicting the rate of flow from such a hopper. Methods for controlling the discharge rate from hoppers such as aeration, vacuum discharge, and screw discharge are included in this review. Jyotaki *et al.* (45) described an analysis of flow behavior for granular material flowing out of a hopper which was supported by two cantilever arms fixed to the side walls. This arrangement allowed the hopper to vibrate continually under the influence of momentum changes as material flowed out.

According to Suzuki and Tanaka (46), the flow of particles through a hopper is too complicated to conclude that the powder throughout the whole hopper behaves as a fluid or as a solid. In the outlet region the fluid analogy may hold; the authors, therefore, measured the flow properties of several powders along a two-dimensional rectangular channel. Their analysis showed how data on individual powders can be interpreted, but experimental data are required for each new material. Since only single powders were used in these experiments, it is not clear whether the fluid dynamic theory can be applied to the far more complex pharmaceutical granulations.

Using a radio "pill" containing a pressure-sensitive diaphragm, Perry and Jangda (47) were able to carry out internal pressure measurements in model bunkers (hoppers) of cylindrical shape with conical bottoms of varying cone angles. An additional hopper was rectangular in shape with a chisel type of outlet. The data indicated the evolution of high dynamic pressures in mass flow hoppers with conical bottoms at the transition point. The chisel-shaped outlet permitted mass flow without the development of such high dynamic wall pressures. Start/stop operations did not alter the pressure patterns when compared to uninterrupted flow conditions. Although hoppers that do not give mass flow have lower dynamic pressures, their flow patterns are neither predictable nor reproducible. These experiments may be of value in the design of large hoppers feeding high speed tablet presses.

Based upon results obtained with a shear cell, two methods for characterizing the flow of powders have been suggested, namely, the flow factor and the shear index. Harwood (48), using data from other workers and his own experiments, stated that both the shear index and flow factor are in agreement in predicting increased flow properties with increased bulk density. A powder, however, will not be more free flowing when compacted than it is at its normal bulk density. A flowmeter designed to measure the relative flow behavior of particulate matter including pharmaceuticals was described in a patent claim (49). Intended for use as a development and quality control instrument, this apparatus measures the mass flow rate of material under gravity from a vibrating hopper into a simulated open-ended die cavity.

Endeavoring to develop a mechanistic interpretation of the resistance to shear of powder beds, Hiestand and Wilcox (50) employed a variety of procedures involving plastic deformation at regions of true contact and such structural changes in the powder bed as consolidation or dilation, blockage to resist unidirectional motion, and particle orientation. Five examples of pharmaceutical substances were selected from the large number tested to illustrate the variety of results obtained. Parameters other than friction coefficient were described as indicative of the flowability of a powder. Quantitative correlations remain to be established.

In assessing the flow properties of solid, granular material, Scarlett and Todd (51) suggested that it is essential to relate the bulk properties of a material to the fundamental properties of the system, which in terms of geometry means the size distribution and shape of the particles. Their experiments were designed to show how the porosity of a bed of particles at the time the material is flowing can be related to the shape and size of the particles. Using a special split ring, annular shear cell, and load assembly, these investigators were able to measure the shear stress, dilation, and critical porosity of free-flowing sand of three different size ranges. The data obtained showed that it is possible to relate the critical porosity of a random, isotropic bed of particles to a random chord size distribution of the bed.

The basic properties of powders that are critical to the behavior of particulate solids in bulk handling equipment were reviewed by Carr (52). Methods for measuring these parameters were discussed, with particular reference to factors influencing bulk flow properties. Attempting to explain why so much activity has cen-

[4] Luviskol VA 64.

tered recently around "such a common thing as a powder," Kaye (53) also reviewed the characteristics of powder systems. Interestingly, he stated that too often the powder technologist does not know what information he requires to describe his powder system. There are certainly many examples of this problem in the pharmaceutical development operation. To characterize a powder with respect to dissolution behavior, surface area is a critical parameter; but other properties, such as agglomeration and wettability, may be equally important. On the other hand, it must be extremely difficult for the pharmaceutical technologist to define what information he needs to characterize a powder with respect to its compression behavior. For such reasons as these, Kaye suggested that future developments in materials science depend on close cooperation between the technologist and the analyst in the search for meaningful methods of characterization.

Ahmad and Pilpel (54) investigated the flow of narrow particle-size fractions and combined size fractions of granular solids through horizontal orifices. The equation used to describe the flow behavior was applicable to materials differing in shape, density, and surface characteristics and to mixtures of up to five different size fractions, in spite of the complicating effects of fines and segregation. Using seven representative materials differing considerably in their shape, rugosity, density, and frictional characteristics of particles, Harwood and Pilpel (55) developed a modified equation of flow for granular materials passing through a circular orifice. The equation was used to predict the flow of simple and binary systems, but the authors concluded that further work is necessary to establish the generality of the relation to granular pharmaceuticals.

From measurements of the angle of internal friction using a shear cell and from angle of repose measurements, Aoki and Suzuki (56) studied the net effects of particle shape on flow and packing properties of noncohesive granular solids. By eliminating the effect of the coefficient of interparticulate friction, the authors concluded that shearing resistance is a maximum for particles with a shape factor of about 0.7, defined as the ratio of the diameter of an inscribed sphere to that of a circumscribed sphere for the particle.

In a series of papers concerned with the flow properties of powders, Kristensen and Jensen (57) discussed the procedures used by previous authors to measure the angle of repose. For several different granular materials, the two-dimensional drained angle was reported to be the most suitable measurement. Consistent results were also obtained for the poured angle of repose independent of the size of the cone of powder. A correlation was shown to exist between these two parameters and the internal angle of friction in a rotating drum. It is generally assumed that tablet weight uniformity will be increased by improving the flow properties of granulations. In fact, the reverse effect may occur since good flow behavior may facilitate segregation of powders. Kristensen and Jensen (58) studied the glidant effect of talc concentrations between 0 and 10% in granulations having different size distributions. In two cases, 2–3% talc produced optimum granule flow properties, but little effect was found in the third granulation. With a granulation containing a large proportion of fines, talc adversely affected the flow behavior. In general, the results confirmed the opinion that the improvement of flow properties by a glidant was associated with better particle packing and, therefore, an increased bulk density. Similarly, when higher concentrations of talc impaired the flow, a decrease in the bulk density was observed.

In a subsequent study, Kristensen (59), using more careful control of experimental conditions, showed that segregation at various stages in the preparation of tablets was greatest with the best flowing granulations. The granulations that consisted of lactose–starch–gelatin granules mixed with ascorbic acid crystals and varying quantities of talc offered good possibilities for segregation to occur. It is valid to conclude that the homogeneity of a powder mix and its segregation tendency must be considered in the evaluation of a glidant and in the choice of glidant concentration for a tablet formulation. From studies using a shear cell, Kristensen (60) concluded that the flow factor is a constant for each powder specimen and can be used as a quality control measurement to define powder properties. Although such measurements are time consuming, the results were considered to provide more detailed information about flow properties than other methods currently available.

From studies of physical properties of crystalline and spray-dried lactose, Kristensen (61) concluded that the flow properties of tablet granulations have a negligible effect on tablet weight uniformity provided the granulations are free flowing. This can be assessed by measurements of particle-size distribution and packing properties of the granulations. A free-flowing granulation will possess a high poured bulk density and a small difference between poured and tapped density, with rapid equilibration of the tapped volume. To assess weight variation of lactose which could not be compressed to form a coherent tablet without other excipients, an eccentric tablet press was modified to permit collection of successive samples of uncompressed powder ejected from the die.

In analyzing the effect of glidants on the flowability of bulk particulate solids, Jones (62) distinguished between the optimization of flow properties by adding a glidant which is chemically dissimilar to the bulk powder and improving flow by the selection of an appropriate size distribution with the correct proportion of fines. Experimental results were discussed, and possible mechanisms of glidant action were summarized in terms of particle separation, antifriction, and antistatic effects.

Gstirner and Pick (63) determined the influence of hydrophilic and hydrophobic colloidal silica on the water uptake by several powders. The effect was largely dependent on changes in the unconsolidated bulk density produced by the additives, since water sorption was retarded in a closely packed powder. Ogawa *et al.* (64) found that the repose angle and bulk volume of potassium bicarbonate increased with increased moisture content, but this effect of moisture could be reduced by glidants such as silicic acid or magnesium stearate.

The influence of various parameters on the flow rate of sodium chloride and lactose granulations was investigated by Danish (65), using a flowmeter of original

design. The lactose granulation, because of greater surface rugosity, required a higher concentration of finer particles to produce a maximum flow rate than did sodium chloride. With equal concentrations of drug and lactose in a granulation, no significant effect on flow rate was observed. It is, of course, unlikely that this concentration relationship would exist for two drugs such as sulfadiazine and phenobarbital in a tablet composition. The author concluded from his experiments that a lubricant acts by reducing surface rugosity through adhesion to coarser particles and by reduction of van der Waals' forces through mechanical separation of individual particles.

Lubricants—Research activity on lubricants appears to be mainly directed toward the testing of new materials for their contribution to smooth operation of tablet presses or toward the methods for determining the effectiveness of lubricants. A broad review by Pilpel (66) included some information on the application of metal stearates as lubricants in the preparation of tablets. The mechanism of action of lubricant powders was studied by Miyaki *et al.* (67) using measurements of bulk density of powder mixes and observations on the electron microscope. Extremely rapid equilibration of apparent density occurred with 1% synthetic aluminum silicate or talc added to microcrystalline cellulose, corn starch, or dibasic calcium phosphate in a V-blender. On addition of calcium stearate, a much greater increase in apparent density occurred but an equilibrium condition was not reached even after 5000 revolutions of the mixer. The lubricating mechanism of talc and aluminum silicate was considered to be a diffusion or diffusion–adhesion process. With calcium stearate, the diffusion–adhesion effect was apparently followed by a transfer-coating phenomenon.

The disadvantages of adding hydrophobic lubricants such as magnesium stearate to tablets were considered by Ganderton (68), using air permeability and liquid penetration techniques. Increasing the lubricant concentration reduced the rate of aqueous penetration, and tablets containing lubricant showed greater variation than unlubricated tablets due to uneven distribution of hydrophobic material. This maldistribution was most evident with coarse granules. A more energetic mixing process ensured more uniform distribution and, therefore, greater resistance to penetration.

By compressing a standard granulation on an instrumented eccentric tablet press, Fuchs *et al.* (69) compared the lubricant effect of two polyethylene glycols and 21 low melting-point surfactants with that of magnesium stearate. A triester of orthophosphoric acid with tetraethylene glycol monocetyl ether[5] dispersed on corn starch was a better lubricant than magnesium stearate but resulted in even longer disintegration times. To ensure optimum lubricant effect with high tablet strength and low disintegration time, the best technique was shown to involve dispersion of the lubricant on lactose and subsequent micronization. A 0.2% concentration of surfactant was then sufficient and the best properties were shown by a defined mixture of glycerol mono- and distearates[6].

Although the concept was not new, Alpar *et al.* (70) presented additional evidence for the effectiveness of polytetrafluoroethylene as a lubricant for tablets containing spray-dried lactose. Reduction in die wall friction during compression and ejection of a 1% concentration was comparable with that for magnesium stearate; in contrast, polytetrafluoroethylene did not decrease the strength or disintegration rate of the tablets. This was attributed to the high yield value of polytetrafluoroethylene which prevents shear spreading. However, using the same polytetrafluoroethylene, La Manna and Shotton (71) found that, when applied to aspirin formulations at equivalent concentrations, the lubricant efficiency was inferior to that of magnesium stearate.

Using the now almost traditional ratio of lower punch force to upper punch force (R value) at an approximately constant applied compaction pressure as a measure of lubrication, Juslin and Krogerus (72) showed an increase in the lubricant efficiency of fatty acids and fatty alcohols as the carbon chain in the molecule increased to 18 atoms. The lubricants were sprayed on the granulations using a solution in chloroform. In most cases, despite variation in the punch forces with the number of tablets compressed in the die, the R value remained fairly constant; but results for dodecanol—a relatively poor lubricant—showed an effect analogous to that reported later by Rees and Shotton (73). The R value decreased progressively during compaction of successive tablets until the value was equal to that for an unlubricated granule. Although the effectiveness of hydrocarbons also increased with an increase in the carbon chain length, they were less effective lubricants, possibly due to a hydrodynamic rather than boundary lubrication mechanism. Similar ratings of lubricant effectiveness were obtained in comparisons involving the measurement of temperature at the lateral and upper surfaces of the tablets during compression (74) and by ejection force measurements (75). More recently, Juslin and Krogerus (76) reported the effects of the various lubricants on the mechanical strengths and disintegration times of the tablets.

In studying the effect of magnesium stearate concentration upon residual and ejection forces in an instrumented single-punch tablet press, Hanssen *et al.* (77) noted that, with increasing lubricant concentration, residual force diminished asymptotically to a limit value. At the same time, ejection force diminished at a slower rate, thereby increasing the difference between the two forces. The role of multiple-compression strokes in such experiments was emphasized as important to the determination of optimal lubricant concentration when an increased number of strokes will have no effect on frictional forces.

Using the flowmeter described in a previous paper (78), Danish and Parrott (79) found no appreciable change in the flow rate of a lactose granulation to which 50% of either phenobarbital, sulfadiazine, or sodium

[5] Hostaphat KW 340 N.

[6] Tegin.

salicylate had been added. The addition of 1% or less of the lubricants investigated—hydrogenated castor oil, glyceryl monostearate, polyethylene glycol 4000, and stearic acid—produced a maximum flow rate of sodium chloride and lactose granulations. For each of the four lubricants at a constant concentration, a maximum flow rate was obtained when the diameter of the lubricant particle was 0.023 cm.

Dines and Brown (80) obtained a patent for tablets completely soluble in water based upon a lubricating system consisting of oil particles coated with oil-insoluble, water-soluble, film-forming substances. According to the inventors, the ability of the coated lubricant particles to mix with dry materials renders the mixture sufficiently flowable for compression into water-soluble tablets. Other lubricants claimed in patents for soluble tablets include adipic acid (81) and fumaric acid (82). Another patent (83) described a technique whereby powders with poor flow properties can be converted into granular material suitable for compression, using stearic acid or other waxy compounds as the sole tableting adjuvant.

Disintegrants—Continuing their investigation of the mechanisms of starch as a tablet disintegrant, Lowenthal and Burris (84) designed a factorial experiment using aspirin with three disintegrants at four different concentrations and three levels of compaction pressure. A second factorial experiment was based upon only one disintegrant, corn starch, at four concentration levels with four different drugs and three levels of pressure. Parameters measured were mean pore diameter, porosity, and disintegration time. The complexity of the interaction of the variables in these experiments prevented the authors from expressing any broad generalizations concerning the effect of pressure, disintegrant or its concentration, and medicament upon mean pore diameter, porosity, and disintegration time of tablets. To industrial pharmacists accustomed to working with a large variety of drugs and excipients, this evidence of complexity is hardly surprising. With reference to the mechanism of starch as a tablet disintegrant, only a negative conclusion could be stated, namely, that the disintegrant effect of starch cannot be explained by its influence on mean pore diameter or porosity. A comparison by Fraser and Ganderton (85) of six types of starch incorporated in the granules of magnesium carbonate tablets wet granulated with acacia showed the rate of disruption in water to decrease in the following order of decreasing particle size: potato, maranta, wheat, corn, waxy corn, and rice. In most cases with these tablets, water uptake was more rapid and the rate was less variable than when starch was added externally to the granules.

In a study of the efficiency of a series of disintegrants in decreasing the disintegration time of lactose and aspirin tablets, Puech and Serrano (86) found it possible to establish a relationship between the activity of the disintegrant and its capacity to absorb water. Weak absorbers such as ethylcellulose had little effect; disintegrants absorbing up to 20% moisture (starch, methylcellulose, or alginic acid) lowered disintegration time; strong absorbers of moisture (sodium alginate, Carbopol 940, and carboxymethylcellulose) increased the time of disintegration greatly. Baichwal and Moghe (87) showed that hydrocellulose, prepared by hydrolysis of absorbent cotton, possesses disintegrant properties at a concentration of 10%. More rapid disintegration of tablets was observed when a 3:1 mixture of hydrocellulose and corn starch was used than if the individual disintegrants were used alone. This was attributed to a capillary action of the hydrocellulose coupled with a swelling of the starch. The influence of the solubility of drugs on the effectiveness of starch as a disintegrant was investigated by Shteingart *et al.* (88). Tablets of water-insoluble drugs prepared with starch disintegrated rapidly, whereas those containing water-soluble drugs disintegrated slowly due to the lowered sorption capacity of the starch.

The influence of the location of different soluble and insoluble disintegrants in tablet formulations prepared by wet and dry granulation techniques and containing a high proportion of active substance was investigated by Delonca *et al.* (89). Changes in disintegration time and tablet friability for each formulation were recorded. The authors concluded that more rapid disintegration was in most cases produced by the insoluble disintegrants regardless of the method of granulation. As might be expected, with a highly soluble, high dose, active substance, the type of disintegrant was unimportant.

By measuring the disintegration times for wet granulated tablets at a range of atmospheric pressures, Huettenrauch and Schmeiss (90) demonstrated an apparently linear relationship between these parameters which they attributed to the air pressure facilitating entry of the liquid disintegration medium into the tablet pore structure. With tablets that were partially evacuated prior to disintegration testing at ambient pressure, a reduction in the air pressure in the pores resulted in more rapid disintegration. Huettenrauch and Jacob (91) commented that, in spite of considerable evidence that capillary effects, wetting, and solubility are responsible for the disintegration of tablets, many investigators still attribute the phenomenon to a swelling of disintegrants. In controlled studies with different macromolecular disintegrants, the swelling conditions were varied by altering the polarity of the solvent using pyridine–water mixtures. Since liquid uptake and swelling tendencies of tablets were not related to the disintegration behavior, they concluded that disintegration is not due to the swelling of disintegrants. Subsequently, they showed (92) that although the swelling effect of a semisynthetic polysaccharide derivative[7] in a tablet decreased with increasing temperature, the disintegration effect increased slightly. This result was also presented as evidence that disintegration is not a swelling phenomenon.

On the other hand, in an attempt to elucidate the mechanism of disintegration by measuring the swelling properties of various substances, Delonca *et al.* (93) concluded that with certain materials such as carbomer[8], a swelling phenomenon may be responsible for the rupture of tablets.

[7] Sephadex.
[8] Carbopol 934.

Working with a tablet composition that was difficult to disintegrate in water, Hirata (94) evaluated several concentrations of crosslinked polyacrylic acid and crosslinked polymethylacrylic acid as disintegrants. The parameters studied included the effects of disintegrant concentration, compression force, and the presence of an organic salt and several inorganic salts on the equilibrium weight of tablets due to swelling. In the system studied, the rate of water uptake was indirectly related to the disintegration time. In a subsequent paper (95) the disintegrant properties of crosslinked acacia were compared with sulfonic acid (styrene base) ion-exchange resins[9] in calcium iodochlorhydroxyquinoline tablets. Except with these resins, a reduction in void space in the tablets increased the time of disintegration.

In an evaluation of five commercially available disintegrants, Khan and Rhodes (96) found sodium starch glycolate[10] and a cation-exchange resin[11] to be most effective for insoluble direct compression systems. The same authors (97) stated that with certain tablet formulations, increased consolidation under pressure can increase the rates of disintegration and dissolution. This was demonstrated for a system of dicalcium phosphate dihydrate containing magnesium stearate, with a cation-exchange resin as the disintegrant.

Following a series of tests of the physical properties of formaldehyde–casein[12], Selmeczi and Liptak (98) concluded that this substance fails to meet the definition of a universal disintegrant. When combined with other disintegrants, however, it may have some potential value in tablet formulation. A similar view was proposed by Sumegi and Kedvessy (99), who compared the disintegration time, hardness, and friability of a readily soluble and a poorly soluble drug formulation with either of two disintegrants. Formaldehyde–casein provided shorter disintegration time, and microcrystalline cellulose yielded tablets with superior mechanical properties.

Disintegrants for use in effervescent tablet formulations have attracted the attention of some investigators. In a German patent application (100), the claim was made that pure sodium dihydrogen citrate can be used as the sole acid component in combination with other usual excipients to produce formulations that need not be processed at low humidity and that are stable under tropical conditions if protected from condensed water. A Belgian patent (101) claimed that glutaric acid is superior to citric or tartaric acid in resistance to caking due to its lower hygroscopicity. A technique developed for treating the surface of acid crystals for use in effervescent tablet formulations appeared in a patent (102). A mixture of sodium carboxymethylcellulose and polyethylene was claimed to be an effective disintegrant in tablets prepared by direct compression (103).

Colorants—Because of previously reported interactions between polymers and dyes, Prillig (104) investigated the effect of a wide variety of colorants on the solubility characteristics of cellulose derivatives commonly used in the film coating of tablets. Both free films and coated tablets were prepared; test parameters included film solubility, tablet coating thickness, tablet disintegration time and dissolution rate, viscosity of dye–cellulose mixtures, and *in vivo* urinary excretion levels of riboflavin-containing, coated tablets. The results confirmed the influence of some dyes on the solubility of the cellulose polymers tested but without identifying a specific correlation with the chemical structure of the dye. Various theoretical explanations for such interactions were offered, but the results of the study pointed to the advisability of individual tests on each dye–polymer combination.

Kornblum and Lopez (105) selected fumed titanium dioxide as an adsorbate for the preparation of color lakes in view of the particle-size range and low content of soluble titanium salts of the fumed variety. In addition to the water-soluble dyes and titanium dioxide, the lake compositions also contained acidifying, binding, and surfactant materials. By spray drying the titanium slurry, the particle-size range was demonstrated to be between 1 and 10 μm. Suspensions of the color lakes in sucrose syrup were applied to rounded, rotating tablets in an automated coating system. Only 8–12 applications of the color suspension were needed to obtain maximum color tone and uniform color dispersion.

Coating Materials—With the exception of the area of polymeric film coating, research activity in coating materials for pharmaceutical purposes is to be found almost entirely in the patent literature, with much of that of minor scientific interest or value. For convenience in classification, this section is divided into the three common groups of coated tablets: sugar, enteric, and film.

Sugar—Pandula and Toth (106) studied a variety of sugar-coating formulations in order to select a composition providing optimal coating properties, friability, and dissolution rate. In one of a series of Japanese patents (107), the claim was made that, by using a mixture of water and a water-miscible solvent, a supersaturated sugar solution which is stable for a long period can be used for sugar coating. Another patent claim (108) stated that a sugar-coating formulation containing specific higher fatty acid esters of sucrose is suitable for tablets containing moisture-sensitive drugs. In earthquake-prone territory (109), the incorporation of short fibrous materials in sugar coatings will increase the resistance of the coated tablets to mechanical shock. The application of alternate layers of a material such as shellac during sugar coating of tablets was reported (110) to improve the appearance and stability of tablets. In a German patent (111), the claim was made that the use of silica in intermediate layers during sugar coating speeds up the process by reducing drying time.

Enteric—The design of enteric coatings, including a comprehensive discussion of appropriate excipients, was the subject of a review by Delporte (112). Enteric coatings should be resistant to gastric enzymes and pH conditions of 1.2–3.5 for up to 6 hr. The mistaken concept of an alkaline pH in the intestine was referred to, as was the short residence time of about 5 min. in the duodenum. The jejunum, where release from enteric-resistant forms should occur, was stated to be about pH 4–5. In this respect, materials such as copolymers of maleic anhydride are of particular value. The author

[9] Amberlite IR-120.
[10] Primogel.
[11] Potassium polacrilin, Amberlite IRP 88.
[12] Esma-Spreng.

stressed the importance of definitive *in vivo* confirmation of the efficiency of an enteric-coating formulation.

On the basis of *in vitro* dissolution studies, Froemming and Sandmann (113) recommended the use of cholic acid derivatives of active substances as enteric forms. The effect was attributed to the inclusion of the active substance in canal-shaped pores of the cholic acid, with *in vitro* release of the active substance occurring at pH 6–7 but not at pH 4–5. No indication of the stability of such cholic acid derivatives at low pH was given.

Film—An extensive review of pharmaceutical aspects of polymer science by Rhodes and Banker (114) included a section on polymer coating. The dissolution of an ethylene–maleic acid copolymer was investigated by Heyd *et al.* (115), using an immersion refractometer for polymer analysis. Solvent pH influenced the dissolution of the polymer through its effect on swelling and hydrated layer thickness. Powell and Banker (116) investigated the potential film-coating applications of poly(methyl vinyl ether–maleic anhydride) in the unesterified form. Water-soluble films could be obtained by mild humidity conditioning of the polymer in the solid state. Such partially converted films disintegrated in the stomach or proximal jejunum in 30–45 min. compared to 10–30 min. for the uncoated tablets. Without preconditioning, the poly(methyl vinyl ether–maleic anhydride) film systems possessed enteric properties dependent primarily upon exposure time to body moisture.

A study reported by Zatz and Knowles (117) was designed to determine the monomolecular film properties of cellulose acetate phthalate, cellulose acetate butyrate, and cellulose acetate stearate. When the subphase pH was raised from about 3 to 6.5, monolayers of cellulose acetate butyrate and cellulose acetate stearate remained unaffected whereas large changes in monolayer properties occurred with cellulose acetate phthalate. It could be inferred that neither cellulose acetate butyrate nor cellulose acetate stearate are capable of functioning as enteric-coating materials. The authors concluded that the utilization of polymer monolayers as a model for enteric and film coatings provides a rapid means for the evaluation of new polymers and polymer mixtures as coating materials.

In order not to prolong tablet disintegration in the digestive fluids, Kuriyama *et al.* (118) investigated the properties of combining single films to make a double-layer film. This was accomplished by forming together, with the aid of a solvent, two single films of equal thickness but of two different types. Water vapor permeability studies on the free films were conducted, and it was found that some double-layer films provided effective protection from moisture when the combined thickness of the layers was less than that of a single film. This phenomenon was interpreted as providing a means of obtaining moisture protection and rapid disintegration by a simple technique.

In a continuation of this study (119), the relationship between water vapor permeability and humidity was shown to depend not only upon the difference in vapor pressure between the higher and lower humidity sides of the test films but also upon the mean humidity conditions to which they were subjected. It will be interesting to see how this approach is applied to the technological requirements of coating tablets. Kildsig *et al.* (120) developed a theoretical equation justifying the graphical representation of vapor permeation data by the reciprocal of rate of water vapor permeation and film thickness. The equation permits calculation of the permeability coefficient of the film as the authors demonstrated with films of unplasticized methylhydroxypropoxyl ethers of cellulose cast from water and an organic solvent.

Lindberg (121) reported that with free films prepared with different viscosity grades of hydroxypropylcellulose and with films deposited from different solvents, there was no significant difference in the water vapor transmission. Various plasticizers and pigments also had no significant effect, but increasing the concentration of polyvinylpyrrolidone in the hydroxypropylcellulose film increased the permeability. Lindberg considered that no effect of the solvent system would be expected since the solvent had evaporated before the films were used. This opinion omits the possibility that the type of solvent might have some effect during film formation.

Using helium pycnometry, Dia *et al.* (122) found that with film-coated tablets the surface was less porous than with sugar-coated tablets. Their claim that the porosity of film coats is more reproducible is hardly justified on the basis of only two replicate batches of tablets. In a Japanese patent (123), a coating material derived from polyvinyl alcohol was described, which, although soluble in gastric fluid, was claimed to impart water-resistant properties to the tablet. A similar claim for a series of cellulose derivatives appeared in a German patent (124).

Surfactants—In a study of 32 different nonionic surfactants used in the preparation of effervescent vaginal tablets, Duchêne *et al.* (125) found the foaming power of the tablets to be related to the chemical structure of the surfactants rather than to their HLB values. There appears to be a direct relationship between the foaming power and the lipophilic part of the surfactant molecule. The foaming power is also dependent on the linkage between the hydrophilic and lipophilic elements of the surfactant, with an ether linkage yielding the best results. An *in vivo* test in dogs, with the aid of radiopaque tablets, showed diffusion to be directly dependent upon disintegration time. In another study, Duchêne *et al.* (126) reported that nonionic surfactants[13] increased the flowability of sulfanilamide granules and dissolution rate of the drug. The influence of these surfactants on tablets was more variable with respect to friability and disintegration time.

PROCESSING

General Principles—Although it is now recognized that the formulation design of dosage forms such as tablets can markedly affect the biological activity of the drug substance as well as the mechanical, physical, and chemical properties of the product, the closely related role of the manufacturing process is not so widely ap-

[13] Myrjs, Spans, and Tweens.

preciated. In view of the importance of the process, pilot plant and scale-up operations represent a critical stage in the development of a pharmaceutical product; yet there are few references to such investigations in the literature.

A technique termed "evolutionary operation," which could find application in optimizing pharmaceutical processes by systematic small changes in the operating conditions for successive investigatory batches, was reviewed by Ridgway (127). Although the example refers to laboratory scale and plant scale implementation of a semisolid mixing process, possible applications in tablet technology could include the selection of the optimum quantity of granulating liquid and mixing time for wet granulations or the most suitable time and temperature conditions in a fluidized bed.

An important factor, which must be controlled if the processing properties of a pharmaceutical dosage form are to be reproducible throughout the various stages of development and during production, is the standardization of the physical properties of the active substances and excipients and the intermediate products such as granules. With solid dosage forms, parameters to be controlled include the individual and bulk particulate properties of the materials. In this respect, much valuable information can be obtained from nonpharmaceutical disciplines. Numerous sponsored investigations in particle technology research in Britain were summarized by Heywood (128), with reference to official specifications for powder characteristics. Proposals were included for standardization of particle-size and particle-shape nomenclature to facilitate comparison of research results. Methods for controlling the size distribution and other properties of powders during manufacture were reviewed by Garrett and James (129), with specific reference to ceramic oxide fuel. Many of the concepts are equally relevant to pharmaceutical particulate materials for incorporation in tablets. In both cases, the powder properties must be dictated not simply by the ease of preparation of the powder but also by the subsequent processing requirements.

The bulk transfer of powdered or granulated material by various methods was reviewed by Ritschel (130). Schematic drawings illustrated three pneumatic and five mechanical types of equipment available. Adherence of particles to containers and to each other during storage and handling can be a serious problem; the various mechanisms involved in adhesion and agglomeration were surveyed by Pietsch (131), with particular reference to caking. Molecular interaction, van der Waals' forces, electrostatic forces, and the influence of moisture on the adhesion of powders were among the topics considered at an international colloquium (132). Electrostatic charges frequently cause problems in powder handling but, as pointed out by Kaeppel *et al.* (133), bipolar charges cannot be determined except by indirect assessment of changes in properties such as flow and bulk density. An ionization device to dissipate bipolar electrostatic charges was described.

In view of the important effect of particle shape on various processes, techniques for sorting particles by shape (134, 135) may find application in tablet development and production operations. The numerous sieves specified by 12 different pharmacopeias for the size analysis of powders were tabulated by Vialard-Goudou and Gimonet (136), with reference to the various arithmetic series on which the sieve sizes are based. An attempt by the International Standards Organization to standardize sieve sizes is reflected in the new editions of several pharmacopeias.

Ridgway and Hersey (137) surveyed over 40 studies relating powder technology to tablet manufacturing processes. Several of these investigations were concerned with the characterization of the initial powdered material. Reports in the field of pharmaceutical engineering in 1968 and 1969 were reviewed by Fowler (138, 139), with reference to particle-size measurement, size reduction, mixing, granulation, and solids handling.

Particle-Size Reduction—Comminution processes such as milling, crushing, and grinding play an important part in many tablet manufacturing operations. Reduced particle size may be important to ensure adequate mixing of drugs with excipients by increasing the number of particles per unit dose of an active substance. In the case of poorly soluble substances, size reduction may increase the dissolution rate by increasing the surface area. Dispersion of pigments and other particulate materials during mixing and granulating operations and in the preparation of sugar- and film-coating suspensions may also be facilitated by a milling process.

The capabilities of various comminuting machinery and the selection of a mill for a specific purpose were discussed in detail by Hiorns (140) in a survey of literature through 1970. The dependence on material properties such as hardness was considered with reference to methods for determining the crushability and grindability. In the grinding zone of a mill, the particle-size distribution is undergoing substantial change and little is known about the flow properties of granular material under such conditions. The strength of particles varies with size, larger ones generally being weaker; but since they are irregular in shape, the direction and magnitude of the force applied to each particle can only be stated in statistical terms. Hiorns explained that since there is no theory of the comminution operation that is firmly based on physical principles, the choice of equipment is usually based on experience coupled with empirical tests, depending on properties of the feed and the extent of size reduction required. Harley (141) attributed the scarcity of information about the unit operation of size reduction primarily to this empirical methodology on which the design of milling equipment continues to be based. In a review concerned with laboratory equipment and large-scale engineering machinery for numerous materials including pharmaceuticals, Harley predicted that although the operating principles are likely to remain unchanged, equipment will become available in the 1970's incorporating the results of recent research and development in grinding mechanisms.

Surveying the use of fluid-energy mills for micronization, McDonald (142) stressed that since the power consumption for size reduction increases as the product fineness increases, a product is usually ground only as fine as subsequent usage necessitates. Equipment design for ultrafine grinding was discussed; the advantages to the pharmaceutical industry were mentioned including

sterilization capability, relatively low product contamination, and ability to mix and mill two components simultaneously even when the proportion of one substance is low. The common problems of agglomeration and packing of material in a fluid-energy mill were not considered.

More recently, McDonald (143) discussed process equipment for grinding, with particular reference to the pharmaceutical industry. An interesting development is a mill that grinds samples under liquid nitrogen and, therefore, can be used for milling certain problematic materials. Size reduction was reviewed from a pharmaceutical standpoint by Ritschel (144), with an explanation of the possible objectives, a summary of the various theories, and a discussion of relevant material properties. The article included a tabulation of appropriate processes and equipment for size reduction of different types of material to specified particle sizes.

Niediek (145) reported extensive studies on the size reduction of crystal sugar. Impact milling and crushing between plates and rollers were compared in terms of changes in size distributions, fracture tendency, energy required, creation of new surfaces, and formation of agglomerates. Between 20 and 100° temperature had no apparent influence on the milling process. A minimum speed of impact was demonstrated, below which no appreciable size reduction occurred and which depended on the size of the original particles. At the point of impact, each particle produced an agglomerate of fine particles, the agglomerate size depending on the impact velocity and the initial particle size. Niediek (145) stated that to define the capability of a milling procedure, the necessary energy to reduce the size of a single particle should be given and not the specific surface energy of the material as is so often quoted. The former value is expressed as the increase in surface area per unit of energy input and was about twice as high with crushing operations than with impact milling. The frictional conditions in a roll mill tended to reduce the formation of agglomerates.

In exploring the kinetics of size reduction, Berg and Avis (146) used a ball mill to comminute sodium chloride crystals, followed by microscopic examination of particle shape, agglomeration, and general appearance. Sequentially, the polycrystalline material first breaks up into its constituent crystals, followed by cleavage of the single crystals into thin platelets which are no longer exposed to shear forces for additional cleavage. With additional milling, the platelets break to a certain size as expected from a stress analysis; from then on, only surface abrasion occurs. Increased surface activity resulting from this abrasion produces agglomerates but, since these are also subject to comminution, only those nearest the shape of a sphere tend to survive.

The effect of time on product size distribution during batch grinding can be represented by a modified first-order kinetic decay of oversize material. Harris and Chakravarti (147) presented data for several materials and milling conditions which support this theory and which show that, in many cases, measurements during the early stages of the process may be extrapolated to predict the size reduction after extended grinding times. Presentation of particle-size distributions and kinetic data for comminution, using log *versus* log and semilogarithmic (*i.e.*, fraction remaining *versus* time) graphical plots, respectively, frequently results in crowding of the data (in the first case, above 50% undersize; in the second example, during the early stages of comminution). Harris (148) described a chart which permits graphical presentation of such data without this kind of congestion.

Mixing—Despite the critical importance of the mixing operation in the preparation of pharmaceutical dosage forms, the literature contains few reports by pharmaceutical scientists relating to the complex process of solids blending. In view of the highly potent, low dose substances that are becoming the rule rather than the exception in pharmaceutical practice, it is highly unlikely that this dearth of information reflects a situation where no problems exist. Fortunately, the mixing process is also important to other industries and there have been a number of useful investigations of the process and equipment by chemical engineers and others.

A thorough and critical review of solids mixing by Fan *et al.* (149) is of particular interest to development pharmacists concerned with the problem of content uniformity in tablets. The various criteria that have been proposed to assess the degree of mixedness were summarized in a table which also listed the materials and types of mixers used by the various investigators. The numerous parameters involved were discussed in terms of the material characteristics, mixing equipment, operating conditions, and sampling procedures. With respect to the simulation of solids mixing processes, the authors recommended Monte Carlo simulation techniques which involve sampling from statistical distributions to approximate the real physical phenomena without reference to the actual physical systems. Covering about 200 relatively recent investigations in clear concise language, the review represents required reading by all tablet technologists. Owing to the large number of products that are processed as relatively small batches in most pharmaceutical manufacturing operations, it is common practice to expect a single type of mixer to be an effective solids blender for several very different mixing processes.

In 1970, Miles and Schofield (150) reviewed the many factors that must be considered when selecting a suitable solids mixer including particle size and shape, flow properties, segregation tendency, size reduction, and moisture content of the materials. A simple test for crude assessment of strong segregation tendency was described which, although not sufficiently discriminating from a pharmaceutical point of view, may be useful in preliminary formulation trials. In view of widespread use in the pharmaceutical industry of tumbling mixers such as double cone and V-blenders, it is important to note that such equipment is likely to cause segregation with free-flowing powders having a wide size or density difference between components (151). Vertical screw mixers are claimed to be more suitable for segregating materials owing to the predominant role of the convective mechanism. Several other reviews of the mixing process (152) and available mixing equipment (153, 154) appeared, including a description of some new mixer designs (155).

In an interesting study of seven mixers, including the air (fluidized-bed), double-cone, and rotating-cube types common in the pharmaceutical industry, Miles and Schofield (156) determined the rate of mixing at the optimum mixing conditions for each mixer. For the relatively simple, two-component, nonsegregating, free-flowing system of particles of uniform density, size, and shape, the air mixer gave the highest output of well-mixed material. However, the nearest approach to a random mixture was obtained with a rotating drum fitted with a simple baffle. The authors were careful to point out that the same conclusions relating to mixing efficiency would not necessarily apply to cohesive or segregating materials. Batch mixing of powders that tend to segregate is difficult and often leads to an unsatisfactory intermediate product being supplied to the next processing stage. Williams and Rahman (157) commented that continuous mixing, with the elimination of intermediate storage and handling, should be considered in such cases. Approaches to the problem of continuous mixing were reviewed, and the performance of a simple continuous mixer was studied extensively under various experimental conditions.

An alternative process, which avoids the potential problems of demixing during material-transfer operations, involves the use of a fluid-bed spray granulator for carrying out the mixing, granulating, and drying operations without unloading the powder mix. Thurn *et al.* (158) evaluated the efficiency of this process for mixing three separate forms of a barbiturate with lactose. Theoretically expected values of mixedness, expressed as relative standard deviations for a series of random samples, were not always obtained, and the reasons for this were discussed. The authors recognized the need for further experiments before proposing any general conclusions.

The idealized study by Bagster and Bridgwater (159) of factors involved in the two-dimensional flow of noncohesive granular material over a moving blade may improve the understanding of the behavior of material in process equipment such as a planetary mixer. The presence of a substantial zone of material that is stagnant with respect to the blade was demonstrated, although surprisingly this region is not immediately next to the blade.

In a study of the mixing of superimposed powder layers flowing down a chute, Ridgway and Rupp (160) showed that the amount of mixing decreased with decreasing sphericity of particles, presumably because angularity causes the bed to resist shear. Reducing the particle size of the upper layer first increased the mixing rate but then introduced a segregation tendency. The authors considered that this type of study is applicable to conditions in a rotary mixer, in which particles flow down the inclined face of the powder charge, and possibly to the flow of material in the hopper and on the die-table of a rotary tablet press, but no correlation was attempted. The mechanism of segregation and blending of particles flowing out of a mass-flow hopper was analyzed theoretically by Shinohara *et al.* (161) for a binary mixture.

Even if the bulk motion of material in a mixer is periodic and regular, the motion of individual particles is random due to collision between particles and with the container wall. A mathematical consideration of the mixing process must, therefore, involve a statistical treatment such as that developed by Inoue and Yamaguchi (162). The results of an ideal mixing process using colored glass balls in a two-dimensional V-blender were shown to agree well with the digital simulation. Hogg *et al.* (163) developed a quantitative theory to describe mixing in particulate systems in which one component is present only as a "trace" quantity. Theoretical predictions agreed closely with experimental data using materials of similar densities, size, and shape, with 1.64% of the minor component—a relatively large proportion by pharmaceutical standards.

Since, in practice, particles generally possess nonuniform physical properties, the mixing process rarely reaches a state of randomness. Williams (164) examined theoretically a nonrandom binary mixture and derived an expression for the variance of the composition of samples drawn from the mixture. When the variance based on a given sample size is determined experimentally, it becomes possible to predict the variance for a different sample size. In addition, an index of mixing which is independent of sample size is obtained. Further development of this concept should be of value in assessing the efficiency of pharmaceutical mixing operations. From experiments with free-flowing materials in a drum mixer, Lloyd *et al.* (165) confirmed that the concept of a random mix is only valid for particles of the same size. A pseudorandomized system can be obtained for particles of different sizes, provided the speed of rotation of the mixer reflects the maximum porosity of the individual components.

Other studies assessed the influence of moisture (166) and the role of mixing aids (167) on the mixing efficiency in binary powder systems.

Although the mixing studies and theoretical treatments that deal with free-flowing uniform materials represent important attempts to define the process of solids mixing more fundamentally, most pharmaceutical mixing operations involve cohesive materials with a range of particle sizes, shapes, and densities. Okada *et al.* (168) studied the early stages of mixing of cohesive pharmaceutical powders in a V-blender. They found that the circulating flow of particles which is observed with noncohesive materials did not occur. By sampling at specified positions, they found that when the mixer was charged with the minor component at the center of the upper surface of the major component, more rapid distribution occurred than if the minor component was introduced first at the apex of the inverted V-blender.

Mixing problems associated with the cohesiveness of minor and major components in two-component systems were investigated by Shotton and Orr (169) using a Lodige-Morton mixer. A free-flowing major component such as heavy magnesium carbonate may facilitate distribution of the minor component by causing dispersion of agglomerates due to shear. Electron microscopy and other techniques were used by Travers and White (170) to show that indentations and irregularities on a crystalline diluent can act as adsorption

sites for a micronized powder, thus reducing segregation tendencies in a powder mix.

Problems associated with the pharmaceutical mixing of solids were surveyed by Polderman and de Blaey (171), with reference to the content uniformity requirements for the final dosage form.

Butters (151) stated that the lack of satisfactory techniques for removal and analysis of samples has reduced confidence in much of the experimental work on solids mixing discussed in the literature. A review by Hersey (172) on sampling and homogeneity of powder mixtures is of particular interest from the point of view of how best to assess the degree of homogeneity. An interesting, though not always feasible, approach which avoids mixing two active substances in the same granulation is the use of "proportionalization" as exemplified by multilayer or cored tablets. In these cases the variability in the ratio of the two substances tends to be reduced, provided the weight ratio of the two granulations is correct. The dosage uniformity of each component still is regulated by the homogeneity of the respective granulations, but this should be improved since the proportion of each component in the granulation in which it appears is higher. In a critical evaluation of procedures for powder sampling, Allen and Khan (173) demonstrated that the use of a spinning riffler was far superior to other techniques and that mixed or unmixed powders can be sampled equally efficiently.

Granulating—For several reasons, it may be necessary to granulate powdered materials prior to tablet compression. A decrease in the quantity of fine powder reduces cross-contamination and machine problems due to dust, and improved flow properties increase the uniformity of the feed rate to the punches and dies, thus improving tablet weight uniformity. An important advantage, omitted by Ritschel (174) in a review of the size enlargement unit operation, may be the increased content uniformity of drugs and excipients present in small quantities, since segregation and demixing tendencies are reduced by fixing the particulate components with respect to one another.

A four-part series by Ries (175–178) summarized the objectives of granulation and established a classification of machines and processes. Numerous photographs and schematic drawings illustrated the wide range of equipment and the shape of the products produced by them. Although the text was not directed toward the pharmaceutical industry, the author's exhaustive analysis provided possibilities for potential applications in the production of solid dosage forms.

Reviews concerned specifically with pharmaceutical granulation include an article by Pilpel (179), which also considered processes such as bowl and dish granulation, spray drying, and fluidized-bed principles; surveys by Ritschel (174, 180) covered spray granulation and briefly mentioned extrusion techniques for thermoplastic materials. Pietsch (181) compared wet and dry pharmaceutical granulation techniques and the possible bonding mechanisms involved. Fast drying of a wet granulation in which the active substance is soluble in the granulating liquid produces a fine crystal structure between the undissolved particles. This produces extremely strong granules, but the dissolution rate of the aggregates may be prolonged compared with a granule that is dried slowly. It is possible that this effect discussed by Pietsch could yield differences in the mechanical and biopharmaceutical properties of granules dried conventionally and, for example, those dried in a fluidized bed. Numerous advantages of dry granulation by roll compaction were discussed. Although Pietsch claimed that a disadvantage of wet granulation is that crystal growth (*e.g.*, of micronized material) cannot be reliably eliminated, it is also possible that dry granulations have an adverse effect on the dissolution behavior of a substance due to agglomeration. An extremely thorough review of the principles and technical applications of roll-type compacting machines by Pietsch (182) is particularly valuable in demonstrating the mechanical design of the rolls that form the shape of the compact. The variety of shapes available is astonishing but not necessarily of importance for pharmaceutical applications since the compaction step is generally followed by comminution and compression on a standard rotary tablet press. In a compactor described by Zschoche (183), the smooth rolls are in a vertical position while the powdered material is fed horizontally by screws. The author found improvements in flowthrough rate using compaction with horizontal flow as compared to the common vertical flow compactors.

Selmeczi *et al.* (184) studied the pressure dependence of several physical properties of tablets prepared with similar compositions but using different granulation techniques. Wet granulated tablets were most resistant to fracture and attrition and possessed longer disintegration times than direct compression formulations or those prepared by dry granulation using slugging. The slugged composition produced tablets with the worst mechanical properties.

Following up earlier reports on the advantages of the vacuum tumbler dryer, Goodhart *et al.* (185) obtained operating data during granulation using a 1 cu. ft. model containing an intensifier bar for the dispersion of liquids. In addition to the evaluation of mixing and drying rates, a series of formulations was prepared and compressed on an instrumented rotary tablet press. Various properties of the tablets were determined. On the basis of the results obtained with this well-organized process study, the authors concluded that the vacuum tumbler is a satisfactory technique for processing some tablet formulations. The efficiency of granule formation when utilizing the fluidized-bed system is dependent upon the formulation introduced into the apparatus and the operational variables associated with the process. Investigating the latter variables, Davies and Gloor (186) concluded that enhancement of the penetrability of the solids by increasing the rate of addition of the granulating solution brings about an increase in average granule size, a decrease in bulk density, and a less friable and more free-flowing granulation. Increased efficiency of the binder solution is also obtained by decreasing either the binary nozzle air pressure or the inlet air temperature during the granulation cycle. The fluid-bed spray granulator used had a maximum capacity of 25 kg., but the results described were based on 10-kg. batches. Whether similar results could be obtained with the larger 60–

120-kg. units operating closer to maximum capacity remains to be determined.

From measurements of the pressure on the wall of a rotary granulator, Toyoshima *et al.* (187) studied the effect of the amount of binder on the wet granulation process. The results were correlated with the strength and other properties of the granules formed. The process of extrusion granulation of a simple binary system of calcium carbonate and water was investigated by Mitsui (188) in terms of the effect of water content and molding pressure on the degree of consolidation and the breaking strength. With both parameters, a critical point, C_1, was observed at the conversion of pendular moisture to the funicular condition; a second point, C_2, was observed during the funicular stage, above which further increase in liquid content decreased the breaking strength. The existence of these critical points was confirmed by an air permeability technique. With various granulating solutions, the same type of effect was observed (189); the amounts of liquid to give the critical points C_1 and C_2 were 30 and 70%, respectively. An increase in the liquid viscosity or surface tension increased the breaking strength of these mixed systems. Since this increase in strength was found to decrease the rate of extrusion of material during granulation, the addition of a surfactant during extrusion granulation was considered advantageous.

Solid, spherical, free-flowing granules with low friability can be prepared by spheronization of extruded pellets of wet granulated material. Suitable process equipment was described (190, 191), consisting basically of a horizontal spinning plate at the base of a stationary cylinder. The importance of controlling the degree of wetting and the solvent content was stressed, and example formulations were quoted (190). Other critical factors include the temperature, plasticity, and adhesive properties of the wet mass (191). Several alternative versions of equipment based on this design were described by Fujii *et al.* (192).

In a controlled study of the granulation process using a horizontal rotating drum, Butensky and Hyman (193) utilized various sizes of glass spheres; they were selected because, being insoluble, they did not influence the granulation mechanism. An interesting technique was used involving gelation of the granulating liquid after a predetermined time so that the "drying" stage did not alter the size distribution resulting from the nucleation and growth stages of granulation. A very rapid nucleation stage was observed, and the granule-size distribution depended only on the initial particle size and on the amount of granulating liquid, not on the process time, drum speed, nor drum loading. A proposed model, which fitted the experimental data well, relates the mean granule size to the amount of granulating liquid under conditions at which the amount of liquid is not sufficient to produce granule growth after the initial nucleation.

A technique described as "microgranulation," which renders a powder suitable for tableting with only minor changes in particle size was discussed by de Jong (194). It is thought that in the presence of the relatively small quantity of granulating liquid used, the particles become coated by a thin film of binder which reduces interparticulate attraction and yields a free-flowing powder which can be compressed to form a coherent tablet. This procedure has been used to make hydrophobic substances hydrophilic and thus dispersible in water.

Using four different binders, Cox and Mulders (195) compared the dissolution rate of phenacetin from tablets and granules prepared by conventional wet granulation, pan granulation, and the microgranulation technique which involves no wet screening. The small-scale sieving techniques employed were reported to produce a similar result to large-scale processing, although no evidence was given. With milled drug in the conventional granulation, *lower* dissolution rates were observed than for unmilled drug; in the microgranulate, the use of milled drug produced the more usual increase in dissolution rate. Microgranulates of milled drug produced the highest *in vitro* dissolution, and an important factor appeared to be the fine granule size. The results underline the importance of standardizing particle size and granulation method if the release rate of a drug from granulations or tablets is to be reproducible. It is apparent that special care is necessary when formulating finely powdered drugs, if the advantage of the small particle size is to be retained. Changes in experimental conditions between the initial study, to select a suitable granulating agent, and the main investigation produced conflicting results for dissolution behavior, but these differences were not explained by the authors.

The effect of granulating agents on the physical stability of hydrochlorothiazide tablets was investigated by Alam and Parrott (196), using changes in hardness, disintegration, and dissolution as parameters. Acacia, starch, and polyvinylpyrrolidone in solution were the wet granulating agents used, with compression on a single-punch press without pressure control. Tablets were stored at 50 and 80° for 14 days, at 37° for 4 weeks, and at room temperature for 12 months. Only with acacia were the changes in hardness, disintegration time, and dissolution rate considered to be significant. The effect of humidity on these physical properties was not investigated, nor is it at all certain that the changes noted with acacia would be biologically significant.

A series of papers dealt fundamentally with the effects of granulation and compression on the relation between pore structure of tablets and penetration by liquids. In the first paper, by Ganderton (68), a decrease in granule size was shown to reduce air permeability of tablets, but all tablets prepared from granules were more permeable to air than those containing ungranulated powder. Results of water penetration studies showed completely the reverse effect, which was explained by an opening of the tablet structure due to weakening of the interparticulate bonds by the penetrating liquid. The presence of small intragranule pores and relatively large intergranule pores creates a wide and often discontinuous pore-size distribution (197). In general, a coarse intergranule pore structure permits a more rapid penetration of liquid than a tablet with the same porosity but a more even pore structure. A rapid penetration isolates other pore areas, however, by preventing the escape of entrapped air. The more even pore structure with weaker granules, and with stronger granules at high pressures, therefore results in more complete liquid saturation.

A subsequent paper (198) showed that granulation of a powder extends the pore-size distribution of resulting tablets. A bimodal pore-size distribution may occur with large, robust granules compressed at low pressures. Smaller, friable granules produce a more uniform tablet structure, and at high pressures the tablet structure resembles that obtained from the ungranulated powder.

A comparison of wet and dry granulation methods for lactose tablets (199) showed that the conditions used for dry granulation had little effect on the pore structure of final tablets because, in most cases, extensive fragmentation of dry granulated material occurred during tableting. Granules formed by wet granulation were apparently more robust, and the influence of granulation conditions was evident even at high tableting pressures. Studies with more complex systems resembling pharmaceutical tablets (200) demonstrated that the aqueous penetration of tablets that disintegrate is not only controlled by the pore structure. The presence of starch did not significantly affect the pore structure or air permeability of the dry tablet, but as the tablet disintegrated, viscous resistance to penetration by liquid was removed. The porosity of a granule mass during processing determines the optimum amount of granulating liquid required (201). Direct comparison of an aqueous, pan-granulation procedure and conventional granulation by massing and screening is not possible, because complex interacting factors such as the moisture content, the contact time, and the forces involved are different in the two processes. Capillary forces and gentle repacking during pan-granulation produces dense granules of lactose, whereas with a Z-blade mixer, the pronounced shear decreases the density of closely packed aggregates and additional shear during screening causes further reduction in density. Tumbling in a pan is inadequate to compact a fine cohesive powder such as calcium phosphate, but massing and screening provide the necessary forces for consolidation.

By measuring the permeability of lactose tablets at different porosities and air flow rates, Rispin *et al.* (202) showed that tablet permeability measurements may involve large errors because the contribution of slip flow is of the same order or greater than that of viscous flow.

After a brief review of the properties of agglomerates and methods for their preparation, Rumpf and Herrmann (203) developed theoretical estimates of maximum transmissible tensile stress for an agglomerate as derived from three models. Mathematical derivations for two of the models were explained, and comparisons were made with experimental results. The relationships between primary particle size of agglomerates, type of bonding, and maximum transmissible tensile stress were presented graphically. Rumpf (204) also showed that his previous theoretical studies on the tensile strength of agglomerates formed from unisized spheres can be extended to the situation involving nonspherical particles.

Linkson (205) described a device which could be used in pharmaceutical development studies or for in-process control measurement of the crushing strength of granules. Crushing strengths of less than 200 g. could be accurately determined, together with the axial deformation of the granule during the test. Gold *et al.* (206) also reported the development of instrumentation suitable for the measurement of granule strength. Their device consists of a mechanical linkage to apply the load at a uniform rate, a strain-gauge instrumented cantilever beam for conversion of the compressive load to a proportional electrical response, and a recorder to measure this response. An overhead cam depresses a plunger which compresses the granule placed upon the platform of the cantilever beam. From the recorder tracing of the granule reaction, the stress pattern is analyzed and the crushing strength calculated. The effect of granule strength on compressibility can be seen in comparing the results obtained for aspirin with those seen with sugar–starch pellets. As shown in Fig. 1, the fractured aspirin granule remains intact between the plunger and the anvil and continues to transmit the compressive load, with only a slight shift in the linearity of the curve. On the other hand, fracture of the sugar–starch pellets is characterized by a sharp break with a large recovery (Fig. 2). The fractured pellet cannot retain its spherical form and collapses into fine particles, thereby abruptly relieving the compressive load.

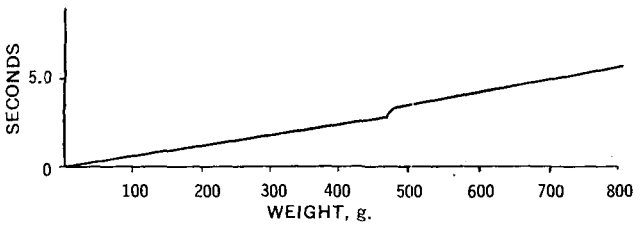

Figure 1—*Typical recorder tracing of an aspirin granule, indicating the magnitude of the breaking point and its breaking pattern (206).*

Bogs and Lenhardt (207) used aspirin mixed with starch, lactose, and gelatin solution as a model system to study the effect of the wet granulation and drying processes on hydrolytic degradation of an active substance. No attempt was made to correlate the experimental results with a derived theoretical relationship.

Drying—Drying of solids is a unit operation which has received little theoretical or practical coverage even in pharmaceutical technology, despite its importance in processes such as the manufacture of tablet granulations.

Although their book was predominantly directed toward chemical engineers, Nonhebel and Moss (208) discussed comprehensively many practical aspects of drying, including scale-up questions, which are of interest to pharmaceutical development scientists.

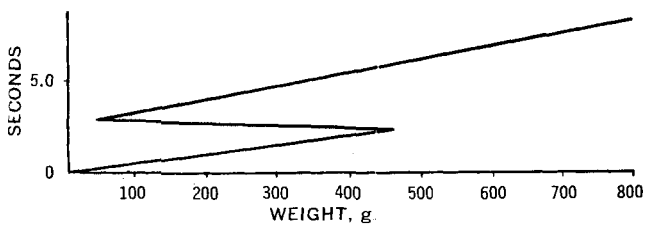

Figure 2—*Typical recorder tracing of a sugar–starch pellet, indicating the magnitude of the breaking point and its breaking pattern (206).*

Migration of solutes during the drying of granules affects their physical properties such as friability, modulus of elasticity, and Brinell hardness (209). By controlled attrition to remove successive layers of spherical magnesium carbonate granules, the distribution of polyvinylpyrrolidone was determined at various stages of drying. A quantitative assay method for polyvinylpyrrolidone involving IR spectroscopy was developed for this study (210).

An important specialized drying operation is spray drying. The technique can be used for coating drug particles with protective materials to improve their stability or to modify the physical properties of active substances and excipients to improve their processing behavior. Takenaka *et al.* (211) spray dried slurries of aluminum silicate or magnesium carbonate with various types of binder to produce fine-particle agglomerates in the size range of 10–80 μm. Scanning electron microscopy was used to examine the surface of the aggregates, and it was found that flow properties were mostly influenced by the size and surface area of the particles. Although the authors reported that the spray-dried materials could be easily tableted, the physical specifications quoted for such tablets were inadequate to confirm this claim. Fell and Newton (212) described an experimental spray drier which they used in controlled experiments to study the effect of variables such as inlet air temperature, air flow rate, and liquid feed rate. Lactose was spray dried from an aqueous solution containing an equilibrium ratio of α- and β-forms. Liquid feed rate was found (213) to be the only factor that affected the physical properties such as size distribution, particle density, and specific surface area of the spray-dried lactose obtained.

Compressing—The entire technology of tablet formulation and production is ultimately limited by the compression machinery available. It is, therefore, surprising that the general principle of operation of tablet machinery has remained basically unchanged for decades. Several improvements in the design of rotary tablet presses have been reported, but none of these represents a radically new concept for the operating principle of compressing equipment. A review by Swartz (214) discussed the specifications of the newer high speed rotary presses available in the United States. Problems resulting from the reduced dwell time of the granulation in the dies were discussed, as well as efforts to reduce or eliminate them such as forced feeding and precompression.

Maekawa *et al.* (215) described a modified rotary machine in which the compression rollers are mounted obliquely, and not perpendicular, to the die table. It was claimed that this arrangement reduces the rate of compaction, increases the dwell time, and minimizes wear of the punches and compression rollers. By using an improved method for securing the dies (216), adjacent die holes can be placed closer together in the die table. A new system for supplying powder to the dies of a rotary press (217) allows the feed material to move continuously with the die table and, therefore, ensures that a large proportion of the material is available for filling the dies even when the die table is rotating at a high speed. A similar principle uses a hopper mounted in such a way that the entire annulus between the upper punch turret and the die table is filled with the feed material (218). Problems of lubrication of the upper punch guides and contamination of the feed material might be expected with this system. A modification designed to reduce such contamination of tablets by machine lubricants involves the use of a felt sealing-ring attached to the underside of the upper punch turret and surrounding the shank of each punch (219). The ejection system of a rotary press was modified to reduce wear on the stationary ejection cam by incorporating an auxiliary roll which loosens the tablet in the die (220). A device was also developed to detect immediately any punches that are binding in the die (221). Prior to this, Goodhart *et al.* (222) reported a method for measurement of forces during the transfer of lower punches across the lower pulldown cam. Frictional resistance associated with movement of the lower punch tip through the die, and of the punch shank in its guide, was recorded using strain gauges mounted on a bolt securing the cam. In factorially designed experiments with a series of formulations, the force measurements were related to the lubrication levels of the formulation and machines, the cleanliness of the machine, and the length of running time.

An interesting technique was used (223) to compress formulations with a strong tendency to adhere to the punches and dies. At one compression station of a two-station machine, a pharmaceutical lubricant composition was compressed at high pressure to clean and lubricate the press tooling. The problematic tablet composition was compressed at the second station. Automatic control of a rotary machine to ensure weight uniformity of tablets was claimed (224). The principle involves servo-adjustment of the die fill volume depending on the measured compaction pressure and is, therefore, the same as that reported previously by Wray (225). A similar system which rejects tablets outside specified limits (226) was used by Ridgway *et al.* (227) to compare direct compression tablet diluents.

One of the most surprising deficiencies in tablet technology was the lack of concern relating to inadequate specifications for the purchase and control of tableting tools. Although the advantages of standardization to the manufacturer of tools was pointed out in 1960 by Gaskell (227*a*) and in 1962 by Swartz *et al.* (227*b*), it was not until 1966 that a committee on specifications was established by the Industrial Pharmaceutical Technology Section of the Academy of Pharmaceutical Sciences. The report of this committee was published by Swartz (228) in the form of a set of dimensional specifications and tolerances for round punches and dies, including a proposed incoming punch and die quality control program. The work of this committee will no doubt be reflected in the economies of tablet production and, what is even more important, in the quality of compressed tablets.

Substances that are difficult to compress can often only be tableted if the dose is small and by careful selection of excipients. Kruse *et al.* (229) considered the reasons why such formulations may compress better on eccentric machines despite the apparently inferior compaction cycle and pressure distribution compared with

a rotary press. It was concluded that even with new precision rotary machines, the variation between physical properties of successive tablets is greater than with an eccentric press due to intrinsic factors such as tooling differences and variation in the position and shape of the compression rolls. The paper reports an apparently successful attempt to resolve this problem using a modified overload mechanism which causes pressure equalization and facilitates the compaction of poorly compressible products on a rotary press.

A device, designed to simulate the compression event in a rotary tableting machine, was described (230); in principle, it could be used in conjunction with a hydraulic press, an eccentric tablet machine, or other single-acting compressing equipment. The system, which involves simultaneous movement of the upper punch and the die, was used with a mechanical testing instrument to compare the mechanism of consolidation of four crystalline materials. Another investigatory technique, developed in a continuing program on instrumentation of rotary machines at The School of Pharmacy, University of London, involves monitoring the radial stress in a Perspex die using photoelastic techniques combined with high speed cine-photography in polarized light (231). Hammond and Schwartz (232) demonstrated that rotation of the die substantially decreases the friction during compaction and ejection of aluminum powder compacts. For example, during compaction in a lubricated stationary die, 20% of the applied stress was consumed by die wall friction, compared to 2% if the die was rotated. Excellent correlation was shown between theoretical and measured values for stress distribution during compaction. Some tableting machines can be fitted with an attachment which rotates the punches during compaction (233); but if a system for rotating the die could be devised, the compaction of certain pharmaceutical formulations which are difficult to compress might be facilitated.

As pointed out by Rahm (234), strain measurement techniques are now widely used to instrument tableting machines in pharmaceutical research, development, and production operations. An enthusiastic evaluation of the contributions made, and to be made, by instrumented rotary tablet machines to tableting technology was presented by Wray (235), with reference to his experience in applying the techniques to troubleshooting and to the assessment of "manufacturability" of formulations on the basis of data concerning compression force, tablet weight, and ejection force. Despite the problems associated with relating the results of preliminary trials with an eccentric single-punch machine to the subsequent compression behavior on a rotary-press, there continues to be much interest in instrumented single-punch machines for use in compaction studies (236–238). In some cases, piezo-electric force measurement devices were used (239, 240).

Jungersen and Jensen (241) instrumented an eccentric machine to measure die wall forces with simultaneous recording of force and dynamic displacement measurements for the upper punch. Dynamic calibration techniques might be preferable to the static loading methods commonly used to calibrate force measuring instruments. Force–displacement curves were obtained by de Blaey and Polderman (242), using inductive displacement transducers mounted directly on the punches in a manner that eliminates the effect of any play in the lower punch. To discriminate between plastic and elastic deformation, the tablet press was modified to allow a second compression, during which the filling and ejection mechanisms were not operating. Quantitative interpretation of the force–displacement curve enabled the net work required for consolidation to be calculated by subtracting the work required for the repeat compression from that required for the first compression. The method of utilizing quantitative force–displacement data was further improved by interfacing the instrumentation with a digital computer (243). Registration and quantitative evaluation of the results are simpler and more precise than with the photographic techniques used by other investigators.

Selecting phenacetin as a classic example, de Blaey *et al.* (244) considered the phenomenon of capping in tablets. Quantitative force–displacement measurements indicated that above a relatively low pressure the work done is largely absorbed by elastic deformation so that no further increase in tablet strength can be expected. The strength in different regions of a tablet varied, apparently due to differences in the extent of elastic recovery. In another paper, de Blaey *et al.* (245) described the use of force–displacement studies combined with tablet strength measurements in the formulation development of a new chemical compound which had also shown capping tendencies in preliminary trials. Compression problems were encountered with the polyvinylpyrrolidone granulations stored at 75% relative humidity due to the marked hygroscopicity of polyvinylpyrrolidone above 68% relative humidity. A comparison (246) of gelatin and polyethylene glycol as binders in tablets showed that elastic recovery was highest in tablets containing gelatin. In all cases the elastic recovery increased with compaction pressure.

Also using an instrumented single-punch machine, Juslin and Jaervinen (247) evaluated the total energy requirements for tablet compaction as the sum of the compression work done by the upper punch and the ejection work done by the lower punch minus the effect of tablet expansion determined from the upper punch force–displacement curve during withdrawal of the upper punch from the die. With the sodium chloride tablets studied, axial recovery was apparently complete even before ejection from the die. The total volume expansion of the tablet due to axial and radial recovery was about 10%. Bockstiegel (248) considered the work involved in isostatic compression of metal powders as the pore volume approaches zero. Although isostatic conditions are not directly related to the compaction of tablets, it is valuable to follow the theoretical approach adopted and to note Bockstiegel's conclusion that mathematical concepts derived from graphical extrapolation of experimental compaction data can lead to dubious conclusions if unsupported by a reasonable physical theory. Führer *et al.* (249) discussed the information concerning elastic recovery, adhesive forces, and friction conditions at the die wall, which can be obtained by measuring the residual force on the lower punch prior to ejection of a tablet from an eccen-

tric compressing machine as well as the ejection force. Measurement problems associated with the rapid ejection event were discussed, and the dependence on machine speed was emphasized.

For a limited range of dimensions applicable to many pharmaceutical tablets, a common linear relation was reported (250) between the compaction pressure and the force lost to the die wall per unit area of apparent die wall contact. Ejection forces were correlated using a similar relation.

Temperature rise on compression was monitored by mounting thermocouples either on the upper punch and the die wall (251) or on the lower punch (252) or by inserting thermocouples into the powder bed (253). Although they concluded that the method is not very sensitive, Juslin and Krogerus (254) used temperature measurements to show that the lubricant effectiveness of fatty acids is greater than that of alcohols or hydrocarbons. Travers and Merriman (253) demonstrated that relaxation of compacts was associated with a fall in temperature. Recompression and relaxation of the same compact repeatedly produced a consistent temperature rise and fall due to elastic deformation and recovery. Sticking problems due to eutectic formation with certain powder mixes were observed by Bogs and Lenhardt (252) as a result of alternate heating and cooling of a tablet press during consecutive compression cycles.

A device for measuring the binding tendency of a tablet surface to the punch face was used (255) in a somewhat uncontrolled experiment to evaluate the ability of several excipients to form tablets without capping or sticking under various compression conditions.

As pointed out by Ridgway (233) in a survey of tablet compression as a unit operation, nobody really knows why particles stick together when compressed; and although several explanations are available, they provide no predictive capability. Certainly this deficiency has been responsible, at least in part, for the appreciable number of recent compaction studies, many of which attempted to clarify the mechanisms involved in the deformation and consolidation of different particulate materials under load. Djiane *et al.* (256) summarized the results of 34 earlier studies concerned with the compaction properties of crystalline substances. The theoretical and experimental work of Karlsson and Spring (257) and Arthur and Dunstan (258) may provide fundamental information which could be used to determine the initial packing arrangement of powders in the die cavity. Vijayan and Venkateswarlu (259) demonstrated the advantage of compacting mixed particle sizes which form close packings and therefore ensure optimum force utilization, lower porosity, and higher compact strength. The correlation for predicting pressure–porosity data of a material with mixed particle sizes from a compaction test conducted with single particles might be useful in optimizing direct compression tablet formulations. Problems of powder segregation that might be encountered during die filling with mixed powder fractions were studied by Lawrence and Beddow (260) using two-component mixes of lead particles. Reducing the size of the fine material increased the segregation tendency up to a point. Beyond this, the flow of fines down through the powder mass was restricted and segregation was reduced. Increasing the rate of die filling was shown to decrease the opportunity for segregation.

A compression modulus of the form log pressure/density is often used to quantify the compaction process; but according to Rees (261), caution is necessary to avoid misleading interpretation of the results. Hersey and Rees (262) reported that the equation proposed by Heckel (263, 264) can be used to distinguish between materials that consolidate with, and without, fragmentation. The deformation of granules during compression was also considered by Egorova and Loksin (265) and Egorova (266). Surface area measurements of magnesium carbonate compacts and size analysis of a suspension of the disintegrated compacts were used by Armstrong and Haines-Nutt (267) to demonstrate fragmentation and aggregation at various stages of compaction. Similar studies were reported with aspirin (268, 269). It may be possible to select optimum conditions of compaction which would produce sufficient fragmentation to provide an optimum surface area for dissolution and yet cause adequate agglomeration to produce a coherent compact (269). Ridgway and Aulton (270) used IR transmittance measurements of potassium bromide disks in an interesting attempt to follow changes in the area of interparticulate contact during compaction.

As a consequence of their differing direct compression characteristics, crystalline and spray-dried lactose were selected for study by several investigators. In analyzing the results of such studies, Fell and Newton (271) stressed that the ability of a powder mass to reduce in volume when compressed does not ensure the formation of a tablet since adequate cohesion in the required geometric form after removal of the applied load is also necessary. There is a linear relation between the work done and the tensile strength of a tablet for both forms of lactose and all the particle-size fractions examined. Since powder consolidation is, nevertheless, a necessary prerequisite to the formation of a compact, Fell and Newton (272) also analyzed consolidation results for crystalline and spray-dried lactose according to several equations which previously were applied to compaction data. They concluded that particle rearrangement is more important in the consolidation of small lactose particles than of large ones. The 75–104-μm. size fraction was most resistant to deformation, and the values of yield pressure differed appreciably from those reported previously (273). Alpar *et al.* (274) found that with small particle-size fractions, spray-dried material produced less die wall friction. Larger size fractions of the spray-dried lactose studied were predominantly crystalline and, therefore, possessed similar properties to crystalline lactose. There was a tendency for tablet strength to increase with a reduction in particle size.

From density measurements at different tableting pressures, Huettenrauch and Jacob (275) concluded that microcrystalline cellulose behaves more like a granular material than a powder. They considered that the variation in mechanical strength of tablets with compaction pressure is larger than with most materials

and attributed this to plastic deformation during consolidation.

Kahela and Krogerus (276) used benzoic acid and several derivatives as model active components to assess the influence of chemical structure on tablet properties. Using mechanical strength and imprecise values for disintegration time and porosity as control parameters, they concluded that the location of hydroxyl groups has a marked effect on compaction behavior. Although the paper represents an interesting approach, the conclusions appear to be unrealistic in view of an apparently inadequate recognition and control of factors such as moisture content and lubricant effect of the active substances which would markedly influence the measured parameters. Similar criticisms apply to subsequent studies (277, 278) in which the same authors related molecular configuration to the rate of release of benzoic acid derivatives from tablets prepared by direct compression with polyvinylpyrrolidone.

In a review of the physical and chemical effects of moisture during tablet manufacture (279), the flow of material into the die and the subsequent compaction operation were considered to be the process stages most susceptible to the influence of moisture. Herrmann (280) showed that compacts of barium sulfate are strongest when pressed under high vacuum. Water vapor reduced the shear strength by decreasing the interparticulate adhesion, and liquid bridges produced no increase in strength. At high humidity, an improved consolidation increased the strength of compacts.

The role of moisture during compaction was also investigated by Rees and Shotton (73), using a particulate system of crystalline sodium chloride and three liquids: water, decahydronaphthalene, and light liquid paraffin. During consecutive compressions the force lost to the die wall increased due to cumulative contamination of the die. Such losses were much less with water than with the other liquids, and this was attributed to boundary lubricant properties of water. All three liquids exhibited interrrelated but opposing effects including die wall lubrication, interparticulate lubrication, hydrodynamic resistance to consolidation, and expression of interstitial liquid to the die wall. For this reason the authors could not find evidence of an optimum lubricant level, but concentrations exceeding 0.5% caused hydrodynamic resistance to consolidation of the compacts.

Using a hydraulic press to study the compaction properties of three granulated materials, Armstrong and Griffiths (281) confirmed earlier evidence (282) that water acts as a lubricant and, therefore, facilitates consolidation; but they claimed that the effect is most significant with materials of low water solubility. Although moisture slightly increased the strength of the phenacetin and acetaminophen (paracetamol) compacts, the opposite effect occurred with dextrose (283). Among other factors, adhesion forces between individual particles determine the strength of agglomerates, and adsorbed layers may cause an increase or a decrease in the strength. Despite the unknown quantities involved, Herrmann and Polke (284) obtained extremely good correlation using a model to relate values of tensile strength, estimated from adhesion measurements, and experimental values of tensile strength for barium sulfate compacts which increased with moisture content.

Despite an intensive effort during the past 20 years to reduce the empirical approach to the compression of tablets, few measurements of the mechanical properties of the particulate solid materials themselves have been reported. Ridgway *et al.* (285) experienced difficulty in measuring the elastic moduli of single crystals of several pharmaceutical materials, using a microtensile testing instrument, owing to the presence of crystal inhomogeneities which cause specimen slip. They found, however, that the compressive elastic modulus and surface microhardness of the materials were in the same rank order, suggesting that the surface hardness reflects the mechanical properties of the bulk crystal. Subsequent work (286) showed that the lower the surface hardness of a material, the larger is the radial force transmitted to the die during compaction. The authors proposed that surface hardness may be a useful parameter to predict the compression properties of a material since good transmission of force to the die wall may be a significant factor in obtaining good tablets (287). A theoretical basis for using uniaxial compression tests with cylindrical specimens to determine Poisson's ratio without the need to determine other basic mechanical properties was discussed by Hammerle and McClure (288).

The advantages and techniques of preparing tablets by direct compression were reviewed by Livingstone (289). He considered that more use should be made of appropriate crystallization conditions to render noncompressible materials compressible. Certainly, this materials science approach to formulation requirements, which depends on cooperation between chemical and pharmaceutical development scientists, is not yet generally adopted in the pharmaceutical industry. Although no experimental justification was presented, Livingstone (289) reported that standard concave or flat bevel-edged punches are more suitable for direct compression tablet compositions because with deep concave punches the pressure distribution is nonuniform. In another review (290), the importance of establishing specifications for the physical properties of materials used in direct compression formulations was stressed.

Commenting on the effectiveness of cellulose powder as a dry binder, Nuernberg and Krebs (291) referred to the importance of avoiding powder mixes with a low bulk density for direct compression. Unfortunately, the experimental results reported for a range of tablet formulations provide insufficient information to assess their suitability from the important standpoint of weight and content uniformity. One major advantage of direct compression quoted by Kanig (292) was the elimination of several process stages at which inadequate control of process conditions may introduce variable bioavailability. Kanig considered, surprisingly, that overhead feeding of tablet presses from bulk storage hoppers is an overzealous objective which should be avoided with direct compression formulations, owing to the tendency for segregation to occur. However, Kanig's proposal that plant operators should "stir" the powder mix when transferring material between containers may well pro-

vide ideal conditions for demixing in certain powder systems.

Coating—Despite the predominant interest recently in polymer film systems for coating of tablets, several studies of the sugar-coating process have been reported, most of which concerned attempts to devise a satisfactory automated manufacturing procedure. Hammer (293) discussed various possible systems for the automation and regulation of processes such as sugar coating. Details were given of equipment and coating suspensions that were found suitable for use in conjunction with a selected automated sugar-coating program.

A method was described by Lantz *et al.* (294) for measuring temperature changes that occur during the application of volatile solutions to pellets in a rotating pan. By recording temperature changes during coating as detected by a thermocouple and thermistors in the pellet bed, it was possible to follow trends during the process. Duplication of thermal patterns was observed at equivalent periods during coating runs on two different days and variation in the rate of application of coating solutions and in pellet drying times produced differences in thermal patterns. The authors suggested that measurement of changes in temperature of a solid particle bed in a rotating pan should be useful in automating the coating process and in evaluating the design of coating pans, baffles, and auxiliary equipment. Using this type of approach to monitor the temperature of a bed of tablets in a coating pan, Courtin and Briner (295) were able to control and minimize the drying time necessary between consecutive syrup applications during sugar coating of tablets. Final drying of the finished coated tablets was also eliminated.

Heyd and Kanig (296) stated that it has not been clearly established that the drying rate is constant for each cycle of a coating process. They pointed out that drying rates differ for each type of coating solution and reflect variations in tablet shape, tablet size, and batch size. Since automatic, timed, tablet-coating procedures fail to take into account either inherent or environmental conditions that are capable of varying the drying time, the authors reported on an in-process control system, using a moisture analyzer based on the high frequency conductance principle, which continuously monitors the degree of dryness as a means for controlling the automated process. Auxiliary switches in the moisture analyzer circuit activate the blower-heater and the exhaust system at the appropriate coating cycle intervals. The analyzer proved to be extremely sensitive to the presence of moisture and to moisture loss from the tablet mass. The sensitivity of the drying cycles to changes in environmental humidity was also shown. The influence of nonaqueous or mixed solvent systems was not investigated, nor did the authors report any data on tablet quality.

Discussing the advantages of not having to rely on the presence of tablet-coating experts in order to ensure continuous production schedules, Rose (297) commented that, for automated coating processes to be successful, the total experience of the coating expert must be translated into appropriate programs which control the coating cycles and ensure accurate duplication. He also stressed the deficiencies of timer-controlled process cycles and the need for sensitive control with automatic compensation for the continually changing condition of the tablet. For example, in addition to monitoring the moisture content of the drying air to control spray cycles, the quantity of coating material applied should be progressively increased to match the gradually increasing surface area of the tablet. It was claimed that with the coating system and self-cleaning spray nozzle described, suspensions containing up to 85% solids can be sprayed into the pan and final polishing can be carried out in the same pan, resulting in a considerable time saving.

The problem of adhesion between shellac-based printing inks and a wax-polishing film on a tablet surface was considered (298). Methods were proposed for coating tablets with a thin unpolished wax film which can be imprinted with legible indicia which are not easily obliterated. After printing, a final protective coating may be applied to the tablets.

Hess and Janssen (299) reviewed the advantages and requirements for film coating of tablets. The processing technology was discussed with particular reference to the use of pigments for coloring the films. In addition to the usual technological advantages claimed for tablets that are film coated as opposed to sugar coated, Muzaffar (300) discussed several economic advantages such as the reduced volume occupied by the coating. This effect increases the batch size of cores which can be processed in a coating vessel, reduces packaging and transport costs, and improves patient acceptability of the smaller dosage form produced. Muzaffar made the totally unacceptable statement that a further advantage of film-coated tablets is that rejected batches can be easily reprocessed following comminution since the small quantity of coating will not cause recompression problems.

A technique involving spraying a film onto a rotating drum was used by Bayer (301) to produce free films under controlled conditions. For the small coating trials involved in this study, an air-spray system was found to be preferable. Scanning electron photomicrographs, water vapor transmission, and mechanical measurements such as deformation behavior, tensile strength, and surface roughness were used to show the influence of plasticizers, pigments, and process conditions on the film structure and properties. As a means of measuring the adhesive bond between film-forming polymers and solid substrates, Wood and Harder (302) and Harder *et al.* (303) used contact angle data and critical surface tension values in studies of the adhesion of film coatings to the surfaces of compressed tablets. By filing the edges of the film-coated tablet, the layer of film on the tablet face was detached from the film on the side of the tablet, and the force required to peel the coating from the surface was measured. Experiments with aspirin tablets of varying composition demonstrated a linear relationship between the cosine of the contact angle of an applied liquid on the tablet surface and the surface tension of the test liquid. The critical surface tension value obtained could be used to characterize the tablet surface, since it was indicative of the cohesion energy density, but further investigation of the role of polar and dispersion forces as they influence wetting,

contact angle data, adsorption, and adhesion was considered necessary. The use of appropriate adjuvants in the tablet composition, resulting in an increase in the cohesion energy density of the tablet surface, would increase the adhesion of a film coating. The authors believed that knowledge of the types of forces acting between the tablet surface and a film coating should advance the comprehension of processes involved in the formation of satisfactory film coatings.

More recent studies (304) indicated that in almost all cases the total surface free energies determined from contact angle data for different tablets do not coincide with experimental critical surface tension values. Since the surface free energy is a measure of the operative cohesional forces in the tablet surface that interact with the liquids, the authors concluded that this parameter should be of greater value than critical surface tension values in explaining and predicting the adhesion of film coatings to tablet surfaces. Experimental results have not yet been obtained to confirm this theory.

A miniaturized, laboratory, air-suspension coating apparatus was described (305) based on the Wurster principle, but utilizing a 34-cm. high conical-shaped chamber of 20° angle. This design reduces the linear velocity as air passes up the chamber so that sedimentation of heavy particles is prevented while ensuring that fine particles are not eliminated with the exit air. Some advantages of the air-suspension technique compared with conventional pan coating were summarized. A commercially available system for film-coating tablets in a fluidized bed was discussed by Feigenbaum and Lefort des Ylouses (306). It is debatable whether such an apparatus is so rapid and efficient that it can replace a battery of coating pans as suggested by the authors.

Film coating in a pan can also be an extremely rapid process, especially in the perforated type of pan. A slightly modified coating pan design was claimed (307) based on the perforated cylindrical drum concept. Drying air is introduced over a part of the drum circumference in the reverse direction to that previously employed. This could conceivably disrupt a spray pattern of coating fluid introduced into the pan.

A method for film-coating tablets under vacuum was patented (308) to remove adsorbed surface contaminants with the objective of improving adhesion of coatings and eliminating defects such as pinholes which, for example, reduce the efficiency of enteric coatings. Studies by Zatz and Knowles (309) showed that at pH values of 2–4, cellulose acetate phthalate monolayers are uncharged and are arranged in a compact, coherent form. Partial ionization and marked changes in monolayer organization follow an increase in pH. Charge repulsion and increased solvation of charged groups expand and decrease the stability of cellulose acetate phthalate monolayers, with the greatest effect at pH 6. The authors suggested that cellulose acetate phthalate is unionized in the highly acid environment of the stomach and is probably quite coherent. In the duodenum at approximately pH 6, ionization of phthalate groups occurs followed by expansion and penetration of water and ions. Even with partial dissolution of the coating, sufficient penetration of water molecules through the coating may bring about disintegration or leaching.

The dispersion of a powder in a liquid, such as during the preparation of coating suspensions, involves wetting and size reduction of aggregates followed by stabilization of the dispersion. Since it is difficult to assess the relative importance of these stages by studying the total dispersion process, Heertjes and Witvoet (310) considered the three mechanisms of adhesion, immersion, and spreading which are involved in the initial wetting of a solid by a liquid. They discussed the influence of geometry of the system and the effect of entrapped air, with reference to the capillary structure of an aggregate. Such information about the wetting process could also be relevant to the dissolution of drugs from dosage forms.

Surveying the technique of coating by compression, Puffer and Willox (311) surprisingly concluded that most of the serious technical problems now appear to have been solved.

BIOPHARMACEUTICS

General Aspects—The publishing explosion in the area of biopharmaceutics continues unabated. Almost 30% of the 500 papers surveyed in this review, which is primarily concerned with the tablet dosage form, fall into the biopharmaceutics classification—papers involving research in pharmacokinetics, GI absorption, biological availability, formulation factors, therapeutic equivalence, dissolution rate testing, and timed-release preparations. As might be expected in any "fashionable" field of research activity, the quality ranges from the inconsequential to the excellent. The importance of *in vitro–in vivo* correlations continues to be emphasized, but progress remains slow due to the need for fundamental advances in the knowledge of GI absorption, the quantitative measurement of drugs in body fluids and tissues, and the biochemical pathways of metabolism and degradation.

Barr (312) classified and compared the usefulness of different *in vivo* and *in vitro* methods and principles which can be used to assess the effects of formulation variables on systemic availability; the onset, duration, and intensity of pharmacological effects; and therapeutic efficacy of drug products. He stressed that clinical observations, although the most relevant method of assessment, are generally the most imprecise and least sensitive and, therefore, are of little value. Nevertheless, biological effects may at times provide a more suitable approach to assess formulation variables, for example, when biological response is not directly related to blood levels or in the absence of precise analytical methods. Although compounds with limited aqueous solubility are most likely to exhibit dissolution rate-limited absorption, Barr tabulated evidence to show that it is a gross oversimplification to consider that only these compounds are susceptible to formulation factors. The dangers of relying on a modified dosage regimen to compensate for incomplete absorption were stressed.

In an assessment of the generic equivalence and inequivalence of oral dosage forms, Wagner (313) summarized the controlled bioavailability studies carried out prior to January 1971 in which two or more commercial drug products containing the same drug in the

same type of dosage form were compared in man. Only 12 drugs were studied intensively in this way; for 10 of these, the products of different manufacturers appeared to be nonequivalent. In light of these statistics, Wagner wondered how anyone can assume that no problems exist with other drugs; he stressed the futility of trying to determine equivalence from an "armchair" in the absence of *in vitro–in vivo* correlations.

Freestone (314) emphatically drew attention to the many different substances that may be included in the formulation of a coated tablet and the possibility of interactions between excipients and drugs enhancing or impairing absorption. Prescott and Nimmo (315) expressed the opinion that the amazing selection of excipients present in "modern" tablets may contribute to clinically significant generic inequivalence in the form of unsuspected toxicity. A comprehensive review by Münzel (316) on the influence of formulation on drug action is important for its consideration of dosage form design. Emphasis was placed not only upon the complete release of the active ingredient but also upon the rate of release. Münzel appears to be critical of the level of progress in biopharmaceutics represented by the USP XVIII dissolution rate test.

Some biopharmaceutical aspects to be considered in the development and testing of tablets were also discussed by Speiser (317), Doelker and Buri (318), and Ritschel (319). The latter drew attention to the need for including drug release rate and bioavailability studies in the stability testing program. However, his proposal that the preliminary stages in the biopharmaceutical assessment of a tablet should include *in vitro* and *in vivo* studies with gelatin capsules containing the active substance with and without excipients would appear to be an unnecessary complication. It is now well known that the formulation of hard gelatin capsules themselves can be a relatively complex procedure in view of the potential effect of the gelatin shell on drug release. Results with gelatin capsules may, therefore, have little significance to the formulation requirements for a tablet. A general review on drug absorption by Rasmussen (320) included some information on controlled absorption from tablets.

The utilization of the rat in bioavailability testing of tablets was reported by Simon and Rasero (321) who prepared 0.32-cm. tablets using a standard concave punch. With a device similar to an intubation cannula, two technicians had no difficulties in administering such tablets to rats weighing 200 g. or more. The data obtained on unchanged drug excreted in urine were satisfactory for demonstrating absorption, a situation not possible with dogs in view of their inability to excrete sufficient quantities of drug in their urine. In reviewing pharmacological and biochemical aspects of the GI tract, Waser (322) posed the question whether pinocytosis could be the primary mechanism of absorption. He reported that without this mechanism, substances such as vitamin *D* and tetracycline could not be absorbed.

Reviewing the impact of biopharmaceutical studies on pharmacopeial standards for solid dosage forms, Mirimanoff (323) referred to the reticence still displayed by most pharmacopeias in considering this aspect of pharmaceutical science. Claiming that, for obvious reasons, results of *in vivo* studies in man could not be required as a pharmacopeial standard, the author concluded that requirements such as crystal structure of active substances, physical properties of materials in the solid state, and *in vitro* dissolution and diffusion through synthetic membranes from solid dosage forms should be envisaged. Since bioavailability tests are not always representative and sometimes worthless, while human studies are usually expensive and difficult to organize, *in vitro* methods have to be introduced into pharmacopeias if a quantitative correlation between *in vitro* and *in vivo* availability for a particular drug can be established. He also referred to the need for *in vitro* test methods for tablets that are intended for administration by routes other than the GI tract and that, therefore, come into contact with relatively small volumes of body fluids. The possibility that compositions and manufacturing details for tablets and other formulations may again be included in future pharmacopeias in conjunction with standards related to *in vivo* effect as a means of assuring clinical equivalence was suggested by Macek (324).

The final paper in a series by Reetz and Speiser (325) concerning the dependence of biological activity on the particle size of a poorly soluble, high dose, oral antidiabetic compound dealt with a comparison between powder and tablet administration. Milling to produce a relatively coarse powder had little influence on the therapeutic effect, but micronization resulted in a pronounced increase in activity, thus reducing the necessary dose. Fine-, medium-, and coarse-particle materials were formulated into tablets prepared by direct compression at a uniform pressure. Changes in surface area during compaction tended to eliminate the relation between activity and original particle size of the powder. Although there was no discussion of the significance of the particle-size changes in tablets, there was apparently a tendency for fine material to agglomerate and for the coarse material to fragment on compression.

In experiments on volunteers, Prescott *et al.* (326) administered oral suspensions and tablets containing phenacetin. Absorption was assessed by estimating the plasma concentrations of phenacetin and its major metabolites at intervals and by measurement of the urinary excretion of free and conjugated acetaminophen (*N*-acetyl-*p*-aminophenol). The results with the oral suspensions demonstrated a definite relationship between particle size and absorption. Since the particle size of the drug in the tablets was unknown, no correlations were possible. The general subject of the significance of particle size to drug absorption was covered by Marshall (327) in a review paper. Attempts by Flanagan *et al.* (328) to elucidate the cause of large variations in blood levels of a potential analgesic administered as compressed and film-coated tablets were reported. Although the film-coated tablets exhibited longer dissolution times and a greater dependency on stirring rate than the uncoated tablets, *in vivo* behavior was found to be independent of dissolution rate. The partition rate between aqueous and organic solvents and *in vitro* studies with goldfish were used in conjunction with absorption studies in the dog and with human buccal absorption

to show that pH at the absorption site was a critical factor.

In a review of the importance of pharmaceutical formulation on drug absorption from tablets, Sjögren (329) presented results for a highly soluble substance, alprenolol hydrochloride, which apparently shows significant differences in availability due to formulation factors. Beckett *et al.* (330) found the physiological availability of pentazocine administered as tablets to be less than when administered by the intravenous or intramuscular route, as an oral solution, and, in some subjects, by the rectal route. If two equal oral doses were administered as tablets 2 hr. apart, the percent of dose recovered in the urine was higher than with a single oral tablet dose, possibly indicating a slow release of drug from the tablet. In an attempt to establish a correlation between plasma level and interdose variation between tablets of aspirin, Oie *et al.* (331) found that although doses of 512.5–600 mg. gave higher plasma levels than doses of 500 mg., this effect was not significant compared with the variation between experiments with the same subject. This may not be the case, however, with other drugs.

An assessment of the physiological availability of phenylbutazone tablets by van Petten *et al.* (332) showed that all of the brands examined produced therapeutically effective blood levels. Although with some formulations the time required to achieve these blood levels was relatively long, it was concluded that this should not be a disadvantage with such a chronically administered drug with a long elimination half-life. The authors stressed that the use of peak blood concentrations to compare absorption from different formulations must be limited to drugs like phenylbutazone for which the elimination rate is much slower than the absorption rate.

From studies using four methods for determining the *in vitro* dissolution rate of phenylbutazone tablets, Withey *et al.* (333) concluded that *in vivo* availability studies are superior to *in vitro* studies because dissolution of drugs from solid dosage forms in the GI tract is a complex phenomenon and more fundamental work is necessary to establish a realistic dissolution test directly related to bioavailability. Reacting to opposite results reported by investigators concerning the effect of dietary components on GI absorption in man, Jaffe *et al.* (334) studied the influence of various test meals with a high carbohydrate, protein, or lipid content on the absorption of acetaminophen tablets. Urinary excretion at 1.5-hr. intervals over 9 hr. was used as an indicator of the rate and extent of absorption. Only with the carbohydrate test meals was there an initial reduction in the rate of urinary excretion of acetaminophen and its metabolites. However, at the end of 9 hr., there was little difference in the cumulative amounts of total acetaminophen and metabolites excreted in the urine.

In extending their studies of solid dispersions of griseofulvin, Chiou and Riegelman (335) compared capsules and tablets of griseofulvin–polyethylene glycol solid dispersions with a commercial tablet of micronized griseofulvin. Only two subjects were used, with urinary excretion data serving as the basis for evaluation of availability. The griseofulvin–polyethylene glycol 6000 (1:9 w/w) tablets were prepared by direct compression on a laboratory pellet press. Absorption from the dispersed griseofulvin was more than twice that of the commercial tablet, thereby leading the authors to suggest a 50% reduction of the dose with the administration of the dispersed form. The technological suitability of tableting such dispersions on rotary tablet presses remains to be investigated in addition to broader based biopharmaceutical and tolerance studies in man.

The particular clinical importance of maximum uniformity of absorption for an anticoagulant such as warfarin prompted Wagner *et al.* (336) to compare plasma concentrations of this drug in two different crossover studies. Six subjects ingested one 25-mg. tablet or five 5-mg. tablets of sodium warfarin; then plasma concentrations were measured by two different methods. The rate of absorption from the five 5-mg. tablets was almost twice as fast as from the single 25-mg. tablets, and relative absorption was also greater. In the second study, 12 subjects ingested two 5-mg. tablets of sodium or potassium warfarin made by three different manufacturers. *In vitro* dissolution rates were determined on five individual tablets of each lot of tablets tested clinically. Availability was equal for all three products tested, and absorption was also complete for each treatment. Correlation between *in vitro* dissolution rate and *in vivo* results in man was excellent, but this was not the case with disintegration time data.

In checking the method of buccal absorption for predicting the relative absorption and excretion of drugs in biological systems, Taraska (337) used clindamycin, an antibiotic readily absorbed from the human GI tract. The results showed that this drug is poorly absorbed from the buccal cavity, possibly as a consequence of surface area, transport mechanisms, and/or pH differences between oral mucosa and the GI tract. The low aqueous solubility and fairly high pKa value of salicylamide suggest that the absorption of this drug would be dissolution rate dependent. This assumption was tested by Bates *et al.* (338) using a suspension as well as experimental and commercial tablets of salicylamide. The results showed that the initial *in vitro* dissolution rate in 0.1 *N* hydrochloric acid correlated with the initial absorption rate in man.

In view of evidence that aspirin-induced GI occult bleeding is a local effect at least partly dependent upon contact area and duration of contact, Leonards and Levy (339) reasoned that the addition of antacids to aspirin tablet formulations would decrease contact time without increasing the contact area. Average daily blood losses in two groups of subjects were determined before and after the administration of either regular aspirin tablets or antacid aspirin tablets. The average daily blood loss in the antacid aspirin group was significantly less than in the regular aspirin group. Although a more elaborate *in vivo* study would be required to decisively reinforce the conclusion, the authors suggested the feasibility of designing aspirin tablet preparations with rapid drug release characteristics and lower GI bleeding liability.

To determine the extent of correlation between *in vitro* and *in vivo* data, Taraska and Delor (340) used three

sulfamethazine tablet formulations with different *in vitro* dissolution rates: fast ($T_{50\%} \sim 1.5$ min.), medium ($T_{50\%} \sim 15$–20 min.), and slow ($T_{50\%} \sim 40$–50 min.). In a single-dose, threeway, crossover study in nine adult subjects, blood and urine samples were collected at specified intervals and assayed for free and total sulfamethazine. The results showed that significantly less drug was absorbed from the slow than from the fast formulation. Although several *in vivo* parameters paralleled the *in vitro* dissolution rate of sulfamethazine from the three types of formulations, not all of the *in vivo* differences were as great as might be expected from the *in vitro* data. The authors explained this situation on the basis of the properties of sulfamethazine as a drug; it is well absorbed and has a relatively long biological half-life.

In an experiment on man, Delacoux *et al.* (341) compared the absorption from compressed aspirin tablets, buffered effervescent aspirin tablets, and tablets of coated microparticles of aspirin. Plasma salicylate curves showed absorption profiles that varied in accordance with the aqueous solubility of the products. Measurements of plasma aspirin concentration indicated that although solubility favored an increased absorption rate, it did not accelerate the hydrolysis of aspirin in man.

In a well-planned crossover study involving the administration of digoxin to normal volunteers, highly significant differences in serum digoxin levels were reported by Lindenbaum *et al.* (342). Differences of four to seven times in serum levels were reached after the administration of various preparations meeting chemical assay requirements. These variations were not only noted between lots of different manufacturers but also between different lots of the same manufacturer. The authors recommended the inclusion of digoxin tablets in the list of drugs in which proof of biological availability is considered crucial. In recognition of the known problems of iron absorption, Blezek *et al.* (343) conducted dissolution rate studies on 12 commercially available ferrous sulfate tablets. Except for three products, hydrochloric acid was critical to the dissolution process.

Timed Release—Although not the earliest effort to control a biological response by pharmaceutical means, the development of timed-release oral preparations provided a powerful impetus to the subsequent rapid evolution of biopharmaceutics as an area of research activity. It is evident from the period under review that interest in timed-release systems, technology, and testing has not diminished, but that a larger portion of the published work reveals a higher level of scientific sophistication.

Two review papers are indicative of this trend. A relatively brief review by Speiser (344) clearly demonstrated the essential relationship between the fundamental technical requirements of timed-release preparations and their biopharmaceutic aspects. The discussion of retard (timed-release) systems was rather brief, with emphasis upon work carried out in the author's laboratory. An extensive review by Hänselmann and Voigt (345) of timed-release preparations, with 328 references, covered basic principles; biopharmaceutic and pharmacokinetic aspects; physiology of the GI tract; absorption; formulation factors; retarding materials; *in vitro* release methods and physiological availability; repeat-action and prolonged-action tablets; matrix systems based on waxes, fatty acids, polymers, and hydrophilic gels; and *in vivo* test methods.

In their first paper on a molecular scale drug entrapment system for use in controlled-release preparations, Goodman and Banker (346) described the basic entrapment method used and the evaluation procedure for *in vitro* and *in vivo* characterization of controlled release. As part of this study, tablets were prepared from acrylic copolymer–methapyrilene hydrochloride entrapment products compressed on a laboratory press. *In vitro* tests demonstrated uniform hourly rates of drug release ranging from 2.5 to 8 hr., depending upon drug concentration and presence or absence of starch. Continuing these studies, Rhodes *et al.* (347) described a procedure involving the addition of a drug and an appropriate carboxylic acid in solution to a polymer emulsion. After washing and drying, the resultant flocculate could be milled, encapsulated, suspended, or tableted to provide controlled-release products. However, experimental drug release data reported in this paper covered only powders and suspensions. In further experiments with their molecular scale, drug-entrapment system, Rhodes *et al.* (348) investigated phenylephrine and phenylpropanolamine preparations using a variety of carboxylic acid anions as binders to acrylic copolymer emulsions. *In vitro* and *in vivo* release studies involved only powders and capsule products.

With the objective of obtaining a controlled, reproducible release rate of low molecular weight substances, Determann and Lotz (349) used copolymers of methyl methacrylate, glycol diacrylate, and acrylamide. After a "dry gel" consisting of crosslinked polymer was prepared, the system was charged with drug by immersion in a solution of the drug in organic solvent, followed by drying. The release of drug from such systems depends on the presence of molecular pores whose size depends on the swelling tendency in water. The authors criticized many previous methods of controlling drug release using polymers, but the proposed system appears to require appreciable development before it could be used commercially for preparing timed-release dosage forms.

Lehmann and Dreher (350) assessed the application of permeable acrylic resins[14] for preparation of timed-release dosage forms. It was claimed that the materials are well defined and since small quantities are required to achieve the desired effect, the release rate is more reproducible than with the use of insoluble, impermeable excipients to form a matrix in which the pore size depends to a large extent on the manufacturing process. Compression of uniformly coated granules to form disintegrating tablets caused failure of the coating and consequent loss of the controlled-release properties. However, by using additional hydrophobic excipients, nondisintegrating tablets could be prepared even from incompletely coated granules. These tablets exhibited

[14] Eudragit.

controlled-release properties independent of compaction pressure. Impregnation of the surface of the tablets by application of a thin film of resin eliminated the initial release of drug and, therefore, ensured a constant release rate.

Speiser and Khanna (351) described a technique called bead polymerization which can be used to control the release rate of drugs. The active substance is incorporated in a liquid monomer system which is subsequently polymerized in the form of beads. These beads can then be formulated in dosage forms. The authors claimed that the system can be prepared free of residual monomer, provided the polymerization is carried out for a sufficient length of time. The use of a water-insoluble cellulose derivative to prepare a timed-release tablet containing nitroglycerin and proxyphylline was described by Ritschel and Clotten (352). Several references were given to previous studies using the same principle. Although these studies indicated that the matrix was not influenced by pH or enzymes, *in vivo* studies showed that nitroglycerin absorption from tablets based on the matrix was pH dependent. To avoid toxic effects which might arise from rapid release in the event of unintentional mastication of the matrix tablets, the nitroglycerin was distributed throughout the matrix itself rather than being incorporated into the pores of the insoluble skeleton.

Injection molding or hot extrusion, a technique commonly employed in various industries to prepare articles from thermoplastic materials, was studied as a process for preparing oral, timed-release dosage forms (353). The influence of pH, ionic strength, and buffer salt concentration on dissolution rates of disks prepared by this technique was evaluated. By using *in vitro* tests, acid-soluble epoxy resins were shown to be potentially suitable for the release of an initial dose of drug in simulated gastric fluid. The use of β-methacrylic acid copolymer matrixes would then permit the incorporation of a sustaining dose which would be released by the action of intestinal fluids.

To check the concept of obtaining timed-release properties through the incorporation of a drug in an enzyme substrate matrix, Javaid *et al.* (354) prepared a sulfamethizole tablet employing a spray-congealed, lipase–lipid–drug system. By means of *in vitro* dissolution profiles, the authors concluded that the release of drug was lipase controlled for the first 1.5 hr. and then was dependent upon lipid hydrolysis. Calcium carbonate in increasing concentrations progressively increased drug release from tablets containing lipase. The variability of enzyme activity in the GI tract could conceivably make correlations with release rates, as determined by *in vitro* methods, a difficult exercise. Polyelectrolyte salt complexes (polysalts) have received little attention in pharmaceutical research compared to coacervates. To remedy this situation, Jablon *et al.* (355) prepared an insoluble drug–polysalt complex of chlorpromazine hydrochloride, sodium carboxymethylcellulose, and protamine sulfate as a model for evaluating the *in vitro* and *in vivo* availability of the interacted drug. *In vitro* release rates showed timed-release properties, whereas *in vivo* studies on rats demonstrated an increased bioavailability of the drug in the form of the polysalt complex. Unfortunately, it was not possible to prepare tablets suitable for administration to rats.

The possible advantages of using a spray-drying technique in the preparation of a drug matrix possessing timed-release properties when compressed into tablets were investigated by Kornblum (356). A slurry of butalbital (isobutylallylbarbituric acid), cellulose derivatives, and diluents was spray dried in a portable spray dryer; following the addition of magnesium stearate, tablets were compressed on a single-punch press. Cumulative data from five batches indicated good consistency of drug release. The author recognized the necessity of conducting *in vivo* tests before acceptance of the proposed process. Equally necessary will be a determination of the operating characteristics of the process when scaled up to effective production size.

Controlled *in vitro* release rates for sulfanilamide were achieved by Chalabala and Starha (357) when the drug was embedded in a matrix consisting of 15–25% of hydrophobic glycerin esters of higher fatty acids. Former studies were criticized for poor reproducibility due to the use of ill-defined mixtures of esters. For this reason, the authors prepared defined materials from lauric, palmitic, and stearic acids purified by vacuum distillation. By using instrumentation which had been previously described by Chalabala *et al.* (358), the release rate was shown to be indirectly proportional to the chain length of the fatty acid carbon chain; the release rate decreased in the order: monoester > fatty acid > diester > triester. Glycerolpalmitostearate was used by Ritschel and Ritschel-Beurlin (359) as the retarding substance in a study of timed-release aspirin tablets based upon the fat-embedment principle. Variations in the parameters tested for *in vitro* drug availability included drug-particle size, granule size, and percentage of glyceride ester in the composition. The relationship of enzyme effect on hydrolysis and availability was also discussed.

The dissolution patterns of a number of spray-congealed sulfaethidole (sulfaethylthiadiazole)–wax products compressed on a Carver laboratory press were reported by Hamid and Becker (360). Release rates were measured in acid pepsin and alkaline pancreatin media using the rotating-bottle method. The addition of increasing concentrations of a surfactant, sorbitan monooleate, resulted in a decrease in the amount of sulfaethidole released in acid pepsin medium, whereas in alkaline medium the opposite effect was obtained. Only initially did the drug release follow the Higuchi model for drug release from inert matrixes. Since the authors suggested that erosion, solubilization, and leaching of the drug represent the mechanism of release as based upon *in vitro* data, the necessity for *in vivo* correlations with the far more complex dynamic biological system is obvious. The possible use of alginates to prepare timed-release tablets by a simple, direct compression technique was studied by Klaudianos (361). The objective was to prepare tablets that GI fluids would convert to a matrix. *In vitro* tests with several substances and the caffeine blood levels in human subjects indicated a potential for this system to obtain up to 8 hr. of drug release.

In the development of a timed-release tablet formulation of potassium chloride based on a waxy matrix,

Gumma *et al.* (362) used scanning electron photomicrography to examine the changes in tablet structure during *in vitro* dissolution of the active substance. Reference was also made to the importance of standardizing the compression pressure to control the porosity and rate of release from the tablet. A series of *in vitro* and *in vivo* trials on a timed-release principle based on an inert plastic matrix was reviewed by Sjögren (363). Dissolution of the drug proceeds at a continuously decreasing rate, but mechanical techniques such as the use of press coating or multilayer compression represent means of modifying the release pattern.

Recognizing that if absorption of a drug from a compressed tablet is incomplete, it would be unwise to administer that drug in a timed-release formulation, Johansson *et al.* (364) evaluated the influence of dissolution rate on the absorption and metabolism of alprenolol when administered as rapidly disintegrating and timed-release tablets. A comparison of serum levels and urinary excretion indicated complete absorption from all of the tablets. Since the dissolution rate had no effect on the completeness of absorption, the authors concluded that absorption is not limited to a short region of the GI tract. The fraction of unmetabolized drug in the urine was slightly lower with the timed-release formulation. Although these results provide no evidence that alprenolol is unsuitable for administration in a timed-release form, the authors stressed that in the absence of a correlation between serum concentration and therapeutic effect, clinical trials of a timed-release tablet are necessary. In a continuing study, using heart rate and systolic blood pressure as clinical parameters in a double-blind crossover comparison of alprenolol administered as 100-mg. normal tablets four times a day or as 200-mg. timed-release tablets twice daily, Johnsson *et al.* (365) concluded that the therapeutic effects were equal. The timed-release tablets did, however, yield more uniform drug serum levels.

Polyethylene as a base for a matrix type of timed-release tablet was claimed in a patent (366), and results were reported for tablets of rutin (367) and scopolamine bromide (368). Formulations of caramiphen hydrochloride and of atropine sulfate with a carboxyvinyl polymer[15] were shown by Baun and Walker (369) to possess relatively uniform *in vitro* release rates over 4 hr. A dry granulation (slugging) technique was used to prepare the tablets. For both drugs, the release rate from the polymer matrix was agitation dependent and was more rapid in simulated gastric fluid than in simulated intestinal fluid.

One early method for *in vitro* testing of release rates involved a continuous extraction of drug, with samples removed for assay at hourly intervals. Bolton (370) presented a method for combining samples in such a way as to make hourly assays unnecessary. Based upon the assumption that drug availability from an oral dosage form can be controlled by regulating the surface area over which the dissolution occurs, Rippie and Johnson (371) investigated the timed-release characteristics of pellets with different surface geometry. Cylinders having circular, cross-shaped, and cloverleaf cross sections were studied; the latter two types were also investigated with the outermost surfaces coated with lacquer to prevent dissolution from these regions. Although the results demonstrated the influence of available surface on the long-term dissolution rate from solid pellets, the rate of dissolution as a function of changing size and shape of the pellet itself and of the fluid dynamics of the adjacent solvent layer render this approach to timed release as too complex hydrodynamically and technically.

A study by Graffner and Sjögren (372) was designed to determine the influence of the *in vitro* dissolution rate of potassium chloride on absorption, using urinary excretion in healthy volunteers as the test method. Five timed-release preparations, two based on embedment in lipids and three based on the insoluble matrix principle, were tested. Although the results showed wide variation in dissolution rate, no significant differences between preparations could be demonstrated. The nature of the absorption process for potassium is probably such that even tablets with slow-release tendencies in the intestine show a high level of availability. The stenosing ulcerations following the administration of some forms of potassium chloride were reported in several papers. Sundell (373) investigated the effect of potassium chloride tablets of three types following their direct introduction into the jejunum of dogs. Timed-release tablets of high and low doses of potassium chloride did not alter the normal peristaltic pattern of the small intestine; rapidly disintegrating tablets produced persistent circular contractions and spasms, followed by an impairment of the local blood supply. The rate of release of the drug rather than the dose appears to play the dominant role in tissue damage.

An investigation by D'Arcy *et al.* (374), comparing prednisone tablets with prednisolone phosphate in a timed-release formulation based upon the plastic matrix principle, made use of plasma prednisolone and plasma cortisol levels as *in vivo* parameters in man. More uniform prednisolone blood levels as well as an absence of high peaks of plasma prednisolone were obtained with the timed-release formulation. An interesting approach to the measurement of the release of the drug from the tablet involved the collection and analysis of the plastic matrixes recovered from the feces of the volunteers.

Using an *a priori* assumption that a correlation exists between *in vitro* dissolution and *in vivo* availability, Cressman *et al.* (375) evaluated changes in dosage form release characteristics *in vitro* before *in vivo* determination of total plasma radioactivity in man. Aminorex base, fumarate, and pamoate were used in solution, regular tablet, or timed-release tablet forms or, in the case of the pamoate and fumarate, in more than one dosage form. Aminorex-^{14}C was used as the radioactive label in a one-compartment pharmacokinetic model which assumes absorption of the intact drug without metabolism or degradation within the intestinal tract. On this basis, good correlation was obtained between *in vitro* dissolution and *in vivo* absorption rates. The mechanism accounting for the timed-release effect was considered to be due to the nondisintegrating properties of the tablets—a conclusion not yet supported by

[15] Carbomer, Carbopol 934.

in vivo observations. Correlation between prolonged levels of radioactivity and prolonged clinical response was reported, but confirming data were not presented in this paper. In seeking a model animal for use in the preliminary evaluation of nondisintegrating, timed-release tablets, Cressman and Sumner (376) found that such tablets prolonged the absorption period of aminorex in both man and dog but that the rates of absorption differed. The authors suggested that the purebred beagle dog represents a pharmacokinetically justifiable model when used to determine whether a given dosage form has affected the rate of absorption, relative to some readily available dose, of the drug under study.

Using a theoretical approach, Robinson and Eriksen (377) derived equations for the calculation of doses and dosing intervals for multiple-dose therapy of timed-release dosage forms. Both zero- and first-order release of drug from the dosage form were considered in the four-compartment model used. Although optimum blood level patterns will not be produced by the proposed calculations since the available kinetics are nonideal, the authors stated that the "practical" approach produces the only satisfactory dosage form.

A novel approach to *in vivo* characterization of timed-release formulations was employed by Schlagel and Sanborn (378), who studied the extent and time course of activity of benzphetamine administered as a single 75-mg. dose, the same dose given hourly in 15-mg. portions and placebo. The pharmacodynamic criteria included electroencephalograms, systolic blood pressure, oral temperature, respiratory rate, pupil diameter, finger-tapping rate, and a digit-letter coding task. The large, single dose of the drug induced a faster, less gradual, more pronounced response than that provided by the simulated timed-release regimen. The authors stated that these results suggest that the virtue of a well-formulated, timed-release preparation may lie in the blunter, smoother type of pharmacological response.

Ebert *et al.* (379) measured plasma and urine concentrations of equivalent pentylenetetrazol-10-^{14}C by liquid scintillation counting following the administration of timed-release and nontimed-release tablets to human subjects. Figure 3 shows the typical rises and falls in plasma-^{14}C levels exhibited by subjects receiving three doses of nontimed-release tablets; in subjects receiving the timed-release tablets, the plasma-^{14}C levels remained essentially smooth for 12 hr. The conclusion reached was that the timed-release tablets of the insoluble matrix type produced absorption and excretion patterns similar to those obtained with three doses of the drug administered at 4-hr. intervals. In both groups the total amount of drug administered was the same.

In view of the low blood concentration of pentaerythritol tetranitrate in man following the administration of timed-release tablets, Banerjee *et al.* (380) investigated the cat as a suitable experimental animal for *in vivo* correlations of release rate. Dissolution rates of the tablets were obtained using a modification of the USP disintegration time apparatus and showed a gradual release of the drug up to a total of 90% in 12 hr. The percentage fall of blood pressure from basal in cats after feeding timed-release pentaerythritol tablets was measured, and a coefficient of correlation with *in vitro* release rate was obtained. Although the dose of drug and possibly other parameters such as size and the density ratio of adjuvants were not the same in the *in vitro* and *in vivo* trials, the authors concluded that the *in vitro* test is satisfactory for use as a quality control procedure.

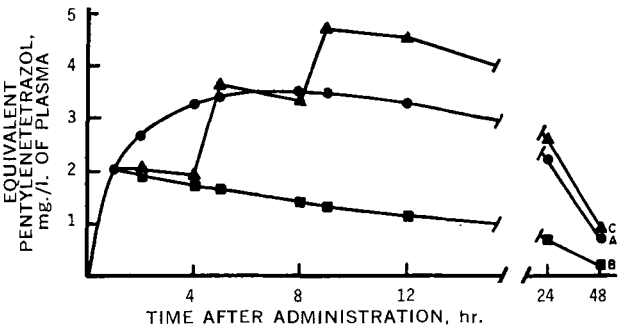

Figure 3—*Average plasma levels of equivalent pentylenetetrazol following oral administration of pentylenetetrazol-^{14}C tablets. Key: Group A, one timed-release tablet; Group B, one nontimed-release tablet; and Group C, one nontimed-release tablet at 0, 4, and 8 hr. (379).*

For an orally administered timed-release tablet formulation of nitroglycerin, Ipsen (381) showed a mathematical correlation between the first-order release rates, the blood nitrate levels, and the therapeutic effects described by skin temperature, systolic blood pressure, and plethysmographic measurements. The double first-order kinetic relations that fitted the blood level and pharmacological data consisted of an exponential function, which correlated with the *in vitro* release, and a second exponential function, which accounted for drug elimination and biotransformation and which depended on the measurement involved.

A clinical case has been reported by Spiegelman and McNabb (382) where 98 tablets of a timed-release iron preparation were recovered from the patient's colon due to the presence of a tumor distal to the trapped tablets. The formulation of these tablets was based on an inert plastic matrix from which the drug was leached out by intestinal fluids. This observation may suggest that a disintegration test may be a necessary specification for tablets to be administered to patients with conditions associated with GI strictures.

Dissolution Rate—During the period under review, research activity in apparatus for dissolution rate testing, factors affecting dissolution rate, and interpretation of results did not diminish. The relative simplicity of much of this work is one explanation for its popularity, but probably the relationship of dissolution rate testing to biopharmaceutics brings such projects into a rather fashionable sphere of pharmaceutical interest.

A review by Hersey (383) of methods available for the determination of *in vitro* dissolution rates of tablets covered 13 methods classified according to agitation and sink conditions. Some procedures measure only the intrinsic dissolution rate, whereas those that measure apparent dissolution rate can usually be modified to measure the intrinsic dissolution rate also.

For standardization of unit tablets for drug availability, intrinsic methods are impractical since disintegration must be allowed to take place. Hersey appeared to prefer the beaker method on the basis of its simplicity

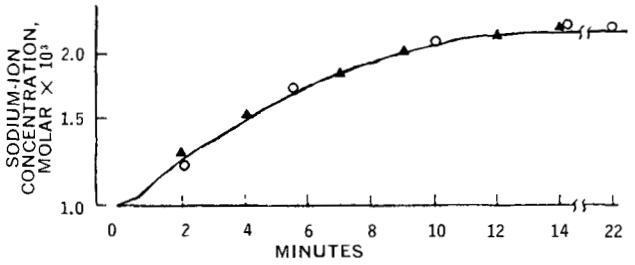

Figure 4—*Electrode response during tablet dissolution* (——). *Key:* ▲, *spectrophotometric salicylate assay; and* ○, *atomic absorption assay for* Na^+; *37* ± *1°, pH 9.0 (390).*

and adaptability. A newer method for *in vitro* assessment of dissolution rate proposed by Langenbucher (384) uses a vertical exchange column containing a fixed bed of drug material traversed by a continuous flow of solvent. Only two, easily standardized apparatus parameters, liquid velocity and mass-specific cell area, are essential to the dissolution process. Reproducibility in the case of homogeneous granules was good, and the correct scale-up to larger dosages or tablet numbers was easily achieved, as were change of solvent and automation. Equations covering dissolution kinetics were derived, and confirmation of the theoretical cube root dissolution kinetics of uniform-size granules was demonstrated.

Cotte (385) reviewed the numerous methods for *in vitro* measurement of dissolution rate from solid, timed-release preparations including dialysis and filtration techniques. He concluded rather surprisingly that the method of Simoons (385*a*) is best since the apparatus presumably simulates physiological conditions in the GI tract. Baun and Walker (386) described a modified Wiley flowthrough apparatus for dissolution rate studies. The results of dissolution tests on compressed tablets of tolbutamide and hydrochlorothiazide were compared with similar determinations in the Levy beaker apparatus.

After a thorough, critical review of dissolution rate testing methodology, particularly with solid dosage forms, Tingstad and Riegelman (387) proposed a continuous flow apparatus, representing modifications of others based on the same principle. The authors strongly expressed the view that a new "standard" dissolution rate method is needed—a need fulfilled by the proposed apparatus. The advantages stated were: greater flexibility; provision of data in the differential form; use of a relatively low volume, homogeneous solvent system; limited accumulation of solute in the system; and provision of solvent flow in a controlled manner related to fundamental dissolution rate equations. The authors attempted to demonstrate the utility of a dissolution rate profile of a prednisone tablet to a formulator. The roughness of the tablet curve demonstrates the uneven release of the drug from the granules as compared to the powder, thereby implying that a smoother curve can be secured by better formulation. How much therapeutic benefit would result from this exercise remains to be demonstrated.

Another apparatus that employs a rotating flask with a sampling port so positioned as to prevent the entrance of fluid into the port was described by Gibaldi and Weintraub (388). Using commercial tablets of aspirin (conventional, buffered, and timed release), the authors were able to obtain an absolute quantitative correlation between absorption and *in vitro* dissolution rate of the drug—a correlation not attainable with the beaker method. In constructing and testing a mechanized apparatus for the USP rotating-basket dissolution rate test capable of handling six dosage units simultaneously, Beyer and Smith (389) discovered variation in results attributable to vibration at 150 r.p.m. or less. They, therefore, proposed control of vibration within a specified limit, as defined by an objective vibration test procedure, or rotation of the basket at a sufficient speed to overcome vibratory effects. The commercial availability of ion-selective electrodes has made it possible to measure conveniently the concentrations of sodium, potassium, calcium, or other ions potentiometrically. Mason *et al.* (390) applied this approach to dissolution rate testing of sodium salicylate tablets. The reliability of the sodium-ion electrode was confirmed by atomic absorption spectrophotometry. Figure 4 illustrates electrode response during tablet dissolution. The primary advantage of the method is the availability of direct readout of drug appearance.

In dissolution rate-limited absorption of poorly soluble drugs considered as proportional to the surface area of the drug, the method used for surface area measurement should, according to Møller (391), be selected for its efficiency in determining the surface that is related to the dissolution process. This involves consideration of the penetration of a liquid into capillaries. For routine control of powders, the author proposed a gas permeability method for determination of specific surface area, estimation of the specific particle number with a hemocytometer, and a layer sedimentation technique to limit the particles of powder to diameters less than 25 μ. Finding it impossible to obtain an accurate drug release profile from timed-release tablets of different companies using the standard disintegration apparatus, Schwarz (392) studied two *in vitro* dissolution methods which were also suitable for use with disintegrating dosage forms. With most formulations tested, the rotating-bottle and flowthrough methods produced equally reproducible results. The rate of flow in the flowthrough cell was not a significant factor; but with tablets that deformed or disintegrated during testing, the rate of flow influenced the rate of release and the reproducibility.

Using the BP disintegration apparatus to measure the dissolution rate of three brands of tolbutamide tablets, Khalil *et al.* (393) assessed the significance of the guided disk and the importance of tube speed. When drug release was rapid, the disk had no significant effect; but a twofold increase in dissolution was observed with a slowly dissolving tablet. A tube speed of 20 strokes/min. without the disk proved to be the most discriminating operating condition. Lerk and Zuurman (394) showed that the pulsation caused by certain peristaltic pumps affected the dissolution rate of aspirin tablets in a flowthrough apparatus.

An automated dialysis method was used by Hersey and Barzilay (395) to measure the dissolution profiles of sparingly soluble tablets of sulfathiazole. The authors

developed a theory which accounts for an increase in the functional surface area due to penetration by the dissolution medium or due to disintegration; this theory also allows for a decrease in the surface area with time. An alternative method of maintaining sink conditions was applied to clomipramine tablets by Richter *et al.* (396), with continuous withdrawal of the solution surrounding the tablet at a constant rate *via* a flow-through spectrophotometer. A simpler yet versatile system which produces sink conditions by a similar principle was described by Marshall and Brook (397). Overcomplexity of design, which they considered introduces other variable factors such as membrane transport, was avoided; only those *in vivo* parameters which, according to the authors, are "easily contrived and reproducible" were included.

Using a 1-cm. sodium chloride cube to represent a standard nondisintegrating substrate, Withey (398) compared the dissolution profiles in seven types of apparatus. By eliminating dissolution variables due to the substrate itself, differences in agitation intensity in the different apparatus could be assessed. The very small vertical agitation component in the rotating-basket apparatus contributed to the poor reproducibility. Although the more homogeneous agitation of the dissolution medium provided by a tumbling cylinder would probably ensure more reproducible results with a disintegrating tablet, the rapid dissolution process is difficult to follow with precision.

The need for a substantial level of dissolution rate testing as a means of controlling manufacturing processes and monitoring production conditions led Beyer and Smith (399) to construct and test a system capable of multiple testing. Based upon the current NF–USP apparatus, the system employs a seven-cell commercial spectrophotometer, a six-channel pump, three water baths, and flow cells. Extensive use of this apparatus in testing provided opportunities for observations of broad significance in dissolution rate testing. These included the influence of vibration on dissolution rate of tablets stirred at low rates and the effect of the passage of tablet particles through the 40-mesh screen on dissolution profiles. The experimental data confirmed the results and conclusions reached by Lin *et al.* (400). A continuous titration technique was developed by Shah (401) for the automated dissolution rate evaluation of both acidic and basic drugs from compressed and enteric-coated tablet formulations. In using the reported titration method, it is necessary to avoid the inclusion of excipients that interfere with the titration assay.

The variety of factors that can influence the dissolution rate *in vitro* is considerable, and a large part of the literature is concerned with identifying and evaluating the extent to which these factors are involved. By microscopic examination of disintegrated tablets, Johnsgard and Wahlgren (402) found that the greater the ratio of excipients to drug, the less was the tendency for aggregates of the active substance to form. *In vitro* studies with tablets prepared by wet granulation showed that such aggregation caused a marked decrease in the rate of dissolution of slightly soluble drugs but not with highly soluble substances. In continuing their studies of the dissolution of poorly soluble drugs, Kornblum and Hirschorn (403) evaluated excipient dilution and compression force effects on dissolution rate. The data obtained demonstrated the importance of the excipient–drug ratio to optimum dissolution rate. Changes in compressive force were more significant with smaller tablets, indicating a less pronounced effect as the dilution factor is increased. In expanding this investigation, these authors (404) used a quinazoline compound and found that the dissolution rate increased as the excipient to drug ratio rose from 3:1 to 7:1 to 11:1. The data supported the conclusion that a larger tablet than is necessary for technical reasons could lead to an optimum dissolution rate.

In determining the effect of different dissolution media on the dissolution rate of hydrochlorothiazide tablets, Alam and Parrott (405) measured the disintegration time and dissolution rate of formulations granulated with acacia, polyvinylpyrrolidone, or starch in distilled water, 0.1 *N* hydrochloric acid, simulated intestinal fluid, and borate buffer at pH 10. Only with the latter was there an increase in the rate of dissolution. No significant alteration in dissolution rate was noted when 0.03% polysorbate 80 was added to the dissolution media, nor could any correlation be established between disintegration times and dissolution rates. Surprised by the failure of previous investigators to use human gastric juice as the solvent in which the dissolution process takes place *in vivo*, Solvang and Finholt (406) used this fluid in studying the effect of granulation and compression on the dissolution rate of phenobarbital, phenacetin, and prednisone. In addition, the effects of particle size and of certain other formulation factors were investigated. Differences in dissolution rate were explained on the basis of surface tension of the dissolution medium, pH effects, complexation, and, in the case of sodium phenobarbital, the failure of the tablet to disintegrate in the acidic medium.

The effect of various surfactants upon the dissolution rate of three steroids of differing aqueous solubility compressed as tablets with magnesium stearate as a lubricant was investigated by Fuchs *et al.* (407). At the concentrations of surfactant and lubricant used (0.2%), no appreciable effect on either the surface tension of the solutions or the solubility of the steroids was observed. However, there was some increase in the dissolution rate from the tablets in the presence of surfactant. The influence of surfactants, physiological surfactants, and certain components of gastric juice on the dissolution rate of drug powder and the effect of premicellar concentrations of surfactant on the dissolution rate of aspirin from a buffered tablet and hard gelatin capsule were investigated by Weintraub and Gibaldi (408). Polyoxyethylene lauryl ether and lysolecithin enhanced the dissolution rate of aspirin from the tablet but not from the capsule. A report by Solvang and Finholt (409) described the effects of polysorbate 80 upon the dissolution rate of tablets of aspirin, phenacetin, and phenobarbital. Only when the particle size of aspirin was smaller than 300 μ did the surfactant cause an increase in dissolution rate. With phenacetin, polysorbate 80 did increase the dissolution rate from granules and tablets, particularly with compositions that were hydro-

phobic. Significant increases in the dissolution rate of phenacetin or phenobarbital tablets occurred when sodium carboxymethylcellulose solution was used as the granulating fluid, but this did not take place when polyethylene glycol 6000 was used.

Although dissolution measurements are now used routinely in the developmental design of tablet dosage forms, this parameter cannot be considered as the sole criterion for assessing the effect of additives on drug performance. An example of the erroneous conclusions that can be drawn was reported by Florence (410) in studies of the dissolution and activity of chlorpromazine hydrochloride tablets in the presence of polysorbate 80. Despite an increased dissolution rate of drug, the activity measured by the death rate of goldfish was decreased, possibly due to an interaction of the drug with higher concentrations of surfactant. Krowczynski *et al.* (411) reported some evidence that tablets prepared with low viscosity binders may tend to release a soluble active ingredient more rapidly than those prepared with higher viscosity binders. No explanation was given as to why gelatin was an exception.

In an attempt to determine the mechanism that explains the alteration of dissolution rates by coprecipitation of drugs with polymers, Simonelli *et al.* (412) selected the sulfathiazole–polyvinylpyrrolidone system. Coprecipitates were prepared from aqueous and alcoholic solutions and compressed into tablets on a Carver press. Dissolution studies were run in an apparatus which supported the tablet within the die but with only one surface of constant surface area exposed. Experiments included: the effect of polyvinylpyrrolidone molecular weight on sulfathiazole release rate; the effect of polyvinylpyrrolidone weight fraction on sulfathiazole release rate; mechanical mix, X-ray diffraction, and solubility studies; comparison of the simultaneous sulfathiazole–polyvinylpyrrolidone release rates; sulfathiazole release into polyvinylpyrrolidone solutions; sulfathiazole release *via* the polyvinylpyrrolidone carrier effect; and theoretical calculations of sulfathiazole release rate. On the basis of these studies, a physical model was derived which satisfactorily explained the observed release rates of all sulfathiazole to polyvinylpyrrolidone weight ratio systems. The results of this investigation showed that the rate of solution of sulfathiazole was greatly increased by the use of coprecipitation techniques with polyvinylpyrrolidone.

During an investigation of the influence of pepsin in the dissolution medium on the dissolution rate of a tablet containing triamterene and hydrochlorothiazide, Yen (413) noted that only the dissolution rate of the latter drug was adversely affected. An incidental and unexplained finding was the significantly lower dissolution rates for both drugs in one of two sets of supposedly identical sets of apparatus.

A review by Wagner (414) summarized in outline form the factors influencing the *in vitro* dissolution rate of drugs from capsules and tablets, with a discussion of the interdependency of some of these factors. Although there are conditions of an *in vitro* dissolution rate test that will give results correlating with *in vivo* results for a variety of tablets containing the same drug, such conditions cannot be applied to other drugs. Equations for interpreting *in vitro* dissolution rate data based upon the surface area concept, first- and second-order kinetics, and exponential release were presented. The relationship between the dissolution rate of drug substances and tablets made from them was analyzed in a review paper by Fuchs and Raptis (415). The mathematical treatment of mechanisms involved in dissolution covered such parameters as temperature, rate of rotation, surface area, surface tension, and viscosity. Types of dissolution rate apparatus and proposed mathematical models were also discussed.

Hom and Miskel (416) recommended soft gelatin capsules as a preferred dosage form for low dose medication of relatively insoluble drugs and for drugs where high blood levels are desirable as rapidly as possible after administration. The data on which this recommendation was based represent dissolution rate comparisons of 10 different drugs in soft gelatin capsules or commercial tablet forms. The inclusion of solvents or surfactants in the liquid system used in the soft gelatin capsule dosage form plays an important role in enhancing the dissolution rate. The authors suggested the advisability of performing *in vivo* studies, but they did not report such data in this paper. It is quite possible that gelatin itself or the additives employed in the capsule form might inhibit absorption in the more complex living organism. The conversion of a commercial tablet dosage form to a capsule in order to conduct a double-blind clinical study is a questionable approach from a biopharmaceutic point of view. Shah and Moore (417) showed that such a procedure leads to an increase in dissolution rates of drugs after conversion to the capsule form. The authors suggested that the primary granules formed by the normal disintegration of a tablet in an aqueous medium differ in some physical manner from the granules obtained by grinding up a tablet. To prepare the capsules from the ground-up tablet, various diluents such as potato starch, urea, and glycine were added before filling into hard gelatin capsules. Such adjuvants had some influence in increasing the dissolution rate. The authors did not investigate the possibility that interaction of some formulations with gelatin might decrease dissolution rate significantly.

Microencapsulation of small ferrous sulfate granules with ethylcellulose by an undisclosed technique was used by Dahlström and Eriksson (418), with the objective of protecting the gastric mucosa from direct contact with the drug cyrstals. Tablets prepared from the coated granules disintegrated rapidly *in vivo*, and *in vitro* tests indicated a rapid dissolution of iron in gastric juice. However, no studies were conducted to confirm whether local irritation of the gastric mucosa was reduced and whether absorption of iron was facilitated or inhibited. In a review of various factors that influence the dissolution rate of crystalline substances, Tawashi and Piccolo (419) suggested the possibility that crystal defects may affect the dissolution; they recommended investigation of this possibility in formulation design.

Claiming that, in many cases, relatively simple *in vitro* tests are largely sufficient to predict the GI availability of a drug from a solid dosage form, Jaminet *et al.* (420) used the beaker method with low agitation

on phenobarbital tablets to distinguish between the effect of process variables and formulation factors. Even if the predictability for the absorption of phenobarbital tablets could be conclusively demonstrated, there is no assurance that similar "simple" tests could be used to predict the absorption of other drugs. In a novel approach to the assessment of the dissolution rate of drugs from solid dosage forms, Ceschel and Mazzonetto (421) used a method based on changes in the electrical conductivity of the dissolution medium due to the progressive elution of high dosage ionic substances into solution. The influence of the excipients used was negligible; and although the authors claimed that even with interfering substances the sum of the partial values due to each component can be determined in advance, this may not be valid in practice when considering differences between formulations. A similar approach has been in use for the routine quality control of timed-release potassium chloride tablets.

In conjunction with 10 collaborators from several laboratories, Alexis *et al.* (422) tabulated the requirements of various pharmacopeias for disintegration times of tablets and reviewed methods for dissolution rate determination. The beaker method of Levy was selected to study the effect of formulation and other factors on the dissolution of methaqualone, partly to show the value of dissolution studies in place of disintegration tests. Reducing the number of tablets used in a dissolution run increased the variation in replicate results. On this basis, the authors concluded that to use the beaker method successfully, it is necessary to take more than one tablet when intertablet variation is large. The reasons for such variation, and methods for reducing its level, were not discussed. A conclusion that precise control of all test conditions is essential to ensure reproducibility will not catch analysts unaware. Using a rapidly disintegrating, wet granulated tablet formulation, the authors noted a marked reduction in dissolution rate of the active substance, partly due to the presence of unsuitable (contraindicated?) excipients and partly due to the effect of consolidation in a tablet. Two alternative tablet compositions—one wet granulated and the other prepared by direct compression—showed more rapid dissolution, probably due to dispersion of the methaqualone in the hydrophilic excipients, which reduced the effect of its hydrophobic nature. In all three formulations studied, there appeared to be no justification for the presence of the large number of excipients.

Research involving the influence of processing variables on dissolution rate is limited in quantity and deals mostly with the effect of compression force (degree of consolidation or compaction). Smith *et al.* (423) studied the relation between dissolution rate and compression force for tablets of lithium carbonate containing polyvinylpyrrolidone as a binder. A maximum dissolution rate at relatively low consolidation apparently depended on the deformation characteristics of the granules and was, therefore, related to the binder concentration. Following a subsequent decrease in dissolution rate due to bonding, a second peak in dissolution rate was obtained which was independent of binder concentration. Kristoffersson (424) attempted to evaluate the effect of

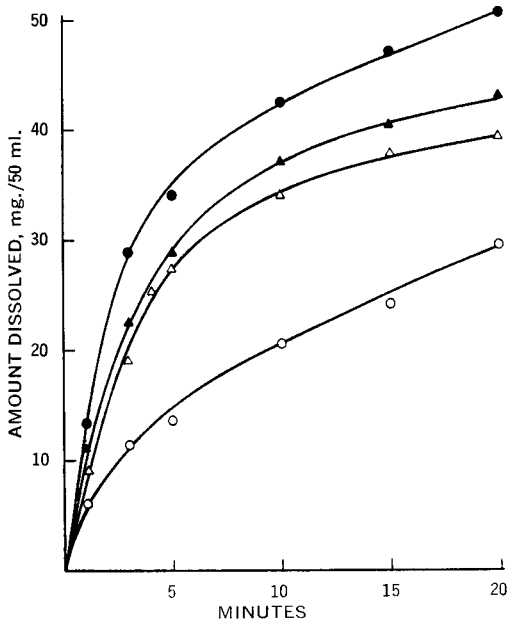

Figure 5—*Dissolution of spray-dried and air-attritioned powders and compressed tablets in 50 ml. aqueous solution at pH 1.2 Key: △, spray-dried powder; ○, air-attritioned powder; ▲, spray-dried tablet; and ●, air-attritioned tablet (403).*

several hydrophilic binders and the influence of compression force on *in vitro* and *in vivo* release rates of hydrophilic drugs. The effects of these two parameters could not be distinguished as separate phenomena. For antipyrine (phenazone) granulated with gelatin, the dissolution rate decreased as the compression force was increased, but in other cases an increase in dissolution rate with compression force was observed. *In vivo* test results generally showed larger variation than did the *in vitro* data. In a rather complicated study involving the effect of different binders and granulating techniques, Van Oudtshoorn *et al.* (425) also presented some results related to compression pressure and dissolution rate.

Monkhouse (426) showed that the rate of solution of relatively insoluble powders can be greatly enhanced by a simple processing technique, which apparently results in molecular dispersion on the extensive surface of an adsorbent such as colloidal silica. The bonding forces were relatively weak so that drug molecules were easily displaced by dissolution media; and since the adsorbent was insoluble in water, the system released free drug into solution which should have been available for absorption. According to Kornblum and Hirschorn (403), dissolution rate studies of various physical forms of a pure drug can be misleading unless a proposed solid dosage form is included in the comparisons. Dissolution rate determinations were made on spray-dried and micronized forms of a poorly soluble quinazoline compound. As can be seen from Fig. 5, the spray-dried powder dissolved more rapidly than the micronized powder. Formulation of these powders so altered the interparticulate aggregation effect demonstrated by the pure forms that the tablet made with spray-dried powder dissolved more slowly than did the one made with the micronized powder. Industrial pharmacists are well aware of the influence of the physical form of the com-

pressed tablet and take this factor into consideration when designing their preformulation and formulation programs.

In an experiment designed to determine the effect of mode of administration of tablets on dissolution rate, Sandell *et al.* (427) prepared phenacetin tablets by wet granulation with gelatin solution and by direct compression. Methods were developed to simulate taking tablets by swallowing whole with a little water, after disintegration in water, or after chewing. The test tablets were dropped straight into the dissolution medium or were allowed to disintegrate in 25 ml. water prior to rinsing into the dissolution beaker with a saliva–water mixture, or they were chewed for 10 sec. followed by rinsing the mouth three times with water before emptying into the dissolution beaker. Dissolution rates for all tablets prepared by wet granulation were approximately equal, but considerable variations were observed with directly compressed tablets. The fastest rate of dissolution occurred after chewing the tablets made by direct compression.

As part of a series of papers by Wagner (428), examples of quantitative correlations of *in vivo* with *in vitro* data were presented for such drugs as penicillin, amphetamine, erythromycin, aspirin, tolbutamide, griseofulvin, and salicylamide. Katchen (429) also attempted to correlate dissolution rate with absorption of diazoxide and griseofulvin in man. For diazoxide tablets, high correlation was found between the dissolution in acid medium and the area under the 0–6-hr. blood level curve. With griseofulvin tablets varying widely in their composition and dissolution characteristics, the dissolution rate in simulated intestinal fluid correlated with the area under the 0–25-, 49–173-, and 0–173-hr. plasma level curve, which corresponded to the effect of a single dose, the plateau region, and the total experimental period, respectively. One tablet was administered daily for the 7-day period. A comparison by McGilveray *et al.* (430) of the USP XVIII limit for the dissolution rate of nitrofurantoin with *in vitro* and *in vivo* availability studies on six tablet formulations led to the conclusion that satisfactory formulation is difficult and that the official test may provide inadequate control.

Using a commercially available model of an apparatus designed to assess the absorption behavior of organic substances by *in vitro* diffusion studies through an artificial lipoid barrier, Stricker reported his results on 19 organic compounds (431) and on tablet formulations of aspirin and potassium penicillin (432). Comparing the *in vitro* dissolution rate of chloramphenicol under various conditions from several different size fractions of powder and three granule and tablet formulations, Andersgaard *et al.* (433) observed more rapid release from tablets granulated with gelatin solutions than from those granulated with carboxymethylcellulose mucilage or an alcoholic solution of polyethylene glycol. In contrast, plasma levels of chloramphenicol in human subjects showed no significant differences between the three tablet formulations, indicating that the dissolution process is probably not the rate-limiting step for absorption. By varying the manner of addition of anagestone acetate to tablet formulations and measuring dissolution rate and progestational proliferation of rabbit uterus after oral administration, Sawardeker and McShefferty (434) established a correlation between an *in vitro* dissolution rate test and a physiological test depending upon the drug's presence at its site of action. Along similar lines, while studying the effect of excipients on the dissolution rate of tablets in the alimentary canal of the dog, Boucard *et al.* (435) abandoned the use of a radiopaque tracer technique and measured changes in the animal's heart rate, which they related to the release of atropine from the tablets. Since factors other than dissolution rate may be involved in this physiological parameter, this method may not be appropriate for precise correlation with dissolution rate.

Table I—Tablets, U. S. Drug Recalls for the 10-Month Period of May 13, 1969–March 9, 1970

Reason for Recall	Number of Recalls	Percentage of Total
Subpotent	21	35
Disintegration	18	30
Content uniformity	11	18.3
Weight variation	4	6.6
Superpotent	2	3.3
Bacterial contamination	1	1.7
Mechanical strength	1	1.7
Organoleptic	1	1.7
Stability	1	1.7
Total	60	100

The dissolution rates of commercial regular, buffered, and timed-release tablets of aspirin were determined at 37° by the rotating-flask method at agitation speeds from 0.9 to 2.4 r.p.m. and were correlated by Weintraub and Gibaldi (436) with previously reported absorption data. Regardless of agitation intensity, the dissolution rate decreased in the order: buffered > regular > timed-release. Aspirin dissolved from the buffered tablet about twice as rapidly as from the regular tablet and about eight times as rapidly as from the timed-release tablet. On the basis of the *in vivo–in vitro* correlations, the authors suggested that the rotating-flask method (437) offers advantages over the beaker method.

Wagner (438) proposed a distribution plot concept as a means of evaluating dissolved time data derived from the testing of conventional tablets and capsules. Linearization of such data by plotting on logarithmic-probability graph paper permits all data derived from a given test to be adequately described by the parameters of the distribution such as the median and standard deviation in the log-normal case. It is then possible to correlate these parameters with *in vivo* data—an obvious advantage in the establishment of regulatory dissolution rate standards.

TABLET QUALITY

The inclusion of new parameters such as dissolution rate and content uniformity in regulatory requirements for tablets has resulted in an intensification of research activity directed toward testing methodology and specifications for the quality of tablets. In a comprehensive review of the control of tablet quality, Cooper and Hersey (439) delineated the current situation and trends in the pharmaceutical industry and in government.

Critical analysis was made of practices and requirements concerning organoleptic properties, mechanical strength, disintegration time, weight variation, content uniformity, dissolution rate, microbiological status, and stability. In view of the general absence of literature reports of specific deficiencies in the quality of tablets on the market, the authors tabulated (Table I) U. S. recalls of tablets during a recent 10-month period. The significant problems appear to be in the areas of drug content and disintegration time, problems that can be solved by improved technology and scientific stability testing. Sinotte (440) reviewed the criteria for tablet quality from the point of view of an experienced director of quality control. While the obvious requirements for final product quality described as "fitness for use" are not neglected, the author indicated but did not discuss in detail the importance of in-process controls, accountability or total material control, control charts to indicate developing trends in a quality parameter, and automated testing.

The possibility of contaminating tablets with nonmicrobial particulate matter during processing steps has only recently received the attention it deserves. In a step-by-step analysis, Lachman and Lantz (441) presented data which showed that particulate contaminants can be found at almost every stage in the manufacture of tablets. Metallic contaminants include iron, stainless steel, brass, and aluminum, whereas hairs, fibers, rubber, wood, paint chips, and paper are representative of the nonmetallic variety. Detection methods currently used are visual, magnetic separation, electronic separation, screening, X-ray, and solution filtration. Sources of contamination from processing steps involve mills, mixers, compactor rolls, scrapers, dryers, feed frames, and punches. The authors presented a well-planned program for keeping nonmicrobial contamination at the lowest possible level.

A review by Slevin (442), in outline form, covered the steps taken by one manufacturer to identify the potential causes of cross-contamination in tablet manufacturing and the steps taken to prevent actual occurrences. The use of a tote-bin system for minimizing cross-contamination by dust containment in the transfer of powders and granules prior to tablet compaction was described by Fox (443). The tote-bins consist of mobile hoppers with a butterfly flow valve at the discharge port. This design does not result in a mass flow profile so, to reduce segregation on discharge, a flow-corrective conical insert is necessary. The author also described other techniques to ensure dust containment in mixing, granulating, and milling operations. Dust collection for product and personnel protection during the manufacture of tablets was discussed by Chase (444), with comments on the feasibility of recovering product from the collected dust in special cases.

A paper by Sykes (445) reviewed the control of microbial contamination of pharmaceutical products. Sources of contamination and data concerning contaminants in drug substances, excipients, and tablets were described. Not surprisingly, the heaviest contamination was found in tablets prepared from drugs such as digitalis, ergot, and thyroid originating in plants or animal tissues. In the author's experience, processing steps in tableting were such that bacterial growth could take place during moist granulation, but subsequent drying and compression rendered the organisms nonviable so that the final product was no worse microbiologically than the original components. In an extensive consideration of the microbiological purity of pharmaceutical preparations, Buehlmann *et al.* (446) stated that harmless saprophytic microorganisms in limited numbers can be tolerated in nonsterile products. In addition to limiting the maximum permissible total count, selective testing for specific organisms of practical significance is sufficient. A section in USP XVIII (15) described tests for the estimation of the number of viable aerobic microorganisms present and for freedom from designated microbial species (*Salmonella*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*) in pharmaceutical articles of all kinds, from raw materials to finished products. Microbiological studies by Wanandi and Speiser (447) on 103 marketed tablets showed that over 60% contained more than 100 microorganisms/g., but only 3% contained more than 10^4 microorganisms/g. Most contaminants were aerobes and spore-producing bacilli, but 4% of the tablets contained enterobacteria. About 97% of the tablets contained fewer than 100 molds/g. Most contamination could be traced to excipients of natural origin, especially starches.

Cox and Spanjers (448) described an interesting method for preparing sterile implants which avoids the need for special precautions during a conventional tableting operation. The drug, usually a steroid hormone, is compressed together with a bactericidal substance such as 1% w/w chlorobutanol, menthol, or camphor which also supplies a lubricant effect. By heating the implant at 80° for 20 hr., the bactericidal agent is removed by volatilization and sterilization is effected. Regrettably, the authors reported no attempt to challenge the effectiveness of the sterilization methods by intentional challenge with spores or viable microorganisms during manufacture.

The inadequacy of indirect methods such as porosity, strength, and disintegration time for studying the physical properties of tablets was referred to by Hess (449). A useful technique for detailed examination of particles and tablet surfaces was shown to be scanning electron microscopy at a magnification of 100–5000 diameters. Photographs of coated active substance after compaction and comparisons of tablets prepared by wet granulation and direct compression demonstrate the exceptionally large depth of field attainable. Fuchs (450) also reported studies using scanning electron microscopy to examine the surfaces of tablets prepared from corn starch, lactose, and cyproterone acetate. Deformation of the starch grains without fragmentation was observed, and the formation of solid bridges between the crystals of lactose and cyproterone acetate was demonstrated. These solid bridges, formed by cold working of the substances, were considered to be undesirable, especially with micronized substances, owing to the resultant decrease in pore volume and surface area which may reduce the rate of drug dissolution. However, corn starch can produce large pores even in

tablets prepared at high compaction pressures, due to elastic recovery following deformation under pressure.

Scanning electron microscopy was also used by Schoepflin and Fuchs (451) to demonstrate differences in the texture of broken surfaces of timed-release tablets prepared at different compaction pressures which were related to the drug release rate. Decreasing porosity and the formation of solid, interparticulate bonds with increasing pressure decreased the rate of drug release, but elastic recovery of tablets prepared at high pressure produced fissures and cracks which increased the release rate. The results stressed the importance of defining and controlling the compaction pressure in such cases. Koehler (452) also studied and reported on the relation between the microstructure of tablets and the release rate of the active drug substance.

Drug Content—The inclusion of requirements for content uniformity of tablets in pharmacopeias initiated a surge of activity in the development of automated analytical procedures and in the search for assay methods of sufficient sensitivity for use with unit doses of potent drugs. USP XVIII (15) permitted the use of automated procedures, provided that the results were of equivalent accuracy to the official procedure, the latter remaining the definitive one in case of differences. NF XIII (16) also accepted automated procedures as demonstrating compliance if the exact chain of chemical and physical steps described in the official test was followed.

Surveying the situation since the quality of reserpine tablets on the U. S. market was first questioned in 1967, Banes and Finkel (453) reported that in spite of a more intensive investigation the results of a second study initiated in 1968 showed an appreciable reduction in the defect rate within a 2-year period. In a total of 956 samples tested, only 35 (3.7%) were defective compared with 9.4% in the previous study. Thirty-three of the defective samples were subpotent, and none was superpotent. The semiautomated analytical technique used to determine the reserpine content of the tablets was described by Page (454). The procedure closely parallels the method of USP XVII.

A review article by Kuzel *et al.* (455), with 293 references, covered developments in the area of automated techniques in pharmaceutical analysis through mid-1968. Although not oriented toward dosage forms, the section on solid sampling methods dealt primarily with unit dose tablet assays. An interlaboratory, collaborative study of the GC assay methods now covered by USP XVIII monographs for tablets of atropine sulfate and of scopolamine hydrobromide was reported by Grady and Zimmerer (456). An added internal standard along with alkaline buffer is used to extract the drug which, following concentration, is injected into the chromatograph. The authors stated that the method is applicable to identity and content uniformity testing.

By measuring the fluorescence intensity of a formic acid–chloroform-treated, powdered, buffered aspirin tablet, Shane and Stillman (457) claimed to have reduced assay time, aside from calibration, to less than 10 min. The authors emphasized that only a monochromatic spectrofluorometer with a solid-state photomultiplier, carefully maintained and periodically calibrated, should be used. To overcome the time-consuming, expert attention required by most official compendia for the analysis of salicylic acid and aspirin, Watson *et al.* (458) described a GC method for the simultaneous analysis of both compounds. Diazomethane in tetrahydrofuran is used to convert the drugs to their methyl esters, which are eluted isothermally from a 5% OV-210 on Diatoport S glass column. When tested by this method, synthetic mixtures of aspirin and salicylic acid as well as commercial compressed and enteric-coated aspirin tablets gave results generally in excellent agreement with USP values. Dechene *et al.* (459) also described the use of GC for analysis of compound aspirin tablets, following preliminary separation of aspirin and phenacetin from caffeine and codeine.

The use of a methyl acrylate–methyl methacrylate copolymer matrix for timed release yields tablets too hard for manual grinding. Sennello (460) described a rapid GLC method for the determination of methamphetamine hydrochloride in tablets of this type; the method provides excellent recovery and precision. Whole tablets are dissolved in chloroform, followed by conversion to the methamphetamine base with potassium hydroxide. As an internal standard, *n*-tridecane is added and an aliquot of the resulting solution is then injected into a gas chromatograph. The method is not applicable to the determination of drug release rate.

An interesting variation in automated spectrophotometry by Ahiya *et al.* (461) involves the use of a dual-extraction procedure for the analysis of phenmetrazine hydrochloride tablets. The first extraction step requires three mixing coils and two separators. In the first, chloroform is separated from the aqueous phase; in the second, chloroform is washed with water, thereby eliminating emulsion problems. The second extraction step involving reextraction of phenmetrazine into dilute hydrochloric acid from chloroform is automated by the use of a continuous digestor in the form of a heated rotating helix.

Abdine *et al.* (462) reported a method using orthogonal functions to correct for irrelevant absorption spectra due to various diluents during the analysis of tablets. The method is proposed as a means of routine analysis without the need to extract active substances from excipients. A colorimetric assay procedure for primary amines in tablets was described by Fontani and Morandini (463). Secondary and tertiary amines and several compounds commonly associated with amphetamine in dosage forms gave no interference. Atkinson (464) showed that multiple attenuated total reflectance IR spectroscopy represents a possible method for the rapid identification of tablets containing barbiturates. Small samples of 1–2 mg. were suitable, and excipients including colorants and coatings had no effect.

In searching for an analytical method particularly applicable to esters, Urbanyi and Lin (465) found IR absorption to be more reliable than any other reported in the literature. For methylphenidate hydrochloride tablets, an automated system consisting of a Technicon SOLIDprep sampler II, a proportioning pump, a continuous filter, and a Perkin-Elmer IR 621 was assembled. Analytically the method involves a simple chloroform extraction and determination of the intact ester car-

bonyl. The authors expressed the view that the advantages of the technique as a new application in automation of tablet content uniformity were demonstrated. The variable composition of esterified estrogens precludes the availability of a valid standard for all batches of tablets. Weber *et al.* (466) solved this problem by using as a standard a sample of the same lot of USP esterified estrogen powder used to prepare the batch of tablets. The automated, analytical procedure employed for the content uniformity test is based on the principle of sulfuric acid-induced fluorescence.

A GC assay for tablets containing belladonna alkaloids in combination with phenobarbital was developed by Zimmerer and Grady (467). After acid extraction of the phenobarbital and curing of the column, the method was sufficiently sensitive to allow assays of individual dose units of hyoscyamine sulfate, atropine sulfate, and scopolamine bromide. Wide variation in content uniformity of digitoxin and digoxin tablets has resulted in recalls from the U. S. market of a number of such preparations. Cullen *et al.* (468) described a sensitive, specific, automated procedure for the unit dose analyses of such tablets based upon the fluorometric measurement of the dehydration products of the cardiotonic steroids as a consequence of their reaction with hydrogen peroxide in concentrated hydrochloric acid. Myrick (469), on the other hand, used thiobarbituric acid as the color reagent for an automated analytical system for testing the content uniformity of digoxin tablets.

Both fluorometric and colorimetric methods were modified by Kabadi *et al.* (470) for the semiautomated analysis of unit doses of reserpine. The fluorometric determination proved to be more sensitive and free from excipient interference. Bryant *et al.* (471) described an automated system for the assay of chloral hydrate in single tablets. Spectrophotometric determination at 605 nm. was used to measure the intensity of the blue complex between chloral hydrate and quinaldine ethiodide in alkaline solution. A detailed description with flow diagrams and photographs for the construction and operation of an automated system for the assay of single tablets appeared in a paper by Beyer and Smith (472). The modular instrumental assembly has the capacity of handling up to six different types of tablets sequentially, with automatic changes in standards or dilutions. The tablet data presented provide examples of the application of the system for unattended UV analysis of a wide variety of steroid tablets. Geller *et al.* (473) described a procedure for the determination of ascorbic acid in multivitamin preparations including tablet dosage forms. Based upon the coupling reaction of diazotized 4-methoxy-2-nitroaniline with ascorbic acid, the method represents an adaptation of a colorimetric test used manually for many years.

The statistical aspects of the USP content uniformity test for tablets received the attention of several investigators. The product specifications in USP XVII and NF XII include rubric limits, weight variation requirements, and content uniformity limits. In the absence of provisions for stating the degree of confidence to be placed on the experimental findings, Comer *et al.* (474) proposed a plan which combines the information from the weights of a large (100–200) number of tablets with information obtained from single-unit assays on a smaller (3–10) number of units from the same lot. Statistical equations based upon tolerance limits for normal distributions were derived, computer simulations were run to justify these distributions, and data from a tablet product involving 20,000 tablet weighings and 1800 assays on 200 lots could be fitted to the proposed formulas. The authors stated that more specific information on tolerance intervals is obtained by the proposed method than by existing tests in the official compendia.

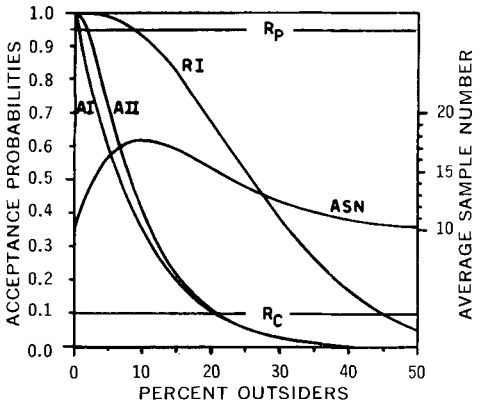

Figure 6—*Characteristics of two-step sampling plan for content uniformity of USP–NF. Key: AI, operating characteristic* (OC) *curve for acceptance after the first sampling* {*10,0*}; RI, OC *curve for rejection after the first sampling* {*10,2*}; AII, OC *curve for acceptance after the second sampling* {*10,1;20,0*}; ASN, *average sample number related to percent outsiders;* R_p, *producer's risk level* (P_a = *0.95*); *and* R_c, *consumer's risk level* (P_a = *0.10*) (*477*).

In further criticism of the compendial test (475), the operating characteristics of the official sampling plans for content uniformity tests were developed and formulas were presented for studying the effect of slight changes in drug content and tablet weight during manufacture upon the probability that a particular lot will meet the official content uniformity limits. These formulas include the proportional process biases for the coefficients of variation of tablet weight and assay data. Due to a difference between the sampling plans in page proof for USP XVIII and the final text in the compendium, Sampson *et al.* (476) reviewed the effect of the new sampling plan on the probabilities of meeting content uniformity requirements for tablets in USP XVIII. Revising their statistical analysis on the basis of the new plan, the authors concluded that the probability of passing a lot, when the coefficient of variation increases, is greater for the new plan than for the old.

Pietra and Setnikar (477) analyzed sampling plans for uniformity of dosage forms as required by 12 different pharmacopeias. The most critical uniformity specification appears to be the two-step sampling plan for content uniformity in the USP and NF. As shown in Fig. 6, the operating characteristic curves show how little the second step adds to the number of tolerated outsiders at the producer's risk level and practically none at the consumer's risk level. The coefficient of variation allowed for content is comprehensive for variability of actual content and for the apparent variability—a reflection of

the effect of analytical error. Depending upon the precision of the analytical method, the allowances for content variability are different for each drug to which the test must be applied.

For a sample of tablets to conform with the requirements of the USP XVIII content uniformity test, the allowable standard deviation of results must decrease as the arithmetic mean value obtained for the sample deviates increasingly from the theoretical mean. The influence of the analytical error on the conclusions reached was considered by Pedersen *et al.* (478), using a computer simulation of a model tablet batch. The results indicated that it is impossible to determine accurately the variation in drug content from tablet to tablet without having calculated the contribution of the assay error on the content uniformity results. Polderman and de Blaey (171), in a survey of mixing problems, concluded that the USP XVIII content uniformity test is a good criterion for solid dosage forms. However, they considered that the limit of 50 mg. of active substance for which content uniformity testing is required is not satisfactory and should rather be defined on the basis of the proportion of active substance in a tablet.

In view of the low dose of drug required in cyanocobalamin tablets, methodology for unit dose assays is complicated by the need for a sample larger than is available in a single dose. Therefore, Nessel *et al.* (479) used radioactively labeled ^{57}Co-cyanocobalamin for a study of the uniformity of distribution of the drug in tablet formulations. Stabilized (protected) cyanocobalamin in 0.1 or 1.0% gelatin compositions or in a 1% resinate composition was used. The degree of mixedness of each formulation was satisfactory. However, statistical analysis of the data showed that after compression and unit dose analysis, ^{57}Co-cyanocobalamin content variations were significantly lower for the 1% gelatin product than for the resin product. Although the 0.1% gelatin product showed lower variability than the 1% resin product, this difference was less marked than with the 1% gelatin product, a difference attributed to the 10-times-greater dilution of the drug.

In the preparation of tablets in which the drug is applied in the form of a coating on a placebo core, Carstensen *et al.* (480) found that tablet size influences variation in drug content uniformity. Since tablet-to-tablet variation decreases with an increasing number of coats, the application of a given quantity of drug is best accomplished with a larger number of coatings of a more dilute coating mixture. The data also supported the view that a higher level of content uniformity is obtained when starting with a large rather than a small core.

Organoleptic Properties—In spite of the fact that examination of the organoleptic properties such as appearance, odor, and taste play an important role in the quality control of tablets, the literature is practically devoid of research papers on this subject. Stone (481) proposed a system of inspection of tablets on both sides, in special trays, under controlled lighting and for a predetermined interval of time. Defective tablets are marked, separated, and then rated in accordance with a table of major and minor defects. The total number of units assayed is related to batch size, and the time interval for inspection is adjusted to the tablet size and the desired intensity of inspection. In taste coverage experiments with four bitter amine drugs in the form of polycarboxylic acid ion-exchange resin adsorbates, Borodkin and Sundberg (482) found a significant reduction in bitterness. Additional taste coverage was obtained by coating the adsorbate particles with cellulose derivatives. Incorporation of the adsorbate into chewable tablets did not result in loss of taste coverage. *In vitro* studies of drug release from adsorbates demonstrated that identical coating levels on different adsorbates did not yield similar release rates, indicating the influence of varying physical properties of the drug substances. It is probable that extensive biopharmaceutic studies would be necessary before any commercial utilization of this procedure for masking undesirable taste characteristics can be adopted.

Weight Variation—Alsos *et al.* (483) discussed the importance of considering the intended (theoretical) weight of tablets when assessing the weight distribution of individual tablets in a batch. The mean weight of a sample is not a suitable parameter on which to base conclusions regarding the entire batch since the tablet weights within the batch may not conform to a normal distribution. Samples of marketed products collected by official inspectors provide inadequate information upon which to base a regulatory decision. The authors suggested that responsibility for complete control must rest with the manufacturer. On the basis of the proportional relationship between tableting pressure and tablet weight, Briner and Courtin[16] (484) designed a strain gauge apparatus for continuous recording of the pressure as a means of monitoring tablet weight. In the event of a significant departure from mean weight, the apparatus can produce a warning signal or automatically stop.

Delonca *et al.* (485) investigated the relationship between die diameter, granule size, and weight uniformity of tablets. Although the effect of die diameter was in some cases inconclusive, for dies of 8–12 mm. the smaller granule fractions between 250 and 800 μm. produced the smallest weight variation. Factors that determine the uniformity in weight of tablets were studied by Bessho *et al.* (486). These factors include compression tooling defects, size ratio of granule to die, flow properties, feed system, level of material in the hopper, and production rate. The authors made the surprising comment that friction, sticking, chipping, and capping during compression are the factors most likely to cause weight variation. It seems reasonable to consider that a tablet composition exhibiting any of these four defects could not be described as adequately formulated, unless defective tooling was responsible.

By using a simple die simulator consisting of a 12-mm. die cavity, the effect of particle shape on the variation of fill was assessed by Ridgway and Scotton (487). Several size ranges of material were separated into batches of different shapes using the method described by Ridgway and Rupp (134). As might be expected, the mean weight and uniformity of die fill decreased as the

[16] In collaboration with Philips AG.

shape became less regular. Tablet weight variation was measured during compression of lactose granules of different size and shape by Ridgway *et al.* (488). The results were correlated with the bulk density and the behavior in a modified annular shear cell, which permitted measurement of the normal force exerted by the granules as they dilated under shear.

Disintegration Test—The popularity of the dissolution rate test has resulted in a corresponding decline in research activity involving disintegration time testing. Klie (489) critically evaluated a commercially available, multipurpose tablet and granule testing instrument with accessories for carrying out various friability, disintegration, and dissolution tests. The discussion included a comprehensive comparison of physical test methods in various pharmacopeias. Klie stated that the rapid disintegration of tablets has always been important in Europe in view of the common practice of patients to disintegrate the tablet in water before swallowing it. While this is undoubtedly true, the practice was related to custom and not to an early recognition of dissolution rate-limited absorption. Klie's comment that in the United States the mechanical strength of tablets was more important than short disintegration times as a consequence of the shipping of tablets in bulk quantities is inaccurate. There were and are no specific regulatory requirements for tablets in the United States, while there has been a legal standard for disintegration time using an apparatus under controlled conditions of agitation with a far more precise end-point than existed in most European countries.

Sanders (490) also discussed the requirements of different pharmacopeias and has proposed a simple method of determining the particle size of tablet fragments after disintegration using an instrument which incorporates a set of sieves. Sandell (491) carried this idea further with an apparatus consisting of three superimposed sieves, with the largest mesh size on the top and the smallest on the bottom. The sieve assembly in a Plexiglas tube is placed in a beaker of water at 37°, with the tablet on the top sieve, and agitated mechanically. After a certain interval, the apparatus is removed from the beaker, the sieves are dried, and the residue on each sieve is weighed. Tests on phenacetin tablets were able to distinguish clearly the far more rapid disintegration and deaggregation of the wet granulated over the directly compressed tablets. In further tests with this apparatus, Sandell *et al.* (492) compared disintegration and dissolution results of isoniazid, sulfamethizole, meprobamate, and diazepam tablets. The residue on the coarsest screen was sufficient to provide discriminatory results for two brands of isoniazid and sulfamethizole tablets. For the other two drugs, the entire screen sieve analysis had to be taken into account in discriminating between different brands. More recently, Sandell and Helmstein (493) compared the wet sieving apparatus with the USP disintegration test. They stated that it would be advantageous to use the sieving technique during formulation trials because the mild agitation permits more sensitive differentiation between preparations than does the USP test with its more intense mechanical agitation. A modified apparatus with only two sieves is now proposed.

Mechanical Strength—To avoid confusion of the term "strength" with potency, the mechanical strength of pharmaceutical tablets is commonly referred to as "hardness," although this term is by correct definition a surface property. A pneumatic microindentation apparatus was used (494) to show that the *surface* hardness of aspirin tablets decreases from the center of the tablet face to the outer edge. As expected, the hardness increased with compaction pressure due to work-hardening. An increase in the initial particle size of the crystals caused a reduction in the surface hardness of the tablets. Such measurements might be extremely useful in both tablet formulation and process development.

Indentation methods are commonly used to assess the hardness of metals. Hiestand *et al.* (495) described an impact test for compressed tablets based on the impact–rebound principle using a pendulum. The energy consumed during impact divided by the volume of indentation produced by the impact of a steel sphere provides an estimate of the mean deformation pressure, and equations were derived for determining the hardness of compacts. This investigation relied heavily on the experience of metallurgists in accepting the validity of the impact method for assessing the hardness of tablets.

To correlate strength measurements for tablets of various sizes, Rees and Shotton (496) quoted the breaking load as a function of the cross-sectional area of contact in the plane of failure. A porosity term was necessary to correct for the decreased contact area due to voids. More recently, Newton *et al.* (497) suggested that results can be correlated using tensile strength values, except when the tablet thickness is small. A theory proposed by Haynes (498), for predicting the tensile strength of *porous* materials, took into account the stress-concentrating effect of the pores.

The strength of pharmaceutical tablets is commonly determined by measuring the resistance to failure in diametrical compression. By coincidence, the circular disk shape of many tablets is such that, under controlled conditions, compression along a diameter produces pure tensile failure in a direction *normal* to the applied force. In a review of the testing of tablets by diametrical compression, Ridgway (499) commented that the use of a groove in the platens of a tester to locate the tablet is, therefore, a bad feature since it alters the stress distribution. Opposed spherical-ended indenters may be more suitable for testing noncircular tablets because the plane stress assumption for tensile failure is only valid with perfect disk-shaped specimens.

Ritschel *et al.* (500) compared eight different instruments for measuring tablet strength. They reported significant differences between the results of different operators, except with the Pfizer and motorized Heberlein instruments. There was no apparent difference in the reproducibility of strength values caused by variations in the rate of loading. Rees *et al.* (501) attributed this negative finding to the low mean strength and relatively large standard deviation in strength of the tablets studied by Ritschel *et al.* With tablets of uniform strength, Rees *et al.* showed that an increase in the rate of loading caused a significant increase in the value

obtained in diametrical compression tests. The measurements with an Instron mechanical testing instrument were also correlated with values obtained using the motorized Heberlein and Erweka testing instruments. In view of this dependence of strength on testing speed, Ridgway (499) proposed that an instrument should be developed to test tablets by diametrical impact.

Pharmaceutical tablets usually contain a number of different substances, and it would be useful to be able to predict quantitatively the mechanical properties of a tablet from a knowledge of the properties of the single components. Studies with three forms of lactose resulted in successful prediction of the tensile strength of tablets prepared from mixtures on the basis of tensile strength measurements for tablets of each material (502). It is sometimes necessary to include suitable padding material between the tablet and the steel platen of the testing instrument to produce the appropriate stress distribution that causes tensile failure of the specimen (503). Conflicting results were obtained concerning the benefit derived from the presence of α-lactose monohydrate in samples of lactose (502, 504); and since each particle of spray-dried lactose may contain all three forms of lactose, *i.e.*, α-lactose, β-lactose, and α-lactose monohydrate, it was not possible to predict the tensile strength of tablets containing spray-dried material.

Investigators in another laboratory (505) also made accurate predictions of mechanical properties for tablets containing lactose and microcrystalline cellulose. A thin blade, inserted through the die wall, was used to slice the compact in a plane normal to the axis of compression and thus to provide an estimate of the strength of cohesive bonds within the compact. More recently, Wray (506) explained how this technique was also used to predict the optimal quantity of binder in a granulation to produce tablets with the required mechanical properties. Because the test is applied to the compacted material in the die, it can be used to measure bonding forces even in powders that would not form a coherent compact on ejection. Wray proposed that the system could be used for quality control purposes to distinguish between batches of a raw material which would possess good and bad cohesion properties in a compressed tablet.

Increases of over 100% in the strength of sodium chloride compacts were observed during the 1st hr. after compression (238). The effect could not be explained by interparticulate crystallization from moisture films and was attributed to plastic flow and increased interparticulate bonding within the compact during stress relief following ejection. The photomicrographs of Hardman and Lilley (507) confirmed that sodium chloride deforms plastically when compacted. Rees (508) pointed out that other tablets containing plastically deforming materials may show a similar effect, in which case different specifications will be necessary for in-process measurements made immediately after compression and for quality control measurements made some time later.

Keymer (509) concluded that with some tablets, it is necessary to accept a low breaking strength in order to ensure adequate disintegration rates. In his opinion, breaking strength is not necessarily a discriminating parameter since even for tablets with an extremely low and inconsistent diametrical breaking strength, he obtained measurements of friability and resistance to dropping that were indicative of adequate mechanical properties.

Stability—The problem of tablet stability is one aspect of the general problem of the stability of dosage forms rendered somewhat more complex by the physical and physiological requirements of various types of tablets and the multiplicity of excipients in tablet compositions. Chafetz (510) defined a stability-indicating assay method as a: "... procedure which affords the selective determination of a drug substance in the presence of its decomposition and reaction products." Such methods are relative and must be approached critically in terms of their utility for monitoring chemical stability in the variable environments that make up dosage forms and their containers. In planning stability studies of tablets, it would appear reasonable to accept the statement by Chafetz that: "... a drug dosage form could be considered as a deliberate contamination of a therapeutic principle, a sophistication which is perpetrated to achieve uniformity and convenience of dosage, product identity, and the physical properties which enable it to be mass produced and shipped in commerce." To this we might say that this sophistication also permits the dosage form to be properly and effectively administered.

Aside from chemical stability, interactions between ingredients in a solid dosage form can result in changes in physical properties such as equilibrium solubilities, partition coefficients, and dissolution rates. Changes of this type are known to have pharmacokinetic effects, and Guillory *et al.* (511) proposed the initiation of control procedures to identify such interactions. Their preference was for differential thermal analysis as having definite advantages over other techniques. Experimentally, it was possible to distinguish between binary systems that interacted and others that did not. Although the authors stated that their differential thermal analysis technique shows promise of adaptability to the examination of dosage forms, no such studies were reported in this paper. The influence of pressure on solid-state interactions was investigated by Forusz (512), using a specially designed punch and die system in conjunction with a hydraulic press. Under pressure, increased moisture caused increased interaction. Quantitative measurements of the solid–solid interactions were made using differential scanning calorimetry and thermogravimetric analyses.

Although not directly involving tablets, the investigation by Lach and Bighley (40) may be of significance in the development of stable tablet formulations. By using diffuse reflectance studies, evidence was found of interactions between chlortetracycline hydrochloride–magnesium trisilicate, tetracycline–magnesium trisilicate, demeclocycline (demethylchlortetracycline)–aluminum hydroxide, dicumarol (bishydroxycoumarin)–aluminum hydroxide, methantheline bromide–talc, and others. Continuing a series of diffuse reflectance studies of solid–solid interactions, McCallister *et al.* (41) proposed a mechanistic interpretation suggestive of chemisorption due to surface chelation. Chelates of dicumarol

(bishydroxycoumarin) and furosemide were prepared, and diffuse reflectance spectroscopy spectra were compared with similar drug–excipient spectra. The authors also reported significant interactions between chloramphenicol, ergonovine maleate, and digoxin with magnesium oxide and magnesium trisilicate. Factors of significance in the nature of the excipient are hydrogen bonding, van der Waals' forces, chemisorption, the amount of adsorbed moisture, and the availability of active sites.

A brief and somewhat inconclusive study of the physical properties and stability of a placebo tablet formulation exposed to a relatively high dose of γ-radiation was reported by Schwenker and Poehland-Heuser (513). The investigation was intended to show the possible effect of sterilizing radiation on the appearance, disintegration time, and mechanical properties of tablets.

The effects of moisture on tablet stability were reviewed by Griffiths (279), including methods for overcoming problems by coating of granules or tablets and the selection of suitable packaging systems for the finished tablets. Rasmussen *et al.* (514) compared various methods for the analysis of moisture content in tablets of potassium phenoxymethyl penicillin—a substance susceptible to hydrolysis. Karl Fischer titration apparently included the theoretical quantity of water of crystallization in the lactose excipient, whereas results by GLC did not. Unfortunately, this was not confirmed by analyzing the lactose itself. Thermogravimetric analyses at 100 and 105° were unsuitable owing to continued dehydration of lactose over a 5-hr. period. The authors concluded that the preferred analytical methods are direct Karl Fischer titration to measure the total water and GLC or Karl Fischer analysis of a methanol extract to detect adsorbed water.

Similarly, Iconomou *et al.* (515) described a GC procedure for the determination of moisture content which they found to be suitable for several granulations and compressed tablets. The results correlated with loss-on-drying and Karl Fischer measurements, and good reproducibility was obtained. Upon tableting with magnesium stearate and microcrystalline cellulose, Carstensen *et al.* (516) found that thiamine hydrochloride degrades to a point of apparent equilibrium when the amount of intact thiamine is a function of the amount of water present and exhibits a minimum at about 5.5% moisture content. On the basis of a proposed model, the phenomenon was explained as resulting from the adsorption of dissolved thiamine on the microcrystalline cellulose, with total degradation of the thiamine in the monolayer and no degradation outside the monolayer. The authors believed that the model is applicable to many systems in which a drug in solution is adsorbed on the main excipient.

In checking the alleged interaction of silica gel with ascorbic acid, de Ritter *et al.* (517) used both model experiments and practical tablet trials on wet granulated materials. Loss of ascorbate in the presence of various excipients and water was demonstrated and stated to be dependent upon pH, water-binding capacity of the excipient, and trace metal content. The importance of proper processing in the preparation of multivitamin tablets in order to reduce the known sensitivity of ascorbic acid to oxidation in the presence of moisture was emphasized. Availability studies in man showed that ascorbic acid is absorbed normally in the presence of silica gel. Kedvessy *et al.* (518) described studies to ensure stability of ascorbic acid in sugar-coated tablets also containing ferrous sulfate. The technique involved reduction in the moisture content of the cores by using a dry granulation procedure with ferrous sulfate dried to contain 1.5 molecules of water of crystallization and by precoating the cores with cellulose acetate phthalate in isopropanol–chloroform prior to sugar coating.

The relationship between stability and biological activity has received surprisingly little attention in the literature. Calvey (519) ascertained that, contrary to an earlier report by Mathews and Turck (520), there appears to be no reason why mannitol-based glyceryl trinitrate tablets should not maintain their chemical and biological potency for over 30 months. Also, in contrast to previous reports, Hammouda and Salakawy (521) observed discoloration of neomycin tablets containing lactose, which they attributed to the Maillard reaction. The effect was associated with an appreciable decrease in pH of a filtered suspension of the tablet, and the reaction was base-catalyzed, acid-inhibited, enhanced by an increase in ambient relative humidity, and retarded by the presence of sodium metabisulfite.

The color stability of hexylresorcinol in a compressed tablet was shown by Polli and Frost (522) to be due to the presence of polyvinylpyrrolidone in the formulation. A strong complexing interaction between the two substances was demonstrated by IR spectroscopy and the solubility isotherm method. This interaction resulted in a reduction of the antimicrobial activity of the hexylresorcinol, indicating the importance of evaluating changes in biological activity as a consequence of complexation.

The popularity of aspirin as a drug is matched by its popularity as a subject for research investigation. In an excellent review of the determination of the decomposition of aspirin in tablets and in tablet compositions with other drugs, Kelly (523) discussed the stability of aspirin in the presence of antacids, buffering agents, and various excipients used in tablet formulations. Along the same lines, Maulding *et al.* (524) investigated the influence of several excipients and antacids on the stability of aspirin formulated as powder mixes, tablets, and suspensions. Relative stability rankings, based on salicylic acid formation after storage for 45 days at 40° in a closed container, were obtained. The similarity of the results for powder mixes and tablets indicates the negative contribution of compression to aspirin stability.

Using simple, slugging formulations consisting of active substance with disintegrant and talc, Delonca *et al.* (525) observed that of five formulations studied, one containing calcium sulfate as disintegrant resulted in the least hydrolysis of aspirin at various dry and humid storage conditions. No details of the physical properties or physical stability of the tablets were given.

Boggiano *et al.* (526) suggested that whereas aspirin–phenacetin mixtures are compatible, the replacement of phenacetin by acetaminophen in many commercial tablet formulations without adequate testing has resulted in

products on the market that contain diacetyl-*p*-aminophenol. The interaction between aspirin and acetaminophen was shown to be considerably accelerated by codeine phosphate and magnesium stearate, and the interaction was greater in tablets than in uncompressed powder mixes. An investigation by Nieminen and Castren (527) of the interaction between aspirin and prednisolone in tablets showed esterification of the steroid to the acetate. Although the authors obtained low values with the USP method, indicating degradation on the 17-side chain, the presence of acetylated prednisolone was not revealed. They suggested the inclusion of TLC analysis in addition to colorimetric and UV spectrophotometric determination in the control of prednisolone tablets.

CONCLUSIONS

Research and development activity in tablet technology during the past 3 years has been appreciable, in proportion to the importance of the dosage form. Experimental design has shown a steady improvement due to a less constricted approach to pharmaceutical problems, as well as external pressure from regulatory agencies. Nevertheless, there is still evidence of a narrow isolated attack on some problems, which involve the interplay of variables.

Methodology for investigating the properties of individual components of pharmaceutical preparations leaves a great deal to be desired in spite of the evolution of a formal discipline of materials science. The literature is almost totally devoid of information concerning the role of the physical properties of active drug substances in processing and drug quality, with the exception of biopharmaceutic implications. The search for new excipients appears to be essentially restricted to diluents for direct compression and new materials for film coating.

In processing technology, a serious gap remains in the study of the mixing operation, and most of the papers reviewed in this report emanate from sources other than pharmacy.

Excessive interest in the instrumentation of tablet machines has undoubtedly led to neglect of other important unit operations involved in tablet technology.

Concern with the problem of content uniformity has led to an intensive search for automated analytical systems, but there is less evidence of corresponding attempts to develop techniques for correcting nonhomogeneity.

Almost 25% of the papers reviewed fall into the biopharmaceutic category; of these, half deal primarily with dissolution rate methodology or *in vitro* dissolution rate comparative tests. In spite of increasing activity at the biological level, the investigational gap in *in vitro–in vivo* correlations involving the *tablet dosage form* remains too wide.

There is no doubt that the general direction that tablet research and development is currently taking is progressive, but considerable room for improvement remains. This is particularly the case with respect to the unit operations involved in tablet technology, operations that are highly developed in other industries from which a great deal of basic information can be readily acquired.

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▲ To whom inquiries should be directed.