Journal of Pharmaceutical Sciences

NOVEMBER 1972
VOLUME 61 NUMBER 11

REVIEW ARTICLE

Disintegration of Tablets

WERNER LOWENTHAL

Keyphrases ☐ Tablet disintegration—uncoated tablets designed for rapid release, review ☐ Disintegration of uncoated tablets designed for rapid release—review ☐ Disintegrants, tablet—mechanism of action, comparative effects, review ☐ Surfactants—effect on tablet disintegration ☐ Compression force and tablet hardness—effect on tablet disintegration, review ☐ Excipients—effect on tablet disintegration ☐ Dissolution equipment—review of tablet disintegration procedures ☐ Dissolution rates, tablets—correlation with disintegration times, review

Complete tablet disintegration is defined by NF XIII (1) as: "... that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen is a soft mass having no palpably firm core." This often makes tablet disintegration a necessary first step to achieve rapid availability of the active ingredient(s). The importance of tablet disintegration was recognized as early as 1879 when a patent recommended that pills be perforated to admit gastric juice for better disintegration (2). This review will only discuss uncoated peroral tablets designed to release all of the active ingredient(s) rapidly.

Many compounds have been proposed as tablet disintegrants. Proposed and presently used tablet disintegrants are presented in Table I.

MECHANISM OF ACTION OF DISINTEGRANTS

Evolution of a Gas—The reaction of sodium bicarbonate with citric and tartaric acids to yield carbon dioxide is the basis of effervescent tablets. The use of certain peroxides is based on the fact that they decompose in the presence of moisture to release oxygen, which is supposed to cause the tablet to disintegrate. In practice, they did not perform well.

Adsorption—It has been proposed that the heat of wetting of the ingredients that occurs when the tablet is immersed in a fluid causes the entrapped air in the tablet to expand, thus producing tablet disintegration (85, 86).

Matsumaru (87) calculated the heat of absorption of water by the Brunauer, Emmett, and Teller method and claimed it is an important factor in tablet disintegration because the decrease of this heat due to tablet compression agrees with the fact that disintegration times increase. This was found with aluminum silicate (86). Prior absorption of moisture by a tablet also decreased the generation of wetting heat (88).

Matsumaru (89) stated that aspirin tablets and tablets containing talc do not disintegrate well because aspirin and talc have contact angles greater than 90°, preventing penetration of water into the tablet. Starch has a contact angle of 80–85°, so water penetrates through canals made of starch grains and causes the tablets to disintegrate. Kolarski and Krowczynski (47), using potato starch and various celluloses, claimed that the wetting time for disintegrant varied with the method of addition to the other ingredients. For aluminum hydroxide tablets, the wetting time decreased with an increase in concentration of the disintegrant. They reported that the wetting of the capillary system alone does not seem to be the only mechanism of tablet disintegration. Surfactants may increase wettability and

Table I—Disintegrants

Disintegrants	References
Starches:	3–25
Corn, wheat, rice, potato, arrowroot sago, tapioca, sweet potato, sorghum, cassava, yam, banana, moriyo, barley, waxy maise	
Dextrinized and swollen starches	26
Starch ester containing hydrophobic groups	27
Starch–agar (1:1)	28
Cold water-soluble ungelatinized starch	17, 29
Compressible starch	30
Amylose	30, 31
Ultraamylopectin	17, 21, 32–34
Amyloform ("condensation of starch")	35
Cellulose and its derivatives:	3, 4, 6, 11, 16–
Methylcellulose, ethylcellulose, sodium carboxymethylcellulose (various viscosity grades), calcium carboxymethylcellulose, hydroxypropyl cellulose, carboxymethylcellulose acid, holocellulose, cellulose, microcrystalline cellulose, beech flour, sycamore wood flour, spruce wood flour, powdered redwood bark, Douglas fir wood flour, (powdered) Douglas fir bark, powdered corn cob, corn cob pith, corn cob wood substance, corn cob chaff, pine flour, birch flour, oak flour	19, 21, 22, 24, 26, 28, 30, 32, 33, 36–53
Citrus pulp	43
Beet pomace	54
Orange peel albedo	17
Sponge, natural and synthetic	17, 43, 55, 56
Alginic acid—salts and derivatives (including various viscosity grades:	2, 6, 9, 10, 20–22, 28, 30, 40,
Alginic acid, sodium alginate, calcium alginate, calcium ammonium alginate, ammonium alginate, propylene glycol derivative of alginic acid	41, 43, 51, 57
Gums and derivatives:	38, 40
Crosslinked gum arabic, arabic acid, elm acid, quince acid, plantago acid, linseed acid	
Agar, laminaria, fucus, Iceland moss, Carrageen moss	16, 58
Guar gum	15, 22, 51, 59
Pectin, tragacanth, locust bean gum, karaya gum, sterculia gum	11, 41, 43,
Proteins:	
Gelatin	57
Formaldehyde–gelatin	17–20, 32, 58, 60–62
Formaldehyde–casein	17, 32, 60, 63, 64
Gelloid 50	43
Enzymes (added to starch, celluloses, or proteins):	
Amylase, cellulase, hemicellulase, protease	65
Carboxymethyldextran—acid and sodium salt	66, 67
Polyacrylic acid and derivatives	2, 4, 6, 38, 68
Polyvinyl alcohol	69
Ion-exchange resins:	18, 70–74
Acid, sodium, and magnesium salt forms of carboxylic acid resins, cationic resins, polyamine resins, sulfonated phenolic resins, and combinations of cation- and anion-exchange resins	
Silicon compounds:	
Colloidal silicon dioxide	18–20, 62
Colloidal magnesium aluminum silicates	4, 22, 28, 43, 75, 76
Aluminum silicate	15–17, 51, 59, 77
Kaolin	51, 78
Bentonite	9, 17, 41, 43, 70, 79, 80
Fuller's earth	70
Peroxides	43
Foam-building material which incorporates air or inert gas under pressure in tablet	81, 82
Dried porous mass, *i.e.*, gelatin foam	83
Organic gas generators	84

hydrophilicity of tablets and decrease disintegration times (84, 90). Immersional wetting might be a controlling factor in the disintegration of tablets, depending on the materials and force (91).

It is questionable if the amount of heat produced can cause a sufficient increase in the volume of air to cause pressures to be built up that break the tablet apart. If this is an important mechanism of action of disintegrants, the heat produced during compression and ejection of the tablet from the press should cause tablets to fall apart. This appears at best to be only a partial explanation. In addition, for this mechanism to operate, moisture appears to be necessary. There was no effect of wetting heat on the disintegration of tablets with crosslinked gum arabic, a cation-exchange resin, or calcium carboxymethylcellulose (18).

Effect of Water Absorption—Billups and Cooper (41) found that the rank order of water absorption of various disintegrants after 4 hr. differed from that after 75 days. No correlation with disintegration time and moisture absorption at 4 hr. was obtained, but high moisture absorption after 75 days produced a longer disintegration time. In another study the order of the decreasing amount of water absorbed was: corn cob, starch, starch-cellulose, and lactose (53). Krowczynski *et al.* (92) found that colloidal silicon dioxide absorbed nine times as much water as the starches, but it took at least six times as long. The authors theorized that an increase in the rate of disintegration time is due to the formation of a larger system of capillaries by starch with smaller grains. Colloidal silicon dioxide and rice starch were considered the best disintegrants because they absorbed the most water. The rate of water absorption was not considered significant.

Disintegrants that absorb about 20% water and are insoluble in water are said to be good disintegrants, *i.e.*, alginic acid, calcium alginate, methylcellulose, and corn, wheat, rice, and potato starches. Those that absorb about 40% water and are soluble in water increase disintegration time, *i.e.*, polyvinyl polymer, sodium carboxymethylcellulose, and sodium alginate; those that absorb water poorly are poor disintegrants, *i.e.*, ethylcellulose (24). Wakimoto *et al.* (93), using microcrystalline cellulose tablets, declared that the amount of moisture absorbed and the volume expanded were rather small compared to those of starch tablets. With increasing pressure, the rates of moisture absorption and of volume expansion decreased.

Jaminet *et al.* (3) reported that the mechanism of disintegration depends on the solubility of the ingredients. An insoluble drug plus soluble disintegrant retards diffusion of water into capillaries much more than viscosity. The rates of disintegration of soluble and insoluble disintegrants are tied to the rate of liquid penetration into the tablet. Water absorption was mentioned as directly proportional to the sodium carboxymethylcellulose viscosity grade but inversely proportional to the sodium alginate viscosity grade. Dried disintegrants absorbed about twice as much as regular ones. Potato starch had a fast initial absorption rate and absorbed less than sodium carboxymethylcellulose and sodium alginate (high viscosity excepted). In various tablets, potato starch was the best disintegrant regardless of the rate or amount of water absorbed. Later it was reported (36) that disintegration times decreased with an increase in the sodium carboxymethylcellulose viscosity grade, and further study indicated that absorp-

tion of water did not explain variations in disintegration times. For sodium benzoate and aluminum hydroxide tablets, no relationship was observed between absorbability of water and tablet disintegration time, but a correlation was claimed for calcium lactate tablets (47).

These studies indicate that the water absorbed by the tablet may be a factor in tablet disintegration, but this depends upon the solubility of the drug and other ingredients. The rate and amount of moisture absorbed by a disintegrant are not directly related to tablet disintegration times.

Swelling—Crosslinked polyacrylic and polymethacrylic acids (68), crosslinked gum arabic (18), carboxymethyl dextran (66), various silicates (70, 92, 94), different gums (11, 19, 67, 95–97), spruce wood flour (52), cation-exchange resin (73), polyvinyl alcohol (69), vegetable drugs (98), natural sponge (55, 67), and various starches (3, 12, 29, 36, 67, 92, 94, 99–101) are among the substances that reportedly swell when moistened. Rank orders of decrease in swelling of various starches under different conditions were described as: wheat, corn, potato, arrowroot, and rice (12); potato, corn, and wheat (67); and potato, wheat, and rice (92).

Tablets made with low pressure have high porosity and, hence, too much space. When starch swells, no pressure is exerted so disintegration is slow. Medium pressure allows just enough space so that when the starch swells, it exerts pressure on the granules to cause disintegration. High pressure, producing low porosity, decreases the ability of fluid to enter, so disintegration is again slow (10, 36).

Starch swelling was claimed to be dependent upon amylose and amylopectin content; the amylopectin expands and the amylose gives osmotic pressure (99). Hirata (68) reported that the swelling of crosslinked polyacrylic acid and polymethacrylic acid increased linearly with an increase in polymer concentration, but it was greater with polyacrylic acid. Swelling increased linearly with tablet immersion time, but disintegration times decreased with an increase in the concentration of polyacrylic acid. Swelling decreased with an increase in pressure. The swelling of crosslinked polyacrylic acid was suggested to be due to its interaction with water (102). Borzunov and Nesmiyan (19) reported that the degree of swelling of acid carboxymethylcellulose was 220%; of sodium carboxymethylcellulose, 400%; of sodium alginate, 450%; and of ultraamylopectin, 1100%. A mixture of starch with 0.1% ultraamylopectin gave maximum swelling while acid carboxymethylcellulose–starch mixture (3:97) gave second greatest swelling. A mixture of ultraamylopectin–starch (2:97) as 10% of a formulation gave best disintegration times, while acid carboxymethylcellulose–starch (3:97) gave the second best disintegration times. It was suggested that starch forms the capillaries and the ultraamylopectin acts as a swelling agent (20). Sager (95) disclosed that corn starch absorbed water faster than rice starch. Agar and gelatin absorbed more water than the starches, so a mixture of corn starch with pectin or agar was recommended. Modrzejewski and Wochna (101) declared that a 0.4–2% solution of sodium lauryl sulfate did not cause an increase in potato starch swelling at room temperature but did cause a 33–44% increase at 37°. Defatting starch caused it to swell 44%. Starch swelling increased with decreasing water content, with dried starch swelling 70% (see also *Reference 92*). Heating starch caused it to swell 88%. Krebs (7) found that the differing disintegration mechanism of rice, corn, potato, and wheat starches is not determined by granule size, water content, or swelling power but by the fat content. A decrease in disintegration was proportional to the water content of the starch. Disintegration times were reported directly proportional to the grain size of the starch.

Modrzejewski and Wochna (17) stated that the decreasing order of swelling for disintegrants was: orange peel albedo (300%), natural sponge (147%), magnesium aluminum silicate, formaldehyde casein from milk, formaldehyde gelatin, bentonite (66%), formaldehyde casein from cheese, cellulose, potato starch (29%), corn starch (6%), and wheat starch (5%). Microscopically, starch swelling reached a maximum in 15–40 sec. (see also *Reference 100*). The grains swelled in all directions uniformly, and swelling was inversely proportional to grain size. They declared that they were able to measure the swelling of certain soluble materials by using Lugol's solution to outline the particles, *i.e.*, ultraamylopectin (1142%), gelatin (400%), and soluble starch (260%).

Chwialkowska and Krowczynski (97) detailed that as the starch content of tablets was replaced by acid carboxymethylcellulose or sodium carboxymethylcellulose swelling increased and the degree of swelling also appeared to increase with an increase in pH (2–8). Starch swelling was only affected at a pH of 8. A similar pH effect was reported by Ingram and Lowenthal (25). Acid carboxymethylcellulose swelled considerably more than sodium carboxymethylcellulose. It was concluded that swelling alone is not an objective criterion for evaluation of a disintegrator and that pH must be considered.

The above-mentioned figures on swelling of various substances do not indicate whether diameter increases or volume increases were meant.

There undoubtedly is some small degree of swelling of starch grains (25, 100, 103, 104). A 10% increase in diameter can result in about a 70% increase in the volume of the grains. Whether this increase is sufficient to cause tablet disintegration is yet to be discovered. An advantage of the starches over the gums is that the starches do not dissolve to cause increased viscosity or form a mucilaginous layer over the tablets (43).

Many substances swell to a greater degree than the starches but are poorer disintegrants. Amylose does not swell but has been stated to cause good disintegration (30).

Porosity—In 1908, it was reported that soluble particles in tablets dissolved first, producing a "honeycombing" effect of the more insoluble materials, thereby causing rapid disintegration (105).

Porosity of tablets has been studied with increasing frequency in recent years, using a variety of materials and numerous experimental methods. Porosity, void space, and pore size decrease as pressure increases (46, 92, 103, 106–118). Potato and corn starches increase

mean pore diameters and porosity (53, 67, 72, 112–114, 119, 120). Pore size and volume decrease as the moisture content of starch increases (110).

The rate of penetration of fluids into a tablet is proportional to mean pore diameter or porosity (107, 108, 121, 122); corn and potato starches increase penetration of fluids into tablets (119, 122, 123). Permeability of tablets decreases as pressure increases (109, 114, 118, 123). The effect of starch on porosity may be due to its poor ability to bond and compress (23, 119, 120, 123).

As porosity or pore diameter increases, disintegration time decreases (9, 18, 46, 53, 116, 124). No correlation was found between disintegration and penetration times, but generally short disintegration times had rapid fluid penetration times (122, 125).

Flow in pores is affected by interfacial tension, contact angle, and geometry of the solid surface. In addition, viscosity and electrostatic charging may affect flow of liquids in capillaries. Surfactants have selectively increased water penetration into tablets.

Surface area in sulfathiazole, sulfadiazine, and lactose–aspirin tablets increased with pressure up to about 1135 kg. (2500 lb.) and then decreased (106, 126, 127). Aspirin gave maximum surface area at 454 kg. (1000 lb.) and lactose at 1816 kg. (4000 lb.). Surface area increased with porosity up to about 10% porosity and then decreased with increasing porosity. Surface area had a linear relationship with pressure, except at higher pressures (126). In later work (128) using sulfathiazole plus 1% starch, it was found that true density decreased as pressure increased, possibly due to pore blockage, and disintegration time increased exponentially with increased pressure.

Wurster and Seitz (129) found that 0.01-cm. (0.04-in.) diameter pores in benzoic acid compacts were somewhat occluded by air and not entirely available to the fluid. A 0.2% sodium lauryl sulfate solution or air evacuation allowed penetration of pores by fluid. Huttenrauch and Schmeiss (130) reported that disintegration times decreased as pressure was reduced from 1 to 0 atmosphere. It was claimed that air in the capillaries hinders liquid absorption and that evacuation causes pores to behave like those in a surfactant solution. Lipophilic pores absorb air more strongly.

Matsumaru (131) disclosed that the disintegration time was lower and the amount of air that appeared to escape from aluminum silicate tablets in water was greater in dried tablets than in undried tablets. The reason stated for these phenomena is that the fine structure of the bottle-neck type capillary (narrow neck and large internal volume) is blocked by condensed water (132).

Ganderton and Selkirk (107) granulated sucrose and lactose with varying amounts of water. They found that with lactose, neither granule size nor amount of water used influenced the relationship between compression force and porosity; with sucrose, the porosity increased as the amount of water decreased. The permeability–porosity relationships were complex, depending on the filler, amount of water, granule size, and pressure. These same factors affected the mean hydraulic radius. A coarse pore structure permitted more rapid penetration than tablets with the same porosity but uniform pore structure. Rapid penetration can isolate pores due to entrapped air so that the percent water uptake decreases with the size and strength of pores.

In another study (108) it was reported that as the porosity of sucrose tablets decreased the pore size range got smaller. Granulation led to an increased proportion of coarse pores and a larger size distribution. Similar results were disclosed for lactose (109). Granule size defined pore size, but as pressure increased and fragmentation became marked, these effects disappeared (108). Changes in permeability of lactose due to granulation with water were smaller than those by slugging (109). Ganderton and Fraser (123) found large differences in porosities and permeabilities between materials and relatively little differences between powders and granules of the same material. With the exception of aspirin, tablets made from coarse powder were less porous and had greater permeabilities to air. Only granulation of magnesium carbonate increased permeability. Aspirin and phenindione made relatively impermeable tablets while lactose was permeable and had the highest penetration rate. It was concluded that factors that determined tablet structure did not entirely determine aqueous penetration of a porous system.

Reich and Gstirner (110) found that pore size is characteristic of a given pressure. At 325 kp./cm.^{2}, 95% of the radii were below 5 μ; at 1265 kp./cm.^{2} pressure, 95% of the radii were below 1.8 μ. Linear relationships between pore volume and the most common pore radius and tablet height were described. In magnesium oxide tablets, mean pore diameter decreased with increasing pressure; *i.e.*, at 0.5 ton the mean pore diameter was 0.197 μ, and at 2.0 tons it was 0.069 μ (112).

Matsumaru (117) compared pore volume distributions with their absorption isotherms. Tablets compressed at 0.76 ton/cm.^{2} had a mode pore radius of 62.4 Å and a pore volume of 148 $\times$ 10^{-4} ml./g.; at 2.9 tons/cm.^{2}, the pore radius was reduced to 21 Å and the pore volume to 60 $\times$ 10^{-4} ml./g. As compressional force increased from 0 to 4.2 tons/cm.^{2}, specific surface area decreased from 400 to 352 m.^{2}/g., heat of absorption decreased from 3.52 $\times$ 10^3 to 2.71 $\times$ 10^3 cal./mole, and void space decreased from 0.353 to 0.075 ml./g.

It was observed in tolbutamide, aspirin, salicylamide, and phenylbutazone tablets that the starch stained with iodine formed continuous chains along the channels between granules even at concentrations below those required to cause tablets to disintegrate. As percent of starch increased, thicker chains were formed, thus enlarging the pores (119).

Patel and Hopponen (103), using transverse sections of tablets scraped smooth, claimed that as the particle size of aspirin decreased the amount of starch grains in the channels between the aspirin crystals decreased. With 60–100-mesh aspirin, the lines of starch around the crystals were discontinuous; and at less than 100 mesh, only scattered grains in small groups with a few channels were observed. Disintegration times increased with a decrease in aspirin particle size, and the degree of penetration of iodine in 50% alcohol was directly proportional to the particle size of aspirin.

The authors claimed that the average volume of starch in a tablet containing 0.3 g. aspirin and 5%

starch was 0.00984 ml. If, on wetting, starch increases 78% in volume (calculated from mean volume diameter and assuming spherical shape), a 0.00768-ml. increase occurs. This increase in volume is close to the total void volume in the tablet (<4.7% void space). Properly located starch could exert force to break the tablet apart. When using 40–60-mesh aspirin plus 5 or 10% starch, increasing compression pressure from 2000 to 16,000 psig. decreased void space from about 7 to about 0.1% with no apparent effect on disintegration times. Since alcohol and glycerin did not cause disintegration but did penetrate the tablets, the authors concluded that the effect of capillarity is minimal.

In aspirin–starch tablets with mercury forced into the pores, disintegration and dissolution times were the same as for the original tablet (133).

Patel and Hopponen (103) also stated that if starch grain contact is not continuous, disintegration time increases. They explained that capillarity *per se* does not appear to have a disintegrating effect, although it may be a limiting factor in hindering water entry. It appeared that small pore diameters cause tablet erosion rather than whole tablet disintegration.

Nogami *et al.* (113), using aspirin tablets of three different particle-size ranges and containing corn starch, found that percent porosity was dependent on starch concentration and aspirin particle size. Potato starch gave similar results but had smaller porosities.

The authors stated: ". . . that there might be a critical amount of disintegrator which depends upon the particle size of aspirin and starch or the relative surface areas of the components which relate to the interfacial character of the capillary wall of tablets." It was suggested that effective pores for disintegration should have the inner wall composed of starch or of starch and aspirin.

Large and medium size aspirin crystals with insufficient starch or small size aspirin crystals with excess starch disintegrated only into large pieces and only slowly into initial particles so that dissolution ($t_{1/2}$) was related to pore diameter. Large or medium size aspirin crystals with 10% corn starch disintegrated rapidly into the original size particles and dissolution ($t_{1/2}$) was independent of pore diameter.

The authors declared that a plot of disintegration time *versus* the reciprocal of pore diameter gave a linear relationship with large size aspirin particles and corn or potato starches. By comparing disintegration times of tablets with the same size capillaries, a more intensive disintegrating effect was observed in potato starch than corn starch due to the smaller contact angle (84.5 *versus* 85°), allowing for more rapid penetration. At 5–10% starch with medium or large size aspirin crystals, the starch was claimed to form continuous pores.

For rapidly disintegrating tablets, the process of water penetration into the tablets, rather than the process of separation of particles, determines the rate of disintegration. Starch affects the process of particle separation, but this occurs more rapidly than the penetration process.

Nogami *et al.* (91) reported that the penetration of tapped powders by water showed that potato starch penetration was greater than magnesium oxide and aluminum silicate and was dependent on liquid temperature. Later it was reported (120) that water penetrated more rapidly and to a greater extent into microcrystalline cellulose than potato starch bed, but the latter had greater water intake/void space. The volume change of a bed of powder after water uptake was larger for starch than for microcrystalline cellulose. Water may just penetrate into the microcrystalline cellulose bed by capillarity, while starch will also absorb water during penetration, resulting in a smaller penetration rate.

Tablets of large aspirin crystals (840/297 μ) disintegrated more rapidly with potato starch than with microcrystalline cellulose. When mean pore diameters were essentially constant, penetration was not always rate determining. A mixture of microcrystalline cellulose and starch may be best because the former enhances penetration; it has a contact angle of 68.5°, so more rapid swelling of starch can occur.

Fuchs (111) used a scanning electron microscope and showed how crystals of lactose and a steroid appeared to melt and fuse together at high pressures, giving smooth surfaces and closing pores and cracks. When a lactose–corn starch mixture (1:1) was used, the lactose sintered between the starch grains; at higher pressures the starch became covered by a thin film. It was suggested that starch grains lie between the granules and that pores exist in interstices between individual starch grains because starch does not fuse. It was hypothesized that elastic deformation of starch caused the film covering to be torn and pores with large pore volume to occur. This may be partially substantiated by the elastic recovery of starch–lactose tablets after pressure is removed, the recovery being proportional to the starch concentration (134).

Starch appears to allow a hydrophobic substance to absorb moisture (114), or it helps to form capillaries which draw water into the tablet (114, 135). It has been often stated that the formation of capillaries and the subsequent absorption of moisture by the tablet, but not swelling, are the mechanisms of action of starch. Porosity is also affected by the drug, binder, and disintegrant (67).

Wicking is due to capillarity of fibers. Stiff fibers of uniform structure and resistance to collapse are required for good wicking. The fibers should have zero contact angle and should not swell (136). This would appear to rule out any wicking effect due to starch or cellulose fibers.

It is easy to hypothesize how chains of starch grains could be formed in tablets, since the starch and lubricant are often added to the dried granules. As the granulation is compressed, the starch remains around the granules, resulting in chains. The more starch used, the bigger are the chains. The chains of starch grains that have been reported have only been observed indirectly and remain to be confirmed microscopically.

The existence of pores or capillaries is not the complete answer to the mechanism of action of disintegrants, because semipolar and nonpolar fluids penetrate into tablets (*i.e.*, 91, 103) yet do not cause the tablets to break. Also, tablets do disintegrate with minimum porosity (103, 114, 133).

In addition to the effects of pressure, starch, *etc.*, on porosity, pore diameters, and penetration (cited in the second and third paragraphs in this section), another fact appears to emerge: the relationship between the particle size of the drug or granules and the particle size of starch and quantity of starch. It seems that there may be a minimum amount of starch necessary for the most rapid disintegration. Commercial tablets are complex mixtures whose particle sizes are affected by all of the variables of the manufacturing process.

Deformation—Führer (137) found that potato starch plastically deforms under pressure, but that the individual grains can still be identified and appear as layers or streaks. It was postulated that compression decreases grain stability, resulting in an energy-rich material being formed so that no more energy is necessary for swelling. Supposedly ordinary starch requires heat to swell whereas deformed starch does not. Starch in starch tablets is held together by cohesion, although 5–10% melting at contact points was suggested. The greater the pressure, the greater is the plastic deformation and the greater is the adhesion. The adhesion is lost spontaneously and contact points are dissolved when water is added. Deformation of corn and waxy maise starches were also observed by others (111, 138), but when water was added the grains did not regain their shapes (138). In some of the scanning electron microscope microphotographs of tablet surfaces, the starch grains appeared to be in contact with each other (111).

Physicochemical Bonding—Fox *et al.* (46) claimed that disintegration is due to entrance of water into the tablet by means of capillaries and the subsequent breaking of hydrogen bonds between adjacent bundles of microcrystalline cellulose. Pressure reportedly caused the matchsticklike bundles of microcrystalline cellulose to line themselves up to decrease bond distances and increase interparticle forces. It was postulated (45) that microcrystalline cellulose in tablets is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. Tablet disintegration occurs when these bonds are broken by water. It was disclosed that as the polarity of disintegrating fluids decreased, disintegration times increased.

Safiulin *et al.* (78) claimed that particles of kaolin acquire a negative charge in the presence of moisture, repelling each other, which causes decomposition of the tablet.

Table II—Effect of Surfactants on Disintegration

Surfactant	Remarks	References
Polyoxyethylene tridecyl ether–urea complex	0.5–5 mg./tablet—good[a]	147
Sodium lauryl sulfate	Various drugs—poor[b]	106, 122, 144, 145, 147
Sodium lauryl sulfate	Various drugs—good	51, 139, 148
Dioctyl sodium sulfosuccinate	Various drugs—poor	144, 146
Dioctyl sodium sulfosuccinate	Various drugs—good	140
Dihexyl sodium sulfosuccinate	Various drugs—good	140
2-Ethylhexyl sodium sulfosuccinate	Variable effect[c]	141
Polysorbate 20	Poor	139, 149
Polysorbate 20	Good	122, 150
Polysorbates 40 and 60	Poor	149
Polysorbate 60	Good	150
Polysorbate 80	Poor	90, 139
Polysorbate 80	Good	122, 150
Sorbitan fatty acid esters	Poor	20, 90, 125
Polyoxyethylene stearates	Good	142
Polyoxyethylene fatty acid ester	Poor	90
Polyoxyethylene fatty alcohol ether	Good	142
Nonionic surfactants	Poor	97, 145
Sucrose stearates	Good	143, 151
Polyethylene glycol	Poor	151
Polyethylene glycol monostearate	Variable effect	141, 151
Triester of phosphoric acid	Poor	145

[a] Good = decreased disintegration time. [b] Poor = increased disintegration time. [c] Variable effect = decreased or increased disintegration time depending on drug.

EFFECT OF SURFACTANTS

The effect of surfactants on tablet disintegration has been variously reported to decrease disintegration time (20, 34, 51, 74, 125, 139–143) or to increase disintegration time (74, 90, 106, 139, 140, 144–146). The effects of various surfactants are summarized in Table II. Sodium lauryl sulfate increased absorption of water by starch or had a variable effect on water penetration into tablets (74, 139). Surfactants were only effective within certain concentration ranges (150, 152). They melted due to their waxy nature, hindering capillary formation (145), or initially made the tablet hydrophobic (*e.g.*, 149, 153). Disintegration time could not be related to surface tension (140). Surfactants were recommended to decrease the hydrophobicity of the drugs (*e.g.*, 34, 147) because the more hydrophobic the tablet the greater the disintegration time (90).

Aoki and Fukuda (141) claimed that disintegration time of granules of water-soluble drugs did not seem to be generally improved by the addition of nonionic surfactants during granulation, but the desired effect of a surfactant appeared when granules were made of slightly soluble drugs. The speed of water penetration was increased by the addition of a surfactant.

EFFECT OF MANUFACTURING PROCEDURE AND EQUIPMENT

The effect of compression force and tablet hardness on tablet disintegration time has been investigated many times under various conditions. The following is a summary of the reported results.

1. Disintegration time increased with an increase in pressure: phenindione–lactose (154), phenacetin (10, 155), aspirin (156), aspirin–phenacetin–caffeine (157), amobarbital (158), nitroguanil (159), sodium chloride (116), sodium bromide (11), sulfathiazole (40, 42), aluminum hydroxide gel (160), lactose–starch (50, 118, 145), lactose (152), miscellaneous drugs (21, 47, 161, 162), starches (26, 30), and microcrystalline cellulose (163).

2. Logarithm of disintegration time increased with an increase in pressure: sulfathiazole (106, 128), sulfadiazine (129), aspirin, lactose, lactose–starch (164, 165), and various other tablets (21, 166).

3. Disintegration time increased with an increase in logarithm of pressure (167).

4. Disintegration time increased with an increase in tablet hardness: sulfa drugs (168) and lactose (169).

5. Disintegration time was not affected by pressure: magnesium oxide (166), calcium carbonate (170), and starch (26); disintegration time was not affected by hardness (171, 172).

Hance (173) in 1902 claimed that the manufacturing process affects disintegration and that no one method is good for all tablets. Kavarana and Burlage (174) listed the factors that influence disintegration as: (*a*) tablet hardness, (*b*) speed of compression, (*c*) nature of lubricant and binder, (*d*) granulation process, and (*e*) percent moisture and dryness of disintegrating agents.

Granule size was variously described as having little or no influence on disintegration time (106, 128, 175), as affecting disintegration time (176), or as giving maximum and minimum disintegration times as granule size changed (155, 177). Higuchi *et al.* (128) noted, with granulated sulfathiazole and 1% starch, that disintegration characteristics are reproducible for a given granulation and that granulations made at different times gave different disintegration characteristics.

Münzel and Kägi (178) studied a lactose–starch mixture and discovered that disintegration times of wet granulation methods in general were shorter than those of the dry granulation methods. They claimed that this is due to the different surface structures of the two granulations. On the other hand, sodium salicylate plus spray-dried lactose gave shorter disintegration times than similar tablets made by the wet granulation method (179).

Addition of the disintegrant to the powders before granulation, addition to the dried granules, and addition to both powders and granules have been subjects of several investigations to determine which procedure would be better. The results have varied. The addition of starches or colloidal silicon dioxide to granules was reported as more effective (13, 47, 92). The addition of starch before and after granulation was described as most effective (7); the addition of disintegrants before and after wet or dry granulation was stated to have no effect (25, 47, 75). No difference between the method of disintegrant addition or slugging also was mentioned (23, 43). With alginic acid as part of the granules, disintegration into fragments smaller than the original granules was described (23). Multiple slugging was reported to have increased disintegration times (133). Tablets made with various algin derivatives added dry, with the subsequent addition of water, generally resulted in low disintegration times (57). Similar results were obtained with other binders (180).

Münzel and Seth (181) found that, with a sulfisoxazole granulation, the eccentric tablet press made tablets that had greater disintegration times than when a rotary press was used. Surface penetration of tablets made with an eccentric press varied, but was the same when tablets were made with a rotary press. The authors also reported (182) that with a starch–lactose granulation, flat-face tablets had slightly longer break-up times than biconvex tablets.

Kolarski and Krowczynski (47) found that the method of addition of disintegrant, the disintegrant concentration, the material, and the particular disintegrant appear to affect disintegration time. Malý *et al.* (21) found that pressure had to be varied, usually decreased as disintegrant concentration increased, to attempt to keep a constant radial hardness. Potato starch and alginic acid with inorganic or organic water-soluble drugs needed slightly increased pressure. Tablet hardness was suggested as a predictor of disintegration times (168). It has been verified that disintegration times also have changed throughout at a compression run, *i.e.*, aminosalicylic acid–sodium aminosalicylate (183).

EFFECT OF FILLERS AND ACTIVE INGREDIENTS

The filler will affect tablet disintegration times (30, 178, 184–186), sometimes depending on its solubility (22, 160). The drug will affect tablet disintegration time if present in a high enough concentration (9, 22, 51, 155, 172, 187, 188). The solubility of the drug may also have an effect (51, 189). The formation of hydrates after compression, *i.e.*, calcium aminosalicylate, will increase disintegration times (190). It has been stated that the nature of the formula or drug affects disintegration more than the pressure used (157).

Colloidal silicon dioxide has been suggested to aid rapid disintegration of tablets containing water-soluble drugs and starch (191). Tablets containing lactose plus various disintegrants disintegrated faster than those containing aspirin (24). Yet another study declared that in tablets containing lactose and starch, the lactose interfered with disintegration. It was disclosed that 45% microcrystalline cellulose reduced the disintegration time of aluminum hydroxide gel, and spray-dried lactose or microcrystalline cellulose were good fillers for amphetamine sulfate (46).

Proshunina (192) found that dried extracts mixed with powders having high compressibility (sodium benzoate and caffeine–sodium benzoate) decreased disintegration time. When extracts were mixed with powders of low compressibility (sodium bicarbonate), disintegration time increased.

Shteingart *et al.* (189) reported that tablets with water-insoluble drugs disintegrated quickly with starch, while those with water-soluble drugs did not disintegrate as well due to the diminished absorption capacity of starch. Halides and benzoates reportedly caused gluing of starch and hindered disintegration. Sodium aminosalicylate also hindered disintegration by forming a gelatinous layer with starch (193).

In a statistical study, Holstius and DeKay (9) used sulfathiazole, sodium bicarbonate, and an aspirin mixture; gelatin–acacia solution, sucrose solution, and starch paste as binders; and arrowroot, corn, potato, sweet potato, rice, sorghum, tapioca, and wheat starches, bentonite, and sodium alginate as disintegrants. They found that sulfathiazole had higher disintegration times than sodium bicarbonate, and the aspirin mixture had the lowest times. Gelatin–acacia had the largest times, followed by sucrose solution, and starch paste gave the lowest break-up times. Bentonite produced much larger disintegration times than the starches. Analysis of variance showed that the main effects were not significant, but the three-factor interaction was. It was concluded that the rate of disintegration was not due to any influence of the three variables singularly

but that certain combinations of these variables had significant effects.

Chalabala and Malý (155) determined that disintegration was affected by the physical properties of the drugs and excipients and by the process. They studied various drugs, fillers, binders, disintegrants, and lubricants in different concentrations. Potato, corn, rice, and wheat starches had less effect on water-soluble tablets than on tablets of lyophobic drugs. Generally, wood cellulose was reported best, except for phenoxymethyl penicillin when potato starch and amylopectin also were effective. They claimed that a significant drug–disintegrant interaction showed that there is no universal disintegrant and that each drug must be tested for an optimum disintegrant.

EFFECT OF BINDER

As early as 1915, it was revealed that binders such as gelatin or glue may result in a 2–3-hr. disintegration (194). Among the many binder comparisons described were: aqueous binder was better than ethylcellulose (102); ethylcellulose was better than gelatin (158); gelatin solution was better than soluble starch (195); starch paste was better than gums (196, 197); increase in molecular weight of polyvinylpyrrolidone or polyvinyl alcohol above 50,000 increased binding capacity but decreased disintegration rate (198); a vinyl polymer caused disintegration times to increase more rapidly with an increase in pressure than did starch paste (158); starch paste was better than polyvinylpyrrolidone or acacia (185); aqueous acacia and methylcellulose increased disintegration times, but an alcohol–chloroform solution of methylcellulose gave rapid disintegration (199); starch paste gave lower disintegration times than syrup, gelatin–acacia, and ammonium calcium alginate (200); bentonite, gelatin, and alcoholic solutions of polyvinylpyrrolidone were better than starch paste, while aqueous polyvinylpyrrolidone and sodium bentonite gave longer disintegration times (201); and use of larch arabogalactan gave similar break-up times to acacia (202).

Among the detailed studies with different drugs made to determine the effect of various binders on disintegration were: triamterene–lactose–starch (203); sodium bicarbonate, ascorbic acid, aspirin, sodium salicylate, and magnesium carbonate (204); sodium chloride, sulfathiazole, aluminum hydroxide, phenacetin, and magnesium trisilicate (57); aminophylline, sulfathiazole, calcium carbonate, lactose, and lactose–calcium phosphate (162); calcium sulfate and lactose (76); sodium bicarbonate, sulfanilamide, sodium phenobarbital, and aspirin–phenacetin–caffeine (205); starch–lactose (180); benzoic acid derivatives plus 250 mg. excipient (161); lactose (206); and aspirin (199, 207).

Disintegration times increased with increased gelatin and soluble starch concentrations (11, 178) and hydroxypropyl methylcellulose and sodium carboxymethylcellulose concentrations (37). Aminophylline tablet disintegration times increased with binder concentration while with sulfathiazole certain binders prevented disintegration (162). In starch–lactose tablets, disintegration times increased with increasing polyethylene glycol concentration (180).

Alcohol seemed to increase the disintegration of sulfamethazine (sulfadimidine) tablets (208); with multivitamin tablets containing malt and 4.6% starch, the disintegration time increased as the percent isopropanol increased (209). Additional binder effects that were recorded were: viscosity due to sodium carboxymethylcellulose did not inhibit rapidity of disintegration (36); magnesium aluminum silicates may be coated by or coat other binders, thereby delaying disintegration (76); polyethylene glycol may cause tablets to dissolve rather than disintegrate (180); and gelatin and methylcellulose may show a plateau or minimum disintegration time as the binder amount is increased (155).

Kwan *et al.* (50) found that binders had a significant effect on disintegration. Starch paste gave the lowest disintegration time compared to gums. Binder effect may be due to rate of dissolution or dispersion of the binder. The effect of binders was dependent upon the nature of the basic materials, binder concentration, and pressure (169).

Chwialkowska and Krowczynski (67) determined the effect of the stepwise replacement of 15% starch by sodium carboxymethyldextran and acid carboxymethyldextran or by a sodium carboxymethylcellulose and acid carboxymethylcellulose combination. When replacing starch in novalgin tablets or sodium benzoate tablets with a sodium carboxymethyldextran–acid carboxymethyldextran combination, disintegration time increased as percent starch decreased or binder concentration increased. In aspirin tablets and sulfathiazole tablets, the starch and binder effects were less marked. Starch replacement by a sodium carboxymethylcellulose–acid carboxymethylcellulose combination resulted in increased disintegration time as starch decreased in the four different tablets, but there was no apparent effect due to an increase in binder concentration.

Gum-type binders may form a gel barrier around the tablet to inhibit disintegration. If the binder concentration is sufficiently large, delayed drug release is obtained (210).

EFFECT OF LUBRICANTS

The following lubricants were reported as causing an increase in disintegration times: magnesium stearate (55, 73, 193, 211, 212), magnesium stearate plus sodium lauryl sulfate (208), calcium stearate (213), stearic acid (178), talc–stearate (211), talc (55), silicone oil (211), and polyethylene glycol 6000 (178, 214). Calcium stearate (151), talc (178), sucrose monostearate (151), silicone emulsion and talc–silicone emulsion (196, 211), and polytetrafluoroethylene (212) were mentioned as not affecting disintegration times. The increases in disintegration times for three lubricants were rated as: magnesium stearate > stearic acid > stearyl alcohol (195).

Disintegration time increases with increased lubricant concentration (155, 213), *e.g.*, polyethylene glycol 1500 and 4000, polyethylene glycol stearates, polyethylene glycol monostearate, saccharose monopalmitate, sac-

charose monostearate, and calcium stearate. Talc concentration was reported (215) as having had little effect. Other lubricant effects described were: stearin hindered disintegration when compared to talc in bismuth subnitrate tablets (73); magnesium stearate (0.5%) increased break-up times compared to 8% talc in lactose–starch tablets (164); and polyethylene glycol stearate, polyethylene glycol 4000, and polyethylene glycol 6000 caused decreases in disintegration time in lactose–potato starch granulations (201).

Selmeczi and Kedvessy (62) found hydrophilic colloidal silicon dioxide decreased disintegration time while hydrophobic colloidal silicon dioxide increased disintegration time. Talc and magnesium stearate were described as increasing the time it took water to penetrate tablets (74, 114).

Jaminet and Hazée (216) studied placebo, antipyrine, and phenobarbital tablets, with glyceryl esters of palmitic and stearic acids as lubricants. When the lubricants were used without potato starch, disintegration time markedly increased. Potato starch reduced disintegration time to a value lower than when an equivalent amount of magnesium stearate was used in place of the esters.

Kwan *et al.* (50) found that lubricants affected disintegration times of starch–lactose tablets. It was suggested that the lubricant effect may have been due to increasing the hydrophobicity of the materials. Talc affected disintegration time less than mineral oil, stearic acid, and calcium stearate.

It becomes apparent from the previous five sections that the process of compression and the materials included in a tablet formula have profound effects on tablet disintegration.

The effect of surfactants varies widely, depending on the ingredients, the surfactant and its concentration, and pressure. Some surfactants have a waxy consistency and dissolve slowly, so a lag time may occur before an effect due to the lowering of the surface tension is seen.

There is no definitive evidence that the time and method of addition of the disintegrant have any notable consistent effect.

A tablet made from a filler that is rapidly soluble in aqueous liquids, with small quantity of drug, should break up readily and a disintegrant may not be needed. There is some evidence that disintegrants are more effective with water-insoluble materials. The compressibility characteristics of the active ingredients and fillers will affect disintegration times; *i.e.*, tablets made from poorly compressible substances will break up more readily. Starch is poorly compressible and weakens the tablet structure. Substances that soften or melt under pressure may present disintegration problems.

The tablet binder may be too efficient, delaying disintegration. It may produce a gel-like barrier around the tablet. Sticking of tablets to parts of the disintegration apparatus is one indication of this phenomenon.

The lubricant may cause the tablets to become hydrophobic, causing them initially to repel the disintegrating liquids. Even some of the water-soluble lubricants are waxy and dissolve slowly.

Tablet disintegration, except for the simplest formulas, is a complex phenomenon depending on the interactions between all of the variables of formulation and processing, so generalizations are difficult to make.

APPARATUS

Between 1902 and 1928, tablet disintegration was determined by dropping tablets in water (173, 217). When 20 samples from 13 manufacturers were tested by this method, disintegration was found to vary from a few seconds to more than 2 days with tablets of the same drug but produced by different manufacturers (98).

Wensley *et al.* (218, 219) described in detail the early equipment. Other equipment, often modifications of the apparatus mentioned by Wensley *et al.*, are described in the literature (79, 118, 220–232). Hand equipment is still being recommended (233–235). Several surveys of methods used for the determination of disintegration of pills and tablets were made (218, 236–238). Equipment that automatically recorded the time of tablet break-up was described (115, 239, 240). Critical comparisons of proposed methods were discussed (67, 115, 224, 225, 241–249).

Most equipment has some type of screen to quantitate the degree of tablet break-up. Disintegration time increased as the screen size opening decreased (75, 115, 233).

Bandelin (230), in 1945, said that disintegration could be mechanical resistance or tablet break-up in a fluid and that tablet hardness is not the sole index of their ability to disintegrate.

Schroeter *et al.* (250) declared: "If each drug incorporated into a given series of compressed tablets is an individual problem then the attempt to establish uniform standards for large number of drugs in many types of compressed tablets is spurious . . . ."

Sandell (251), in 1970, explained that a disintegration test should be: ". . . developed and improved so that it will express the ability of tablets and capsules to disintegrate and deaggregate in such a way that the original drug particles are formed. . . ." He used a 3-cm. diameter Plexiglas cylinder containing three sieves. The top one had a 2-mm. opening, the middle one a 0.5-mm. opening, and the bottom one a 0.1-mm. opening. The tube was raised and lowered 1 cm. every 10 sec. in water at 37°. Tablets weighing 0.4–0.5 g. were necessary, and after 10 min. the granules on the sieves were dried and the amount on each sieve was determined.

In 1955, O'Brien *et al.* (252) suggested plastic disks to give clear end-points by pushing soft residues through the screen. These disks were later adapted by the compendia. It was claimed that the disks are gentle and will not force unacceptable tablets through the screen, nor reduce disintegration times for plain tablets.

Kaplan and Kish (253) recommended a rubber gasket between the tablet and screen to minimize sticking of the tablets to the screen or disk and to increase turbulence and flow around the tablet. Later (254), comparisons using the USP method with and without disks or gaskets on 25 different commercial tablets were made. The USP apparatus with gaskets gave the lowest times and generally the lowest standard deviations and coefficients of variation of products, with disintegration

times between 5 and 70 min. Five products that did not disintegrate in 70 min. in the USP apparatus had times that were less than 70 min. with disks or gaskets.

Chapman *et al.* (255) modified the USP apparatus by using a 3-l. beaker, rubber disks for light rubbing action, and perforated plastic disks inserted into the tubes to standardize the distance traveled by the tablets. The tablets were placed for 30 min. in a simulated gastric juice and then in a simulated intestinal juice. Disks gave smaller error variances, smaller percent coefficients of variation, and sharper end-points. There was no statistical difference in the position in the basket or in days. Differences in times with and without disks varied with the type of tablet, and occasionally tablets stuck to the disks. Cook *et al.* (256) determined that a plot of disintegration times without disks *versus* times with disks gave a slope of 0.65. Disks gave shorter times which could mask differences, so they suggested that the apparatus be run slower. Dissolution times were found roughly inversely proportional to starch content. When using water-soluble fillers, disks caused decreased disintegration times compared to tests without disks (186).

Widmann (257) investigated the use of a polyethylene bag containing 12 ml. liquid. The bag was moved up and down in a water bath at 37°, and disintegration was observed by a mirror placed in the bath. Advantages of the bags were removal for observation, minimal tablet sticking, and disposability.

Richter and Steiger-Trippi (242), in 1962, compared the USP apparatus, a modified USP apparatus, and a modified Kantoapotheke (K-A) apparatus. The K-A apparatus consisted of a glass cylinder with 50 ml. water at 37°, the cylinder being turned 180° every 5 sec. so that the tablet falls and hits the stopper. The tablets used were made of potato starch. The modified USP apparatus had a smaller stroke and cylinder height and a smaller screen opening. The USP method had the smallest and K-A modified apparatus had the largest experimental error. With the USP apparatus and the modified USP apparatus, test times, replicates and disintegrants, and test times times replicate interaction were statistically significant.

Kühni *et al.* (247) compared the Swiss Pharmacopoeia V method and a method similar to that of the BP 1948 by using 15 kinds of tablets and five investigators. The error of the Swiss compendium method can be large because only one tablet is used. At least five tablets and a fixed time limit, based on an average with a standard deviation not to be surpassed by any single tablet, were recommended. The coefficients of variation of the two methods did not produce significant differences, but there were large variations due to investigators.

Kockel (225) studied a tumbling device for determining disintegration and the USP, the Swiss Pharmacopoeia, and the French Codex (Medicamentarius Gallicus) equipment. It was disclosed that disintegration times decreased as screen size increased from 2 to 2.5 mm., but times did not significantly decrease when the openings were increased from 2.5 to 3 mm. Disintegration times decreased as temperature increased, so that the 4° temperature range in the USP test may have had an effect in some instances. The author recommended that the effect of temperature be determined for each tablet to find the temperature variation permissible during the test. The Swiss and French methods gave the longest times, and the USP method had slightly longer times than the tumbling method but it had a smaller coefficient of variation. The USP method had no error due to personnel factors, and the author claimed that manual tumbling is without a human error factor. It was reported that disintegration times increased directly with tablet weight. Variability for tablets that disintegrate in less than 1 min. should be up to 30% and only up to 15% for those disintegrating in 3–5 min.

Nogami *et al.* (258) determined tablet disintegration by thermal analysis, claiming that it was possible to determine the exact disintegration time due to a temperature rise from a reaction of tablet ingredients with the fluid. This is actually due to dissolution of the ingredients. The determination of particle-size distribution was also claimed. For calcium carbonate tablets, a pH 4.2 acetate buffer was used. The addition of potato starch as the disintegrant gave a rapid increase in temperature to the maximum in about 2 min., compared to dried paste which had a maximum in 8 min. Another study reported that starch caused a negligible temperature rise while magnesium carbonate gave a 1.85° rise. With acetate buffer, it was stated that granules with potato starch dissolved or disintegrated faster than those without starch. No effect due to pressure was noted by this method, yet with the USP method a linear relationship of log disintegration time *versus* pressure was noted and the Japanese Pharmacopeia method showed an arithmetic relationship. Aspirin tablet disintegration in a sodium citrate solution was also determined by this method (259).

It was disclosed that the USP apparatus gave more uniform values than the Erweka apparatus (100). When the BP method and the Erweka apparatus were compared, the latter gave slightly lower average values, standard deviations, and coefficients of variation (260).

Effect of Fluids, Temperature, and Agitation—In performing disintegration tests under various conditions with different formulas, little or no difference between water, diluted hydrochloric acid solutions, simulated gastric or intestinal juices, or sodium bicarbonate solution was seen (4, 67, 115, 226, 244, 245, 261–263). That acidic solution and simulated gastric juice resulted in faster disintegration time than water also was reported (27, 48, 49, 67, 94). An increase in agitation (tumbling, basket movement, *etc.*) caused faster tablet disintegration (225, 226, 244, 261, 264). Disintegration times decreased with an increase in temperature in the 20–40° range (115, 225, 226, 261, 264) or it was described as having had no effect (262). Polysorbate 80 in the disintegrating fluid had no effect (265).

Effect of Mucoid Substances and Viscosity—Viscosity of the test solution affected disintegration in certain instances (240). Addition of gastric mucin to the disintegrating fluid caused disintegration times to increase (221, 266), and this increase was proportional to the viscosity of the mucin or methylcellulose (266–268). It was recommended that a mucoid substance or methylcellulose be added to the test fluids (266, 267). Pretreatment of tablets by an artificial saliva also increased disintegration times (266, 267).

Münzel and Kuhn (268) showed that an increase in viscosity retarded fluid entrance into pores and that methylcellulose in tablets affected their porosity. Methylcellulose also could cause the screen in the test equipment to become coated and thus retard tablet disintegration time. It was reported that the number of molecules, and not molecular weight, of methylcellulose or polyvinylpyrrolidone affected disintegration. They suggested that only natural gastric mucin was capable of reflecting the true influence of the mucoid substance on the *in vitro* disintegration.

STANDARDS

Sperandio *et al.* (249) defined disintegration as the time required for a tablet to break up into granules of the size from which it was compressed. An 8-mesh screen was recommended since the majority of tablet granulations do not exceed that size.

The term disintegration has been confused with dissolution (173, 194, 249, 269). In addition, the time it takes tablets to fall into granules or into powder may differ (115). The reviews of Smith (270, 271) should be read for some past standards for tablet disintegration.

In 1919, it was emphasized that tablets should disintegrate readily in warm water (272); NF V declared that tablets should disintegrate in a few minutes when dropped into water (273). Since then, various time limits have been suggested, *e.g.*, 1 (32, 60, 227), 3 (234), 5 (225), 10 (262), 15 (274), 30 (230, 275), and 60 (276, 277) min.

An average of the disintegration time of six tablets rather than the upper time limit stated in compendia monographs was recommended (265). The average was explained to be better because one tablet that takes a long time to break up is not indicative of the other five tablets. In another study (278), it was pointed out that if the mean is about 30 min., a 30-min. range of time for disintegration may be acceptable. But if the mean is about 60 min., a range may allow tablets having too long a break-up time to pass the disintegration requirement. This was demonstrated with phenylbutazone when only one product failed the test if a 60-min. mean and range were used and three failed if a 30-min. mean and range were used. The three products also had poor *in vivo* availability and the longest dissolution time ($t_{50\%}$).

The number of tablets to be used to represent a production batch varied from 2 to 20, at one time or sequentially (*e.g.*, 279).

Several investigators classified tablets according to the time required for disintegration or their intended use. Standards were set up for hypodermic, sublingual, buccal, and vaginal tablets and for tablets meant to dissolve before taking (280). Tablets have been classified as: lozenges, sublingual, those that dissolve in 3 min. before use, and those swallowed whole (188). Éwe (281) indexed products as: (*a*) uncoated tablets intended to disintegrate or dissolve in the stomach, 10-min. maximum; (*b*) same as (*a*) except a 120-min. maximum; (*c*) hypodermic tablets, 1-min. limit; (*d*) uncoated tablets intended to dissolve or disintegrate in water at room temperature within 5 min.; and (*e*) uncoated tablets intended to pass into the intestines and be disintegrated there, with no time limit set.

Over the years, various equipment and disintegration test liquids have been recommended and various time limits have been set. These are all arbitrary. In spite of all the rationalizations, the *in vitro* tests do not resemble *in vivo* conditions. Yet the disintegration tests, official and otherwise, are useful as quality control procedures once the results can be correlated to *in vivo* data.

COMPARISON OF DISINTEGRANTS

Generally, disintegration time will decrease as the disintegrant concentration increases (*e.g.*, 11, 13, 22, 47, 74, 193, 282). Occasionally, there may be no concentration effect noted (144), or even an increase in disintegration times with increased disintegrant concentration may occur (37, 53, 155, 282).

The following is a summary of the reported effectiveness of various disintegrants and comparisons between disintegrants: Polish bentonites were poor disintegrants (94); American bentonites were recommended (79); purified cellulose was better than starch (48); powdered natural sponge was better than starch, but powdered synthetic sponge increased the disintegration time (55); 5% powdered natural sponge added during granulation and 2% starch added to dry granules were a good disintegrant combination (56); cation-exchange resin was better than starch (73); formaldehyde–casein was better than sodium carboxymethylcellulose, ultraamylopectin, or starch (32, 63); starch was better than purified cellulose (49); holocelluloses were better than potato starch in aminosalicylic acid, sodium salicylate, and analgesic tablets, but the starch was better with aspirin (44); purified cellulose, magnesium aluminum silicate, and alginic acid showed minimum disintegration times at the 5% level in calcium sulfate and starch–lactose tablets (22); sodium chloride tablets disintegrated more rapidly with 10% starch than without it (118); in soluble tablets, starch and alginic acid accelerated disintegration while sodium carboxymethylcellulose slowed it down (6); kaolin was better than starch (78); starch was better than desiccated starch paste (7); alginic acid and acid carboxymethylcellulose were better than starch, while other gum acids were less effective than starch (40); in sodium bicarbonate and aspirin tablets, a starch ester containing hydrophilic groups was better than starch, which was much better than purified cellulose (27); and when various celluloses, potato starch, alginic acid, amylopectin, and sodium lauryl sulfate were compared in tablets of different compounds, the celluloses generally decreased disintegration times but potato starch was best for aspirin (33).

Generally, various celluloses, especially microcrystalline cellulose, have been reported to increase tablet strength without adversely affecting disintegration time (*e.g.*, 21, 33, 283). Heating microcrystalline cellulose or moisture had no effect on disintegration (31, 284). Humidity may soften microcrystalline cellulose tablets, but the effect is reversible (45).

Fakouki *et al.* (53) compared microcrystalline cellulose, starch, various wood flours, and the three sections of corn cob. Powdered corn cob was claimed

superior to starch in certain tablets. Another comparison of disintegrants showed a 1:1 mixture of starch and microcrystalline cellulose to be better than microcrystalline cellulose alone, which was better than starch. Ten percent corn cob and 15% starch were considered optimum concentrations.

Various gums, polymers, algin derivatives, starches, and magnesium aluminum silicate, when compared in aspirin tablets, gave similar break-up times, with the exception that the addition of a carboxyvinyl polymer and sodium alginate gave long disintegration times (4). When comparing alginic acid, magnesium aluminum silicate, starch–agar, starch, and methylcellulose, a different order of effectiveness was obtained for sodium bicarbonate and aluminum hydroxide tablets (28). Starch was generally better than microcrystalline cellulose in sodium bicarbonate and aspirin tablets (46). When starches, effervescent combinations, gums, and cellulose derivatives were compared in tablets of various drugs, the starches were generally better (11). Corn, potato, and wheat starches had the maximum effect at 10% concentration, and rice starch had the maximum effect at 20% concentration (155). Guar gum with calcium lactate and Sago starch with other drugs were reported better than magnesium aluminum silicate and banana or corn starches (59). Moriyo starch was shown to be slightly better than other disintegrants (15); and the addition of barley starch, in several formulas, resulted in lower break-up times than when other common disintegrants were used (16). In lactose, sodium bicarbonate, and calcium carbonate tablets, cassava and yam starch were about equal but better than potato starch (14). Tablets containing dextrinized and swollen starch disintegrated more rapidly than those containing untreated starches. With digitalis, lactose, thyroid, and sulfathiazole tablets, guar gum was a better disintegrant than starch at a 1.5% concentration (282). Sodium alginate and sodium carboxymethylcellulose were less effective as disintegrants than ultraamylopectin–starch (2:98) or acid carboxymethylcellulose–starch (3:97) combinations (19).

For sodium carbonate granulated with polyethylene glycol 4000, it was revealed that a high viscosity grade of sodium carboxymethylcellulose was a better disintegrant than lower viscosity grades, and disintegration was improved when smaller size sodium carboxymethylcellulose particles were used (37). Barbital, digitalis, phenobarbital, and thyroid tablets disintegrated more rapidly with alginic acid than potato starch (10).

Manudhane *et al.* (30) disclosed that with calcium phosphate, 4 or 8% alginic acid was a better disintegrant than compressed starch, amylose, or starch. With aspirin, starch, compressed starch, or amylose was better at 4 and 8% concentrations. Starch, compressed starch, amylose, and alginic acid are more effective with insoluble drugs such as aspirin and calcium phosphate than with a soluble substance like spray-dried lactose. Amylopectin was shown to be a poor disintegrant in all instances.

Gross and Becker (43) used lactose and zein as binders to compare many different disintegrants. The disintegrants were added to the filler before granulation, or 5% was added with the lubricant (2% leucine). A total of about 17% disintegrant concentration was used. Powdered natural sponge was discovered to be the best, followed (in order) by citrus pulp, locust bean gum, calcium carbonate with pectin or citric acid, colloidal oakmeal, methylcellulose 4000 cps., magnesium peroxide, and then starch. Over a dozen other substances were poorer disintegrants than starch.

EFFECT OF AGING

Tablets of varying compositions have been stored under different conditions of temperature and relative humidities to determine the effect of aging. Increases in disintegration times have been reported (15, 59, 188, 285) but, in some instances, no apparent effect was cited (20, 286). Others reported a variable effect due to the storage conditions (16, 39, 282, 287–290).

Ward and Trachtenberg (51) studied the effect of 5% disintegrants and aging tablets 1 year. In amphenidone and sulfadiazine, magnesium aluminum silicate and starch–20% sodium lauryl sulfate showed the least effect. They recommended starch plus 20% sodium lauryl sulfate, kaolin, purified cellulose, and starch in that order because of their low average disintegration times and the short range. The more soluble drugs disintegrate more rapidly.

Alam and Parrott (185) checked 50-mg. hydrochlorothiazide tablets made with lactose filler. At 80° there was no change in disintegration times for polyvinylpyrrolidone or starch binders. Acacia caused increases in disintegration and dissolution times at elevated and room temperatures. Starch caused no changes at elevated or room temperatures, and polyvinylpyrrolidone had only a slight increase in dissolution time after 1 year at room temperature.

CORRELATION OF DISINTEGRATION AND DISSOLUTION TIMES AND BIOAVAILABILITY

Miller and Heller (291) stated the USP and NF added a disintegration test to ensure that tablets will break up, but the test "... was never meant to serve as an indicator of the degree that the drug content might be absorbed by the body or even as an index to the extent it was presented to the body in a form 'available' for absorption ...." The lack of correlations between disintegration times and dissolution rates or times has been disclosed (208, 265, 278, 292–297), as has the lack of correlations between disintegration time and drug blood levels or *in vivo* activity (235, 295, 297–301). Disintegration times of water-soluble drugs were found to be independent of the dissolution rate (240). Other reports showed disintegration times correlated with dissolution rates (157, 208, 250, 256, 302–306), or they showed rank correlations with dissolution times (179, 296, 307). Disintegration time was correlated to penicillin blood levels (308, 309). Long disintegration times were blamed for ineffective products (276, 277, 302, 303, 307, 310–313).

Some other correlations of disintegration times and dissolution times are described below. Dissolution times increased, dissolution rates decreased, and disintegration times increased with increases in binder concentration (30, 127, 208, 305, 314). Dissolution rates were re-

ported to increase as starch concentration increased (30, 127, 179). It was disclosed that the botanical origin of starch affected the dissolution rate of salicylic acid tablets (315). Reformulation of spironolactone tablets with a water-soluble base helped to reduce the effective dose of the drug (316). Knoechel *et al.* (157) reported, for aspirin–phenacetin–caffeine tablets, that disintegration times and dissolution rates increased as pressure increased, but the nature of the formula or the drug affected these times more than the pressure. In starch–lactose tablets containing $Na^{131}I$, it was found that a maximum of ^{131}I was released when the tablet disintegrated (314). Krowczynski and Stozek (208) found that when magnesium stearate or sodium lauryl sulfate was used, increasing the lubricant content slightly increased disintegration and the $t_{50\%}$ times. Increasing the surfactant content increased disintegration time but decreased the $t_{50\%}$ times of sulfamethazine (sulfadimidine) tablets. When using calcium carbaspirin, buffered aspirin, and plain aspirin tablets, it was revealed that the amount dissolved in 10 min. and the amount of drug absorbed were inversely proportional to the disintegration times (299). Manudhane *et al.* (30), using calcium phosphate tablets containing 0.1% amaranth, showed that compressed starch at high and low pressures released dye better than plain starch.

The time for 80% dissolution was reported to be much longer than the disintegration time (179). Disintegration could not distinguish between rapid and slow dissolving granules (299, 317). Tablets that disintegrated into fine particles had faster dissolution rates than those that disintegrated into large clumps (306). The formation of fine particles was not dependent on disintegration time, so it was suggested that particle size should be determined after disintegration to ensure product effectiveness (318). Sandell *et al.* (319), using the apparatus consisting of three screens (previously described), found that for isoniazid and sulfamethizole the granules that remained on the coarsest sieve correlated with dissolution rate. With meprobamate and diazepam tablets, some correlation with the amount left on the three sieves and dissolution times occurred.

Hersey and Barzilay (127), using sulfathiazole tablets, stated that "disintegration time" is the difference in lag times to reach dissolution equilibrium between the powder and tablets. The lag times were: powder, 1.75 hr.; 10% starch, 2.5 hr.; and 5% starch, 3.5 hr. Therefore, disintegration times became 0.75 and 1.75 hr. for 10 and 5% starch, respectively. It was claimed that pharmacopeia tests could not distinguish between tablets and that a change in particle-size distribution due to compression and formation of a mucilage by starch around some of the particles might be factors affecting dissolution rates.

A small amount of aminobenzoic acid in the tablets was recommended to indicate how rapidly tablets disintegrate after ingestion, because the aminobenzoic acid is rapidly absorbed and detected in the urine (320).

Chapman *et al.* (276), in 1957, said that a 60-min. time limit on disintegration for tablets is necessary based on riboflavin excretion. In another study (235), three out of 25 tablets had disintegration times greater than 60 min. but were considered bioavailable because the riboflavin was leached out of the tablets without their complete disintegration. The authors explained that all *in vitro* tests are an empirical approach which must be correlated to bioavailability at some stage. The use of simulated gut juices and disks helped establish these correlations. Middleton *et al.* (300) reported that disintegration tests do not reveal clear evidence of a separation into acceptable and unacceptable aminosalicylic acid products, although a previous study did show this separation. It is possible to have tablets disintegrate rapidly but the drug dissolves slowly.

In 1958 it was claimed that two patients exhibited Cushing's syndrome when given cortisone tablets that had disintegration times longer than the BP requirement (312, 321). Yet it was argued that a disintegration time of 22.5 or 30 min. for cortisone did not matter (322, 323), and poor therapeutic results could also have been due to a nonspecific assay and the wrong drug being used (323). Prednisone tablets, found therapeutically inactive in one patient, disintegrated in less than 6 min. with disks but in greater than 1 hr. without the the use of disks. Therapeutically effective tablets disintegrated in less than 6 min. with or without disks. The inactive tablet had a $t_{50\%}$ of 100 ± 53 min., while the active tablet had a $t_{50\%}$ of 4.3 ± 1.3 min. (302, 303).

Jacob and Plein (304) reported the pounding action of disks gave fast and fairly uniform disintegration times of commercial phenobarbital tablets; only 1 out of 13 failed the disintegration test, while disintegration times without disks indicated that only 1 in 13 passed the test. The tests without disks appeared to correlate qualitatively better with dissolution rate.

Schroeter *et al.* (250) determined, for 12 lots of tablets of an anti-inflammatory steroid, that the regression of $t_{50\%}$ *versus* disintegration time gave highly significant linear correlation with a slope of 1.02. Seven lots of a sulfonamide showed that a formulation with sodium chloride had a slope of 1.82, while a formulation without sodium chloride gave a slope of 1.10. Seven lots of tablets of an antidiabetic drug showed no correlation between $t_{50\%}$ and disintegration times determined either with or without disks. A plot of $t_{50\%}$ calculated *versus* disintegration time gave a slope of 0.56 for 16 lots of aspirin–phenacetin–caffeine tablets made from a single granulation. Average disintegration times with disks *versus* times without disks gave a slope of 0.67, with the line going through the origin. The authors explained that disks may mask differences between lots because they cause more rapid disintegration. That there may be *in vivo* and *in vitro* correlations specific for a drug and formulation was revealed by this study.

X-rays have been used to determine *in vivo* tablet disintegration (233, 324). Levy (325) reported that aspirin tablets disintegrated *in vitro* in 3.5 min., but X-ray seemed to indicate that disintegration *in vivo* just began in about 13 min. Steinberg *et al.* (326) used tablets containing barium sulfate pellets that disintegrated in 10.25 min. *in vitro*. Roentgenograms taken after 89 nonfasting and 19 semifasting subjects swallowed two tablets with water showed that about 52 tablets disintegrated in 15 min., about 90 in 25 min., 55 in 45 min., and the remainder in over 45 min. There appeared to be a low degree of agitation in the stomach. Tablets that

disintegrated in 30–40 min. *in vitro* reportedly disintegrated in more than 2 hr. *in vivo;* those that disintegrated in 18 min. *in vitro* lasted 66 min. *in vivo*, while those that had a 15-min. *in vitro* break-up time had 50-min. disintegration *in vivo*.

It was claimed that the amount of drug needed to achieve clinical results must be considered, so it may be necessary to sacrifice availability to protect drugs from decomposition by stomach contents, cover bitter taste, achieve prolonged effect, or reduce GI irritation (327). Kingsford (328), in 1966, claimed that in many cases *in vitro* disintegration time cannot be used as a direct indication of *in vivo* dissolution time and *in vitro* and *in vivo* correlations need to be determined for every preparation. Disintegration tests are useful but lack the discrimination required for critical assessment.

French *et al.* (238) said: "Specifying simple set of conditions, it (*disintegration test*) represents a physical method of pharmaceutical quality control which allows a drug manufacturer or distributor to check his products for uniformity of performance from batch to batch without recourse to complex and expensive apparatus or personnel requiring advanced academic training. . . ." The break-up times must be correlated to *in vivo* data because *in vitro* results alone cannot be relied upon as indexes of availability. Physiological conditions cannot be duplicated, and fast disintegration does not guarantee availability, nor does slow disintegration indicate nonavailability. The formula is of sufficient importance that the manufacturers must give this information to the proper government agency. Dissolution tests were considered more important because disintegration tests only measure the time needed to form granules, yet even dissolution tests require *in vivo* correlation.

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ACKNOWLEDGMENTS AND ADDRESSES

Received from the *School of Pharmacy, Medical College of Virginia, Health Sciences Center, Virginia Commonwealth University, Richmond, VA 23219*