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Review Articles

Solid-state properties of powders in the formulation and processing of solid dosage forms

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Introduction

Powdered drugs are not generally used alone when formulating solid dosage forms. A variety of excipients, such as diluents, disintegrants, binding agents and lubricants, the vast majority in powder form, are included for particular functions. These are then processed into convenient forms for drug administration. Whilst full chemical profiles of drugs and additives are generally well defined for quality assurance purposes, it is also relevant to understand their fundamental powder and processing properties since these parameters can significantly affect the manufacture and performance of solid dosage forms. In addition, with the increasing sophistication of processing equipment with regard to speed and automation and the complexity of certain formulations, such as controlled release preparations, the selection of drug species and additives has become more critical. Subtle variations in solid-state properties, here regarded as the intrinsic properties of component crystals, between batches and between suppliers, can lead to manufacturing problems (Jones, 1981).

Increased understanding of powder properties now allows powder characteristics to be defined more fully permitting a more quantitative approach to formulation design and processing than by the more traditional empirical methods. In this article, the significance of the solid-state properties of pharmaceutical powders is considered in terms of the selection of drug species and additives in formulations, and the processes involved in the manufacture of solid dosage forms.

Powder property classification

Powdered materials represent complex systems for fundamental characterization. At the bulk powder level, they are non-homogeneous in structure, composed of

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particles of different shapes and sizes with interparticle voids. As a result, powders contain a multitude of interacting surfaces which leads to wide ranging physicochemical and mechanical properties. Alternatively, the component size of powdered materials can be examined at the particle or crystal level, where an increased degree of homogeneity will be observed. Jones (1977) has identified 3 groups of properties based on consideration of different unit component size—basic material, or solid-state, properties; particulate material properties; and bulk-derived properties. Recent reviews have considered the influence of bulk-derived and physico-technical properties on formulation design and processing (Jones, 1977, 1981; Rees, 1973, 1978; York, 1980a). It is also appropriate to evaluate the significant role played by the solid-state properties of powdered materials in these important areas.

Solid state properties: stresses during preparation and processing

Most drugs and additives are crystalline materials, or possess a high degree of crystallinity, and over recent years the subject of solid-state evaluation has received considerable attention from pharmaceutical scientists. Properties which have been identified as being of particular importance in formulation and processing are listed in Table 1 together with a listing of stresses to which the powders might be exposed during their processing or manipulation into solid dosage forms. The procedures commonly used are also given in Table 1. Recent evidence suggests that variations in solid-state properties, occurring for example between batches of the same material or resulting from alternative powder treatment procedures, can modify formulation requirements as well as processing and product performance (e.g. Chiou and Kyle, 1979; Hansford et al., 1980b; Hanssen et al., 1970; Huettenrauch, 1978; Muller, 1977). Careful evaluation of solid-state properties and the effects of different stresses

TABLE 1

SOLID-STATE PROPERTIES AND POTENTIAL PROCESSING STRESSES DURING IDENTIFIED PROCEDURES USED IN SOLID DOSAGE MANUFACTURE

Solid-state properties	Processing stresses	Manufacturing procedures
Crystal structure	Temperature	Crystallization
Crystal hardness	Pressure	Precipitation
Crystal habit	Mechanical	Milling
Polymorphism and solvate forms	Radiation	Mixing
Wettability, surface polarity and moisture sorption	Exposure to liquids	Drying
	Exposure to gases and liquid vapours	Granulation
		Compression
		Storage
		Transport
		Handling

upon these parameters is therefore important when defining formulation and processing requirements as well as in optimizing product performance.

Crystal structure

All crystalline solids contain within their lattices, defects which can influence their physical and mechanical properties and their processing, as well as the properties of the final dosage form. The most common defects include screw dislocations and lattice vacancies. For example, frequency of defects can be related to the ease of fracture during milling (Pilpel, 1977) as well as deformation during compression (Wert and Thomson, 1970; Huettenrauch, 1977). An understanding of the role of crystal structure in the compressional process might therefore lead to predictive features in tablet formulation and processing.

Recently, Hess (1978) has considered the changes taking place in crystal structure and shape during compression. Such structural changes are opposed by intermolecular forces which restore the crystal to its original form, as in the case of elastic

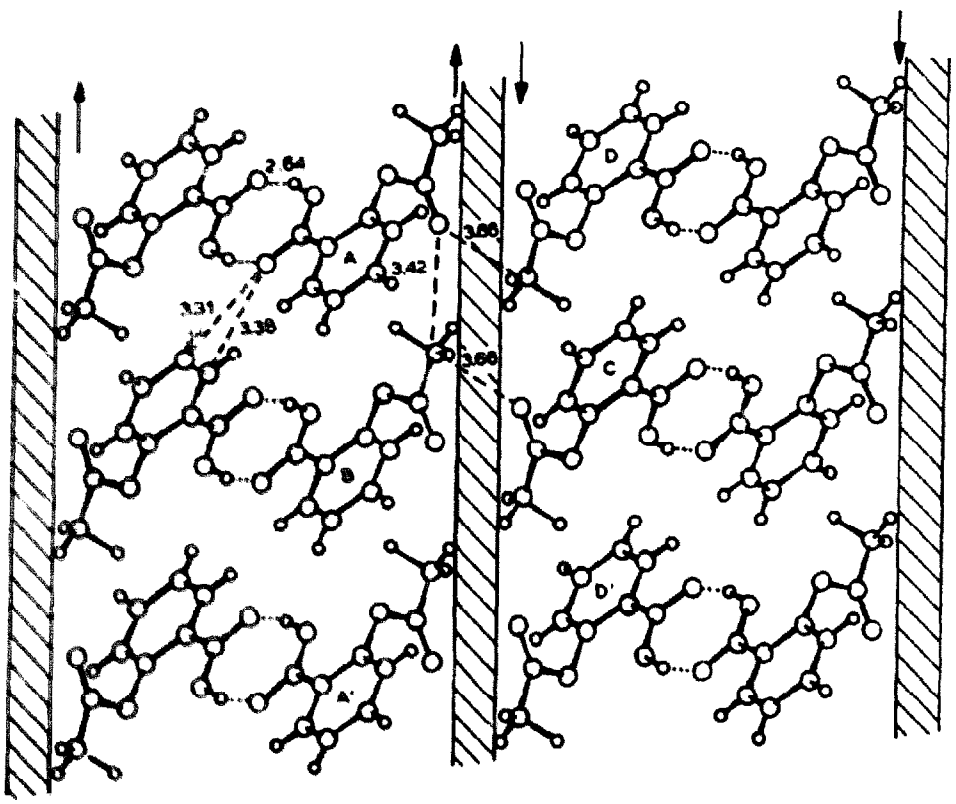


Fig. 1. Illustration of postulated structure inside an aspirin crystal (Hess, 1978). A–D represent individual aspirin molecules (A^1 and D^1 being the positions reached by translation of A and D). Crosshatched areas are possible displacement planes in the direction of the arrows. Atomic distances are in angstrom units.

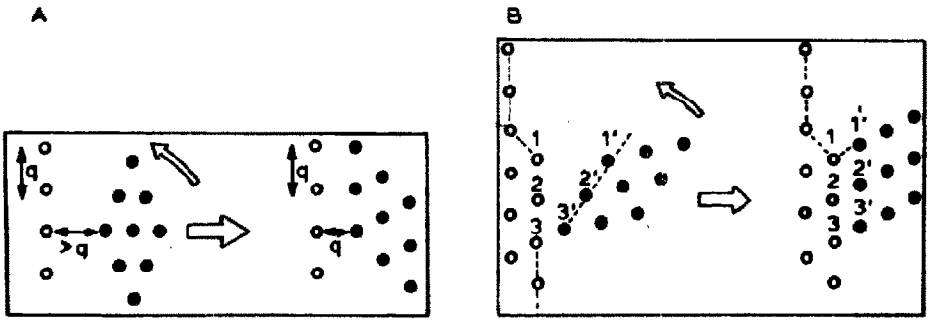


FIg. 2. Illustration of postulated alignment of (A) two plane surfaces in a crystalline powder, and (B) two surfaces with finite rugosity (Carstensen, 1980). q represents interatomic distance.

materials. If the intermolecular forces are exceeded, then plastic or permanent deformation results and, if the stress is continued, plastic flow will continue. Hess (1978) demonstrated that where stepwise displacements are in evidence as for aspirin crystals (see Fig. 1) the displacements occur along slip planes inside the crystal. As a

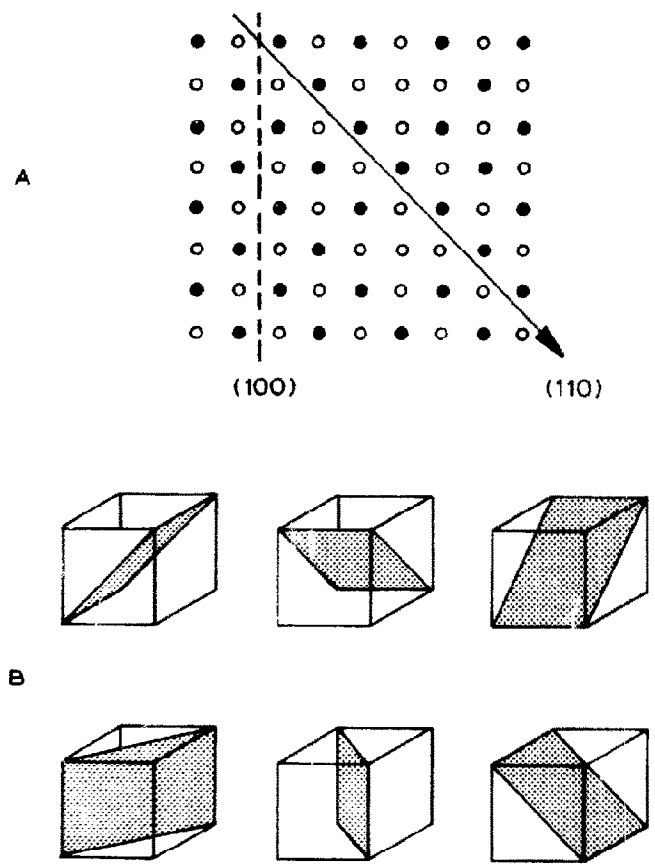


Fig. 3. Illustration of postulated behaviour of sodium chloride crystals under mechanical stress. A: cleavage (dotted line) and mechanical translation (continuous line) planes. B: the 6 equivalent translation planes (Hess, 1978).

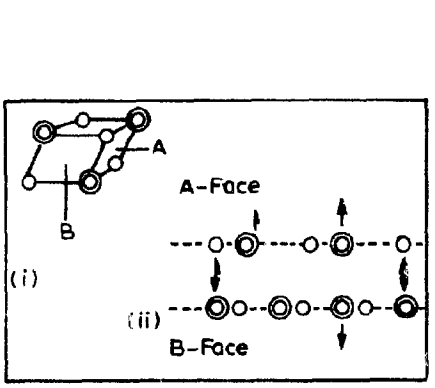
result the displaced elements move in an orderly manner to a new location with equivalent molecular packing arrangement to the starting point. In this way, the internal packing arrangement is maintained whilst the external crystal shape is changed.

However, Carstensen (1980) has pointed out that for materials with steps in approaching crystal faces only portions of the faces will approach to distances equal to the lattice constant (see Fig. 2). As a result, pores will remain at positions of crystal face irregularity which may cause points of strain resulting in crack formation upon pressure release (Carstensen, 1980).

Alternative mechanisms for plastic deformation are identified for highly symmetrical crystals such as cubic crystals of sodium chloride (Hess, 1978). These crystals possess numerous potential slip planes to produce plastic deformation and Fig. 3 illustrates possible cleavage and translation planes for ionic sodium chloride crystals. In sodium chloride crystals, all planes parallel to '110' plane are potential slip planes whilst planes parallel to '100' plane can become cleavage planes. Unlike the layering effect observed for aspirin, Hess reported that shearing effects were not observed in scanning electron micrographs for sodium chloride and the shearing must occur on the molecular level. Substances in more complex crystal systems have lattice arrangements which differ from face to face (see Fig. 4) and only one out of a number of faces will match up with a given face of another crystal (Carstensen, 1980).

The fracture of crystals in brittle materials is associated with crystal lattice defects and imperfections (Hess, 1978). Defects are thought to develop into breakage planes if the applied stress continues, is sufficiently large, and if the rate of break is faster than the rate at which the stress can be reduced by the material deforming plastically.

Most drugs and some excipients show a tendency to fracture on compression. Materials such as sodium chloride, potassium chloride, aspirin and lipids exhibit



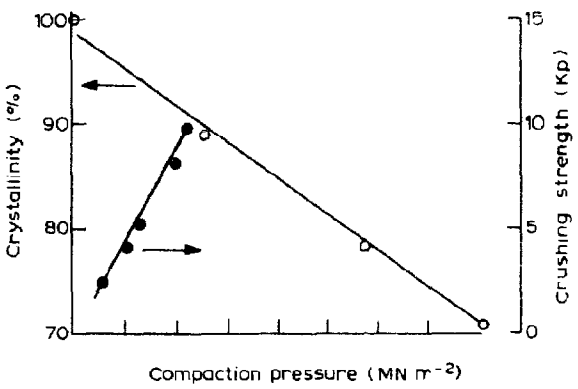


Fig. 4. Illustration of postulated alignment of two non-equivalent surfaces (Carstensen, 1980). ○ and ◎ indicate different groups of molecules which are at or close to the surface of the crystal. Arrows indicate attraction or repulsion.

Fig. 5. Relationship between crystallinity, tablet crushing strength and compaction pressure for α-lactose monohydrate (Huettenrauch, 1977a).

TABLE 2

STRUCTURAL AND MORPHOLOGICAL CHARACTERISTICS AS A FUNCTION OF COMPACTION PRESSURE FOR ALUMINIUM OXIDE (ZIEGLER, 1978b)

Densification range (kbar)	Compaction pressure (kbar)	Relative density % theoretical density	Mean particle size [a] (μm)	Weight fraction of particles $< 2\ \mu m$ [b] (%)	Morphological changes	Lattice distortions (%)	Crystallite size (μm)	Densification mechanism
(I) ≤ 24	6	86	4	4.5		0.065	0.135	
	24	90	3.8	7	(i) Fracture of large particles (ii) Increase of the fraction of fine particles (iii) Mechanical bonding of fine particles on surfaces of large particles (iv) Beginning of formation of agglomerates with and without occluded pores	0.15	0.145	(i) Advantageous packing arrangement of particles (ii) Beginning of particle size reduction by friction between particles and fracture of large particles

(II) 24–48	39 42	92	2.3	12.5	(i) Fracture of large particles (ii) Increase of the fraction of fine particles (iii) Formulation of agglomerates with and without occluded pores (iv) Irregular and serrated particle surfaces	0.34	0.075	(i) Considerable particle size reduction (ii) Plastic deformation
(III) > 48	63 66	94.5	1.8	14	(i) Very dense packing (ii) Particle boundaries no longer detectable in some places	0.31	0.05	(i) Further particle size reduction (ii) Plastic deformation (iii) 'Welding' of particles
	108 114	93			(i) Strong particle deformation (ii) Particle size analysis no longer possible	0.35	0.05	

[a] Mean particle size from cumulative frequency distribution.
[b] Sedimentation analysis.

plastic deformation whilst starches and celluloses demonstrate elastic behaviour at low pressures and deform plastically at high pressures. The mixed behaviour of starches and celluloses has been attributed to the fact that adjacent amorphous and crystalline regions exist in these materials and reorientation of regions may occur during compression (Hess, 1978).

Preferred orientation of crystals during compression has also been reported for several materials including aspirin, ascorbic acid and talc (Nakai et al., 1978a, 1978b; Nakagawa et al., 1979). The '100' faces of aspirin crystals were found to show a preferred orientation parallel to the upper flat punch face during compression. The extent of the orientation was affected by the size and morphology of the crystals and influenced the tendency of compressed tablets to laminate.

Huettenrauch (1977b, 1978) has also considered changes in crystal structure during tablet formation. Decreases in crystallinity and order in deformed crystalline materials are thought to produce an unstable activated state, the intensity of which determines the properties of the resulting product. Experiments with lactose demonstrated that its crystallinity decreased as the compaction pressure increased, producing stronger tablets due to the more activated crystals dissipating acquired energy by interparticle bonding (see Fig. 5). The effects of particle size, lubricants, humidity and wetting agents (Huettenrauch, 1978; Huettenrauch and Jacob, 1977a, 1977b, 1978) are considered to be in accordance with the alteration of crystallinity. Ziegler (1978a and b), working with alumina, has successfully related the morphological changes occurring in compressed powders, assessed using scanning electron microscopy, to changes in crystal structure characteristics. The increasing energy content due to lattice defects and very small crystallites as well as the plastic deformation of the particles were determined by measuring the crystallite size and lattice distortions by X-ray line breadth analysis. Such data (see Table 2) enable conclusions to be drawn regarding the densification mechanisms occurring at different compressional ranges. Whilst similar crystal structural analysis for most pharmaceuticals will be more complex, this technique has considerable potential for examining and under-

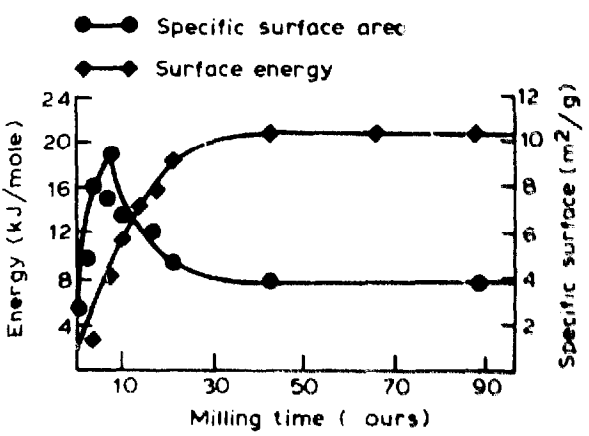


Fig. 6. Effect of milling on surface energy and specific surface area for sucrose (Dialer and Kuczaner, 1973).

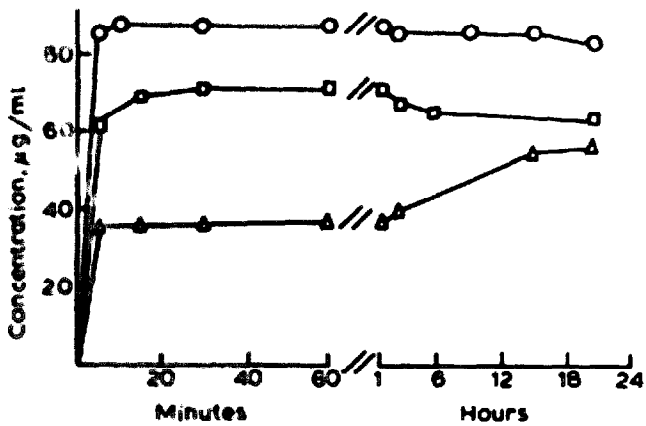


Fig. 7. Dynamic solubility study in water at 37°C for an untriturated (bottom), freshly triturated (top) and triturated and stored (2–5 months; middle) digoxin powder (Chiou and Kyle, 1979).

standing structural features and densification mechanisms in pharmaceutical systems.

Further examination of relationships between crystal structure and bonding mechanisms on compression is likely to lead to knowledge of required crystal properties for direct compression materials. However, a thorough understanding of crystal structure and crystal modifications also has clear pharmaceutical implications in other relevant areas. Recent work has reported modifications to crystals on milling or physical manipulation for several pharmaceutical powders. These include digoxin (Florence et al., 1974; Florence and Salole, 1976; Chiou and Kyle, 1979), digitoxin (Chiou and Kyle, 1979), spironolactone, oestradiol (Florence and Salole, 1976), methisazone (Lee and Hersey, 1977), lactose (Huettenrauch, 1977a and b; Huettenrauch and Keiner, 1979; Krycer and Hersey, 1981; Lerk et al., 1981), sucrose (Dialer and Kuessner, 1973) and microcrystalline cellulose (Nakai et al., 1977). Dialer and Kuessner (1973) found that when sucrose was milled in a vibratory ball mill, the ordered crystal was transformed into a glass-like structure. In addition these workers found that the increase in surface energy of milled sucrose, measured by heat of solution, could not be accounted for by an increase in surface area alone (see Fig. 6).

Techniques used to demonstrate the modifications to crystals include X-ray diffraction, electron microscopy, density determination, and thermal analysis. Crystalline disorder throughout the crystal is readily recognized by X-ray diffraction and thermal analysis but these techniques do not readily identify changes that take place only at a particle surface for only a few nanometers into the crystal. Surface changes, which may have far reaching formulation and processing effects, may therefore not be observed. It is thought that most crystal modifications occurring during processing are manifest only at surfaces and possibly only at localized points or hot spots (Hersey and Krycer, 1980). Nevertheless, these effects will influence the manufacture of dosage forms and may affect the bioavailability of drugs. Increased surface energy and/or formation of amorphous states on milling, with resulting higher dissolution

rates, is likely to occur (see Fig. 7). In addition, crystal modification on processing causes changes in other properties such as drying rate (Huettenrauch and Friche, 1981), drug stability (Chiou and Kyle, 1979), agglomeration, ordered mixing and increased tablet strength (see Fig. 5) (Hersey and Krycer, 1980). It is apparent that these subtle, yet significant, changes in crystal structure on technological processing require further study.

The relationship between induced crystal defect density and dissolution has been examined by Burt and Mitchell (1981) who grew potassium perchlorate crystals by allowing potassium chloride and perchloric acid to diffuse into silica gel. Octahedral crystals were selected, cleared to expose the '001' plane and etched with a mixture of sodium sulphite and hydrochloric acid. The crystals which had been grown most rapidly had the greatest density of dislocations and a positive correlation between dissolution rate and content of dislocations was evidenced. Other workers have used alternative techniques which interfere with crystallization procedures, such as solid solutions (Allen and Kwan, 1969), solid dispersions (Chiou, 1977), co-precipitation (Chiou and Riegelman, 1971; Simonelli et al., 1976), nanoparticles (Kopf et al., 1976; Marty et al., 1978) and inclusion compounds (Jones, 1981), with the objective of preparing materials which exhibit increased dissolution rates. These processes lead to crystal or lattice deformations which impart irregularities to crystal structure. The importance of increasing the dissolution rates of sparingly soluble drugs may be associated with improved drug bioavailability and therapeutic performance. Further and fuller understanding of the crystal form and structure existing in these systems may permit the formulator to increase predictively the solubility and dissolution rate of a given drug.

Crystal hardness

Crystal hardness can be defined as a measure of the resistance to local permanent deformation (Bowden and Tabor, 1969) and can be measured by micro-indentation techniques (Aulton, 1977). Indentation hardness is measured by a non-destructive indentation or scratch test using either static impression or dynamic rebound methods. Whilst extensive work has been carried out using single crystals in the chemical engineering field (Mullen, 1972), few studies of this nature have examined pharmaceutical materials, presumably because of the problems associated with producing large and reproducible crystals which may possess different properties from crystals of the sizes usually employed (Aulton, 1977). Ridgway et al. (1969) measured the hardness of crystals of several pharmaceutical materials (see Table 3) and examined the relationship between crystal hardness and radial pressure during compaction. The observation of larger radial force transmission for crystals with lower surface hardness values has been linked with the ability of such materials to form good tablets (Aulton, 1977) since it has been shown that good force transmission to the die wall results in tablets with superior mechanical properties (Windheuser et al., 1963). Ridgway and Aulton (1971) found that preparative conditions for producing single crystals influenced their hardness, with the lower hardness figures

TABLE 3

HARDNESS OF SINGLE CRYSTALS (RIDGWAY ET AL., 1969)

Crystal	Vickers hardness number (MPa)
Aspirin	85
Urea	89
Hexamine	130
Salicylamide	148
Potassium chloride	174
Sodium chloride	208
Sucrose	624

observed for rapidly grown crystals associated with increased defects and imperfections. Other hardness and mechanical strength studies have attempted to eliminate problems associated with crystal preparation by examining particles (Markova and Balbudkin, 1979) or compressed tablets (Aulton and Marok, 1981). The mean mechanical strength of the particles was found to vary between materials, and the hardness of tablets with compression force as well as between materials, but clearly results from such systems will be influenced by preparative conditions of the test samples.

Cooper and Rees (1972) have nevertheless suggested that hardness testing might be useful in both tablet formulation and process development as demonstrated by the test distinguishing between 'good' and 'poor' tabletting materials (Aulton et al., 1974; Aulton and Tebby, 1976). Correlation of results from such tests with crystal structure and an understanding of crystal behaviour under compression may enable tabletting characteristics and product properties to be predicted.

Crystal habit

Crystals can also be modified by crystallizing the material in different ways to produce different habits (e.g. needles, plates, etc.). Habit is the description of the outer appearance of a crystal. If the environment of a growing crystal affects its external shape without changing its internal structure, a different habit results. Techniques for producing different habits include rapid cooling, crystallization by sublimation or change of crystallization solvent. Since processing properties such as powder flow and dissolution rate can differ for various habits of the same material, this aspect is of pharmaceutical interest. Garti and Tibika (1980) achieved crystal habit modifications for nitrofurantoin crystallized from formic acid mixtures. They suggested that when more regular crystals are precipitated, bioavailability and solubilization of the drug increase although no supporting experimental data was presented. Using the additive adipic acid, it has been shown (Michaels and Colville, 1960; Fairbrother and Grant, 1978, 1979) that reproducible modification of crystal habit by the deliberate addition of trace amounts of non-toxic impurities during

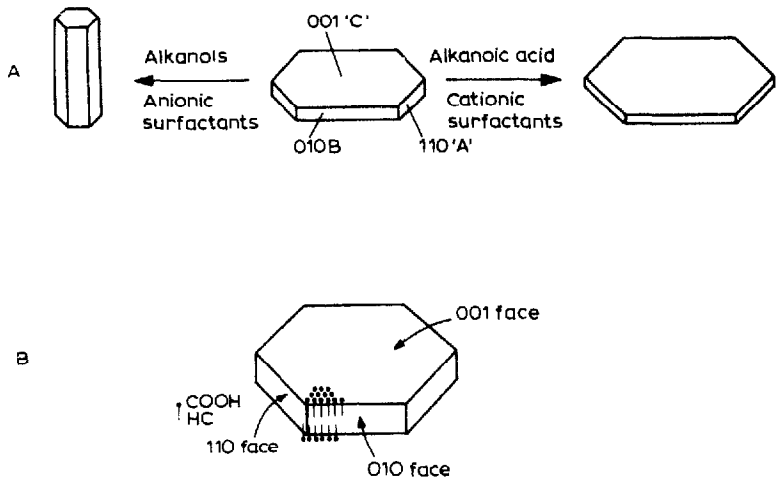


Fig. 8. A: effect of alkanols, alkanoic acids and anionic and cationic surfactants on the habit of adipic acid crystals (after Michaels and Colville, 1960; Fairbrother and Grant, 1978). B: diagrammatic representation of arrangement of molecules at adipic acid crystal surface (Florence and Attwood, 1981).

crystallization can facilitate the production of powders with desirable physical properties. By using traces of *n*-alkanoic acids in the crystallization medium (Fairbrother and Grant, 1978, 1979), additional crystal faces developed on the regular hexagonal plates of the adipic acid crystals. The retarding effect on growth rates of the '110' and '100' faces was attributed to selective adsorption of the trace additives on the various faces altering their relative growth rates (see Fig. 8).

Surfactants in the crystallization medium can similarly modify crystal habit. Michaels and Colville (1960) demonstrated that crystallization of adipic acid in aqueous solutions containing high concentrations of anionic surfactants produced long thin needles, whilst in the presence of cationic surfactants, thin flaky plates

TABLE 4

INTRINSIC DISSOLUTION RATE CONSTANTS FOR PHENYLBUTAZONE COMPACTS PREPARED FROM SAMPLES CRYSTALLIZED IN AQUEOUS SOLUTIONS CONTAINING DIFFERENT CONCENTRATIONS OF POLYSORBATE 80 [a] (AL-MESHAL AND YORK, UNPUBLISHED DATA)

% w/v Polysorbate 80 in crystallizing medium	Intrinsic dissolution rate constant ($cm \cdot min^{-1}$)
0.0	0.195
0.1	0.297
0.5	0.351
1.0	0.324
5.0	0.343

[a] Intrinsic dissolution rate constant estimated using a constant surface area apparatus containing compacts compressed at 10 kN in phosphate buffer (pH 7.5) at 37°C.

were produced (see Fig. 8). The inhibition of growth rate of crystal faces was found to be dependent upon the propensity for adsorption of the surface-active agent molecules.

Enhancement of dissolution rate can also result from the crystallization of poorly soluble drugs in aqueous solutions containing surfactants (Chiou et al., 1976; Naggar et al., 1980). This has been demonstrated for chloramphenicol, sulphathiazole, prednisone powders (Chiou et al., 1976) and phenylbutazone both in powdered (Naggar et al., 1980) and tabletted (Al-Meshal and York, unpublished observations) form. The presence of trace amounts of surfactant in surface-active agent treated crystals, indicated from thermal analysis studies, would increase the wettability of the powder and thereby increase the dissolution rate. In addition, the uptake of surfactants onto the crystal during crystal growth might produce a defect in the crystal structure making the crystal thermodynamically unstable and hence, dissolve faster (Chiou et al., 1976). Values of intrinsic dissolution rate constants for phenylbutazone compacts do, however, suggest that there is a relatively low optimal concentration of surfactant required in the crystallization medium to achieve maximum dissolution rate (see Table 4). Further work examining the location and concentration of surfactant molecules and crystal structure for such systems is indicated together with an assessment of their in vivo bioavailability compared with unchanged parent drug crystals.

In earlier work, Shell (1963) demonstrated the effect of crystal habit on tablet properties. To evaluate the tabletting behaviour as influenced by crystal habit he quantitatively described crystal habits by measurement of preferred particle orientation and related this parameter to the compressional characteristics of the powder. Hiestand et al. (1981) demonstrated mechanical property changes in ibuprofen compacts made from crystals prepared at different crystallization rates. The variation in indentation hardnesses was attributed, at least in part, to differences in particle size whilst it is likely that dislocation density also varied in the crystals. In addition, a linear relationship between hardness and maximum force of compression to produce a given solid fraction compact was shown, further indicating the significance of crystal properties in tabletting behaviour.

Staniforth et al. (1981) have also examined alternative crystallization conditions in order to design excipient crystals with preferred habits for direct tablet compression and non-segregating properties in low dose mixes with small-sized drug particles. Using mannitol seed crystals and an aqueous crystallization medium containing industrial methylated spirits as a co-solvent, highly porous surfaced mannitol crystals were obtained. A mix of model drug and the modified mannitol crystals was also found to be consistently more resistant to vibrational segregation than a similar mix of model and anhydrous lactose, the latter being an example of a direct compression tableting excipient. The technique of including a water-miscible organic solvent in the crystal mother liquid has also been used to produce crystalline lactose particles with increased surface rugosity (Staniforth, 1979).

It is likely that further work in this potentially valuable field developing the concept of 'crystal engineering' will enable material with improved handling, processing and/or dissolution characteristics to be prepared and thereby improve manufacturing and bioavailability efficiency.

Polymorphic and solvate forms

Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystal species (e.g. carbon as diamond (cubic) or graphite (hexagonal) and is associated with different internal packing arrangements of atomic components or molecules, or differences in the orientation of atoms or molecules at lattice sites. It has been suggested (Haleblian and McCrone, 1969) that probably every organic medicinal compound can exist in different polymorphic forms and the choice of proper polymorphs will determine whether a pharmaceutical preparation will be chemically or physically stable or tablet well, or give an appropriate blood level to produce the correct pharmacological response. The extent of polymorphism was assessed by Kuhnert-Brandstatter (1965) who reported that of 48 steroids, 40 sulphonamides and 38 barbiturates examined, 67%, 40% and 63%, respectively, exhibited polymorphism. The subject of polymorphism has attracted the wide interest of formulators and several excellent reviews have appeared recently in the literature (Haleblian and McCrone, 1969; Rosenstein and Lamy, 1979; Mewada et al., 1973; Haleblian, 1975).

Since polymorphism involves differences in crystal structure, different polymorphs will have different energy contents, the energy difference being associated with their molecular binding energies. For a given set of physical conditions the polymorph with the lowest free energy is the most stable and other polymorphic forms, termed metastable, will tend to transform to the most stable form. As a result, polymorphs may differ substantially with respect to certain physicochemical properties; for example, crystal shape, density, melting point, hardness, solubility, dissolution rate, as well as bulk behaviour characteristics such as flow properties and compaction behaviour. Whilst it has been suggested that when the free energy

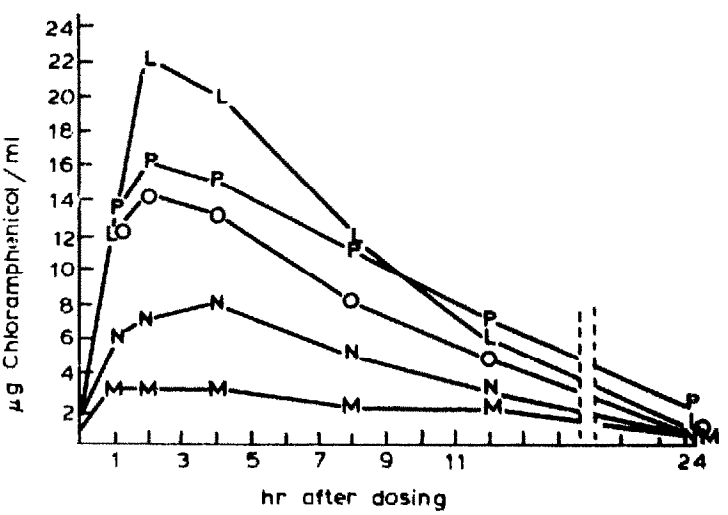


Fig. 9. Comparison of mean serum blood levels obtained with chloramphenicol suspensions containing varying ratios of α and β polymorphs, following single oral dose equivalent to 1.5 g chloramphenicol (Aguiar et al., 1967). Percentage polymorph β in the suspension: M, 0%; N, 25%; O, 50%; P, 75%; L, 100%.

differences between polymorphs are small there may be no significant differences in their bioavailability (Aguiar and Zelmer, 1969), it may be required on occasion to search for a different polymorphic form of a drug to eliminate a specific stability, processing or bioavailability problem. The different clinical performance of polymorphs of chloramphenicol (Anguiar et al., 1967; Anguiar and Zelmer, 1969), chlortetracycline (Miyazaki et al., 1974) and esters of prednisolone (Florence and Attwood, 1981) illustrate the relevance of selecting appropriate polymorphs to optimize bioavailability (see Fig. 9). However, it should be stressed that if a metastable form is indicated, the integrity of the selected form under a variety of processing and storage conditions must clearly be assured. For example, polymorphism has been shown to occur during spray-drying for hydroflumethiazide (Corrigan et al., 1982), β-lactam antibiotics (Pikal et al., 1978), lactose (Fell and Newton, 1970), phenobarbitone (Corrigan et al., 1982), and phenylbutazone (Matsuda et al., 1980). Sodium salicylate (Kawashima et al., 1972) and sulphamethoxazole (Takenaka et al., 1980, 1981) when spray-dried with excipients resulted in alteration of the crystal form of the drug. Examples where chemical stability is affected by crystal polymorphic forms include penicillin G and amitryptyline which decompose more readily as amorphous solids compared to their crystalline forms, and the two forms of methylprednisolone which exhibit different stability profiles (Lieberman and Lachman, 1980).

Several interesting studies have examined the processing characteristics of different polymorphs. Two polymorphic forms of tolbutamide, which did not reveal significant in vivo differences, have been reported to possess different powder flow and compression characteristics (Simmons et al., 1972; Sekiguchi et al., 1974). In a preliminary study on a rotary tablet press, polymorphic form B was responsible for both powder bridging in the hopper and extensive capping problems during tabletting. This behaviour was attributed to the plate-shaped crystals of form B and could be corrected by using the non-plate-like form A. Working with different crystal forms of phenylbutazone, Tuladhar et al. (1981) reported differences in dissolution characteristics for the polymorphs following compaction with excipients, and Ibrahim et al. (1977) observed polymorphic transitions during milling and compression.

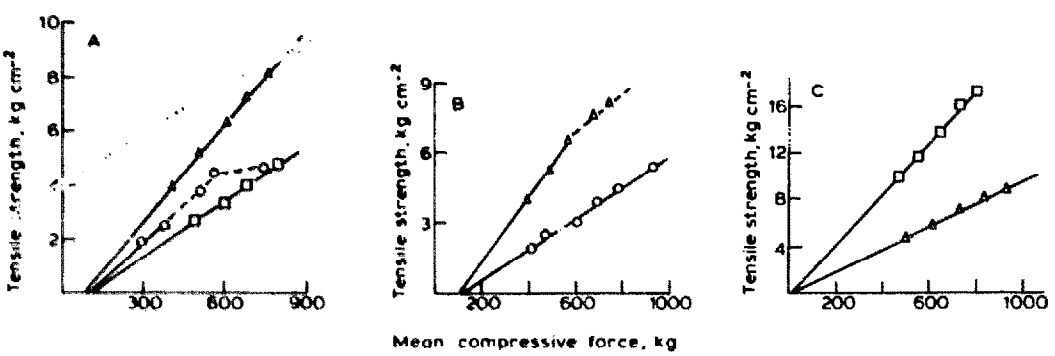


Fig. 10. Tensile strength of compacts prepared from different crystal forms (Summers et al., 1977). A: barbitone (104–152 μm); ○, form I; □, form II; △, form III. B: sulphathiazole (104–152 μm): ○, form I; △, form II. C: aspirin (250–353 μm): △, form I; □, form IV.

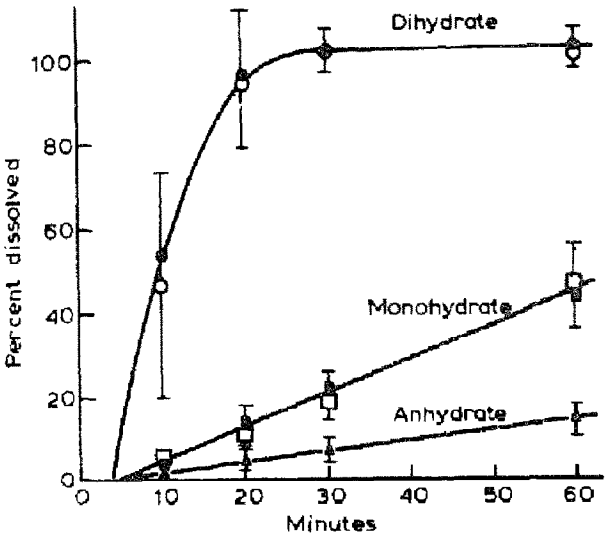


Fig. 11. Dissolution behaviour of erythromycin dihydrate, monohydrate and anhydrate in phosphate buffer (pH 7.5) at 37°C (Allen et al., 1978).

Similar transitions have also been reported by Cruaud et al. (1981) when compressing sulphanilamide polymorphs. Summers et al. (1977) have demonstrated that different polymorphs of sulphathiazole, barbitone and aspirin differed significantly in their compression characteristics (see Fig. 10), although the controversy concerning the polymorphism of aspirin remains unresolved (Chopra and Dhall, 1981). All these reports point to the importance of identifying and examining the properties of polymorphs and their potential use in solid dosage formulation and processing.

During crystallization from a solution, the crystals separating may be of a pure component or be a molecular compound. Molecular compounds may have two or more constituents that have satisfied valency force requirements and crystallize out as a single crystalline form. Solvates are molecular complexes that have incorporated the crystallizing solvent molecule into their crystal lattice, hydrates being formed when the solvent is water. To distinguish solvates from polymorphs, the term pseudopolymorph has been used and indeed polymorphism can be exhibited by solvates, as for example in the ethanolic solvates of fluocortolone, and the hydrates of fluprednisolone and succinylsulphathiazole (Kuhnert-Brandstatter and Gasser, 1971a, 1971b). Other compounds of pharmaceutical interest forming solvates include caffeine, chlordiazepoxide, cortisone, fluocortolone, fluprednisolone and theophylline (Bouche and Draguet-Brughmans, 1977) as well as many antibiotics such as ampicillin, cephaloridine, chloramphenicol, erythromycin and griseofulvin (Chopra and Dhall, 1981). Attention for potential solvate formation must therefore be given during crystallization as well as granulation since the latter process involves the use of a solvent. Alternatively if the crystal form is initially a solvate, the drying process associated with many manufacturing procedures may cause transition to a desolvated form.

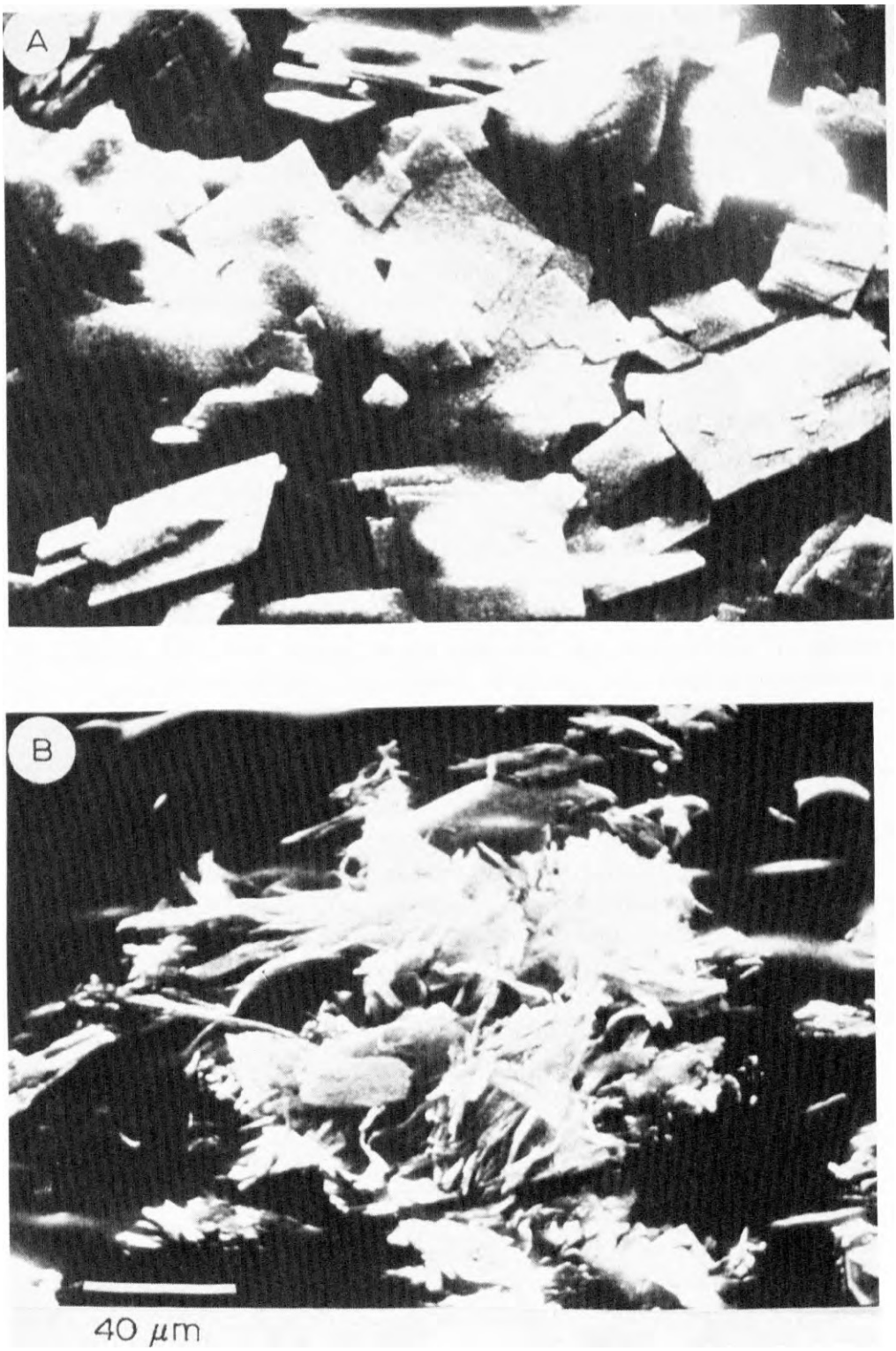


Fig. 12. Scanning electron photomicrographs of pure magnesium stearate (A) plates and (B) needles (Miller and York, unpublished data)

The ability of a drug to form solvates can greatly increase the number of available possibilities for modifying and controlling processing, dissolution, stability and bioavailability (Haleblian, 1975). As examples, Fig. 11 illustrates the different dissolution behaviour of erythromycin dihydrate, monohydrate and anhydrate (Allen et al., 1978), and differences in absorption rate of ampicillin in trihydrate and anhydrous form have been reported (Poole et al., 1968), although the clinical significance is doubtful. In terms of processing, the reported pseudopolymorphism of the tabletting lubricant, magnesium stearate, provides an interesting example. Although generally used in relatively unpure form, differences in its physical form between suppliers can be quite marked (Butcher and Jones, 1972) and batch differences have been found to significantly affect the failure properties of powder beds (Butcher and Jones, 1972), tablet die wall friction (Hanssen et al., 1970) and tablet dissolution (Billany, 1981). Working with pure samples, Muller (1977) has suggested that the different crystalline forms of magnesium stearate—plates and needles—(see Fig. 12) are associated with different hydrated states and has indicated that its lubricating efficiency can be correlated with its crystalline structure which in turn can be affected by thermal drying (Muller, 1976). Recent work, however, indicates that the water molecules are incorporated into the different forms in an irregular manner during preparation and that the preparative conditions prevailing during manufacture control the form obtained (Miller and York, 1982). Further work is required to elucidate the particular characteristic of this material which confer upon it the property of punch and die lubricant during tabletting.

Wettability, surface polarity, moisture sorption

Crystal surface characteristics, such as wettability and polarity, are also important properties with regard to the formulation and processing of solid dosage forms as, for example, in granulation, penetration of dissolving fluid into tablets and granules prior to dissolution and the adhesion of film coatings to tablets.

Wetting is an important factor in the dissolution process but the extent of that role has not been clearly defined (Florence and Attwood, 1981). Conversion of hydrophobic drug surfaces to a more hydrophilic character by granulation with a (water-miscible) binder (Solvang and Finholt, 1970), by spray-drying with acacia (Kawashima et al., 1975), or by coating with a hydrophilic material (Lerk et al., 1978) resulted in enhanced dissolution rates.

The wettability of powders can be assessed using the contact angle of a particular solvent, generally water or a saturated aqueous solution, on the powder. Low angles represent relatively easily wetted surfaces. Several relatively simple techniques have been recently employed to assess the contact angle of liquids on pharmaceutical powders. These include direct observation (e.g. Fell and Efentakis, 1979) and the sessile drop technique (e.g. Lerk et al., 1976, 1977, 1978; Fell and Efentakis, 1978, 1979) both using samples of material in compact form. A third method makes use of the Washburn equation (Washburn, 1921) and involves measuring the distance a liquid penetrates into a bed of powder, or a compact (e.g. Hansford et al., 1980b).

Lerk et al. (1976, 1977, 1978) who published tables of contact angles for a listing of pharmaceutical powders (see Table 5) have demonstrated that the wettability of crystalline materials can be related to their chemical structure, as shown in Table 6 for a series of substituted barbiturates. The more hydrophobic the molecule, the more hydrophobic the crystal is likely to be, resulting in a high contact angle, a value above 90° implying little or no spontaneous wetting. Contact angle values can also be seen to be affected by crystal structure (see chloramphenicol palmitate in Table 5). Lerk and his co-workers have further demonstrated that reversible changes in powder surface characteristics occur on milling, which is in accord with the finding of Huettenrauch and other workers previously discussed. Data in Table 7 show the increased hydrophobic nature of compacts prepared from milled aspirin crystals which reverted on standing. Contact angles of typical formulation excipients have also been examined (Gissinger and Stamm, 1980; York, 1981).

In an interesting recent study, Hansford et al. (1980b) used both the sessile drop and liquid penetration techniques to estimate the contact angle of 6 griseofulvin samples prepared by alternative procedures—crystallization, controlled precipitation, dry grinding and wet grinding. Whilst the two measuring methods gave significantly different numerical values for contact angles, both sets of data demonstrated that differences existed in the surface and wetting properties of the different powder samples and that this was a function of the powder pretreatment history

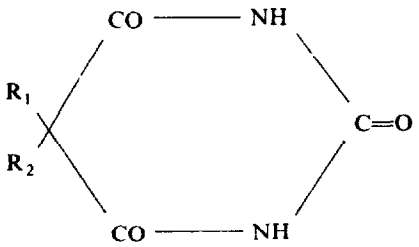
TABLE 5

CONTACT ANGLES OF SOME PHARMACEUTICAL POWDERS ESTIMATED USING SESSILE DROP METHOD (LERK ET AL., 1977, 1978)

Material	Contact angle (ϑ)
Acetylsalicylic acid	74
Aminophylline	47
Ampicillin, anhydrous	35
Ampicillin, trihydrate	21
Calcium stearate	115
Chloramphenicol	59
Chloramphenicol palmitate (α-form)	122
Chloramphenicol palmitate (β-form)	108
Diazepam	83
Digoxin	49
Indomethacin	90
Lactose	30
Magnesium stearate	121
Phenylbutazone	109
Prednisolone	43
Prednisone	63
Stearic acid	98
Sulphacetamide	57
Theophylline	48
Tolbutamide	72

TABLE 6

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND CONTACT ANGLE WITH WATER FOR A SERIES OF BARBITURATES (LERK ET AL., 1977)



Material	R_1	R_2	Contact angle (θ^0)
Barbitone	Et	Et	70
Butabarbitone	Et	$CH(CH_3)CH_2-CH_3$	82
Pentabarbitone	Et	$CH(CH_3)CH_2-CH_2-CH_3$	86
Amobarbitone	Et	$CH_2-CH_2-CH(CH_3)_2$	102
Aprobarbitone	$CH(CH_3)-CH_3$	$CH_2-CH=CH_2$	75
Butalbitone	$CH_2-CH(CH_3)-CH_3$	$CH_2-CH=CH_2$	87

rather than of the batch powder. This work was extended to examine the surface energetics of wetting of the griseofulvin samples (Hansford et al., 1980a).

Measurement of contact angle would therefore seem to provide a useful parameter for comparing raw materials as well as batch and supplier variability. However, the techniques used do present difficulties. In the direct observation and sessile drop techniques, problems of optical siting of the interface and swelling of compact can occur. It should also be recognized that during sample compaction, the properties of crystal faces may be changed and the contact angles measured on compact surfaces may not be consistent with values obtained using a different principle, such as the

TABLE 7

VARIATION OF CONTACT ANGLE OF ASPIRIN WITH TIME AFTER JET MILLING (LERK ET AL., 1976)

Time after milling (h)	Contact angle (θ^0)
0	106
24	91
30	87
48	80
72	77
120	77

TABLE 8

CONTACT ANGLES, POLARITY INDEXES, TIMES FOR 50% DRUG DISSOLUTION FROM CAPSULES ($t_{50\%}$) FOR SOME PHARMACEUTICAL POWDERS AND BINARY MIXTURES (YORK, 1980b)

Material	Polarity index (Po)	$t_{50\%}$ [a] (min)
Barbitone	0.36	25.1
Lactose	0.93	–
Maize starch	0.99	–
50% barbitone: 50% lactose	0.89	4.8
50% barbitone: 50% maize starch [b]	0.98	18.1

[a] Powder(s) packed into No. 1 clear hard gelatin capsules and 50% porosity.
[b] Moisture content of powder mix = 7.1% w/w.

liquid penetration technique. This latter method suffers, however, from the problem of non-uniform solvent movement during measurement.

Zograffi and Tam (1976) have extended the concept of powder wettability and proposed a polarity index ($P_0 = \gamma_s^P/\gamma_s$) by splitting the surface free energy term for a solid, γ_s, into polar, γ_s^P, and non-polar, γ_s^d, components. The polarity index is estimated by measuring contact angles using two test liquids with known values of polar and non-polar surface free energies. Figures given in Table 8 indicate that the presence of hydrophilic diluents such as lactose or maize starch at the 50% level in binary mix swamp the hydrophobic nature of drug barbitone, causing an increase in drug dissolution rate from capsules (York, 1980). These studies indicate that measurement of contact angles and polarity indices may prove useful measurements when optimizing formulation and drug release characteristics for hydrophobic drugs.

Whilst the wettability and polarity of crystal surfaces are clearly important

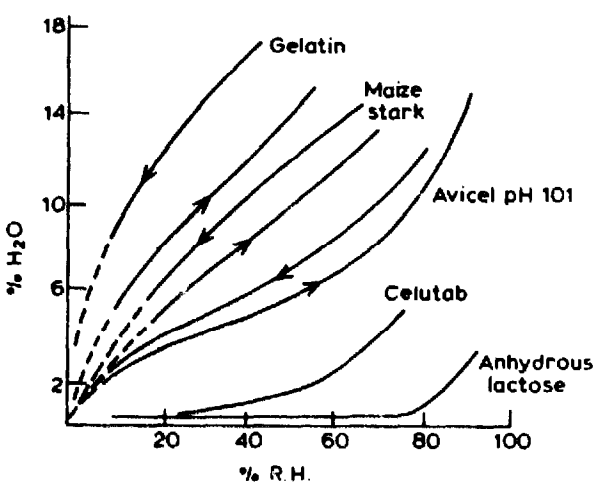


Fig. 13. Moisture sorption profiles of some pharmaceutical additives (Jones, 1977).

factors in formulation and processing, another closely related and significant characteristic is the rate and extent of moisture uptake—moisture sorption. Adsorbed moisture is particularly important with respect to the physical and chemical stability of drugs. In addition, the equilibrium moisture content (the amount of moisture in a solid for a given temperature and moisture level in the surrounding air) is likely to influence the flow and compression characteristics of powders and the hardness of granules and tablets. Knowledge of the rate and extent of moisture uptake or loss in drugs and excipients permits the formulator to take corrective action where required—as, for example, in defining storage or drying conditions or package specifications. Van Campen et al. (1980) have recently published an excellent review on the hygroscopicity of pharmaceutical solids.

Fig. 13 illustrates the moisture sorption profiles of several pharmaceuticals over a range of relative humidities and some materials—such as gelatin, starch, microcrystalline cellulose—exhibit hysteresis in their sorption cycles. Changes in ambient humidity can therefore result in different moisture contents in sensitive materials causing deleterious phemonena with respect to formulation and processing such as caking, solution formation and recrystallization. For materials exhibiting hysteresis, additional problems may result since ultimate moisture content is dependent upon its previous sorption history (Scott et al., 1963).

Whilst the mechanism of sorption hysteresis is not completely understood, Young and Nelson (1967a, 1967b) proposed 3 locations for moisture and associated hysteresis phenomena with the relative ease that internally held moisture could be taken up or lost during sorption and desorption, respectively. A moisture distribution pattern can be obtained by analyzing sorption data using the theoretical relationships derived by Young and Nelson (e.g. Jork, 1981). The moisture distribution pattern (i.e. surface or internally held) can have significant effects, for example, on powder packing or flowability, since the presence of surface moisture modifies interparticle attractive forces.

One method which has been successfully used to characterize comprehensively specific solid–liquid interface interactions and to describe the wetting of hydrophilic and hydrophobic solids is to combine the powerful techniques of calorimetry and vapour sorption (e.g. Young and Healy, 1954). Hollenbeck et al. (1978), examining sorption hysteresis in microcrystalline cellulose, used immersional calorimetry and moisture sorption techniques to estimate differential free energy, enthalpy and entropy changes accompanying the adsorption process (see Fig. 14). Using these data, these workers were able to conclude that the hysteresis was of both enthalpic and entropic origin and suggested that the experimental method is potentially valuable for routine characterization of hydrophilic powders. Since immersion into an aqueous environment is the ultimate fate of most solid dosage forms and since most problems encountered in the production and performance of solid dosage forms can be resolved in terms of solid-liquid (water) interactions (Hollenbeck et al., 1978), studies of specific solid–liquid interactions for drug powders, formulated systems and water are likely to prove a fruitful area for research work.

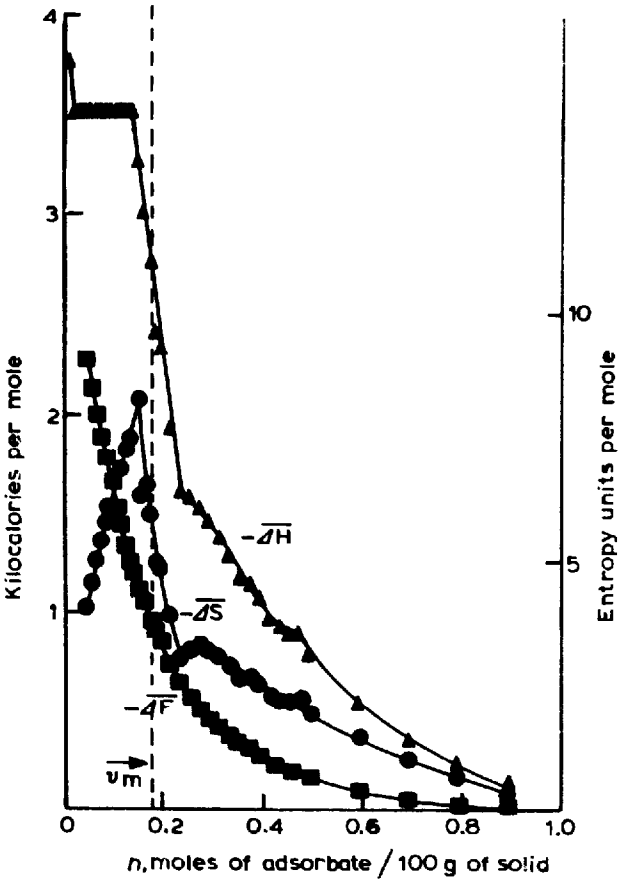


Fig. 14. Differential thermodynamic properties of the microcrystalline cellulose–water system (Hollenbeck et al., 1979). ▲, differential enthalpy; ●, differential entropy; ■, differential free energy; v_m, BET monolayer capacity.

Concluding remarks

The widespread use of powdered drugs and additives by the pharmaceutical industry and the increased sophistication of formulations and processing equipment has highlighted the need to consider the solid-state characteristics of the powders. Problems with powders, in terms of formulation and/or processing, can be particularly serious and lead to reduced efficiency for a process or may adversely affect the quality of the product. In this review the role of solid-state properties in the formulation and processing of solid dosage forms has been examined. It is evident that, whilst a complex inter-relationship exists between some of the characteristics, and a single property can influence a range of formulation and processing factors, a fuller understanding of these properties is likely to lead to a more rational and predictive approach to formulation design and solid dose manufacture.

Acknowledgements

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