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CRYSTAL ENGINEERING AND PARTICLE DESIGN FOR THE POWDER COMPACTION PROCESS

Peter York

Pharmaceutical Technology
School of Pharmacy
University of Bradford
Bradford BD7 1DP
UK

ABSTRACT

The historical background to the subject of crystal engineering of pharmaceuticals is briefly reviewed with reference to materials as diverse as insulin and direct compression tablet excipients. In the light of the limited scientific and practical information available on the topic two questions are posed -

Is it possible to prepare 'designer' materials with preferred processing, specifically compressive, properties giving optimised product characteristics?

How can such materials be efficiently manufactured?

In order to consider these questions, several important elements of data-base requirements are regarded as essential. These include knowledge of the crystalline phases of pharmaceutical solids, full understanding of the fundamental mechanical constants and moduli of particulate solids, and the relationships describing the influence of crystallographic structure on the mechanical properties of crystals and powders. At the same time the effects of preparation, pretreatment and

processing effects on crystal structure, crystallinity and thermodynamic properties of powdered solids must be established.

The topics of material based compaction problems, property groupings of pharmaceutical powders with particular emphasis on crystal structure and mechanical properties are discussed. The review then considers recent and current research work examining the compaction behaviour of modified or engineered materials, prepared using alternative crystallisation conditions and the incorporation of low level additives. Specific examples include modern direct compression excipients, 'spherical' drug particle production and high purity lubricant (magnesium stearate) powders.

In conclusion, the future potential of the concepts of crystal engineering and particle design is considered in terms of predicting mechanical and processing properties from fundamental molecular and structural information.

HISTORICAL BACKGROUND

The concept of engineering materials with improved properties is widely applied in many industries. Examples include the use of metallic alloys, semiconductors and polymer composites. However until relatively recently, applications in the pharmaceutical industry have been minimal.

Whilst the topic of crystal engineering and particle design for the powder compaction process is receiving considerable current research interest, a small number of examples is available in the literature where the concept of manipulation of crystal and particle properties has been employed. Perhaps the most historically important crystal manipulation in drug delivery concerns the polypeptide hormone insulin.

After the discovery of the role of insulin in the treatment of diabetes in 1921 (1), three main types of insulin preparations have been developed - short, intermediate and long acting - which relate to the duration of therapeutic effect, ranging from eight to thirty six hours. This has been achieved by using a solution phase for rapid action, suspensions with varying proportions of amorphous and crystalline forms for the intermediate effect, and suspensions of complexed forms of insulin with,

for example, zinc salts and protamine sulphate, for long acting action. These modifications were developed more than forty years ago (2-4). Of particular importance was the work of Hallas-Moller et al (5) which revealed that the solubility of insulin was determined by its physical state (amorphous, crystalline, size of crystal) and by the zinc content and the nature of the buffer in which it was suspended.

In terms of powder compaction, the major area of activity in particle engineering has centred over the last twenty five years on the design of excipients for direct compression. The manufacture of tablets by direct compression offers advantages over conventional wet granulation procedures in reducing the number of individual unit operations (typically from six down to two) and the elimination of exposure of formulation components to water or solvent, and applied heat. The mixing of direct compression excipients with drug powder followed by compression of the mixture provides an attractive manufacturing route, although it is clear that this process imposes stringent demands on the properties and characteristics of the direct compression excipient (6)

The important properties required for direct compression excipients are good flow properties, high 'carrier' capacity for drug powders (typically limited to 25% of drug in mixtures), the ability to consolidate and bond under pressure and maintain interparticle bonds on ejection from the tablet machine.

The first directly compressible excipient, spray dried lactose, was reported in 1963 (7) and other direct compression filler/binders have been developed and marketed subsequently (see Table 1). Of particular relevance to crystal engineering has been the recognition that the different mechanical properties exhibited by the various direct compression forms of lactose can be related to the crystallisation and pretreatment (8). Slow crystallisation produces single crystals with defined crystal faces for α-lactose monohydrate (Figure 1a), whilst rapid crystallisation or dehydration produces aggregates of microcrystals for anhydrous α-lactose and anhydrous β-lactose (Figure 1b). On compression, the aggregates undergo intensive fragmentation, leading to higher tablet

TABLE 1

Dates of introduction of some direct compression filler binders

Year of introduction	
1963	Spray dried lactose
1964	Microcystalline cellulose (Avicel)
	Anyhydrous ß-lactose
	Dicalcium phosphate dihydrate (Emcompress)
	Direct compression starch (Starch 1500)
1967	Spray-crystallised dextrose/maltose (Emdex)
1982	Calcium sulphate dihydrate (Compactrol)
1984	Tricalcium phosphate (Tri-Tab)
1985	Anyhydrous ∝-lactose (DCLactose 30)

crushing strengths compared with tablets prepared from ∝-lactose monohydrate (8,9). The superior bonding ability of spray-dried lactose (Figure 1c) when compared with ∝-lactose monohydrate has been attributed to an amorphous phase of lactose which exhibits plastic flow on compression.

A restriction to the general applicability of direct compression excipients is the fact that, as mentioned above, the drug carrying capacity is limited to around 25% drug. However, since approximately one third of marketed tablets contain less than 10mg of drug and another third contain 10 to 100 mg of drug, it is clear that the compressibility of the direct compression excipient will be the controlling factor. In the remaining one third of tablet formulations, the compressional characteristics of the drug substance itself will dominate and over recent years, some research in crystal engineering and particle design has been addressed to consider the controlled modification of the physicochemical and physicotechnical properties of drug particles.

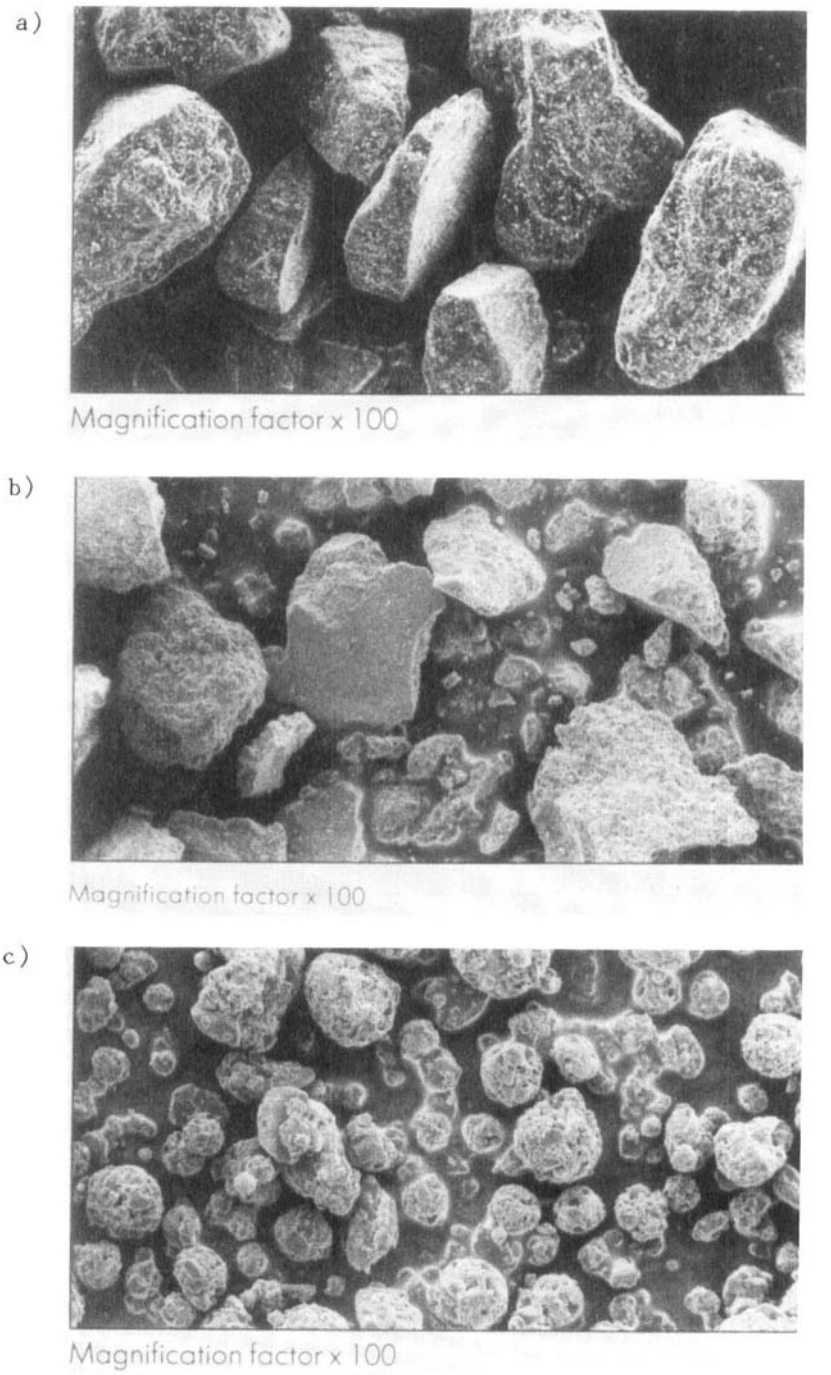


FIGURE 1

Scanning electron photmicrographs of a) α-lactose monohydrate, b) anhydrous ß-lactose, and c) spray-dried lactose

TABLE 2

Material based compaction problems

MATERIAL PROPERTY		POTENTIAL/POSSIBLE COMPACTION PROBLEM
Unsuitable mechanical property	-	capping lamination excessive elastic recovery crushing strength
High strain rate sensitivity	-	change of mechanical characteristics on scale-up to high speed tablet machines
Hygroscopicity	-	handling and processing difficulties
Variation in solid-state (crystal) properties	-	batch to batch, and source variation problems
Low aqueous solubility	-	inadequate drug dissolution

MATERIAL BASED COMPACTION PROBLEMS

If crystal and particle engineering of drugs and excipients is to play a significant role in the design of materials for compaction, then the driving force for controlled modification must be to provide the required properties for direct compression or good compressional behaviour, and/or overcome deficiencies in unmodified material which lead to tabletting and compaction problems. Table 2 lists some features of material based problems which lead to tabletting difficulties. It is clear that if deficiencies and inadequate properties in drugs and excipients are to be reduced (or 'designed out') then a fundamental knowledge base establishing causative and predictable relationships between the chemical

TABLE 3

Physicochemical and physicotechnical properties

PHYSICOCHEMICAL	PHYSICOTECHNICAL
Chemical composition	Mechanical properties- compression comminution
Melting point	Packing
Solid state properties	Flowability
Particulate properties - size, shape, surface	
Organoleptic properties	Corrosive, abrasive tendency
Solubility	Dissolution

and structural properties of materials on the one hand, and their mechanical and processing properties on the other is required.

PHYSICOCHEMICAL AND PHYSICOTECHNICAL PROPERTIES OF PHARMACEUTICAL POWDERS

In an attempt to classify the spectrum of properties of pharmaceutical powders, Table 3 identifies two broad groups - physicochemical and physicotechnical. The physicochemical properties are those relating primarily to the chemical composition and structure of the material whilst those characteristics determining principally its mechanical behaviour are termed physicotechnical properties. The physicochemical group includes a number of crystallographic or solid state properties which, as discussed later, are important in determining processing and product performance. The important solid state

TABLE 4

Solid state properties

Crystal density
Crystal habit
Crystal hardness
Crystal order/disorder state
Crystal structure/system
Hygroscopicity
Polymorphism, solvates, hydrate forms
Wettability, thermodynamic properties

TABLE 5

Mechanical Properties

Brittle/ductile transitions
Fracture stress
Indentation hardness
Poisson ratio
Stress/strain relaxation
Yield pressure
Young's modulus

properties are listed in Table 4, whilst a breakdown of the major characteristics grouped under mechanical properties in the physicotechnical properties is listed in Table 5.

It is also apparent that the physicochemical properties of materials influence and, in certain situations, predetermine their physicotechnical characteristics, with the scale of scrutiny changing between groups from molecular through particulate to bulk powder scale. Certain properties, including many particulate bulk and surface properties, bridge between the two major groups.

At the same time, knowledge of the pretreatment, as well as the processing stresses must be incorporated into the data base (see Figure 2). It is well recognised that alternative crystallisation procedures and

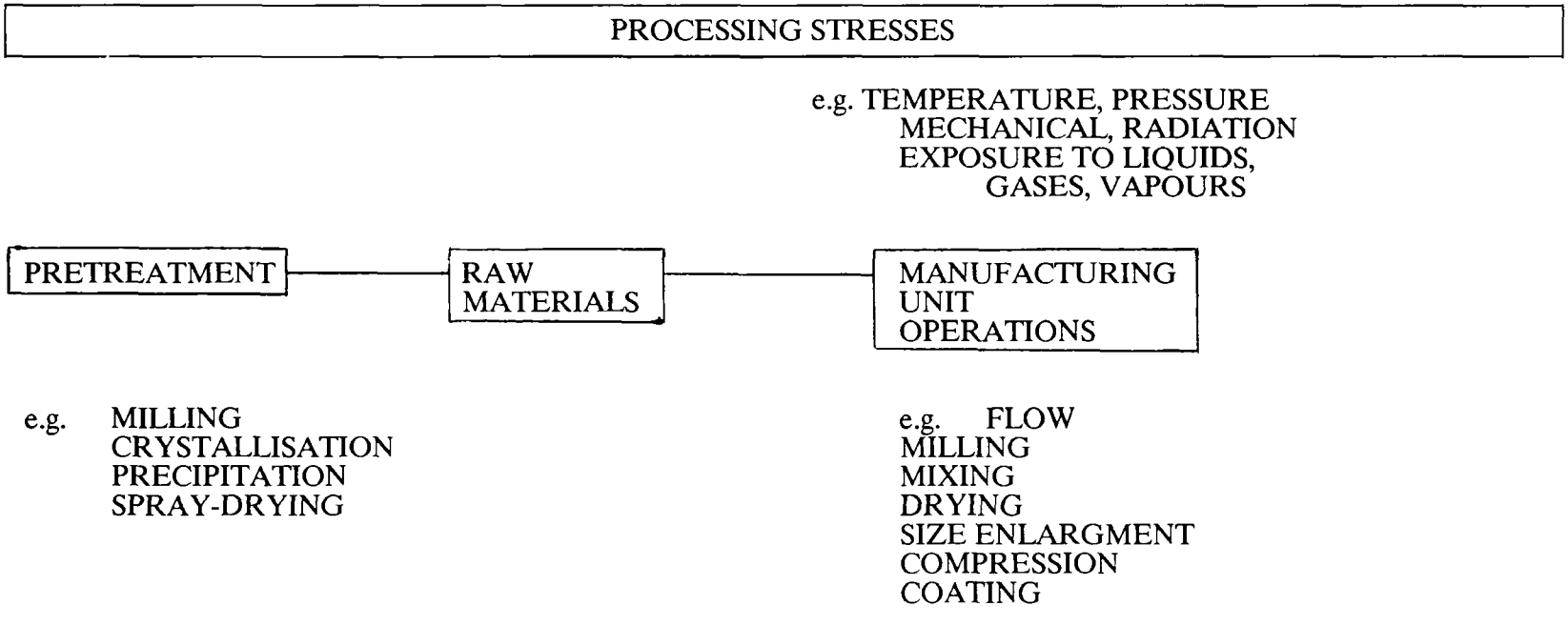


FIGURE 2

Pretreatment procedures, processing stresses and unit operations involved in solid dosage form manufacture

various processing operations can lead to changes in material properties. Examples of stress and time dependent changes in materials include the variation in wettability and surface contact angle after milling in aspirin powder (10), recrystallisation phenomena on tablet surfaces after compression (11) and polymorphic transitions under compression (e.g. 12-16). If predictive functions are to be established then these behavioural factors must be recognised and considered.

PRIMARY CHALLENGES OF CRYSTAL ENGINEERING AND PARTICLE DESIGN

Whilst the scientific demands involved in designing materials with preferred properties remains a formidable challenge, several exciting areas of research are showing considerable promise, particularly with regard to powder compaction. The remaining sections of this review consider a number of these approaches. These studies must clearly address the following two questions -

Is it possible to prepare 'designer' materials with preferred processing, specifically compressive, properties giving optimised product characteristics?

How can such materials be efficiently manufactured?

In an attempt to answer these questions, it is first necessary to consider the structure of the pharmaceutical materials in question at the molecular and crystal level.

CRYSTAL STRUCTURE

The crystal lattice can be regarded as a highly ordered structure which repeats itself regularly in three directions. In real crystals lattice disturbances and imperfections are extremely numerous. Imperfections include defects (e.g. vacancies, impurity defects, interstitial occupancies), line defects (e.g. edge and screw dislocations) and plane defects (e.g. particle boundaries and crystal surfaces). Such disturbances develop during crystallisation and pretreatment operations (17) and their nature

and frequency (i.e. concentration) change during pharmaceutical processing as a result of the prevailing stresses and strains (18). These operations include drying, sorption, milling as well as compression.

Crystal lattice imperfections are known to influence the physicochemical and physicotechnical properties, of pharmaceutical materials such as chemical reactivity (19), dissolution rate (20), as well as formulation and processing of pharmaceuticals (18). Even traces of additives or impurities can exert major effects on the physicochemical properties of materials, as exemplified by the changes in crystal habit (shape), energy, entropy, surface properties and dissolution rate of adipic acid and acetominophen (21-25). These changes are thought to be mediated by increasing concentration of crystal defects. Since the nature and frequency of crystal imperfections and impurities often vary from one batch to another, this property may represent an important source of batch to batch as well as lot to lot variation. Such variation frequently gives rise to problems in formulation and processing, and often cause lack of reproducibility and poor performance in the final product (26,27).

The quantification of crystallinity, taking into account the fact that increasing crystal imperfection will reduce crystallinity, is therefore important in characterising the solid state, in probing relationships between molecular structure and processing performance, and in considering the controlled modification of crystalline powders by various techniques such as alternative crystallisation. Up to relatively recently, the techniques of density, x-ray diffraction, IR spectroscopy, thermal methods (DSC, DTA, solution calorimetry) and kinetic studies, have been used to assess crystallinity in solid samples. However, even when data is normalised to give a crystallinity scale ranging from 100% for the 'perfectly' ordered crystal down to 0% for the 'completely' disordered amorphous solid state, quite divergent values of crystallinity for a given sample are obtained (18, 28-31) (see Figure 3).

Suryanarayanan and Mitchell (30) have pointed out the influence of the degree of crystallinity on diverse physicochemical and physicotechnical properties of pharmaceutical solids. They illustrated two

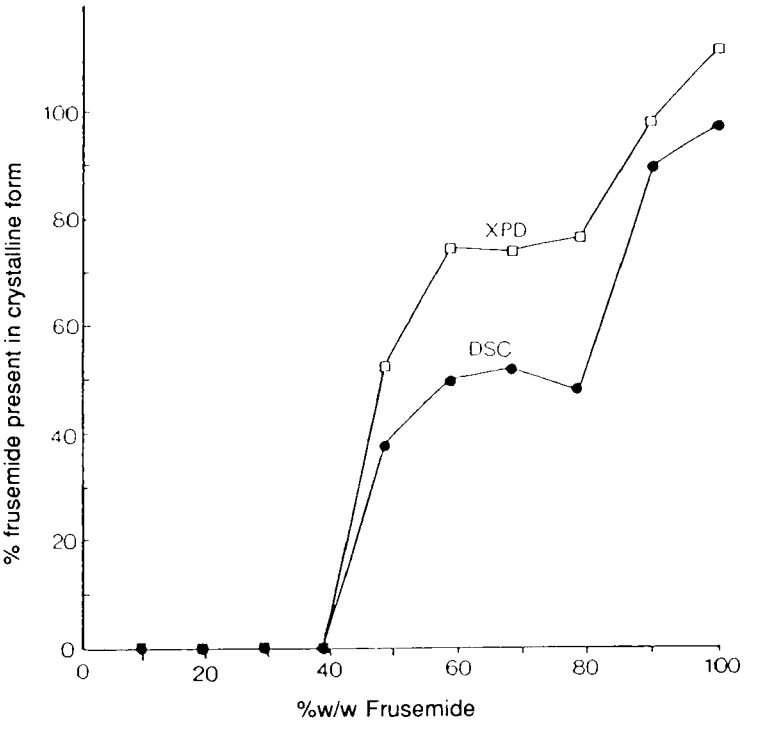


FIGURE 3

Comparison of crystallinity data by x-ray powder diffractometry (XPD) internal standard and DSC methods for frusemide-PVP solid dispersions containing 10-100%w/w frusemide.

concepts regarding the degree of crystallinity (see Figure 4). The two state model, the concept implicitly adopted by pharmaceutical compendia, assumes solids to be either 100% crystalline or 100% amorphous or a mixture of the two states. Alternatively, and more realistically, the one state model indicates that the degree of crystallinity varies between 0% and 100% with no sharp distinction between the crystalline and amorphous states (18). However, the requirement of empirical assignment of reference materials is still required.

An alternative approach is to use the thermodynamic term entropy as a measure of the concentration or density of crystal imperfections since

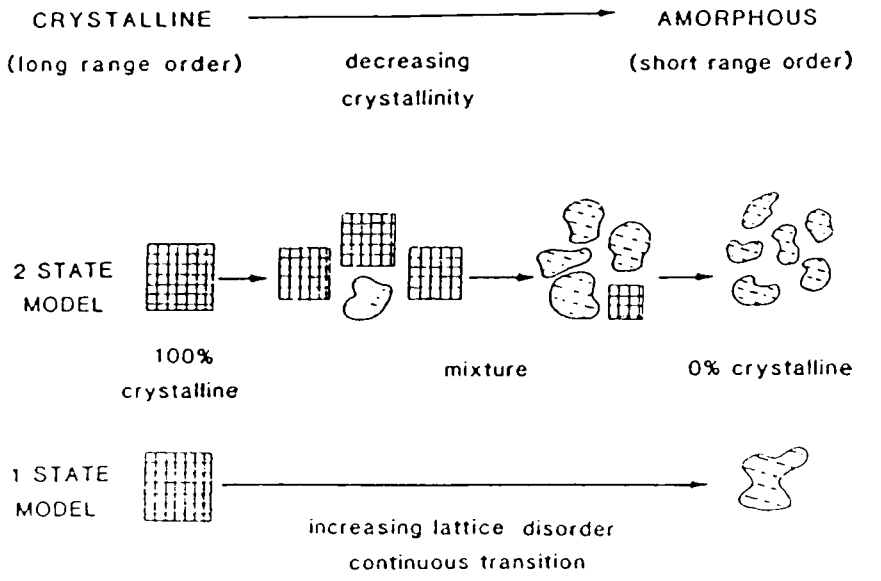


FIGURE 4

Schematic representation of the two models of crystallinity. Squares represent the lattices of perfect crystals, while irregular shapes represent the amorphous state; no assumptions are implied regarding the structure of the latter (from Suryanarayanan and Mitchell (30)).

this term, S, represents a direct measure of the disorder of the system (32-34). The effects of low level additives or impurities as well as processing effects can be monitored by quantifying changes in entropy (ΔS) between untreated materials and treated (processed) samples. The terms disruption index (d.i.) and entropy of processing (ΔS^P) have been used to quantify these changes. Figures 5 and 6 illustrate how d.i. and ΔS^P can be calculated from the latent heat of fusion of samples using DSC analyses. These terms can also be derived from enthalpy of solution data (32-34). A rigorous thermodynamic treatment has also verified the viability of this approach (35).

Figure 7 shows a plot of ΔS^F versus ΔS^M_{ideal} for phenylbutazone samples containing low levels of the surfactant Pluronic F68(36). The

DISRUPTION INDEX - Quantifies the influence of the guest (i.e. additive, impurity, retained solvent) on the difference in entropy between the more or less crystalline host and the liquid host (ΔS^F)

At the melting point, $T_M, \Delta G^F = 0$

Thus $\Delta S^F = \frac{\Delta H^F}{T_M}$

where ΔG^F = Free energy of fusion

For mole fractions of guest up to 0.05:-

$$\text{d.i.} = \frac{\delta(\Delta S^F)}{\delta(\Delta S^M_{ideal})}$$

where ΔS^M_{ideal} = change in entropy associated with the substitution of an additive into the host's lattice (or into the liquid host) so as to give an ideal solid (or liquid) solution,

and $\Delta S^M_{ideal} = -R\Sigma x_j \ln x_j$

where R = universal gas constant

x_j = mole fraction of a component substance;

d.i. < O - presence of guest molecules creates less disorder (entropy) in the host's crystal lattice than in liquid host
- not yet observed

d.i. = 0 - solid state is as sensitive as the liquid state to the disordering effect of the guest
- examples are ideal and regular solutions

d.i. > O - presence of guest molecules creates more disorder (entropy) in the host's crystal lattice than in liquid host

Range d.i. values

0-1	e.g. Partial dehydration of cephaloridine monohydrate
1-10	e.g. Organic molecules as additives in organic crystals
10-100	e.g. Polymeric additive in phenylbutazone
100-1000	e.g. Fatty acid additivies in adipic acid

FIGURE 5

Derivation of disruption indeces (d.i.) from latent heat of fusion (ΔH_F) and compositional data

ENTROPY OF PROCESSING - Difference in entropy of the solid sample under investigation and the entropy of the same amount of reference sample (e.g. a pharmacopoeial reference standard)

At the melting point, T_M, -

$$\Delta G^F = O$$

$$\text{Thus } \Delta S^F = \frac{\Delta H^F}{T_M}$$

For a drug (D) in pure or modified form, which may contain a ligand or complexing agent (A) and/or a solvent (W) such as water:-

$$\Delta S^P_{solid} = -\Delta S^F_{solid} + X_D \Delta S^F_D + X_A \Delta S^F_A + X_W \Delta S^F_W + \Delta S^M_{liquid}$$

where X = mole fraction of component

ΔS^M_{liquid} is taken as ΔS^M_{ideal}

FIGURE 6

Derivation of entropy of processing (ΔS^P) from latent heat of fusion (ΔH^F) and compositional data

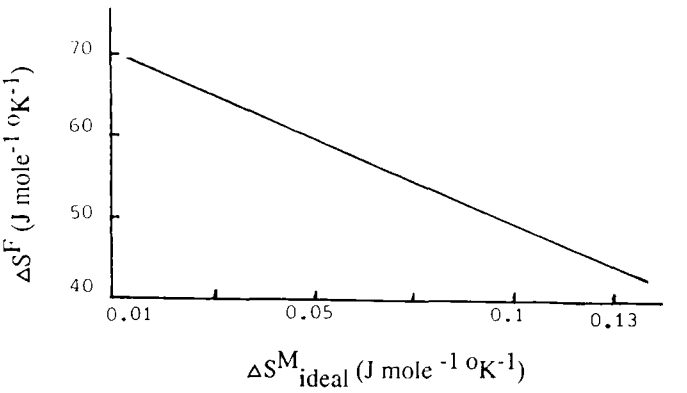


FIGURE 7

Correlation between ΔS^F at melting point and ΔS^M_{ideal} for phenylbutazone - Pluronic F68 samples.

TABLE 6

Entropy of processing and crystallinity data for various cephalothin sodium samples (after Pikal et al, (29))

Sample	Form	Entropy of processing ($J K^{-1} mol^{-1}$)	Crystallinity[1] (%)
1.	Crystalline, vacuum dried	0	93
2.	Commercial sample, recrystallised four times	- 6.0	100
3.	Ground sample (from 1)	3.6	
4.	Freeze dried amorphous form	78.2	
5.	Sample 4, annealed at - 5°C	32.4	54
6.	Spray dried, partially	38.9	47

high value of d.i. (obtained from the slope in Figure 7) indicates major disturbance of the crystal lattice of the host by the additive.

Entropy of processing, ΔS^P, used as a measure of crystal disorder, is shown in Table 6 to reflect the increased severity of processing conditions for a series of cephalosporin samples using published values of heats of solution (29). Interestingly, the data from Hendriksen (37) can be used to demonstrate a positive linear relationship between the powder intrinsic dissolution rate of a number of experimental and manufactured scale batches of calcium fenoprofen and ΔS^P. This observation indicates the potential of this approach in quantifying crystallographic differences between batches of the same chemical entity and relating these changes to important pharmaceutical properties. Other analyses have shown links between ΔS^P and chemical stability and milling times (34). It can be

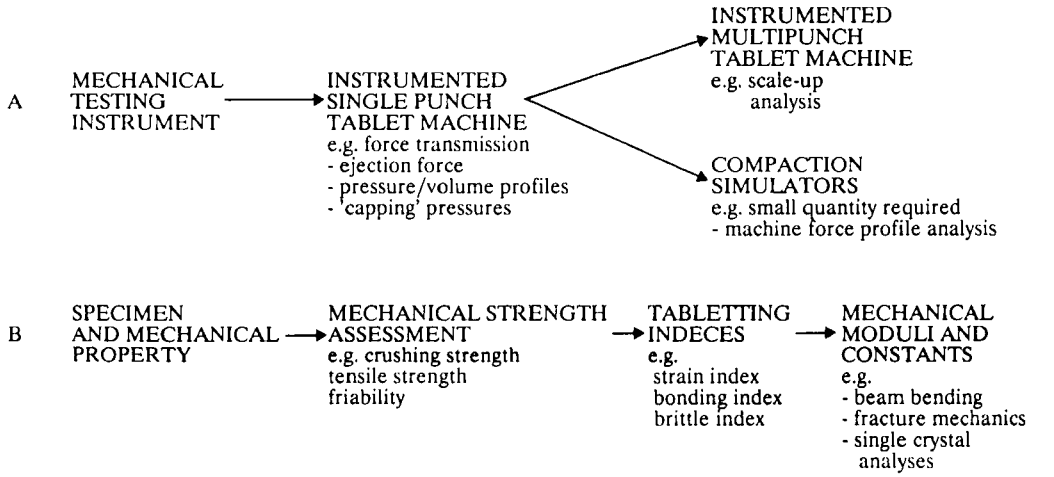


FIGURE 8

Sequences of development of (A) instrument and (B) analytical procedures for compaction studies

anticipated that similar changes in crystallinity will influence the behaviour of materials on compaction.

MECHANICAL PROPERTIES

It is now approaching 40 years since the idea of instrumenting a mechanical press or tablet machine was developed to study the compression and compaction behaviour of pharmaceutical crystals and powders (38). Since that time, the sophistication of measuring and monitoring systems has improved and this has been mirrored by improvements in the procedures used to analyse and evaluate derived data. Figure 8A illustrates diagramatically the sequence of the development of measuring machinery. The parallel improvement in analytical procedures and approaches is shown in Figure 8B. It is generally recognised that the use of routine analyses of, for example, force-displacement plots or the effects of speed of compression will solve practical problems in formulation design and material processing.

However such data will not provide a scientific rationale for predicting the compaction behaviour of new materials or multicomponent systems. Such a requirement is much sought after by pharmaceutical scientists and this goal has clear implications in terms of designing crystals and powder particles with preferred tabletting characteristics.

As highlighted in Figure 8A a range of procedures has been developed and reported in the literature to examine material consolidation mechanisms and compact properties. For example, a number of workers (e.g.39,40) have found the Heckel relationship (41,42) particularly useful. This equation defines a pressure-volume relationship where the reciprocal of the linear portion of the plots of $\ln \frac{1}{1-D}$, where D=relative density, versus applied pressure has been shown to be equal to the yield pressure, P_y, of the material under test (43). Information can also be obtained from these plots regarding the degree of particle rearrangement and repacking during the first stages of consolidation (44) as well as the elastic recovery postcompression (40). In terms of the mechanical properties of compacts, comparison of the tablet crushing strengths, or tablet tensile strengths where tablets fail in tension under diametral loading across a diameter, has proved extremely useful if data is compared at equivalent porosity (ε).

In terms of crystal engineering and particle modification, Marshall et al (45-47) have reported on the influence of crystallisation solvent induced solid state and particulate modifications on the compaction behaviour of nitrofurantoin and ibuprofen. From earlier published work, it was known that the crystal habit of these materials could be changed by the use of alternative solvents of crystallisation (48-49). Tables 7 and 8 list, respectively, the particulate characteristics of the nitrofurantoin and ibuprofen samples examined, with Figures 9 and 10 giving scanning electron photomicrographs of these materials. Representative Heckel plots are shown in Figure 11 for nitrofurantoin and Table 7 lists derived vales of P_y. From these data and figures, it is apparent that prehistory and crystallisation conditions influence both the particulate properties of

TABLE 7

Particulate and mechanical properties of nitrofurantoin samples.

Figures in brackets are standard deviations

	Solvent of crystallisation	True density ($g.cm^{-3}$)	Aspect ratio	Projected median diameter (um)	Yield pressure (MPa) under load	Yield pressure (MPa) after ejection
A	Formic acid	1.646 (3.95×10^{-3})	1.29 (0.31)	78.90	59.3	113.6
B	Formic acid/water (2 : 1)[1]	1.574 (2.85×10^{-3})	7.09 (2.85)	88.55	69.4	255.1

[1] : the monohydrate formed was dried at 125°C for 2 hours

TABLE 8

Particulate properties of ibuprofen samples crystallised from various solvents.

Figures in brackets are standard deviations

	Solvent of crystallisation	Aspect ratio	Roundness
A.	Dimethylformamide	1.656 (0.380)	1.255 (1.079)
B.	Hexane	2.531 (0.893)	1.540 (1.039)
C.	Methanol	1,569 (0.336)	1.205 (0.535)

the resulting samples as well as their compaction behaviour, as reflected by the P_y values.

For nitrofurantoin, the more needle shaped (elongated) particles, with a high aspect ratio which were crystallised from the more polar solvent, are more brittle than the more equidimensional particles. The former sample was also found to exhibit a higher degree of axial elastic recovery after compression and tablets prepared from this sample failed to break in tension.

For ibuprofen, the sample crystallised from hexane, the least polar solvent, were the most elongated. The samples crystallised from methanol and dimethylformamide were compressed at different punch velocities using a compaction simulator, and found to exhibit different degrees of sensitivity to axial recovery and tensile strength/pressure plots between samples.

Another series of modified crystals, achieved by the formation of a range of salts based on the parent compound para-aminosalicylic acid (PAS) has produced samples with diverse solid state and crystallographic

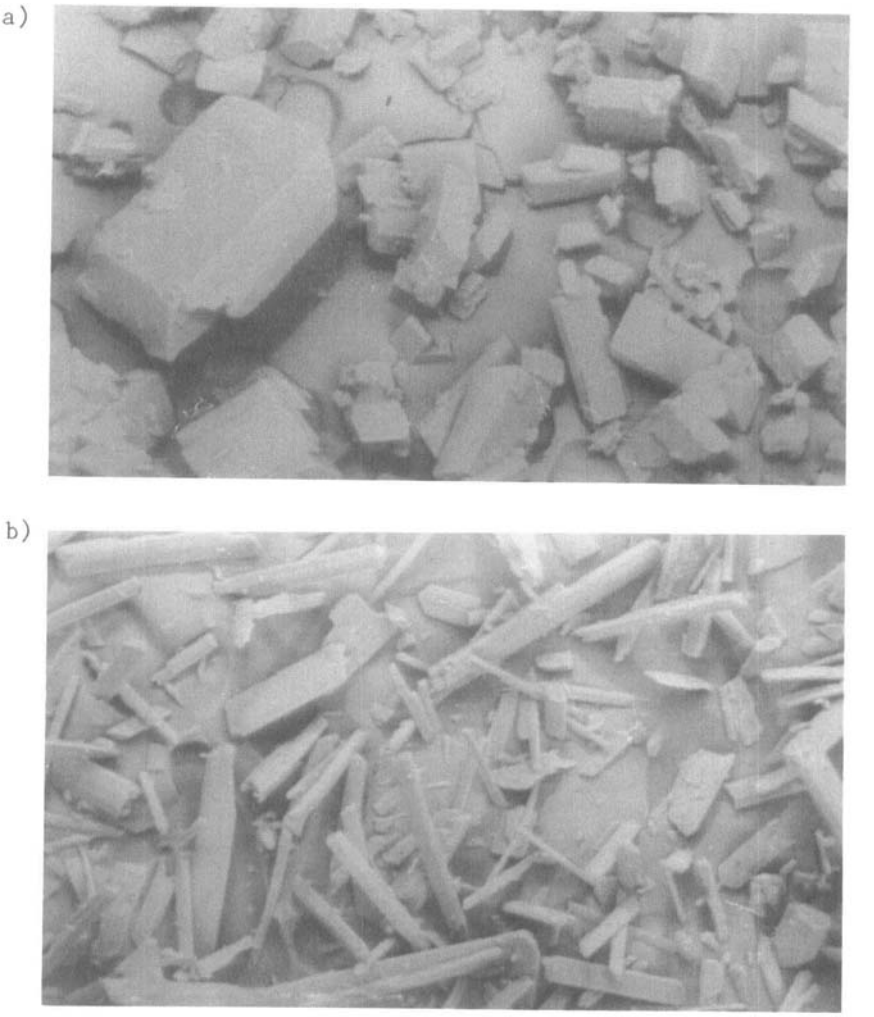
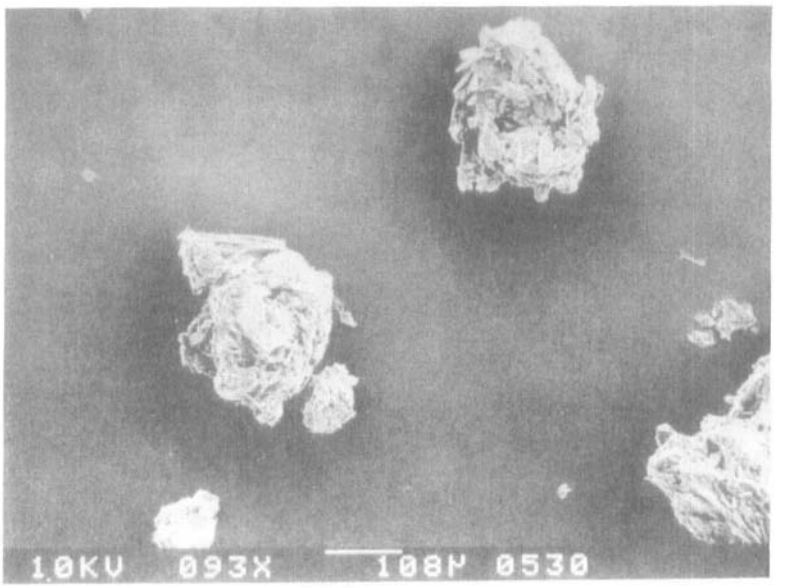


FIGURE 9

Scanning electronphotomicrographs of nitrofurantoin crystallised from A) formic acid, and B) formic acid/water (2:1) after drying. (magnification x 75)



Magnification x 93

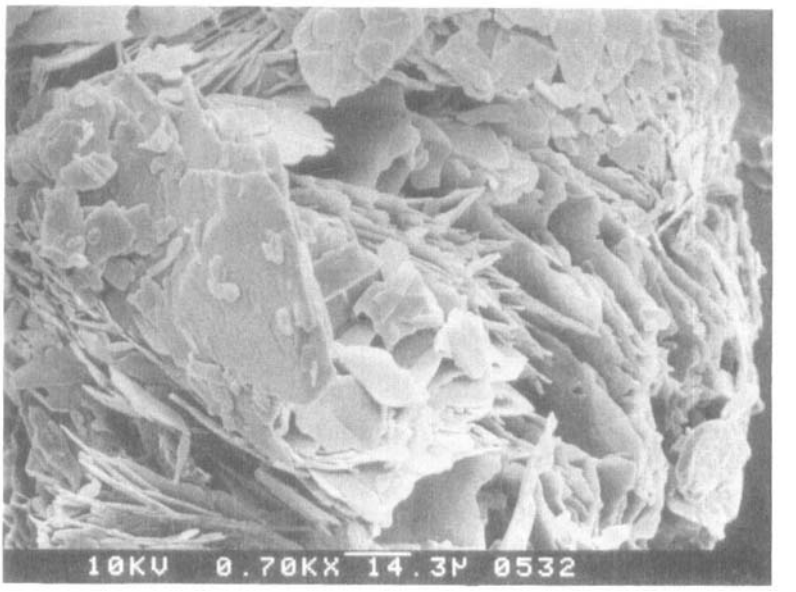


FIGURE 10

Scanning electronphotomicrographs of ibuprofen samples crystallised from A) dimethylformamide, B) hexane and C) methanol. (Magnification x 250)

c)

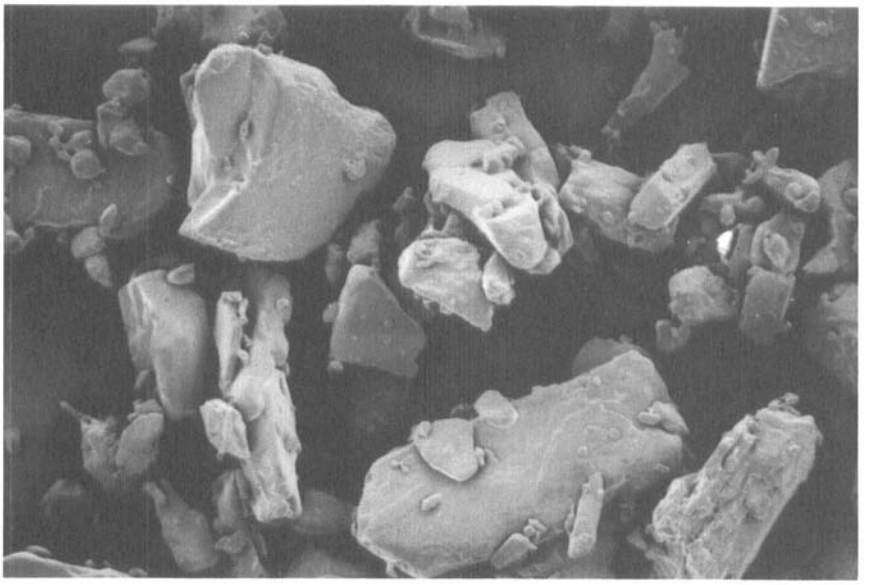


FIGURE 10 (CONTINUED)

structure (50) and particle shape(51). PAS and a number of the salts have been compressed and data analysed by exploring relationships between a range of factors thought to be important in controlling compaction behaviour of powders and tablet mechanical properties, including P_y and particle shape factors (axial ratio and form factor), flow assessment (Carr compressibility index), and particle size parameters. Whilst the large variation in P_y values between the various salts (greater than four-fold change) indicated that different particle and deformation mechanisms occurred between salts, initially attributed to alternative crystal structures, the strongest linear correlations were found between P_y and the shape factors($p < 0.001$). This finding supports the concept, as reported by other workers for aspirin (52-54) that preferred orientation of particles occurred during die filling and compression. Thus, both internal and external crystal features should be considered when selecting appropriate crystal modifications to optimise tabletting performance.

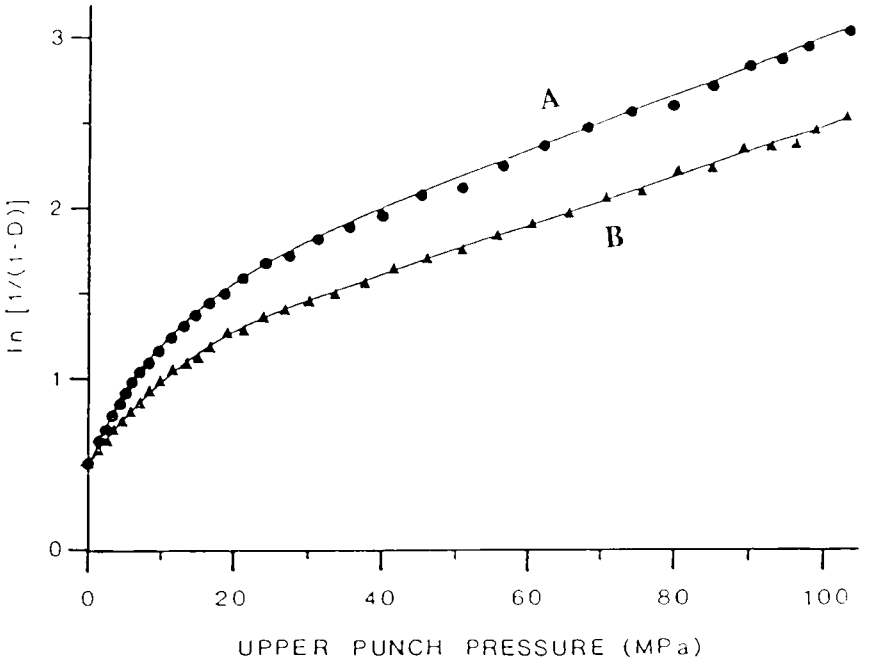


FIGURE 11

Representative Heckel plots for nitrofurantoin samples A and B obtained during compression (D = relative density)

A stimulating and recent development in understanding and testing compaction behaviour was the development of 'tabletting indeces' by Hiestand and Smith (55). They proposed three indeces - the bonding index, the strain index and the brittle fracture index - which were found useful in assessing the compression behaviour of pharmaceutical materials and identifying batch variation in materials. Absolute mechanical constants and moduli were not used in the final equations defining the indeces, but the ratios of fundamental mechanical properties demonstrated the value of such terms in describing material behaviour.

More recently a number of workers (56-64) have adopted methods used more commonly in engineering to derive the basic mechanical constants of pharmaceutical crystals and powders (see Table 5). If such

material constants and moduli can be derived and related to processing and compaction behaviour, then controlled modification with quantified changes in such properties will enable crystals and particles to be engineered with preferred properties. If, in addition, a molecular basis for the origins and magnitude of mechanical properties can be developed, the directed and controlled modification required will be able to be achieved from analysis of structural and constituent molecular information.

In the approaches adapted from engineering, involving fracture mechanics, samples of materials prepared into rectangular beams, with and without notches, have been employed to determine Young's modulus (E), critical stress intensity factors (K_{IC}), fracture toughness (R) and indentation hardness (H). By extrapolating data obtained from beams at known porosities back to zero porosity the material constants of E_0, K_{IC0}, and H_0 can be derived. In addition, the value of the yield pressure, P_y, at different strain rates (punch speeds) has been examined using a compaction simulator and been found to be a particularly useful term (defined as the strain rate sensitivity - SRS)(62). This function demonstrates how the mechanical behaviour of materials, particularly plastic materials, can change with strain rate. These various terms, now quantified for individual materials, reflect the three main types of mechanical behaviour observed in pharmaceutical materials during compaction. E indicates elasticity, K_{IC} and R reflect brittleness, and H and P_y measure plasticity (see Table 9).

In Table 10, the derivation of the SRS is illustrated, and Figure 12 shows how the mechanical character of specific materials can be interpretted from parts of the data base generated. Thus with such information available for both drugs and excipients the opportunity to predict their compaction behaviour is available. Interestingly recent work has also considered the issue of prediction of E_0 for mixed systems, so the important issue of considering 'real' formulations is being addressed (65).

Whilst these approaches represent exciting opportunities, the data base for modified crystals at present is minimal. However some

TABLE 9

Methods of determining the mechanical constants of powdered materials

MECHANICAL CONSTANTS		
MECHANICAL PARAMETER	MATERIAL PROPERTY	MEASURING TECHNIQUE
E - Young's modulus	Elasticity	Beam-bending
P_Y - Yield pressure	Plasticity	Instrumented press Compaction simulator
K_{IC} - Critical stress intensity factor R - Fracture toughness	Brittleness Brittle-ductile transition	Notched-beam fracture

TABLE 10

Derivation of the strain-rate sensitivity (SRS) of powdered materials

$$SRS = \frac{P_{Y2} - P_{Y1}}{P_{Y2}} \times 100$$

where P_{Y1} = yield pressure at slow strain rate ($0.033\ mms^{-1}$)

P_{Y2} = yield pressure at fast strain rate ($300\ mms^{-1}$)

HIGH SRS = PLASTIC MATERIALS

LOW SRS = BRITTLE MATERIALS

PREDICT 'SCALE UP' BEHAVIOUR

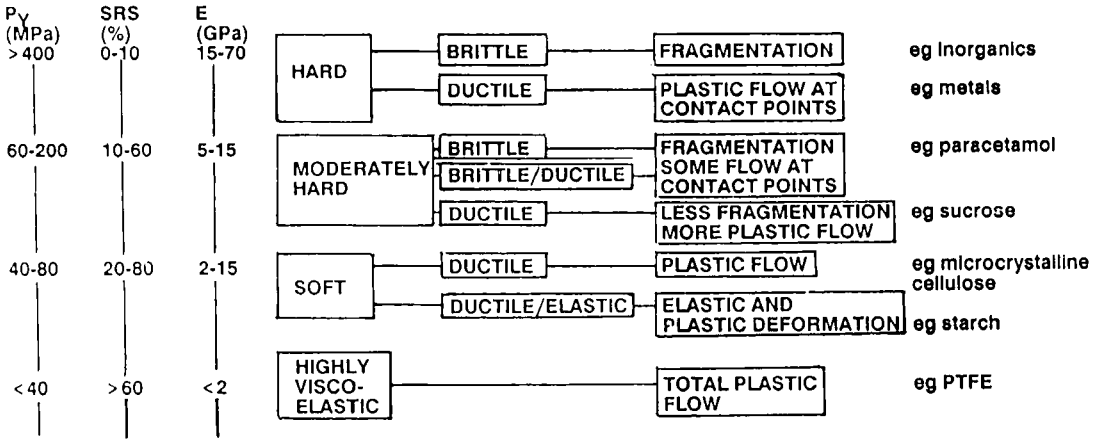


FIGURE 12

Relationships between material properties and compaction behaviour

interesting data is available for the effect of monohydrate formation on the behaviour of theophylline crystals (66). Figures 13 and 14 illustrate the effects of porosity on E and H respectively, the latter being determined by indentation studies on prepared beam specimens. Derived mechanical properties listed in Table 11 show that the monohydrate of theophylline exhibited higher Young's modulus, surface hardness and beam tensile strength, and a lower P_y than the anhydrous theophylline. Thus a different pattern of mechanical property and thereby mechanical behaviour is demonstrated between the two materials. The data suggest that for the monohydrate, more bonds survive unloading, ejection and elastic recovery after beam (or tablet) formation and that the anhydrous form is more brittle than the monohydrate. These differences can be attributed to the lubricating action of the water of hydration as well as the increased hydrogen bonding between in the monohydrate sample.

CURRENT WORK AND FUTURE POTENTIAL

In the light of the foregoing discussion and examples, a response to the two questions posed earlier can be made. This will be considered

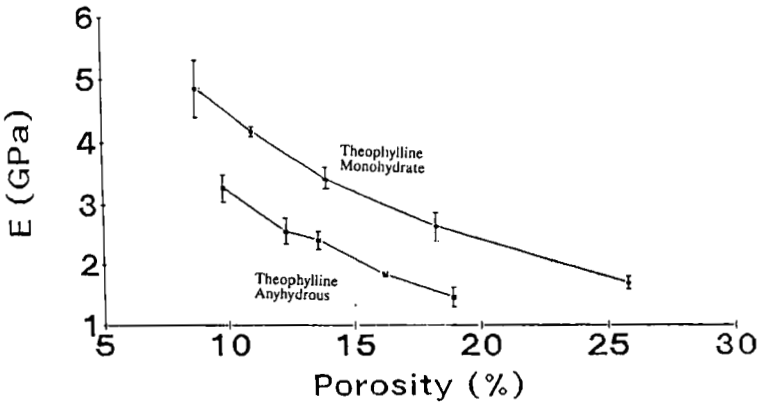


FIGURE 13

Effect of porosity on the Young's modulus (E) of beams prepared from monohydrate and anhydrous theophylline

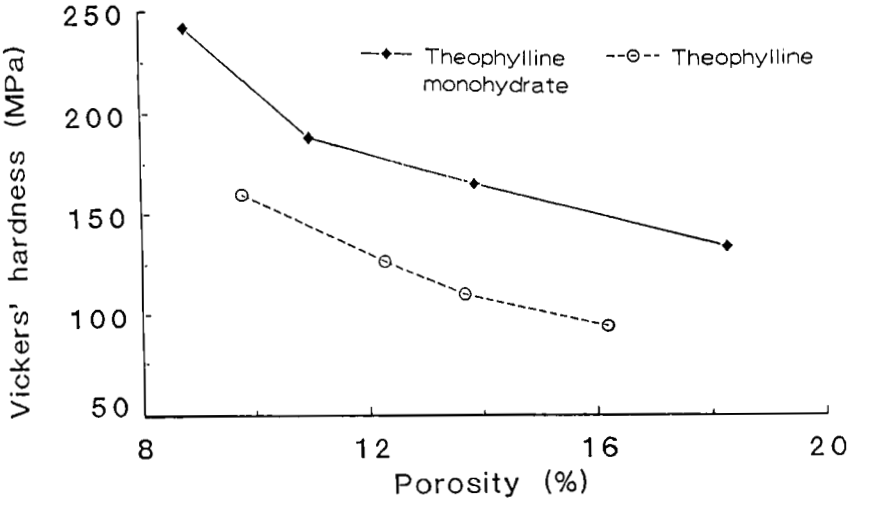


FIGURE 14

Effect of porosity on the indentation hardness (H) of beams prepared from monohydrate and anhydrous theophylline

TABLE 11

Mechanical properties of rectangular beams prepared from theophylline and theophylline monohydrate

	Theophylline anhydrous	Theophylline monohydrate
Young's modulus (E)[a] (GPa)	2.01	3.20
Yield pressure (Py) (MPa)	148.9	90.9
Hardness (H)[a] (MPa)	103.0	157.0
$\frac{\text{Yield strength}^{b}(\sigma_o)}{E}$	2.5×10^{-2}	9.4×10^{-3}
Tensile strength[a] (MPa)	2.50	4.20

[a] : determined at 15% porosity
[b] : estimated from $\sigma_o = \frac{Py}{3}$

under the three headings - crystallisation studies, novel excipients and predicting mechanical properties from molecular structural data.

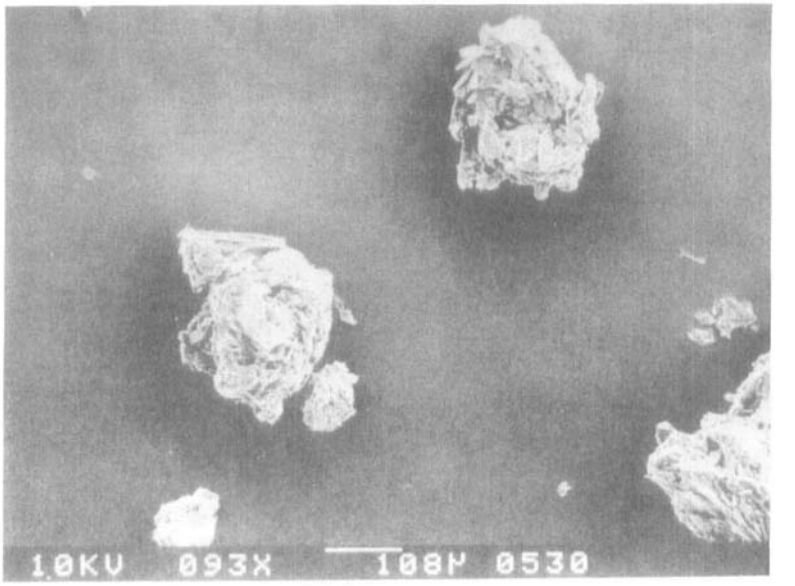
CRYSTALLISATION STUDIES

Over recent years a number of examples have been reported in the literature whereby improved control over the crystallisation or particle preparation stage has been used to advantageously obtain material with preferred properties. Workers have demonstrated the capacity to relate crystal structure and shape and compute the shape of crystals from their crystal structures (e.g.67,68). Attention has also been directed to predicting the effects of low level additives on the habit of 'doped' crystals

(e.g.69,70). The powder lubricant magnesium stearate also provides a good example. Commercial samples have been shown to exhibit considerable batch-to-batch and between supplier variation in terms of both structural, particulate and mechanical properties (71,72). By controlling the manufacturing operation as well as the quality of the chemical components, an improved particulate form with batch consistency as well as improved mechanical properties in certain situations, has been prepared (73-75).

Crystal morphology can play an important role in the compaction behaviour of materials, and many drugs in high dose formulations are unable to be compressed directly, due to poor flow properties and/or poor compressibility. The work of Kawashima et al (76-79) has demonstrated the potential of alternative crystallisation techniques in the formation of spherical agglomerates of drug substances. The techniques used are referred to as quasi-emulsion solvent diffusion (QESD) and solvent change (SC). The spherical agglomerates have been shown to exhibit good flow properties and improved compressibility compared with parent drug crystals. In the QESD method, the drug is dissolved in an organic, non aqueous miscible solvent and quasi-emulsion droplets are formed immediately when this solution is added to an aqueous solution containing a suitable surfactant. As a result of agitation, the non aqueous solvent gradually diffuses from the quasi-emulsion droplet into the water and the process of crystallisation begins at the surface of the droplet. After complete diffusion, spherical agglomerates of drug are formed which retain the shape of the initially formed quasi-emulsion droplets. In SC, the drug is crystallised out as microcrystals in water when an (e.g.) ethanolic drug solution is added with agitation. A non-miscible solvent is then added and phase separation occurs, liquid bridges are formed by small amounts of the non-miscible solvent retained between the particles and the particles agglomerate. On agitation, the drug particles make repeated contact to form spherical agglomerates.

Gordon and Chowhan (80) have recently used these techniques to prepare spherical agglomerate forms of naproxen (see Figure 15). From



Magnification x 93

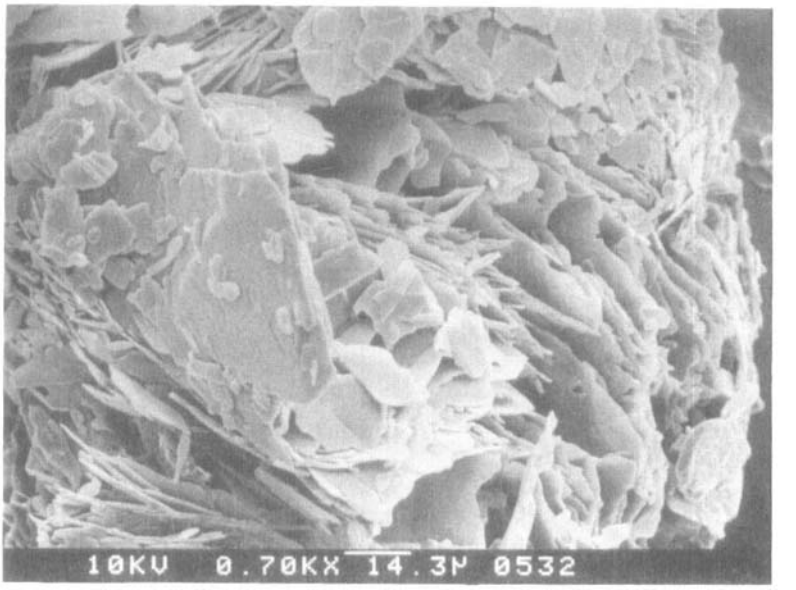


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FIGURE 15

Scanning electron photomicrographs of naproxen crystal aggregates, prepared with toluene as the agglomerating solvent (80).

TABLE 12

The Intrinsic Compressibility of Nonagglomerated (Control) Naproxen and of Spherically Agglomerated Naproxen Batches, with the Column Heading Noting the Agglomerating Solvent Used. (80)

	Batch 0 (Control)		Batch 7 (Hexanol)		Batch 8 (Octanol)		Batch 9 (Toluene)	
Compression Pressure (Lbs)	Tablet Weight (Mg)	Tablet Hardness (Kp)	Tablet Weight (Mg)	Tablet Hardness (Kp)	Tablet Weight (Mg)	Tablet Hardness (Kp)	Tablet Weight (Mg)	Tablet Hardness (Kp)
1000	300 + 3	3.0 + 0.7	307 + 3	10.3 + 1.5 [1]	359 + 1	3.3 + 0.4	278 + 4	11.3 + 2.0 [1]
1500	-	-	302 + 4	13.6 + 1.3	357 + 7	5.2 + 0.4	269 + 3	14.9 + 1.1
2000	299 + 1	4.8 + 0.5	301 + 2	13.9 + 2.0 [1]	360 + 8	7.7 + 0.4 [1]	265 + 10	11.4 + 0.4 [1]
2500	-	-	302 + 3	10.5 + 0.5	362 + 7	8.7 + 1.9	259 + 3	8.5 + 0.9
3000	299 + 4	6.3 + 0.6	304 + 3	9.7 + 1.5 [1]	368 + 6	8.3 + 0.8	271 + 4	9.7 + 0.6 [1]

[1] Statistically significantly different from the control batch, using a Student's t test at the p=0.05 level.

the SC method with either hexanol, octanol or toluene as the non-miscible solvent, compact spherical aggregates of plate shaped crystals were formed. The spherical forms exhibited improved compressibility and flow characteristics and were able to be directly compressed (see Table 12).

These examples clearly illustrate the potential of improving particle properties by control of the crystallisation process and use of alternative crystallisation conditions. Indeed, the final stage of raw material preparation should be regarded as the first step in formulation, and interaction between scientists concerned with fine chemical production and pharmaceutical formulation should be encouraged and promoted so that preferred forms of raw materials for further formulation and processing operations can be identified and prepared. It is also apparent that when materials are produced under controlled and defined conditions then the efficient manufacture of modified materials is readily possible.

Indeed it should be emphasised that relatively minor changes in crystallisation conditions can produce significant changes in crystal and powder properties. Brown et al (81) working with a programmable small scale batch crystalliser on the crystallisation of ibuprofen from solutions in acetonitrile have demonstrated that changes in the linear cooling rate influence the equivalent spherical diameter, bulk density, true particle density and enthalpy of fusion (see Figure 16). Results showed that a more uniform particle size is obtained for the sample prepared at the fastest cooling rate. Interestingly, the true density and enthalpy of fusion were found to exhibit small but statistically significant ($p<0.05$) differences, suggesting that the molecules of the crystal are becoming less tightly packed with increasing cooling rate. Whilst the consequences of these changes on the compaction behaviour of the samples are currently being studied, these differences in the solid state and particulate properties further demonstrate the vast potential of material manipulation by careful and critical control of the crystallisation environment. Clearly further research work in this important area is indicated.

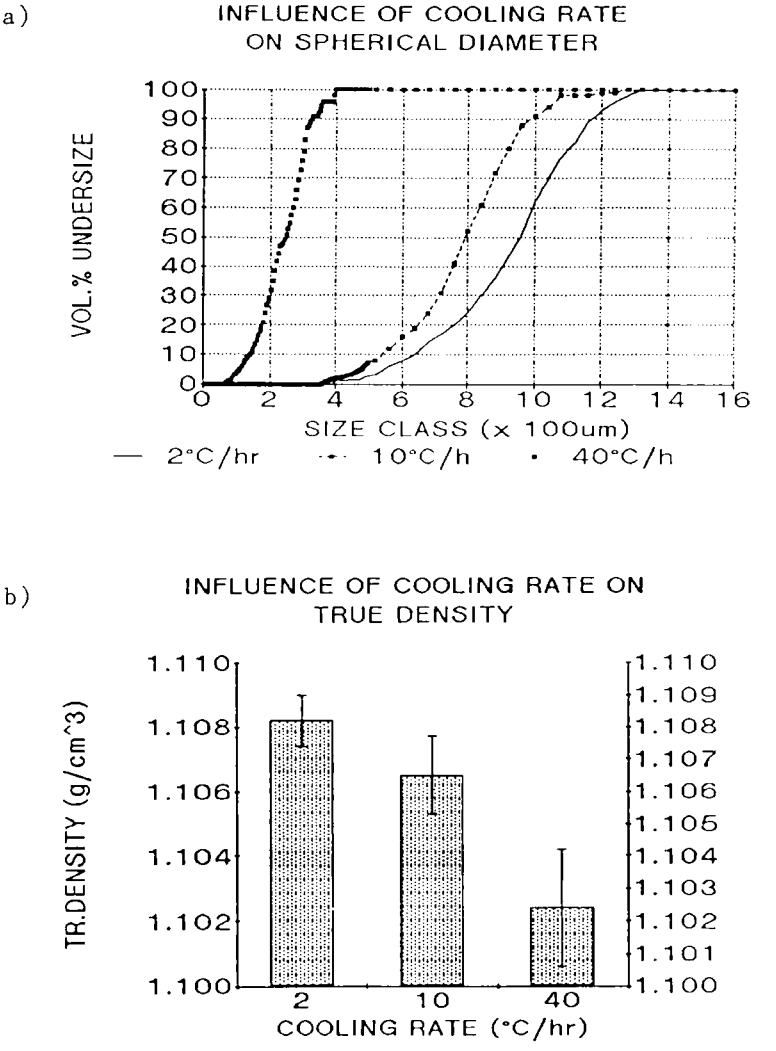

FIGURE 16

Influence of linear cooling rate during the crystallisation of ibuprofen from acetonitrile solutions on A) spherical diameter, B) true particle density

NOVEL EXCIPIENTS

A recent addition to the range of direct compression filler-binder excipients is Cellactose (Meggle Milchindustrie GmbH). The preparation and availability of this material illustrates how the advantageous properties of two individual materials - lactose and microcrystalline cellulose - can be combined in a single, specially prepared form to reduce the negative characteristics of the two components (82). In preparing this composite excipient, it was projected that the good solubility and flow properties of lactose should be combined with the water absorption and disintegration characteristics of microcrystalline cellulose whilst maintaining the good compaction behaviour of both materials. Scanning electron photomicrographs are shown in Figure 17.

The preferred combination ratio was found to be lactose:cellulose 25:75. Whilst physical mixtures showed some improvements, the coprocessed and agglomerated Cellactose with microporous structure gave superior properties in terms of crushing strength, flow properties and disintegration time (see Table 13). Thus the use of a specially prepared combined product duplicates the advantages of the individual components whilst overcoming their respective disadvantages.

This product also illustrates the potential for particle design and the achievement of superior particulate and compressional properties by manipulation of processing conditions and careful selection of individual components.

PREDICTING MECHANICAL PROPERTIES FROM MOLECULAR STRUCTURAL DATA

One of the major goals for the future in the field of compaction and tabletting must be the facility to predict material processing and compaction behaviour of pharmaceutical powders to direct the design of optimal formulations. Within this objective, the desired refinement would be to use structural, molecular data thereby eliminating the need for conventional and routine material testing.

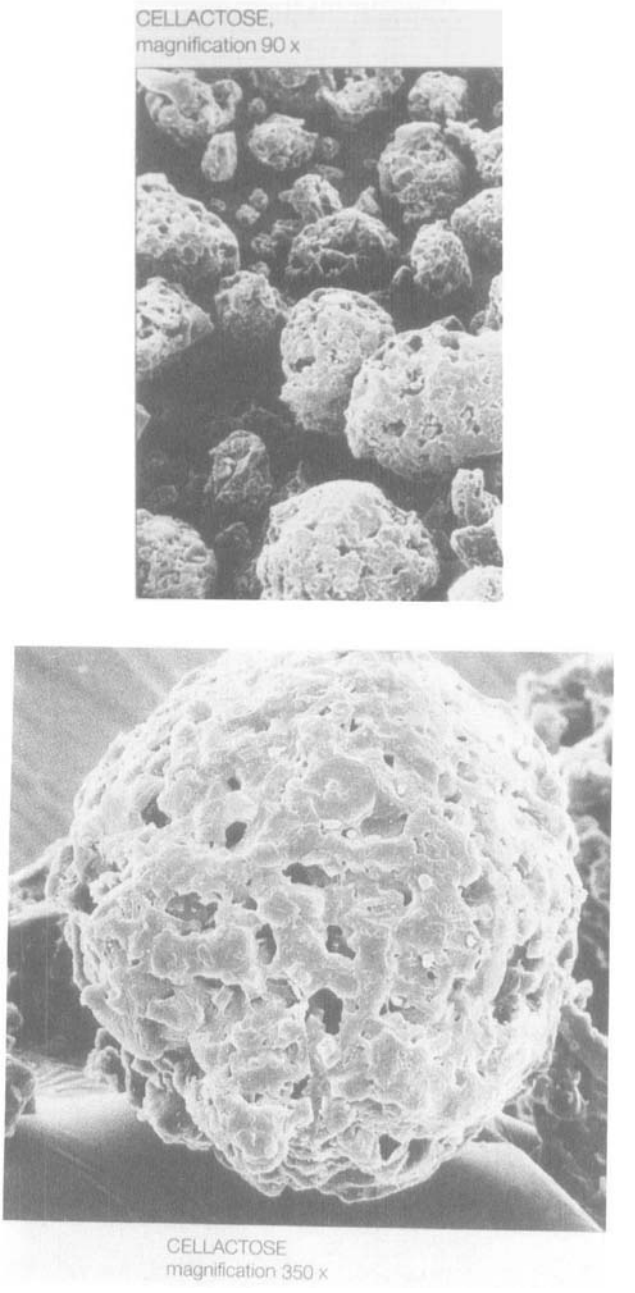

FIGURE 17

Scanning electron photomicrographs of Cellactose (82)

TABLE 13

PARTICULATE AND TABLETTING PROPERTIES

OF CELLACTOSE

	Agglomerated lactose[1]	75% agglomerated lactose; 25% microcrystalline cellulose[2]	Lactose cellulose granulate[3]
Flow characteristics			
Angle of repose	35.7	35	35
Hausner ratio	1.19	1.21	1.16
Crushing strength (N) Compression force (KN)			
at 10KN	17	31	68
at 20KN	49	75	152
at 39KN	80	118	235
Disintegration and friability (at equal crushing strength of 45N)			
Compression force required (KN)	13.30	15.78	7.54
Friability (%)	0.13	0.16	0.12
Disintegration time (seconds)	44	62	39

1: Tablettose
2: Avicel
3: Cellactose

TABLE 14

ASPIRIN

Values of elastic modulus, E

METHOD	GPa
Lattice Dynamics (Kim et al, 84)	7.1
Brillouin Scattering (Kim et al, 84)	8.5
Beam bending (Roberts et al, 83)	7.5
Solubility parameters (Roberts et al, 83)	7.4

TABLE 15

Water to ion bond distances and threshold temperature of dehydration, T_t, for PAS salts.

salt cation	T_t (^oC)	water to metal bond distances (Å)
Na^+	46 (2.5)*	2.4 and 2.9
Ca^{++}	110 (4.7)	2.4
Mg^{++}	107 (2.1)	2.0 and 2.1

* brackets denote standard deviation, n = 3

Recent exciting work by Roberts et al (83) has extended the report by Kim et al (84) on the crystal structure of aspirin to predict its Young's modulus at true particle (crystallographic) density (i.e. zero porosity) using single crystal elastic potentials. Values obtained experimentally using beam bending techniques as well as by a solubility parameter approach, estimated from constituent groups after Hansen (85), are listed in Table 14. An excellent agreement between predicted and experimentally determined values of E is demonstrated indicating, for perhaps the first time in molecular organic crystals, the potential for predicting mechanical properties from molecular structural and constituent data. These findings offer enormous potential in the field of crystal engineering and particle design in many ways, not least the notion of 'molecular manipulation' to modify material properties.

Other recent work has shown (50), using single crystal x-ray diffractometry, a relationship between hydrate stability in a metallic salt series based on para-aminosalicylic acid and the hydrogen bonding distance between water molecules and the counter ion (see Table 15). The water loss in the sodium salt is also facilitated by a 'channeling' structure of the water molecules in the crystal lattice.

With the advent of high resolution analytical instruments now able to examine crystal and powder samples directly without pretreatment, fundamental solid state, molecular and structural information can be made available to the pharmaceutical material scientist. Such knowledge and information will be particularly beneficial in the research and study of crystal engineering and particle design at the molecular level as theoretical models and predictive relationships between structure and mechanical properties are probed.

CONCLUDING REMARKS

It is clear from the discussions above that there is an increased interest and research activity in manipulating the physicochemical and physicotechnical properties of pharmaceutical crystals and powders to solve formulation, processing and compaction problems related to

inadequate material properties. However it is also apparent that for predictive, directed and controlled engineering of the crystals and particles, fundamental causative relationships will need to be established between the molecular, structural characteristics of the pharmaceuticals and their physicotechnical properties. Recent studies probing these areas of research are beginning to provide the necessary theoretical models, scientific arguments and experimental data to test the hypotheses. Further research will undoubtedly provide an expanding basis for the commercial development and preparation of modified materials for use by pharmaceutical scientists.

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