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Some observations of the penetration and disruption of tablets by water

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The effect of compressibility, particle size, granulation and the addition of starch on the pore structure on tablets of aspirin, calcium carbonate, lactose, magnesium carbonate, phenindione and sucrose has been measured using air permeability and liquid penetration techniques. The addition of starch to the various materials produced no significant effect on the pore structure of the dry tablet but caused disruption and alteration of this structure when the tablet was penetrated by water. This disruptive effect produced by starch depends on the compressibility of the constituent material and the pressure used to form the tablet.

The aim of the tablet formulator is to produce a hard tablet which, when ingested, disintegrates to give a particulate system of similar size distribution to the original powder blend before processing. Such disintegration is achieved by penetration of the strong compact by gastric fluids and by the disruption of the bonds which unite it.

The rate of penetration of liquid into the tablet is determined by the balance of the capillary forces promoting movement of fluid towards the interior, and the viscous forces opposing it. Since the latter increase with penetration whereas the former remain reasonably constant, penetration rate into a tablet that retains its overall structure during penetration, will fall as saturation proceeds. When disruption of a tablet occurs, an increased rate of penetration is achieved because the viscous forces acting along the disrupted pore system are reduced while capillary forces remain unchanged. This arises since the curvature of the meniscus of the advancing liquid, on which capillary activity depends, is determined by the dry undisrupted pore system.

Although the extent to which the balance between capillary and viscous forces is influenced both by the physical properties of the liquid and the pore structure of the tablet, pore structure is the only factor which the tablet formulator can control. This paper reports a quantitative examination of some of the variables in formulation which may influence pore structure. The factors investigated here include the effect of tabletting pressure, differences in the compressibility of the materials comprising the tablet, the particle-size distribution of the powders and the granulation process.

EXPERIMENTAL

Materials and granulation

Aspirin was used in three forms: fine powder, coarse crystals, and granules prepared by massing fine powder with absolute ethanol (31·5% by weight).

Calcium phosphate was used as fine powder and as granules prepared by massing with 10% dextrose solution (50% by weight).

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Lactose was studied in the form of coarse powder, fine powder, and granules prepared by massing the coarse powder with water (20% by weight).

Magnesium carbonate was used as coarse powder, fine powder, and as granules prepared by massing the fine powder with a 10% gum acacia solution (45% by weight).

Phenindione was studied in three forms: coarse crystals, fine powder, and as granules prepared by massing the fine powder with 10% dextrose solution (70% by weight).

Sucrose was examined as fine powder and as granules prepared by massing with water (8% by weight).

All granular materials were screened and those fractions passing a 16 mesh sieve but retained on a 22 mesh sieve were selected for study.

Granules of the above materials were also prepared including, before massing, 10% by weight of potato starch. A proportionately larger quantity of binding solution was used.

Particle-size analysis

The particle-size distributions of sucrose, fine lactose, potato starch and fine aspirin powders were measured by microscope, those of fine phenindione and fine and coarse magnesium carbonate powders by Coulter Counter and the sizing of coarse lactose, coarse aspirin and coarse phenindione powders was by sieving.

Compression

A weighed quantity of material was placed in a lubricated die, sealed at one end by a spigot. The upper punch was inserted and the assembly compressed over a pressure range of 12–300 MNm^{-2} between the platens of a hydraulic press. Compaction pressure was measured as described by Shotton & Ganderton (1960) by means of strain gauges affixed to the shank of the punch. The porosity at any given pressure was calculated from the weight and volume of the tablet whilst still in the die: the tablet was therefore under radial constraint when the measurements were taken. These conditions were reproduced in the permeability and penetration studies by testing the tablet in the die.

Permeability and penetration measurements

The permeability of the tablets to air was measured with an apparatus similar to that designed by Lea & Nurse (1939) and the permeability coefficient calculated was that defined by Ganderton & Selkirk (1970). The rate at which water penetrated the tablet was measured in an apparatus similar in design to that described by Ganderton & Selkirk (1970). The values quoted in Fig. 4 are those occurring when the liquid had penetrated 1 mm into the tablet.

RESULTS AND DISCUSSION

The pressure adopted for the manufacture of compressed tablets is usually determined by the strength of the tablet, its disintegration characteristics having been assessed during formulation. It is probable that common pressures are usually within the range 50–200 MNm^{-2}. The interaction of tabletting pressure with the other variables of formulation is therefore considered over this range.

PERMEABILITY STUDIES

Effect of compressibility

A comparison of the permeability and porosity of tablets made at the same compression is shown in Table 1. There are wide variations in both permeability and porosity factors and also in the compressibility of the powders, expressed in Fig. 1 as the relation between porosity and tabletting pressure. For example, the porosity of calcium phosphate compressed at 100 MNm^{-2} is over 42% whereas that of an aspirin tablet made at the same pressure is only 4·4%. Thus, in normal tabletting a large difference in porosity can be expected between a tablet containing a high proportion of an incompressible diluent and a tablet of a compressible drug.

Table 1. *Permeabilities and porosities of tablets compressed to* 100·0 MNm^{-2}

Material	Porosity (%)	Permeability (m^2)
Aspirin powder	4·4	$6·7 \times 10^{-15}$
Aspirin coarse powder	3·2	$6·4 \times 10^{-15}$
Aspirin granules	6·0	$6·6 \times 10^{-15}$
Calcium phosphate powder	42·0	$2·7 \times 10^{-14}$
Calcium phosphate granules	39·1	$2·4 \times 10^{-14}$
Lactose powder	15·9	$1·7 \times 10^{-13}$
Lactose coarse powder	11·6	$6·0 \times 10^{-13}$
Lactose granules	16·8	$3·3 \times 10^{-13}$
Magnesium carbonate fine powder	42·2	$1·1 \times 10^{-14}$
Magnesium carbonate coarse powder	39·6	$7·4 \times 10^{-14}$
Magnesium carbonate granules	36·4	$1·9 \times 10^{-13}$
Phenindione powder	8·2	$5·3 \times 10^{-15}$
Phenindione coarse powder	7·6	$7·4 \times 10^{-14}$
Phenindione granules	6·7	$4·2 \times 10^{-15}$
Sucrose powder	14·5	$1·6 \times 10^{-13}$
Sucrose granules	14·3	$3·1 \times 10^{-13}$

The effect of tabletting pressure on the permeability of tablets is given in Fig. 3. If tablets prepared from powders of the same particle size distribution are compressed at the same pressure, differences in permeability can be ascribed mainly to the compressibilities of the starting materials. The size distributions in Fig. 2 show that lactose can be compared with aspirin, and magnesium carbonate with phenindione. The results in Table 1 show that lactose, which is intermediate in compressibility, gives tablets 25 times more permeable than those of aspirin which is compressible. Comparison of the finer materials showed that magnesium carbonate, which is incompressible, was 13 times more permeable than phenindione.

Effect of particle size

The effect of particle size distribution on porosity and permeability was examined by comparing coarse and fine samples of the same material. Although tablets prepared from coarse powder were less porous, their permeabilities to air were greater, with the exception of aspirin. Tablets prepared from coarse phenindione powder were ten times more permeable than those compressed from the fine powder. The effect of particle size distribution on permeability was less marked with magnesium carbonate and lactose and was absent with aspirin.

Effect of granulation

Granulation of coarse magnesium carbonate powder increased the permeability coefficient of tablets prepared at 100 MNm^{-2} from $7·4 \times 10^{-14}$ to $1·84 \times 10^{-13} m^2$.

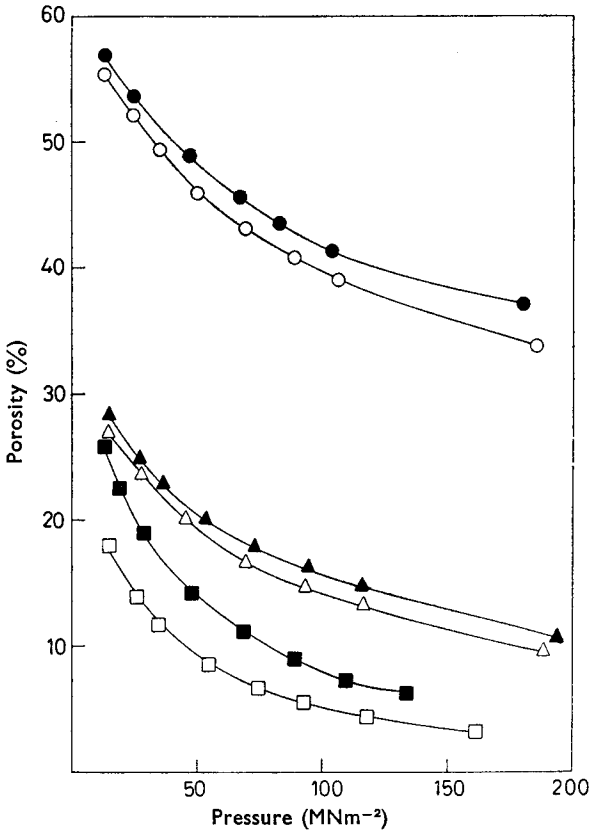

FIG. 1. Compression characteristics of the powders used for granulation. ● Calcium phosphate. ○ Magnesium carbonate. ▲ Lactose. △ Sucrose. ■ Phenindione. □ Aspirin.

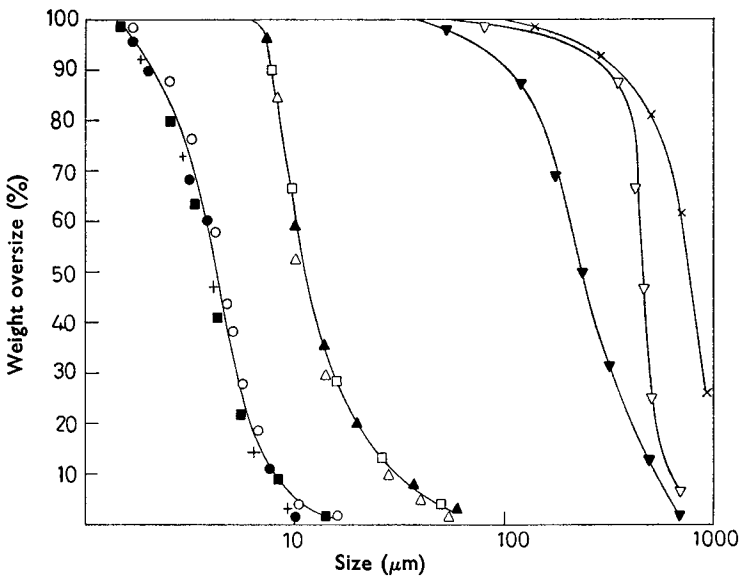

FIG. 2. Particle size distribution of powders. ● Calcium phosphate. ○ Magnesium carbonate. ▲ Lactose. △ Sucrose. ■ Phenindione. □ Aspirin. ▽ Potato starch. + Fine magnesium carbonate. X Coarse phenindione. ▼ Coarse aspirin.

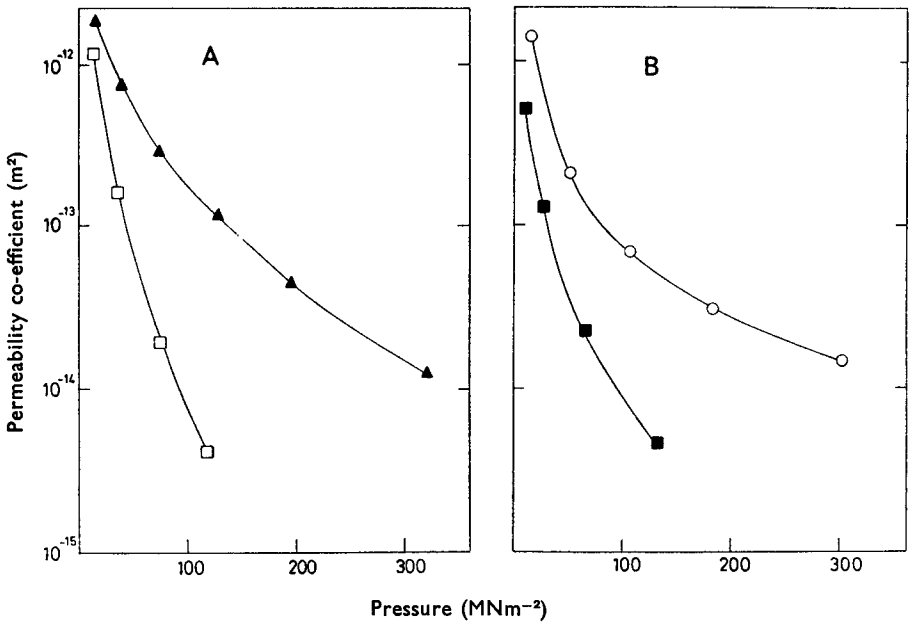

FIG. 3. The permeability-pressure relation of ungranulated powder. A. ▲ Lactose. □ Aspirin. B. ○ Magnesium carbonate. ■ Phenindione.

With sucrose and lactose, the increase in permeability with granulation was small. Granulation produced no effect with calcium phosphate, aspirin and phenindione. These differences are probably explained by the fact that the granulation techniques used produced hard gritty granules of magnesium carbonate, whereas granules of aspirin, phenindione and calcium phosphate were soft, reverting to powder when pressed with a spatula. Lactose and sucrose granules were of intermediate strength.

Effect of starch

Comparison of Tables 1 and 2 indicates that the effect of potato starch on the porosity and permeability of tablets is largely additive. Starch has the same compressibility as lactose and sucrose and when added to these materials its effect on the porosity of tablets compressed at 100 MNm^{-2} was negligible. The presence of starch in phenindione and aspirin tablets increased the porosity of tablets prepared at 100 MNm^{-2}. When mixed with the relatively incompressible calcium phosphate or magnesium carbonate the porosity of these tablets decreased.

Table 2. *Permeabilities and porosities of granules containing* 10% *potato starch compressed to* 100 MNm^{-2}

Material	Porosity (%)	Permeability (m^2)
Aspirin	6·6	$1·1 \times 10^{-14}$
Calcium phosphate	36·0	$2·9 \times 10^{-14}$
Lactose	16·3	$3·3 \times 10^{-13}$
Magnesium carbonate	33·4	$2·8 \times 10^{-13}$
Phenindione	8·1	$7·6 \times 10^{-15}$
Sucrose	14·7	$3·0 \times 10^{-13}$

The permeability of lactose and sucrose tablets containing starch was unaffected whereas tablets of all other materials showed a small increase in permeability consistent with the introduction of a component of much larger particle size.

Conclusions

The interaction of compressibility and particle size distribution has given permeability differences of over one hundred fold in tablets compressed at 100 MNm^{-2}. This indicates marked variation in the capillary network within the tablet. Compressible materials in fine particle form produced impermeable structures. The effect of granulation on pore structure is smaller and appears to be restricted to granules which strongly resist deformation. The introduction of up to 10% by weight of potato starch has only a small effect on the pore structure of a tablet.

THE EXTENT OF PENETRATION BY WATER

Compressibility and particle size distribution, which largely dominate gross variations in permeability have the same influence on rate of liquid penetration.

When comparative liquid penetration studies are made, factors in addition to those which determine pore structure of a dry tablet must be considered. Most important are the wettability of the tablet ingredients, and the varying degrees of disruption caused by the penetrating liquid. Nevertheless, the general form of the relation between penetration rate and tabletting pressure is similar to the permeability-pressure relation described by Fig. 3. The results, presented in Fig. 4, show that the rates of penetration for aspirin and phenindione, both of which give impermeable

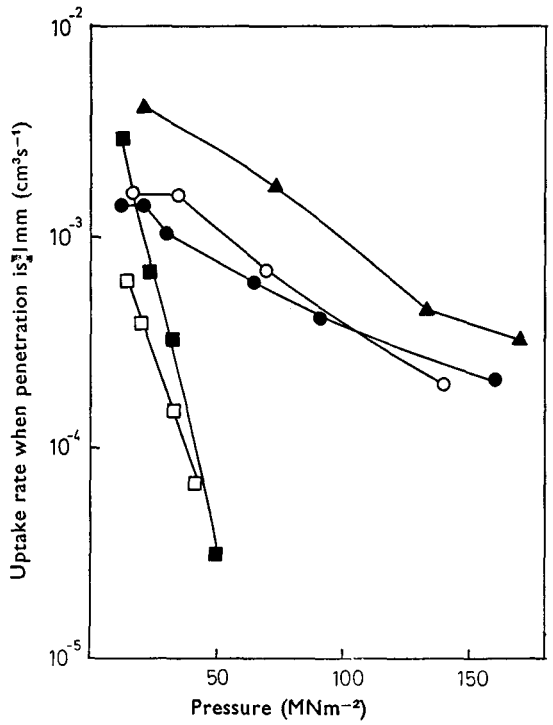

FIG. 4. The aqueous uptake rate into compacts of granules containing no starch when penetration is 1 mm.

tablets, declined rapidly becoming immeasurably slow for tablets compressed at 50 MNm^{-2}. Lactose which gave the most permeable tablets also had the highest penetration rate.

Differing wettability appears to play a subordinate role in liquid penetrability and this role cannot be precisely identified from these experiments. Contamination of the powders by granulation fluids would probably reduce differences in the wettability of the powders used in this study.

Disruption by an aqueous penetrant occurs only with calcium phosphate and magnesium carbonate tablets produced at low pressure. Increase of tabletting pressure had a small effect on the penetration rate of tablets of all materials even though the marked reduction in permeability, shown in Fig. 3, indicated large changes in pore structure. Tablets prepared at pressures up to 50 MNm^{-2} showed softening of the wetted portion so that viscous resistance to penetration was never fully developed.

At pressures above 50 MNm^{-2}, tablets of calcium phosphate and magnesium carbonate retained their shape during liquid penetration and further increase in pressure gave a commensurate decrease in penetrability. All tablets prepared from granules of lactose, aspirin and phenindione retained their shape after penetration by water. A decrease in penetrability was therefore observed over the entire pressure range studied.

Effect of starch

Starch, which produces only small effects on pore structures, profoundly affected penetration rate. For example, addition of starch to lactose affected neither porosity nor permeability of the tablet produced at 100 MNm^{-2}. The effect on aqueous penetration is, however, dramatic. As shown in Fig. 5, the initial phase of penetration is similar in form to that of lactose without starch—although somewhat faster. This is followed by a period in which wetting of the starch–lactose tablet is almost instantaneous. Viscous resistance to penetration disappeared as the result of tablet collapse. Severe and sometimes explosive disintegration occurred with all materials to give the increased penetration rates reported in Table 3.

The actual mechanism by which starch acts as a disintegrant has long been the subject of dispute. Two theories, disruption by swelling (Patel & Hopponen, 1966), and the formation of a capillary network (Curlin, 1955) that accelerates the wetting of a tablet, have been proposed. The rate of penetration of water into lightly compressed tablets of phenindione (Fig. 6), is only slightly increased by the inclusion of starch. This is commensurate with the small increase in the permeability coefficient which starch produces. Thus, evidence of a significant change due to the formation of a capillary network of different wettability is lacking. In the absence of starch, further compression only decreased the rate of saturation of the pore network by water (Fig. 6A). When the phenindione tablets contained starch (Fig. 6B), the changing form of the saturation curve indicated that disruption became more pronounced as tabletting pressure increased. After a period of slow penetration, relatively high rates of saturation were observed even in tablets produced at a pressure of 75 MNm^{-2}, but at 100 MNm^{-2}, saturation rates became slow again and the degree of tablet disruption decreased.

The failure of starch to disrupt tablets that had been lightly compressed (15 MNm^{-2}) was also observed with lactose and aspirin during the penetration test. Magnesium

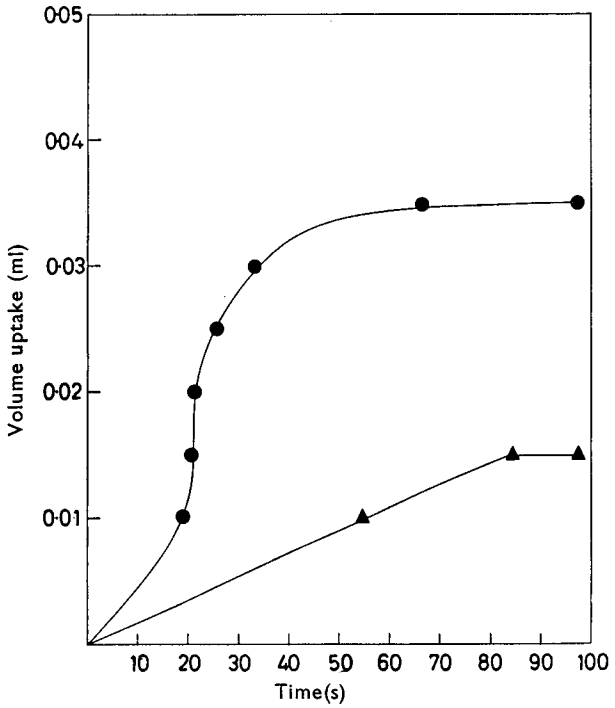

FIG. 5. Aqueous penetration of lactose tablets prepared from granules compressed to a porosity of 10%. ● 10% potato starch. ▲ No starch.

carbonate and calcium phosphate, on the other hand, slowly collapsed. At higher pressures, i.e. 75 MNm^{-2}, the pattern of aqueous penetration of all tablets showed the same dependence on tabletting pressure as that of phenindione. The observation that starch does not fully exert its disruptive capacity in tablets produced at low pressure is in accordance with the explanation of its effect by a swelling mechanism since swelling would be more effective in rigid tablets of low porosity. However the penetration rates given in Table 3 show that the effect of starch is much modified by the structure of the tablet. Phenindione which, in the absence of starch, was the least permeable and most slowly penetrated tablet, retained these characteristics when starch was added. Lactose, in the absence of starch, was most permeable and the most rapidly penetrated tablet on addition of starch. Of the other materials, starch was more disruptive in aspirin tablets than in tablets of calcium phosphate.

Table 3. *Times for* 30% *saturation of tablets prepared from granules compressed to* 100 MNm^{-2}

Material	Time (s)	
	Without starch	With starch
Aspirin	300	14
Calcium phosphate ..	52	20
Lactose..	26	10
Magnesium carbonate	80	30
Phenindione	600	215

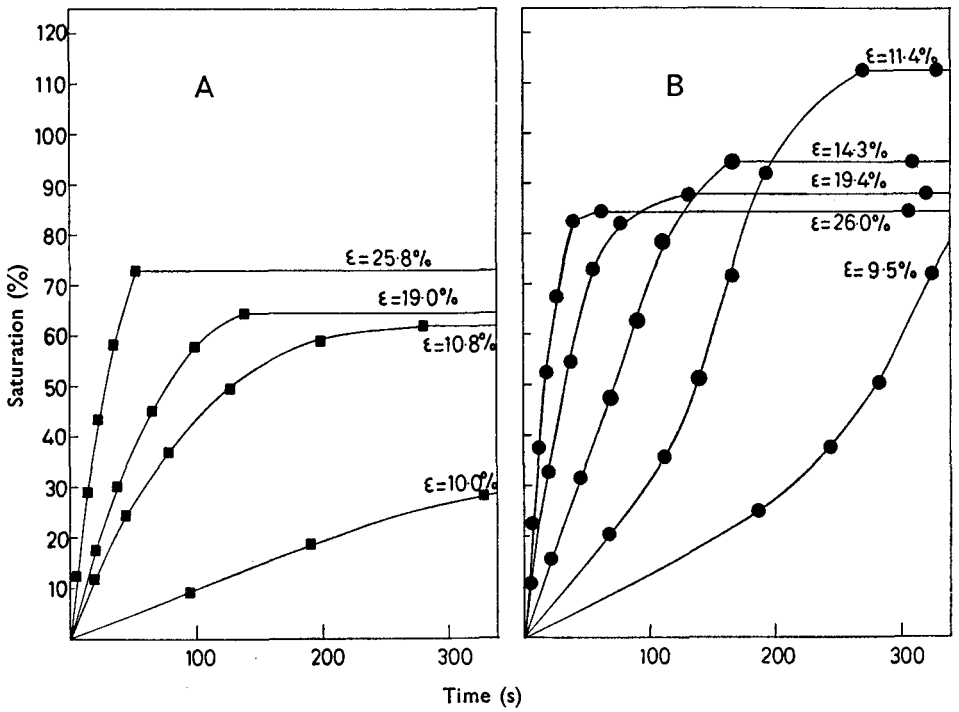

FIG. 6. Saturation of phenindione tablets prepared from granules. A. ■ No starch. B. ● 10% potato starch. (ε=tablet porosity)

The factors that determine tablet structure do not therefore entirely determine the aqueous penetration of a porous system which is being disrupted. It is probable that when starch is present the extent of bonding will also influence the susceptibility of the tablet to break-up when water causes the starch grains to swell.

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