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THE DESIGN AND USE OF TABLETING EXCIPIENTS

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DEFINITION

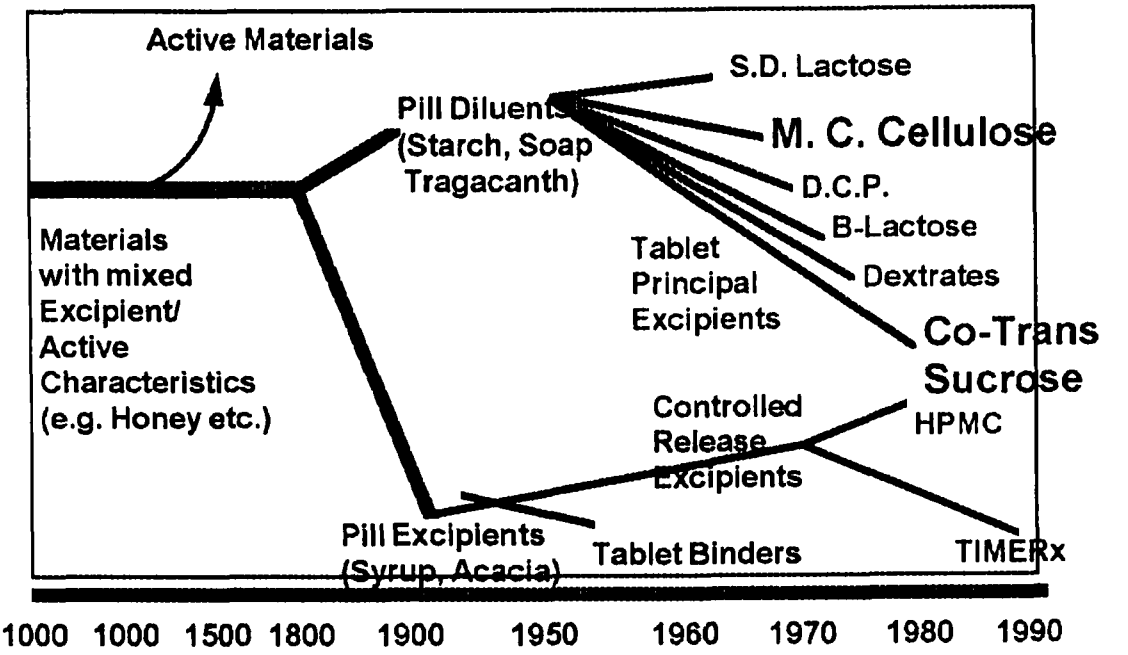
EXCIPIENT: a substance mixed with a medicine to give it consistence or used as a vehicle for its administration (L. excipere, to take out, receive - ex, from, capere, to take) [1]

Although drugs are responsible for therapeutic activity, it is a medicine and not a drug which a patient receives in the treatment of an illness. The difference separating a medicine from a drug is the presence in medicines of pharmacologically inert ingredients or excipients which modify a whole variety of physical, physico-chemical and physico-mechanical properties of the drug and these may lead to changes in the biopharmaceutical performance of the system.

BACKGROUND

Tablet excipients have a synchronology with materials used in the preparation of pills, and earlier inactives used in the preparation of solid oral dosage forms such as cachets and powders (table 1). Very early excipients may have been used not only for their physical characteristics but also for some supposed therapeutic benefit (eg honey, alcohol) etc. However, some texts relating to use of inert materials for pill preparation introduce the concept of distinct physical functionality of different excipients [2]. Diluents, which included starch and tragacanth, were used to increase the pill mass, and were distinguished from excipients such as glucose, glycerine, syrup and acacia gum which had the function of providing a cohesive mass. The functionality of early tablet excipients was limited to fairly undemanding performance requirements in categories such as: diluents (the direct descendants of pill diluents), binders (descended from pill excipients), disintegrants (incorporated without an understanding of the exact mechanisms of action), lubricants, glidants, anti-adherents and a number of other

Table 1. The Synchronology of Excipients



categories of a more specialized nature such as wetting agents, gas producers, flavours, colourants etc.

This method of categorization of excipients by function is analogous to the pharmacological categorization of drug action by therapeutic function eg anti-asthmatic, anti-hypertensive, anxiolytic etc and just as a drug such as propranolol could have activity in more than one functional pharmacological performance category, so an excipient could have activity in more than one physical performance category. Recently, it has been the deliberate aim of excipient design not only to optimize a single excipient function, but also to broaden the spectrum of excipient activity.

INTRODUCTION

It is this aspect of broad-spectrum activity which will be considered in more detail here. The major activity of a Principal Excipient is its ability to dilute the quantity of drug so that the tablet produced will be of an easily handled size. Such excipients are also

expected to be capable of "carrying" the drug in tablets which are strong enough to withstand further processing and handling and yet breakdown sufficiently quickly in contact with gastrointestinal fluid to yield the drug into solution promptly and reproducibly. Other requirements of the finished tablet, mediated through excipient performance are that it should possess pharmacopoeially acceptable weight and content uniformity adequate to ensure consistent drug dosage according to national or international standards. Principal excipients should be capable of fulfilling these objectives irrespective of process, whether direct compression or wet granulation. It is considered that the objectives of broad-spectrum activity and reduced process sensitivity can only be achieved by a more complete understanding of the physical, mechanical and chemical interactions in tablet formulations made possible by more sensitive characterization techniques.

The critical performance characteristics which a well-designed Principal Excipient should promote and conserve are drug homogeneity and tablet integrity. Since both functionalities result to a greater or lesser extent, from surface interactions, they will, in some circumstances, be interdependent.

(a) Drug Homogeneity

In setting standards for tablets, many pharmacopoeiae [3,4] use the test of uniformity of weight as a control of content uniformity. However, Train [5] used a statistical approach to show that in formulations where the drug constituted less than half the gross compression weight, the tablets could comply with pharmacopoeial standards despite many individual tablets being outside the specified dose range. The variation could be as high as four times the official assay limits in most cases and eight times or more with one or two formulations. Analysing practical systems, Moskalyk et al [6] found excessive dosage variation in individual tablets from batches which had passed the official tests for content uniformity.

In the past, it has been a fairly common misunderstanding that Wet Granulation or Multi-Operation Processing (MOP) prevents such inhomogeneity through granule formation, whereas Direct Compression Technology (DCT) promotes inhomogeneity because it does not produce granules. This is a fallacy. Both of the above examples are for tablets produced using Multi-Operation Processing, and Selkirk [7] and Spring [8] have demonstrated separately that production of wet granulations does not on its own prevent loss of homogeneity. Some excipients used in Direct Compression Technology also produce segregation of the drug component and it is therefore clear that drug inhomogeneity is related to the performance of excipients in both MOP and DCT.

Powder Mixing

Correct design of excipients may be used to overcome problems of poor mixing and segregation in formulations for use in either Direct Compression Technology or Multi-Operation Processing.

Table 2. Beneficial characteristics of microcrystalline cellulose as a tableting excipient.

- Highest excipient compactibility (42, 43)
- High ductility (30, 44)
- Non-destructive recoverable deformation (30, 45, 46)
- High dilution potential (46)
- Rapid disintegration (47, 48, 49)
- Good lubricity (50)
- Good blending characteristics (51)

Although unsatisfactory content uniformity of tablets may result from the segregation of powder mixes during processing, it may be attributable to incomplete mixing of the drug and excipient during initial processing prior to tableting. To minimize the probability of a batch of tablets or capsules failing a content uniformity test it is necessary to understand the intermediate processes taking place between the initial preparation of the powders and the final compression or encapsulation [9]. A recent review article with special emphasis on pharmaceutical powder mixing and segregation covers the theory of mixing and segregation and the mechanisms and process conditions leading to their production [10]. As a generalization, powders behave macroscopically as though the component particles were non-interacting (classical random mixes) or as though they were interacting (classical ordered mixes). In between these 2 extreme types of behaviour lies an intermediate form in which some particles interact and others are non-interacting; this composite system has been termed partially ordered random [11]. In terms of ability to form homogeneous mixes, all three types of particle association are capable of producing drug/excipient mixes of equally low variance of sample content, given the appropriate correct selection of powder mixing equipment for each type of powder mix being processed. However, the 3 different types of powders will perform quite differently in terms of their ability to resist segregation during subsequent processing.

Hersey [12] first introduced the concept of ordered mixing to explain the behaviour of interacting particles in a powder. Fine particles adhere to other, usually coarser

Table 3. Disintegration times for tablets prepared from ungranulated and granulated microcrystalline cellulose.

Drying method / material	Wet mass batch	Compaction force (kN)	Tablet tensile strength (MPa)	Tablet work of failure (J m^{-2})	Tablet relative density	Disintegration Time (sec)
Ungranulated MCC	---	15.1 ± 0.12	5.8 ± 0.21	1060 ± 105	0.85	330 ± 30
	---	10.8 ± 0.06	4.1 ± 0.14	744 ± 52	0.79	210 ± 26
	---	4.9 ± 0.03	1.8 ± 0.08	392 ± 21	0.66	80 ± 10
Granules:						
Microwave-vacuum dried, "high" process type	1	15.1 ± 0.03	4.1 ± 0.15	480 ± 42	0.85	79 ± 6
Freeze dried	1	15.1 ± 0.04	3.9 ± 0.11	464 ± 21	0.85	70 ± 9
Fluidised bed dried	1	15.0 ± 0.04	3.7 ± 0.05	402 ± 17	0.85	52 ± 7
Ambient conditions	1	15.0 ± 0.05	3.6 ± 0.10	374 ± 20	0.86	45 ± 8
Tray dried, "just dry"	1	15.1 ± 0.04	3.5 ± 0.10	386 ± 16	0.84	54 ± 5
Tray dried, "over dried"	1	15.1 ± 0.05	3.4 ± 0.08	375 ± 24	0.84	39 ± 3
Vacuum dried	1	15.1 ± 0.03	3.2 ± 0.12	360 ± 22	0.84	38 ± 4
Radio frequency dried	3	15.0 ± 0.04	3.2 ± 0.07	299 ± 21	0.86	34 ± 4

particles to form so-called ordered or adhesive units. It is the formation of these adhesive units which produces the stabilizing effect seen in ordered mixes, absent in random mixes and which therefore makes ordered mixes more segregation resistant than random mixes. Indeed a comparison of the forces responsible for stabilizing particles in adhesive units of an ordered mix with those responsible for formation of wet granules shows little difference between the 2 types of particle association: granule or dry mix adhesive unit. The potential adhesive forces shown in table 3 related to formation of adhesive units in dry powder mixes were described by Hersey [12] and others [13, 14, 15]. The only significant difference between the list in table 3 and one compiled by Rumpf [16] solely for granules, is the absence from table 3 of solid bridges as a class of forces responsible for formation of ordered units.

It now becomes clear that in order for excipients to perform optimally in terms of homogeneity and segregation resistance, that adhesive, or interactive mixes should be produced. Staniforth and Rees [17] tested 2 chemically similar excipients designed for use in Direct Compression Technology. Both excipients had comparable, coarse particle size distributions and were used to form homogenous powder mixes with a fine-particle model drug. When the 2 mixes were subjected to vibration conditions similar to those found during routine tablet production [18], only one mix remained homogeneous, the other mix was found to segregate. The physically stable mixture contained the excipient Emdex and the unstable mixture contained Dipac. Further work suggested that Emdex produced stable mixes due to 3 effects [19] related to surface porosity, which promoted increased interparticle forces in comparison with smoother surfaced excipients which produced weaker adhesive units on mixing drugs and excipients [20].

In addition to the direct beneficial effects on content uniformity and stability of powder mixes through formation of adhesive, or interactive, mixes, recent work has shown that there are other advantages in producing tablets using Direct Compression Technology to promote interactive mixing. Because formation of interactive mixes, requires finely divided drug particles to be spread over coarser excipient carrier particle surfaces, the efficiency of tablet dissolution can be improved through exposure of higher reproducible surface area of drug to dissolution fluid [21]. Other workers have also reported improvements in dissolution rates especially for sparingly soluble drugs mixed with soluble carrier excipients such as Emdex [22, 23, 24]. However, it should be realised that although most excipients for use in Direct Compression Technology, which formed interactive drug mixes produced enhanced dissolution properties, a variability in effect was found for different excipients. This was considered due to difference in solubility of different excipients and also differences in drug/excipient and excipient/excipient interactions [24, 25].

Throughout this section, work has been reported on formation of interactive mixes between fine drug particles and coarse carrier excipient particles such as microcrystalline cellulose, although the flow properties of such mixes may be less acceptable than using coarser excipients, such as Emdex. Another important

application of these highly stable interactive mixes is that they retain the free flowing characteristics which are vital to producing tablets with acceptable weight and content uniformity [26, 27, 28].

(b) Tablet Integrity

The integrity of a tablet is dependent on the strength and resistance of the compacted powder in withstanding external disruptive forces, until the tablet is administered. The purpose of compaction is to bring particle surfaces into close proximity and to enhance intermolecular or other forces, thereby enabling interparticulate bonding [29]. The mechanical properties of the resulting compact are dependent on both the intra- and interparticulate bond strength and on the area of interparticle bonding resulting from powder compaction and decompression [29].

Compactibility may be affected by both the physico-chemical characteristics of the material under consolidation as well as the tableting conditions. Krycer et all [30] showed that powders exhibiting high compactibility had a high particle friability and porosity. Important functional characteristics also include the ability of particles to bond following deformation [31], particle roughness and shape [29, 32, 33] size and size distribution [34, 35, 36] moisture content [37] and the amount of elastic recovery occurring during decompression [31, 38]. Many of these factors have been used in manipulating the functionality of different tableting excipients:

Particle Size Distribution Modifications -	Dicalcium Phosphate Dihydrate (eg Emcompress)
Physical Transformation -	physical modification of crystal type (such as by spray drying or granulation of lactose (eg Fast Flo, Tablettose)
Physico-chemical Transformation -	chemical treatment of cellulose by partial acid hydrolysis to remove the amorphous portions of alpha-cellulose and produce microcrystalline cellulose (eg Avicel, Emcocel)
Physical Co-Transformation -	co-crystallization of sugars with small concentrations of other materials such as sucrose and maltodextrin (eg Dipac, Microtal, Emdex

In designing an excipient to exhibit and retain improved characteristics during tablet processing for example, using one of the techniques described above, it is very important to use characterizations which can adequately distinguish differences in compactibility. A number of tests for distinguishing brittle and plastic materials have

been reported in the literature. Some tests, such as work of compaction and stress relaxation studies, rely on measuring changes occurring during the compaction process, whereas others such as normalized work of failure and apparent failure viscosity measurements, are made on finished tablets. Some of these tests are more sensitive than others and provide more useful information for the interpretation of excipient performance in use.

Design Characteristics

When designing a new excipient based on a brittle material, such as sucrose, it is important to quantify the influence of changes resulting from co-transformations on tabletability. Sucrose transformation is a continuous process of crystallization with no by-products. A hot sucrose syrup is stored in a tank (A, fig 1) and usually has a solids content between 50% and 80% by weight. From this tank the syrup is passed to a plate evaporator (B, fig 1) where it is concentrated by removal of water, to form a sucrose syrup which may have a solids content of 90% or more by weight. This is then passed through a second evaporator (C, fig 1) which is heated by steam where the syrup is further concentrated by removal of water. The highly concentrated syrup at a temperature greater than 123°C is passed through a colloid mill (D, fig 1) which applies a sufficiently high shear to induce nucleation. The syrup emerges as a concentrated slurry in which crystals are in the process of forming and flows onto a heated conveyor band (E, fig 1). Sucrose crystallization is an exothermic reaction and the heat generated during this stage of crystal formation aids drying of the final product which can be milled to the desired particle size range. Other, normally polymeric materials can be introduced during this process, with the aim of modifying the inherent brittle nature of sucrose to one which promotes ductile deformation on compaction.

In-Die Characterization of Compactibility

(a) True Work of Compaction

Determinations of true work of compaction were carried out for differently co-transformed sucrose and other principal excipients. At all compaction rates, there was a decay in the work carried out after the first compression to a constant value after a maximum of approximately 13 re-compressions. The shapes of the work decay/recompression number profiles were similar for both ductile materials such as MCC as well as for more brittle materials such as sucrose (fig 2). However, the degree of force decay was greater for co-transformed sucrose than for MCC at all compaction forces and rates of compaction (fig 2). For example, a co-transformed sucrose compressed at approximately 8kN showed a decrease from 8500 N at the first compaction to a near-constant value of 5200 N after the 11th re-compaction. In the case of MCC, the decrease was from 8200 N to a constant value of 7400 N after the 8th re-compaction. This would suggest that although having a more resistant structure may be associated with desirable excipient compactibility, this characterization method was not considered especially sensitive to positive design changes made during co-transformation of various sucrose excipients.

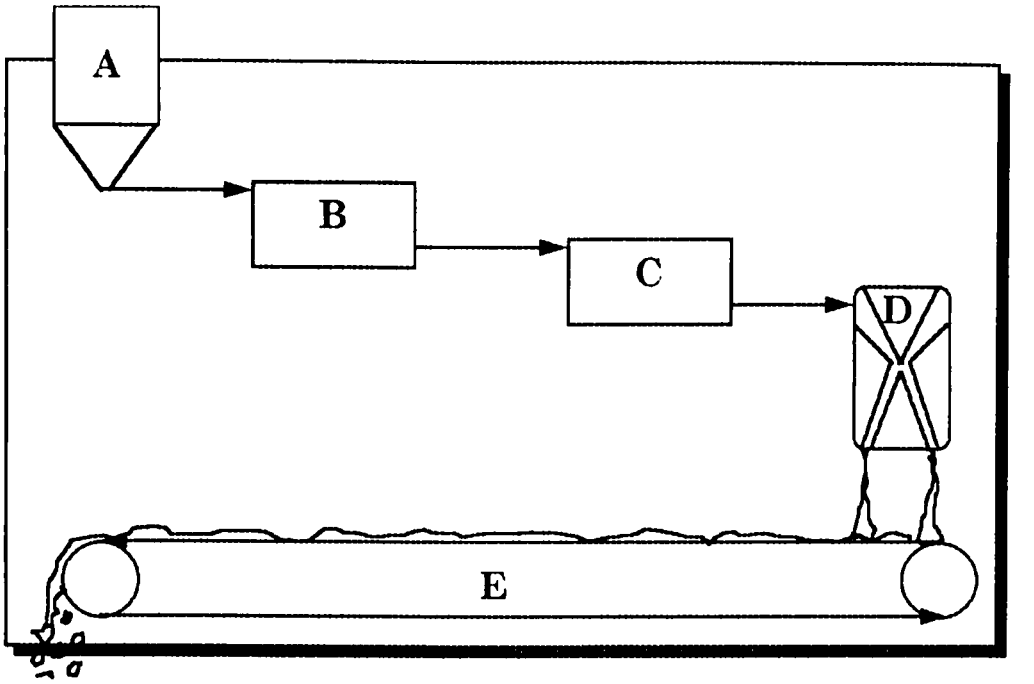
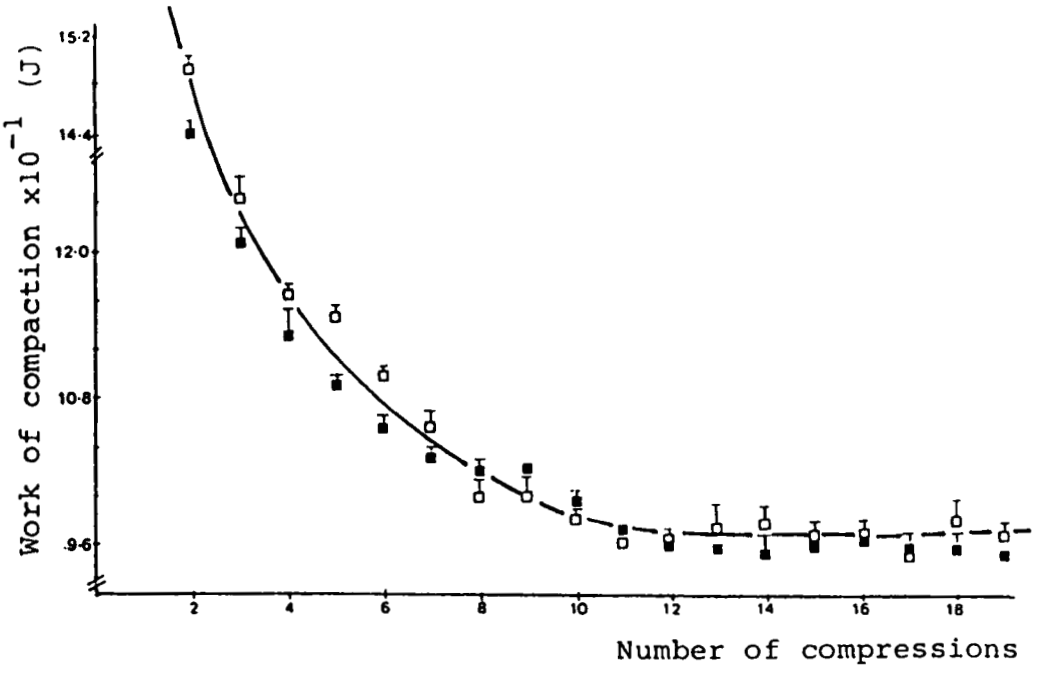


Figure 1 Continuous Sucrose Crytallization
(Tate & Lyle plc UK Patent # 1460614)

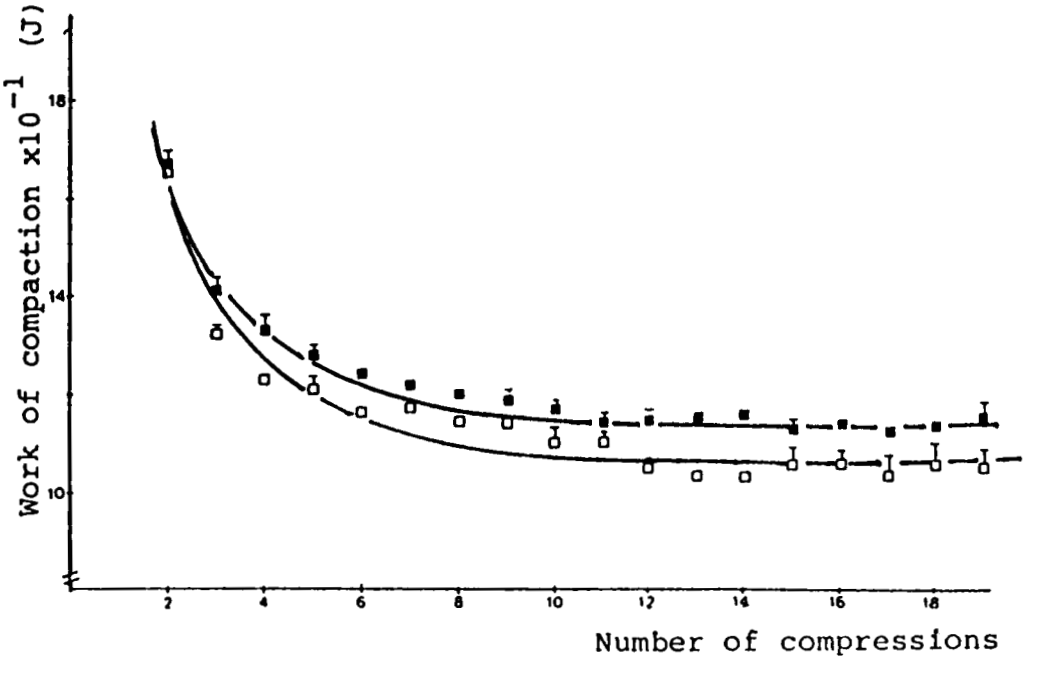
(b) Creep Compliance and Creep Relaxation.

In principle, determinations of creep compliance or creep relaxation should provide a more complete rheological evaluation of material behaviour than for example, stress relaxation studies.

Fig 3 shows an example of a creep compliance curve showing separation of the different rheological characteristics which can be quantified for comparison of the behaviour of different excipient designs. Region AB (fig 3) represents elastic behaviour equivalent to DE for elastic recovery; region BC represents visco-elastic behaviour equivalent to EF, for visco-elastic recovery. Finally, region CD shows plastic deformation, which has no equivalent on the recovery cycle, since such deformation is permanent. The aim of using creep determinations for excipient design work is to enable such behaviour to be separated in order to maximize non-recoverable deformability and minimize recoverable deformability (fig 4). Unfortunately, the inability of displacement transducers to differentiate "useful" deformation from "non-useful" deformation has limited the application of this characterization for sensitive measurements [39].

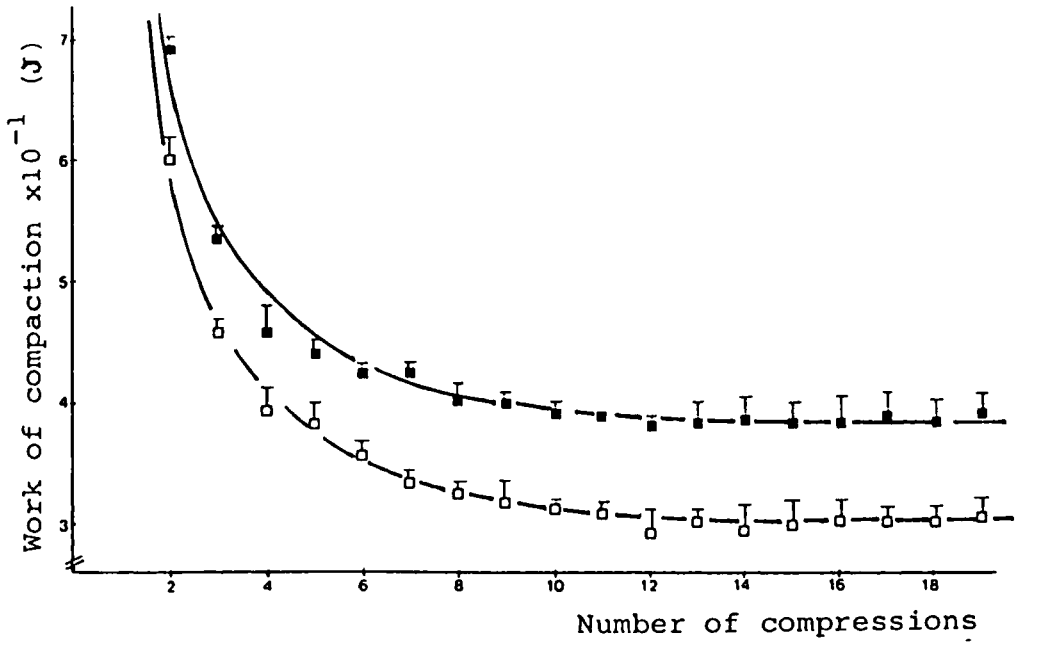


a. Contact time (□) 15.04 and (■) 10.70 seconds x10^{-2}.

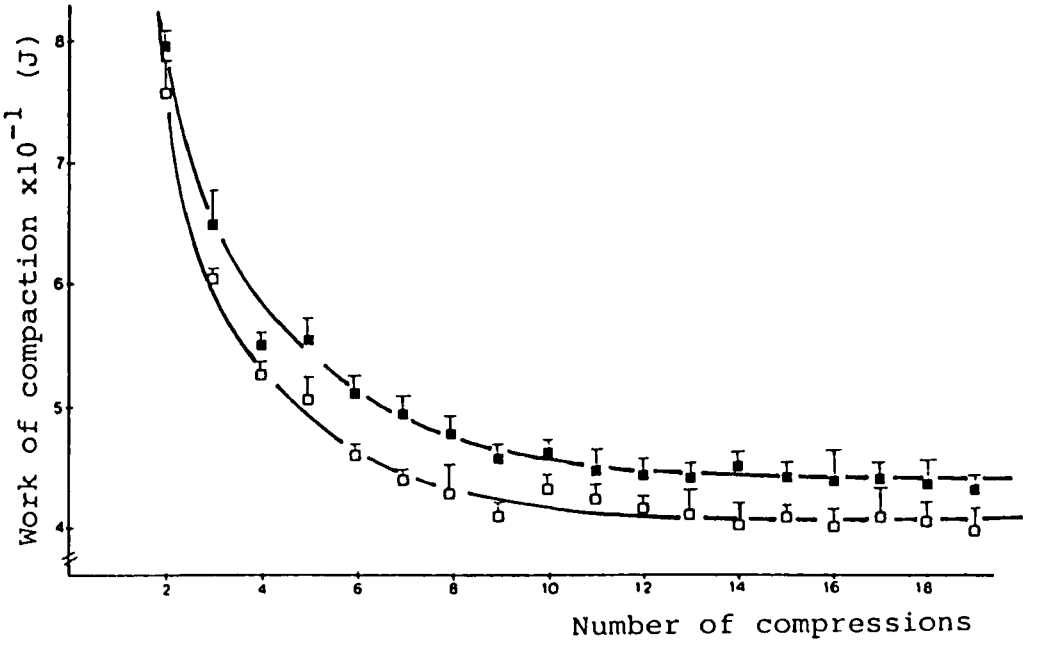


b. Contact time (□) 11.52 and (■) 9.17 seconds x 10^{-2}.

Figure 2 (i). Relationship between Work of Compaction and Number of Compressions for microcrystalline cellulose, compacted at 8kN. Compaction rate is effectively represented by contact time.



a. Contact time (■) 11.65 and (□) 7.68 seconds x10^{-2}.



b. Contact time (■) 10.11 and 6.77 seconds x10^{-2}.□

Figure 2 (ii). Relationship between Work of Compaction and Number of Compressions for co-transformed sucrose compacted at 8kN. Compaction rate is effectively represented by contact time.

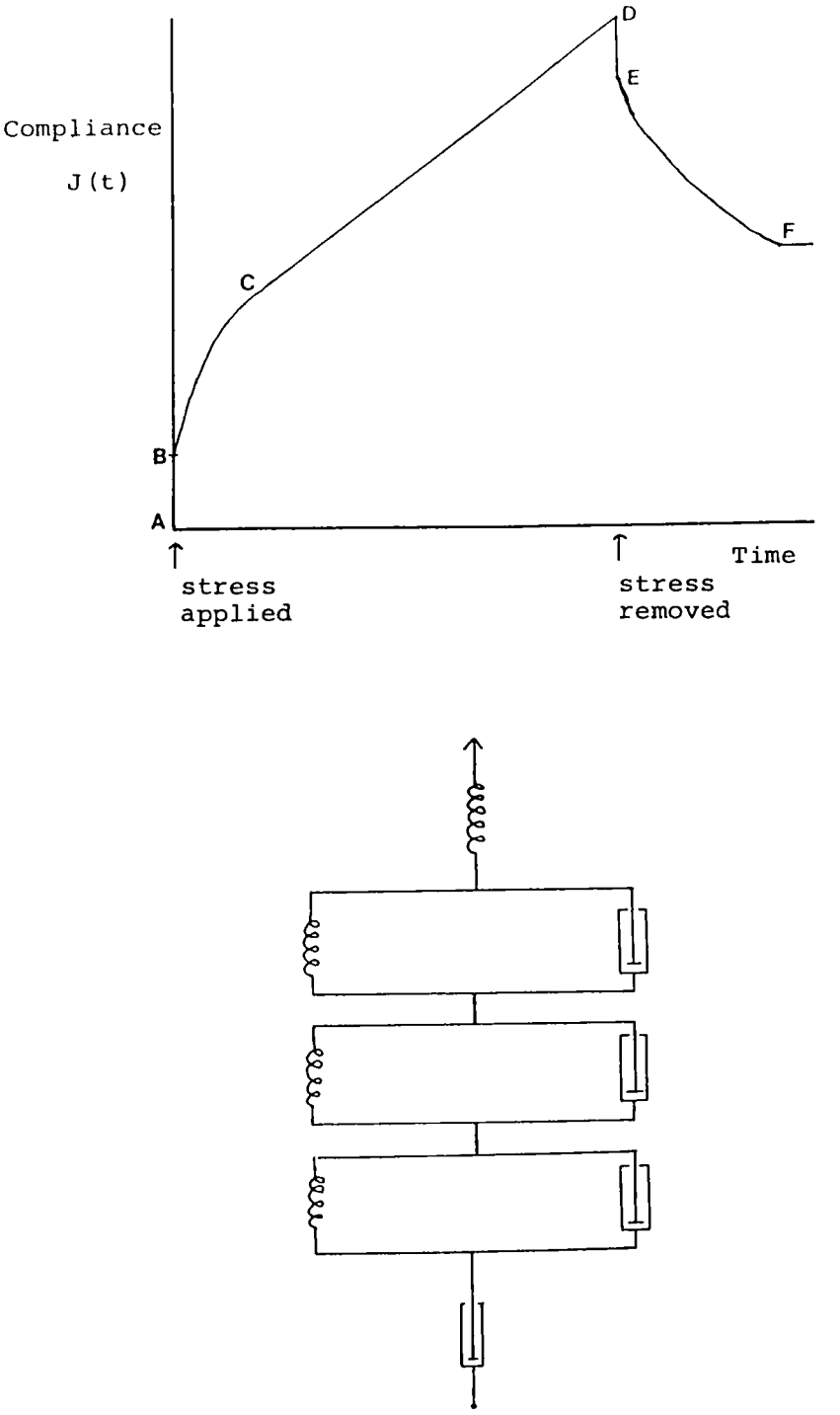


Figure 3. Creep compliance curve and canonical model used to describe creep curve

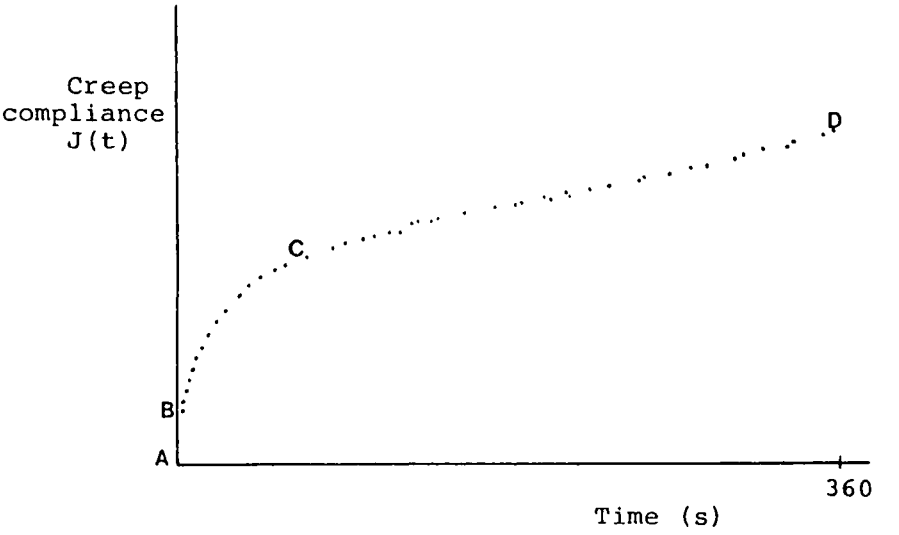


Figure 4. Creep compliance curve obtained over a 360 second time interval for microcrystalline cellulose.

Post Compaction Testing

(a) Fatigue Strength of Tablets

The relationship between the number of cycles required for fatigue failure with increasing compaction force for some direct compression excipients is shown in figs 5 and 6. For Avicel PH102 and co-transformed sucrose tablets - Microtal and Dipac, the number of cycles required for fatigue failure was found to increase with increase in compaction force (fig 5). This is the result of an obvious relationship: increase in compaction force results in an increase in the areas of intimate inter-particle contact, thus increasing the degree of inter-particle bonding and consequently the tablet possessed greater resistance to mechanical damage. MCC tablets required the highest number of cycles for fatigue failure at any given compaction force (fig 5). No data for MCC tablets compacted above 16 kN compaction force was obtained, since these tablets were found not to undergo fatigue failure, even after 60,000 cycles (approximately 3 days). Fig 6 shows that there was no influence of compaction force on the number of cycles required for fatigue failure for either Emcompress or Tablettose tablets. This behaviour was unexpected since normalised work of failure values were previously found to increase with increase in compaction force for these tablets.

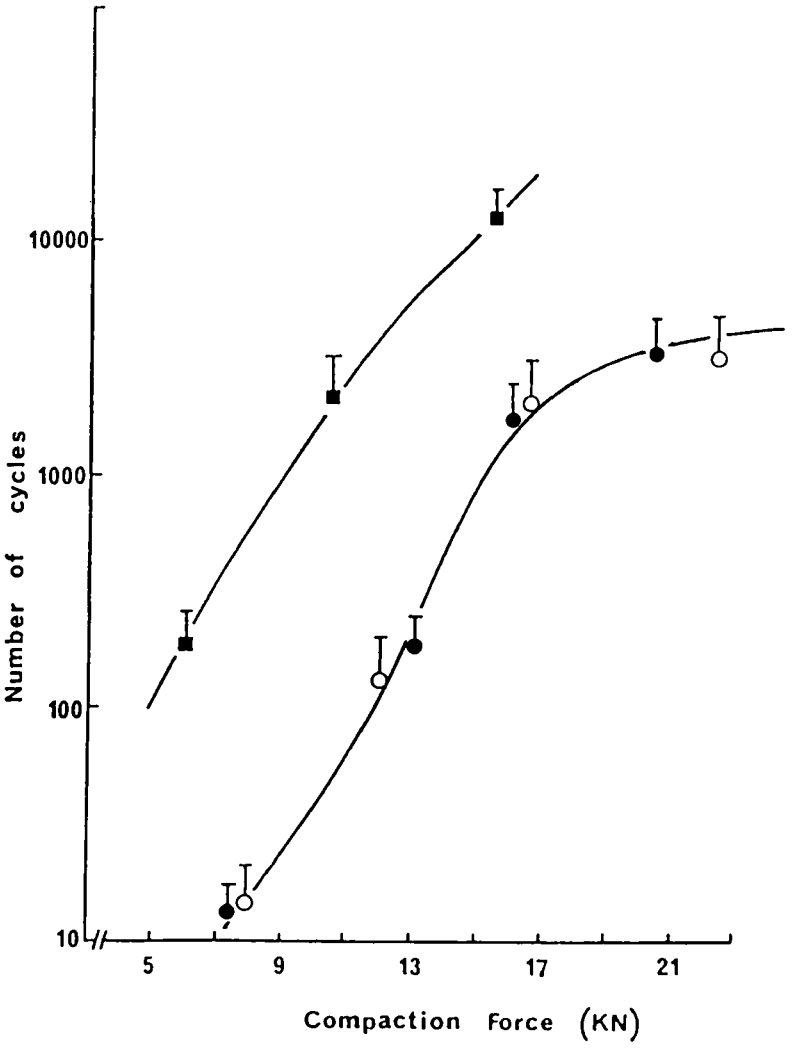


Figure 5. Influence of compaction force on the number of cycles required for fatigue failure of ■ microcrystalline cellulose, ● co-transformed sucrose, Microtal, ○ Dipac tablets.

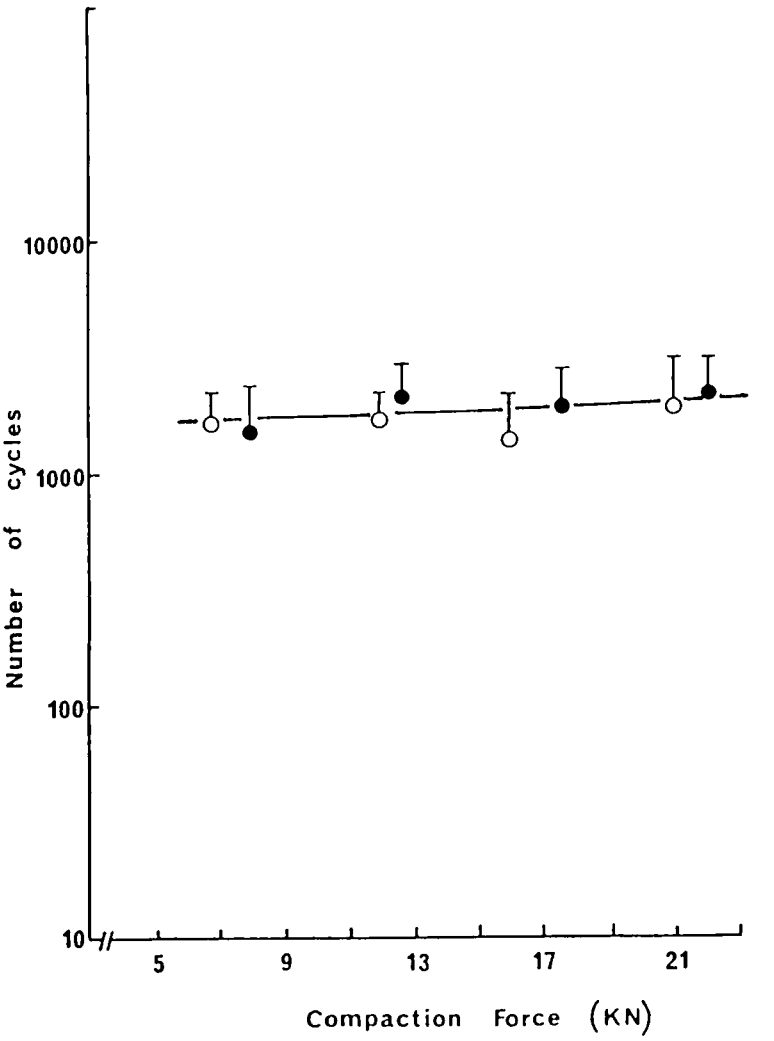


Figure 6. Influence of compaction force on the number of cycles required for fatigue failure of ● dicalcium phospate dihydrate, ○ Tablettose tablets.

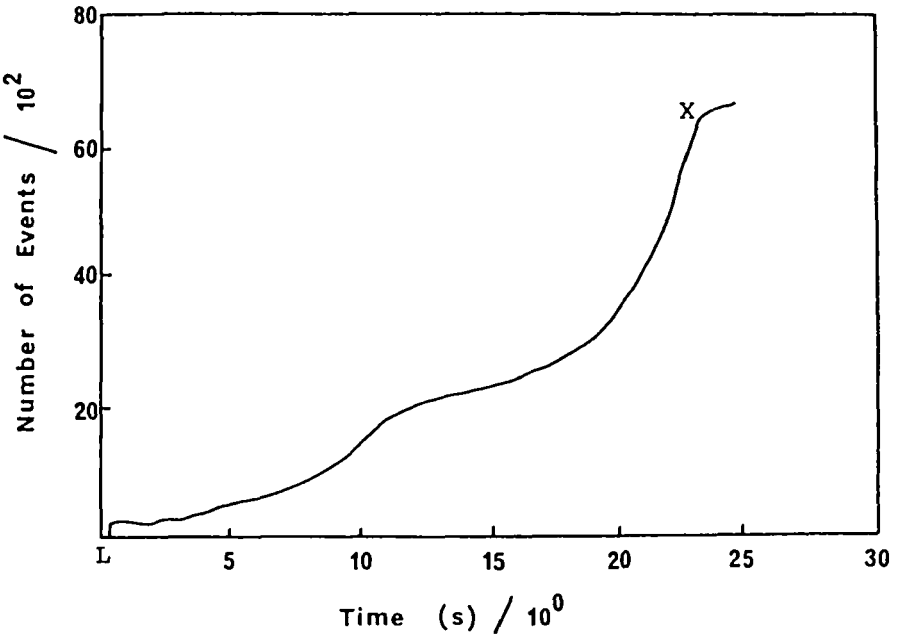


Figure 7. Cumulative number of AE events recorded with time during fatigue testing of a co-transformed sucrose tablet compacted at a force of 8kN. Note: L, is the point of loading and X, is the point of fatigue failure

Nevertheless, fatigue strength determinations appear to provide a method of distinguishing classically brittle tablets from those which have been plasticized, on the basis of a change in the shape of the fatigue failure profile. The degree of excipient ductility was found to be related to the number of cycles required to cause failure.

The different trends observed in figs 5 and 6 are a result of differences in the fatigue crack propagation (FCP) rates, since all variables, except those of a physico-chemical nature (material variables) of the powder in the Paris equation were kept constant:

$$da/dn = A(\Delta K)^m \qquad \text{Paris Equation}$$

where da/dn is fatigue crack growth (change in crack length, a, with number of cycles); ΔK is the stress intensity factor range given by Kmax - Kmin; A, m are functions of material and test variables, such as temperature, cycling frequency, stress ratio and environment.

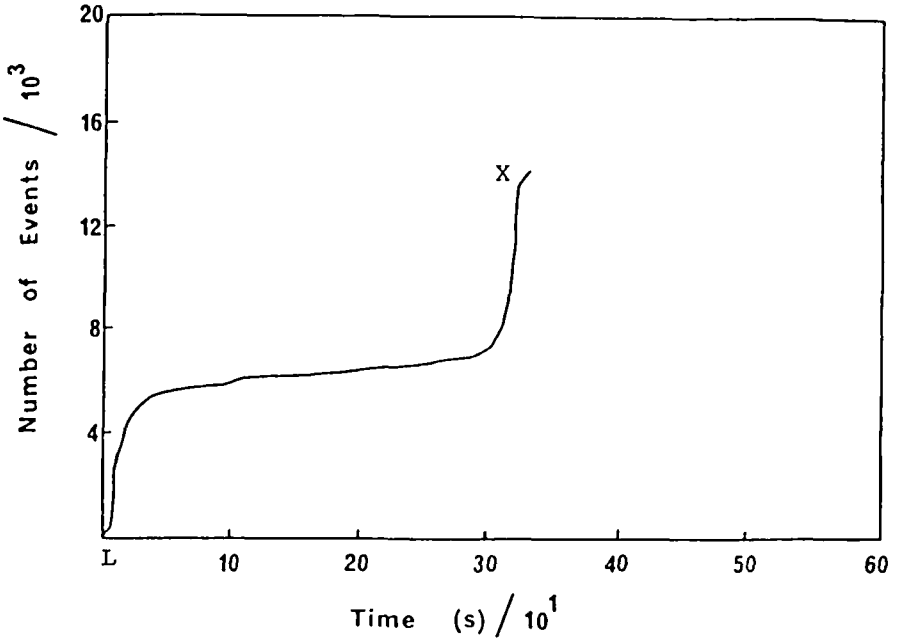


Figure 8. Cumulative number of AE events recorded with time during fatigue testing of a co-transformed sucrose tablet compacted at a force of 12kN. Note: L, is the point of loading and X, is the point of fatigue failure

Irwin [40] stated that the stress field at a crack tip increases rapidly as the radius of curvature at the crack tip decreases and the rate of crack propagation is rapid, but if plastic deformation were to take place in the crack tip zone, crack tip blunting would occur. It is thought that during fatiguing of MCC tablets, these tablets undergo some degree of plastic deformation at the crack tip zone, consequently increasing the radius of curvature at the crack tip.

(b) Non-Destructive Testing - Acoustic Emission

Acoustic emission (AE) monitoring provides a means of following the damage in a component, especially crack propagation [42]. The formation of a crack and its subsequent propagation are associated with release of elastic energy, which can be detected by placing a sensitive pizoelectric acoustic sensor on the surface of the component. Figs 7 and 8 show AE data acquired for co-transformed sucrose compressed at 8 and 12 kN. Not surprisingly, AE for a 12 kN tablet was found to be much greater than that for an 8 kN tablet, due to differences in the degree of interparticle bonding. This is clearly shown on the

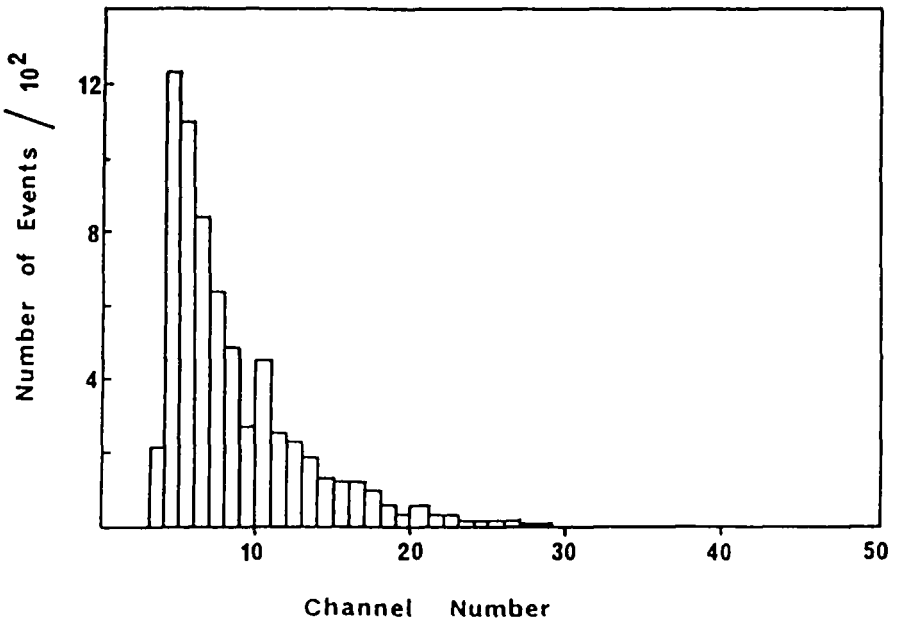


Figure 9. The distribution of AE energy levels during fatigue testing of a co- transformed sucrose tablet compacted at 8kN.

histogram of the number of events, versus channel number (figs 9 and 10). The channel number represents a classification of the AE based on energy level, the higher the energy emitted, the higher the channel number in which it is recorded. Between channels 0 and 10, a 12 kN co-transformed sucrose tablets showed greater AE than 8 kN tablets, indicating that the fracture (de-bonding) in a 12 kN tablet occurred with a larger release of elastic energy. In both cases, after the point of loading (L), which caused a burst of AE suggesting some fracture, there was a gradual increase in AE up to the point of fatigue failure (X) The sudden bursts of AE in Emcompress suggest that once a crack was initiated, the FCP was rapid. This supports the hypothesis that due to absence of mechanisms which would cause blunting of the crack tip, stress concentration at the crack tip would be large. However, these bursts were short-lived, indicating that the path of the crack was short. This is the result of brittle fragmentation producing a heterogeneous, galleried tablet structure.

The data suggests that AE may provide a useful non-destructive test capable of distinguishing brittle from ductile characteristics in compacted tablets.

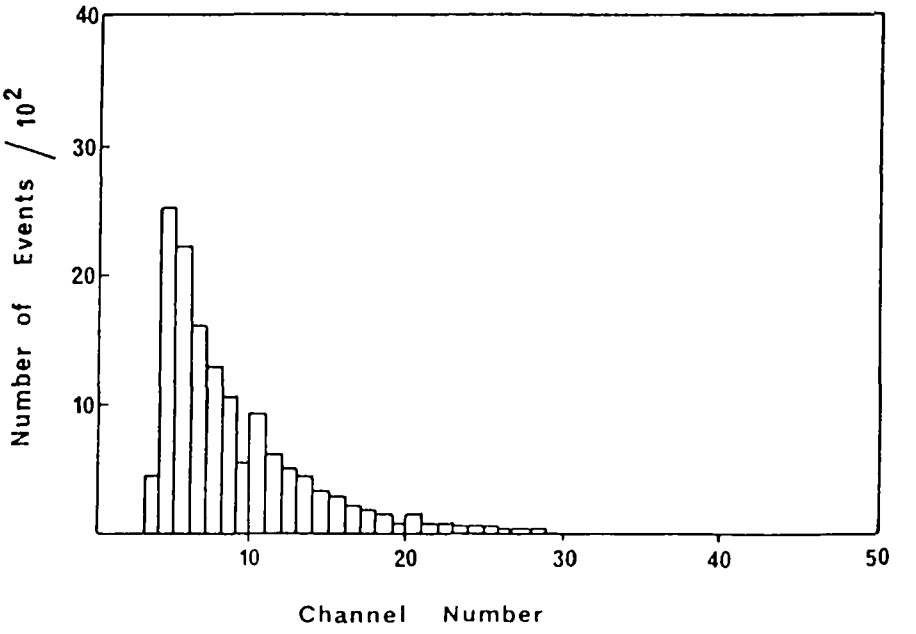


Figure 10. The distribution of AE energy levels during fatigue testing of a co- transformed sucrose tablet compacted at 12kN.

(c) Normalized Work of Failure

One of the simplest and most sensitive tests for characterizing the physico-mechanical properties of excipients has proved to be measurement of normalized work of failure.

In studies of co-transformed sucroses, this method was capable of distinguishing optimum concentrations of crystallization additives used. It was found that for sucrose co-transformed with maltodextrin, the optimal concentration was approximately 1%w/w (fig 13) which was lower than expected. It was considered that the increased plasticity found in sucrose co-transformed with 1% maltodextrin was due to relaxation of the sucrose lattice resulting from the presence of low concentrations of oligosaccharides. Further increases in concentration have a lower plasticizing effect and although the reason for this is not clear, it may be due to the reduced influence of maltodextrin as a formulation mixture component in comparison with its action as a crystal poison.

When the concentration of maltodextrin incorporated with sucrose was 1% w/w, the NWF profile was found to be comparable to that for anhydrous lactose.

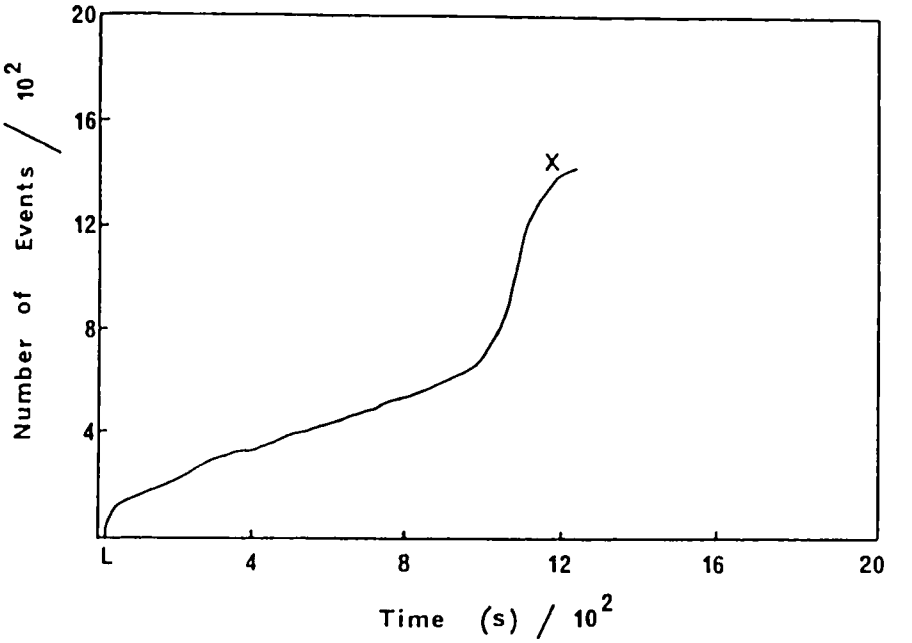
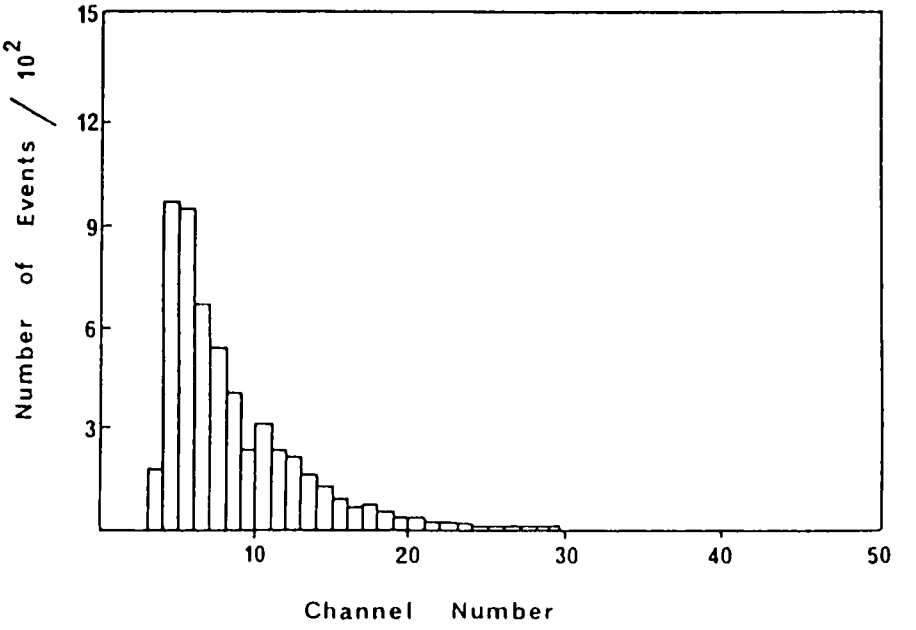


Figure 11. (a) Cumulative number of acoustic events recorded with time during fatigue testing of a microcrystalline cellulose tablet compacted at 6kN. Note: L, is the point of loading and X, is the point of fatigue failure.



(b) The equivalent AE energy level distributions during fatigue testing

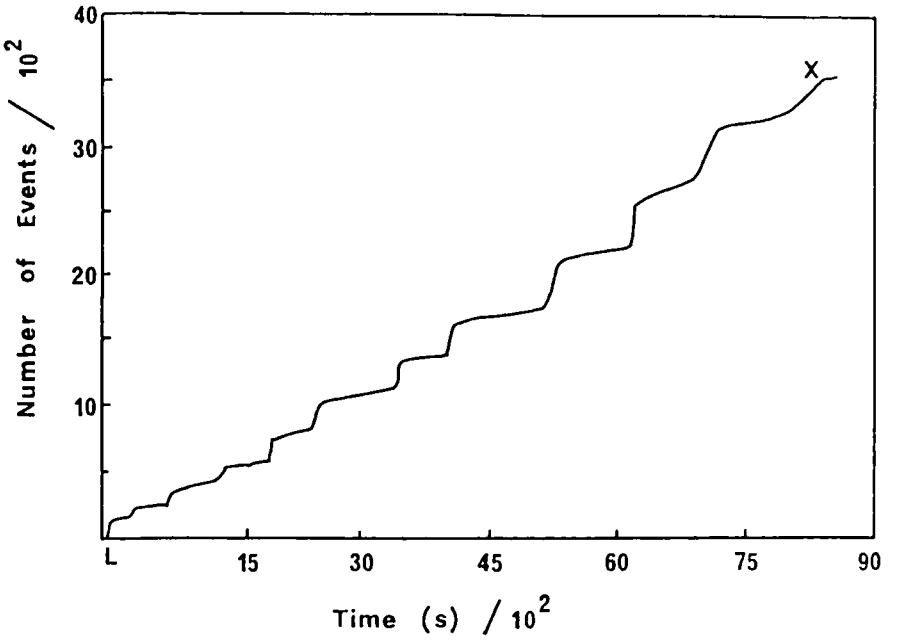
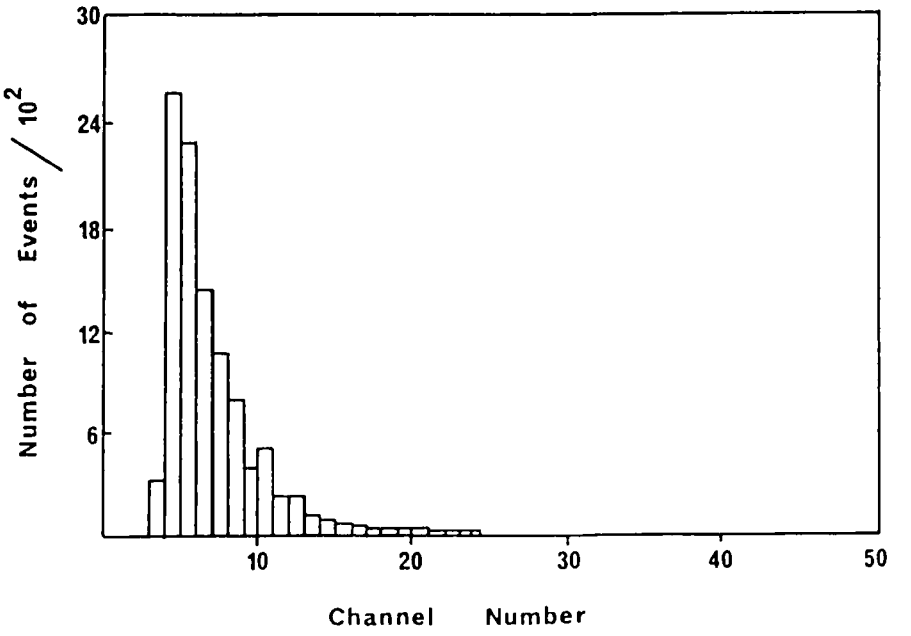


Figure 12. (a) Cumulative number of acoustic events recorded with time during fatigue testing of a dicalcium phosphate dihydrate tablet compacted at 20kN. Note: L, is the point of loading and X, is the point of fatigue failure.



(b) The equivalent AE energy level distributions during fatigue testing

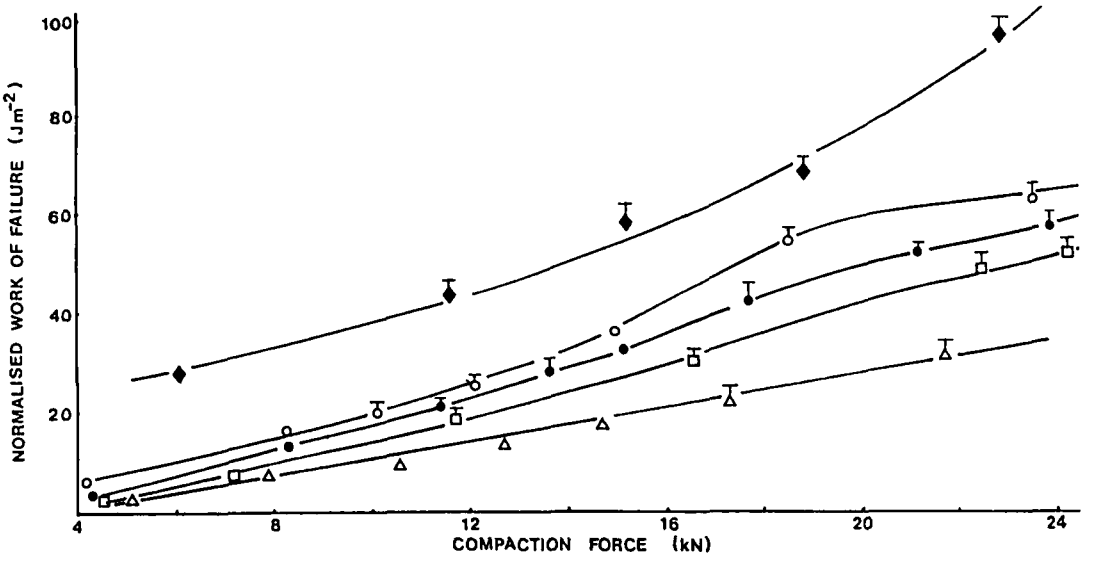


Figure 13. Influence of the concentration of sucrose co-transformed and compaction force on the normalized work of failure of tablets. ◆ 1% maltodextrin, ○ 3% maltodextrin ● 5% maltodextrin and □ 10% maltodextrin. Pure transformed sucrose compactibility is shown △ for comparison.

However, the moisture level of the co-transformed sucrose at the point of compaction was only 0.2% of total dry powder mass, compared with approximately 0.8% for anhydrous lactose. It is therefore possible that the water content of anhydrous lactose provided the plasticizing effect obtained by addition of maltodextrin with sucrose.

The incorporation of 1% gelatin was found to have a larger plasticising effect on transformed sucrose than 1% maltodextrin when judged according to NWF profiles (fig 14). It is probable that gelatin possessed a greater inherent plasticity than maltodextrin, possibly because gelatin has a more coiled molecular shape with greater molecular space than maltodextrin. It might be expected that the plasticity of tablets compacted from co-transformed product would increase as the concentration of gelatin incorporated was increased. However, the results shown in fig 14 show that, in fact, there was a decrease in NWF at concentrations of 3 and 5%, similar to that found previously for incorporation of maltodextrin. The increase in plasticity found in tablets containing 1% gelatin was found to be produced by an effect other than moisture acting as a plasticizing binder. The effect was also apparent using gelatins with different Bloom strengths.

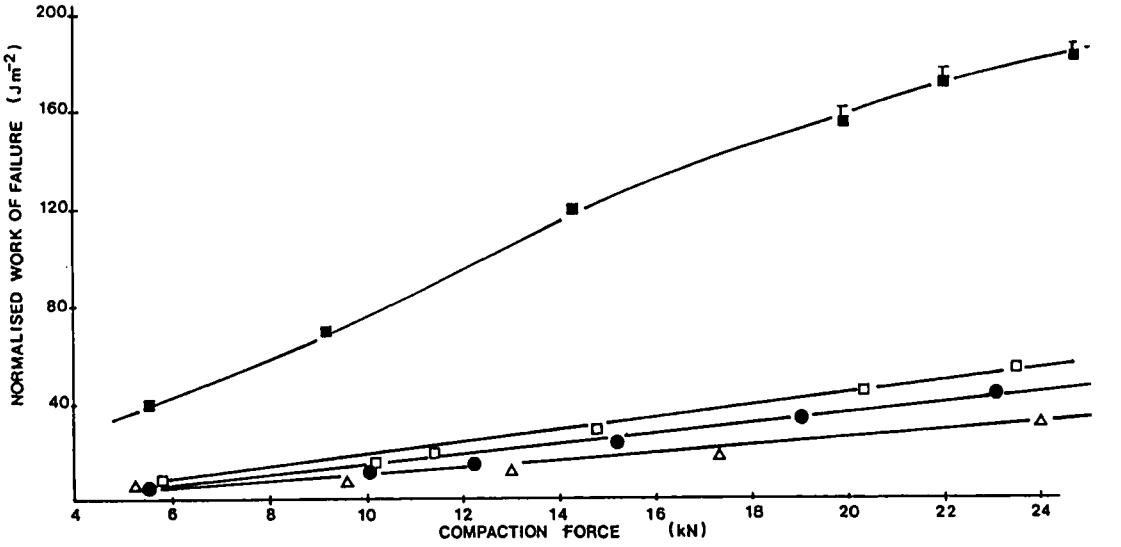


Figure 14. Influence of the concentration of gelatin B.S. 60 and compaction force on the normalized work of failure of tablets. ■ 1% gelatin, □ 3% gelatin ● and 5% gelatin. Pure transformed sucrose compactibility is shown △ for comparison.

It was hypothesized earlier that alteration of the sucrose lattice by small concentrations of crystal poisons could significantly increase plasticity and tablet toughness. Sucrose crystals with a larger quantity of impurities are found in third crop recovery of refinery sugar which is the residual product after a third re-crystallization stage of refining sugar. A commercial crystallized sucrose was used as a control. The moisture content at the time of compaction for the third crop sample was approximately 0.32%. Fig 15 shows the influence of impurities in the sucrose crystals on the NWF-compaction force profile. Compared with pure sucrose crystals, the third crop crystals showed greater plasticity than pure sucrose or transformed sucrose. The data appears to support the hypothesis of beneficial crystal poisoning in producing a plasticized excipient with enhanced physico-mechanical characteristics.

Use Characteristics

It is widely known that another Principle Excipient with broad-spectrum functionality, microcrystalline cellulose NF has a very high compactibility and is probably the single most useful principal excipient. In past studies, various workers have demonstrated the beneficial characteristics of microcrystalline cellulose, some of which are listed in table 2.

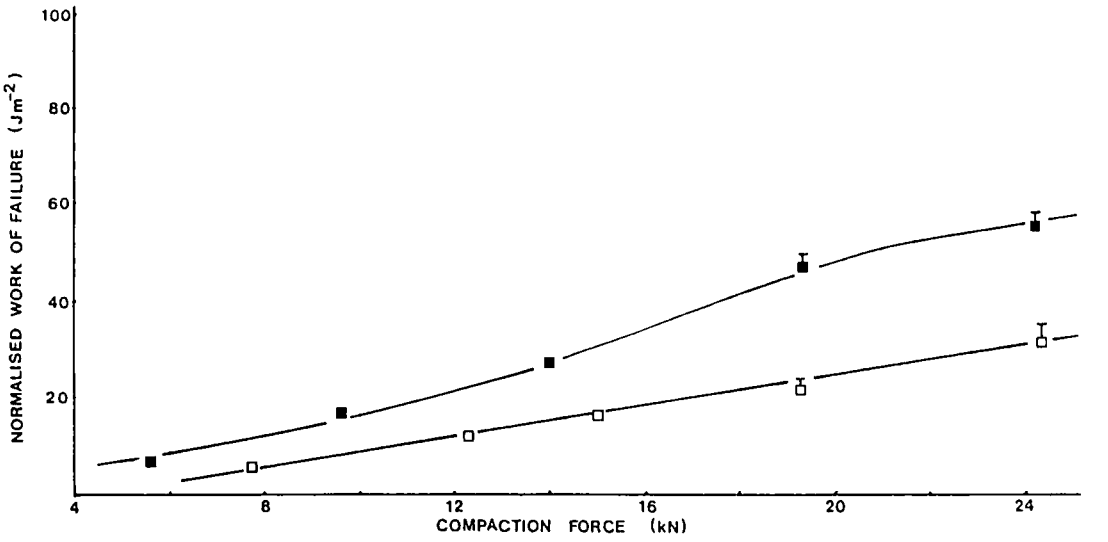


Figure 15. Influence of the impurities in sucrose crystals and compaction force on the normalized work of failure of tablets. ■ Pure transformed sucrose compactibility is shown □ for comparison.

However, it has been found that many of the beneficial characteristics, especially those related to tablet strength, can be lost during subsequent processing, whether this be in a direct compression formulation caused by blending with lubricant powder (fig 16) or in multi-operation processing, caused by aqueous granulation (fig 17).

Conservation of Compactibility

We have found that the beneficial characteristics of microcrystalline cellulose can be conserved during either direct compression or multi-operation processing, by selection of appropriate formulation and process criteria.

(a) Direct Compression Processing

(i) Process Changes

The compactibility of MCC can be conserved by judicious selection of process conditions in order to minimize the exposure of clean MCC particle surfaces to bond-weakening adsorbed layers or adhered particles. It has been found that:

- Reduction of mixing times

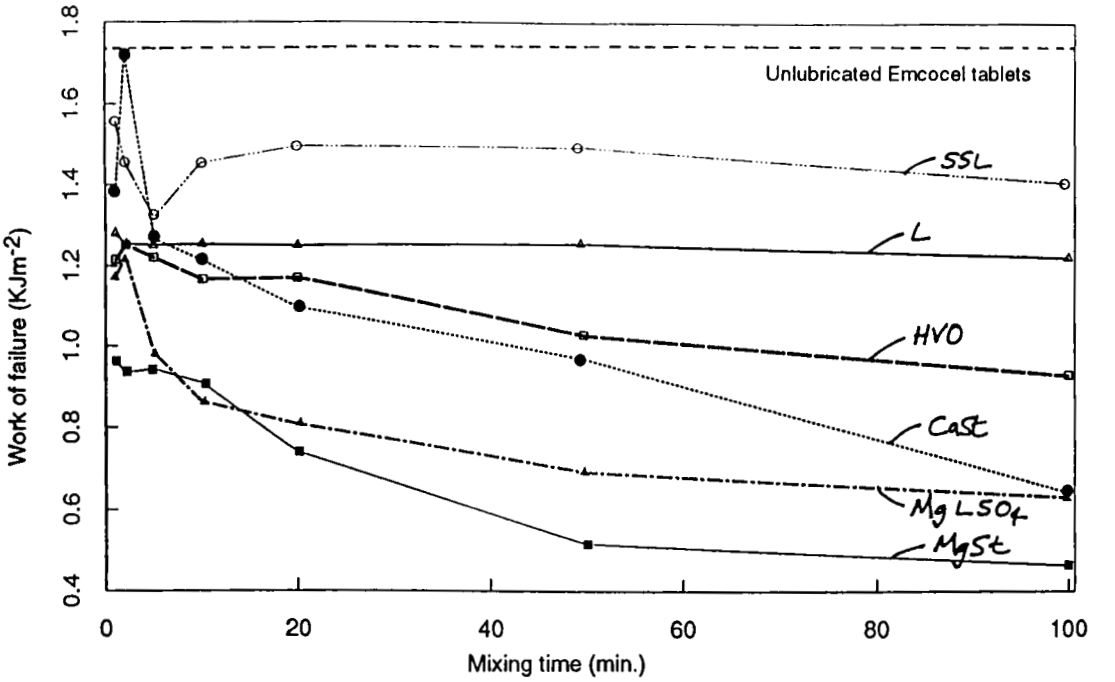


Figure 16. Effect of different lubricants on the toughness of tablets containing microcrystalline cellulose powder after different mixing times . Key: SSL = sodium stearoyl lactylate, L = L-Leucine, HVO = Lubritab, CaSt = Calcium stearate, MgLSO4 = Magnesium lauryl sulphate, MgSt = Magnesium stearate.

- Use of low-shear blenders
- Introduction of a 2-stage blending process to minimize exposure time of MCC to other components.
- Extrinsic lubrication system

All help to conserve the compactibility of MCC.

(ii) Formulation Changes

Similarly, the compactibility of microcrystalline cellulose can be retained, and in some cases, restored by appropriate selection of formulation additives.

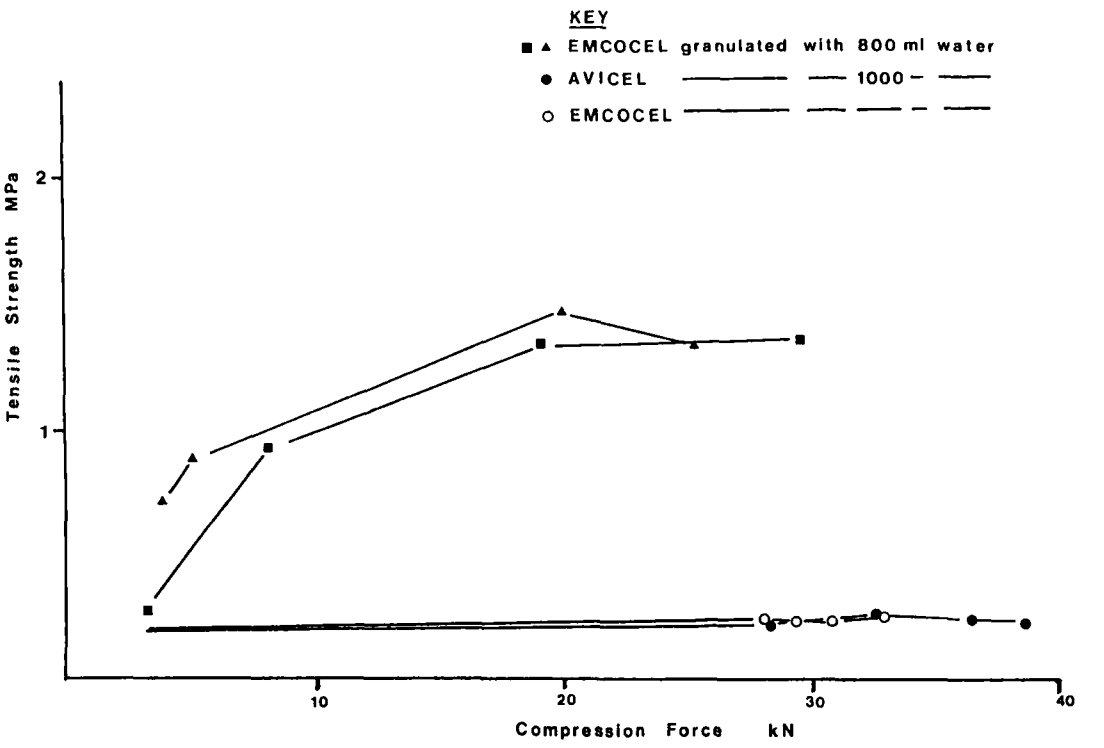


Figure 17. Effect of granulating microcrystalline cellulose with different volumes of water on tablet strength profiles.

Again, the objective is to conserve the strong-bond forming potential of pure MCC surfaces. This has found to be possible by

- Reduction of lubricant levels
- Protection of MCC by coating with colloidal silicon dioxide (fig 18)
- Production of a pre-blend of magnesium stearate and colloidal silicon dioxide (fig 18) without loss of lubricity
- Removal of magnesium stearate from the formulation and substitution with an alternative (fig 19)

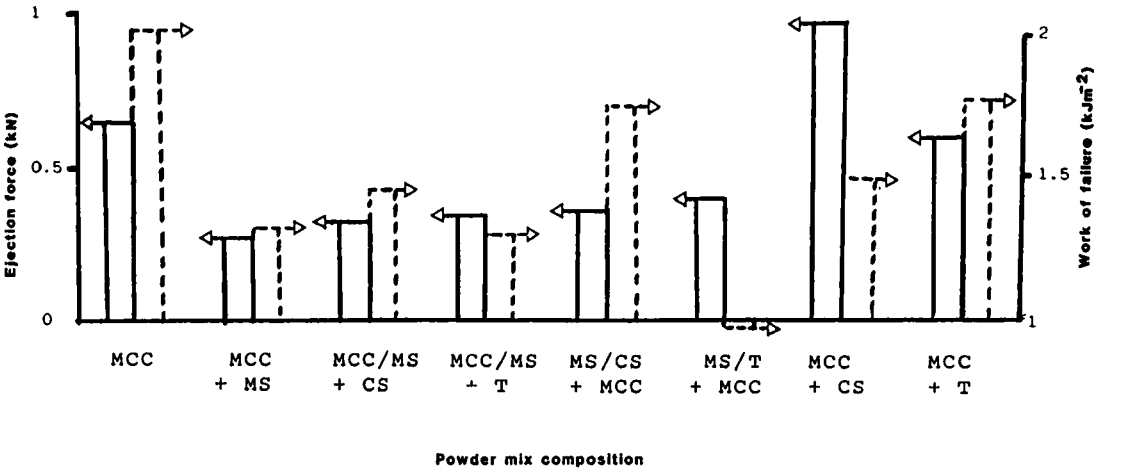


Figure 18. Summary of the relationship between tablet ejection force, work of failure values and powder mix compositions. Key: MS = Magnesium stearate, CS = Colloidal silica, MCC = Microcrystalline cellulose.

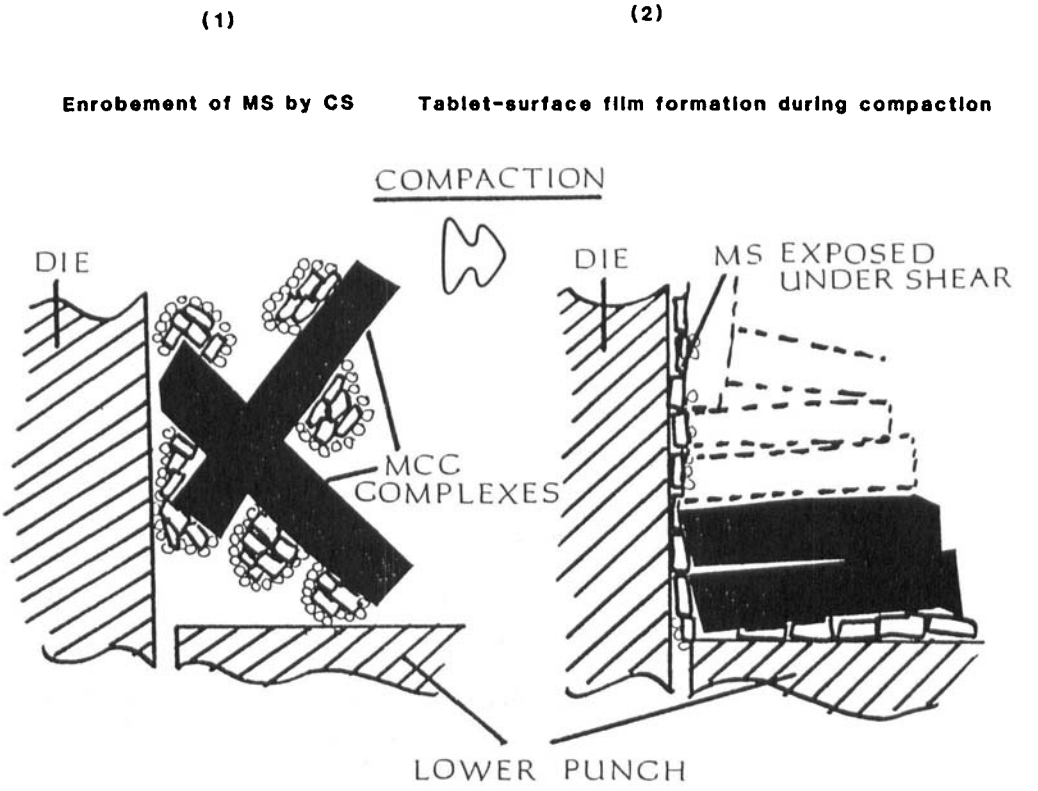


Figure 18 continued. Compaction conservation mechanism of Colloidal Silica.

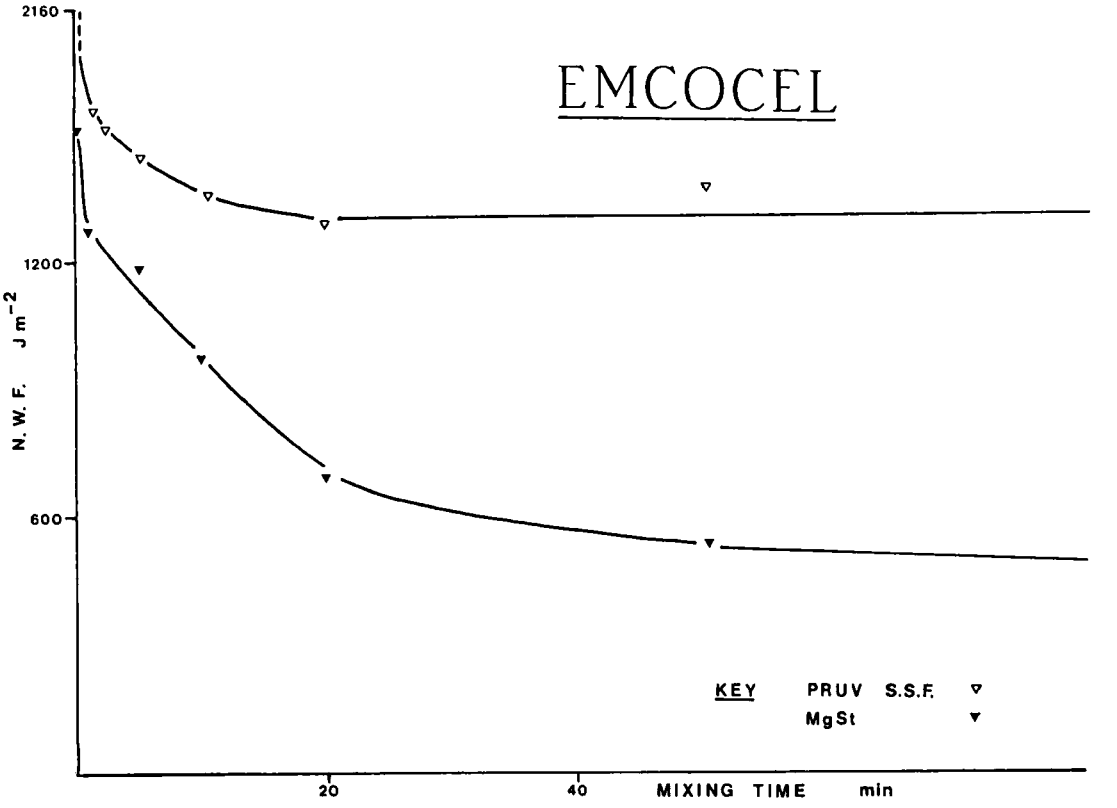


Figure 19. Conservation of microcrystalline cellulose compactibility by substitution with another lubricant.

(b) Multi-Operation Processing

(i) Formulation Changes

We have found that MCC granule compactibility varied with the level of water used during wet massing (fig 20). The compactibility decreased with an increase in water concentration between 26.8% and 41.2% w/w. The granulation water level resulting in minimum compactibility occurred at approximately 40% (which was less than the water level giving maximum bulk density and minimum friability). This supported the theory that the surface characteristics manifested in bulk properties vary independently of and may be mechanistically different from internal structural characteristics.

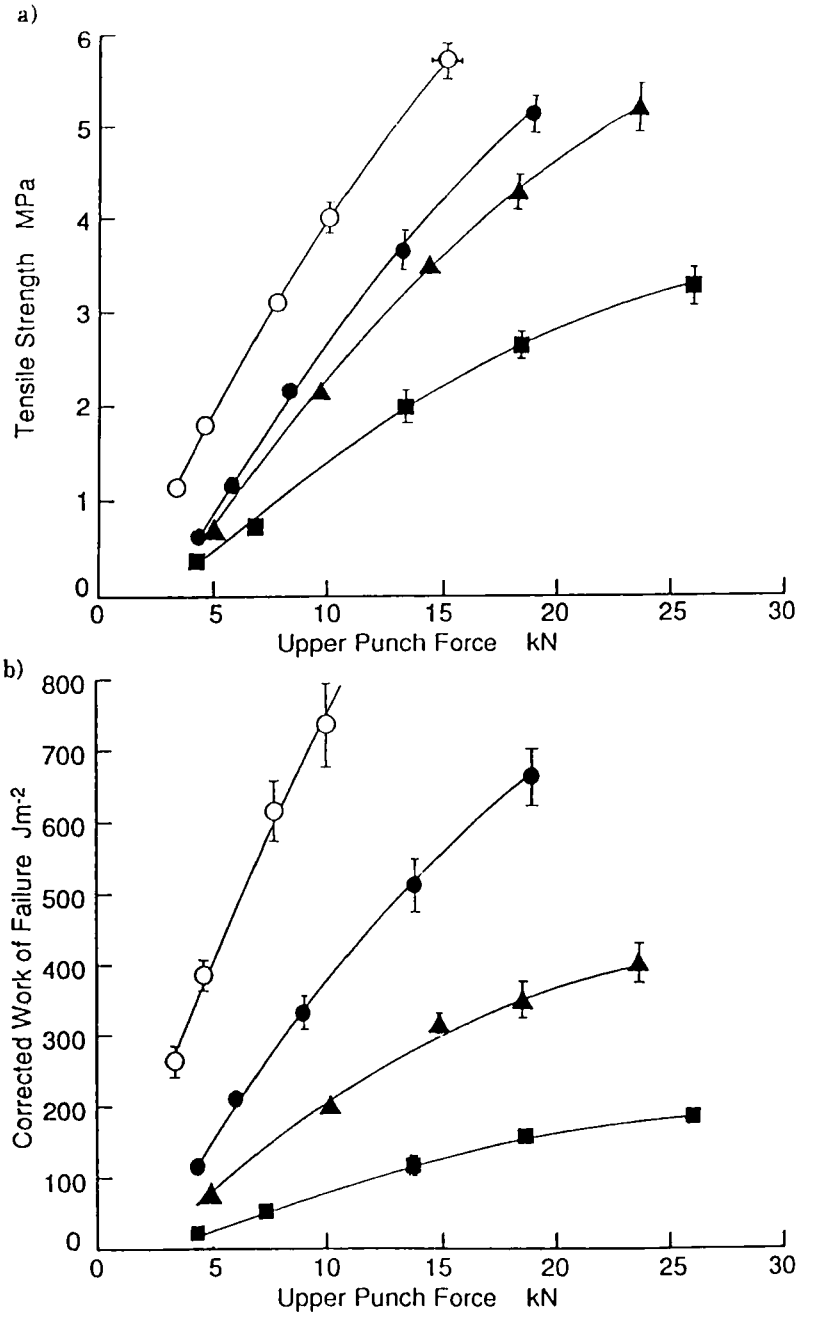
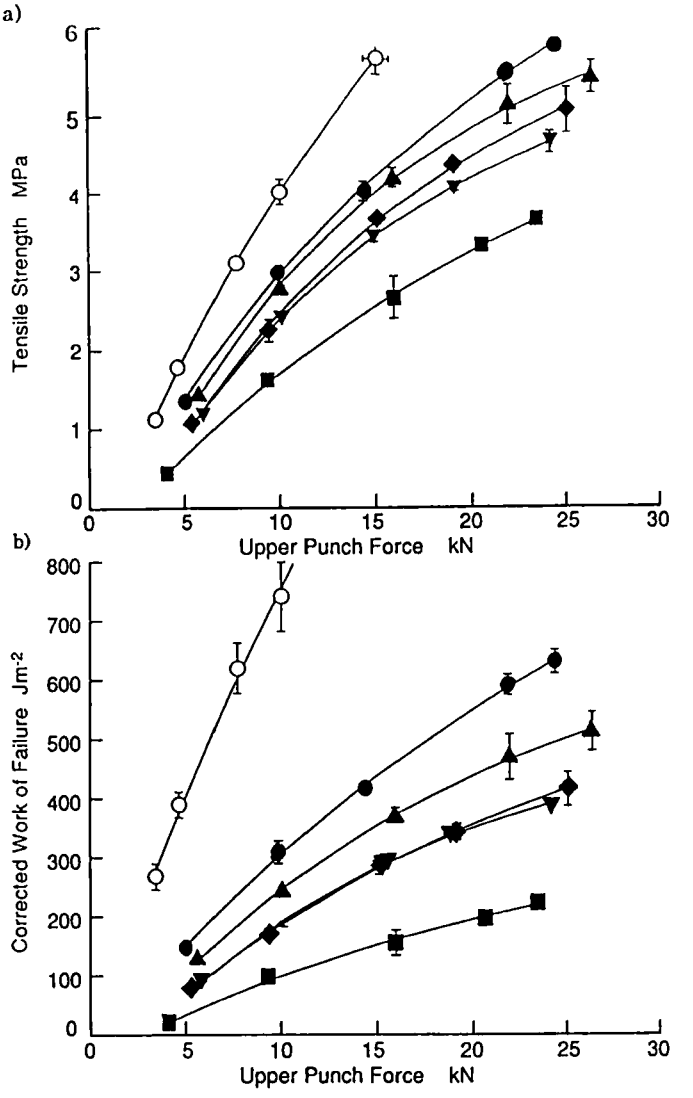
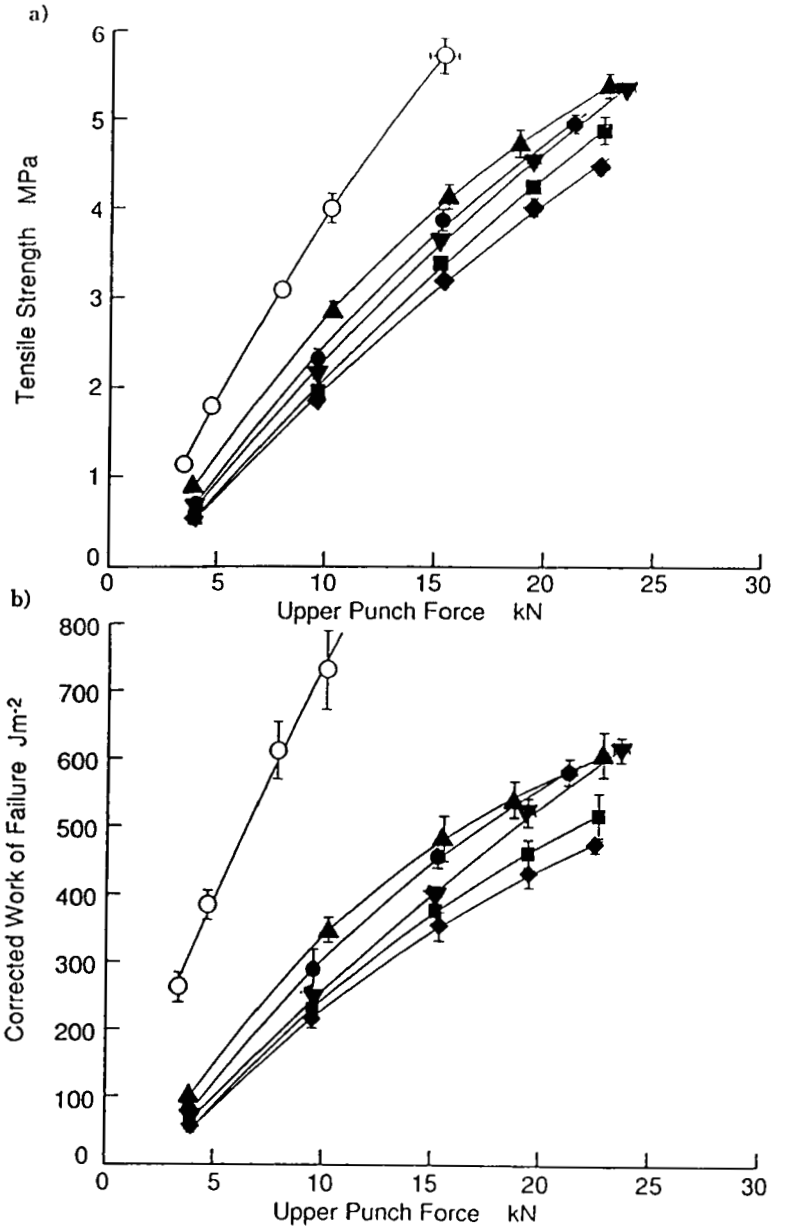


Figure 20. Relationship between (a) tensile strength, and (b) corrected work of failure, and compaction force for tablets produced from granules prepared using different concentrations of water. Key: ○ Ungranulated microcrystalline cellulose. Granules prepared from: ● 26.8%w/w water; ▲ 31.85w/w water ; ■ 41.25w/w water.



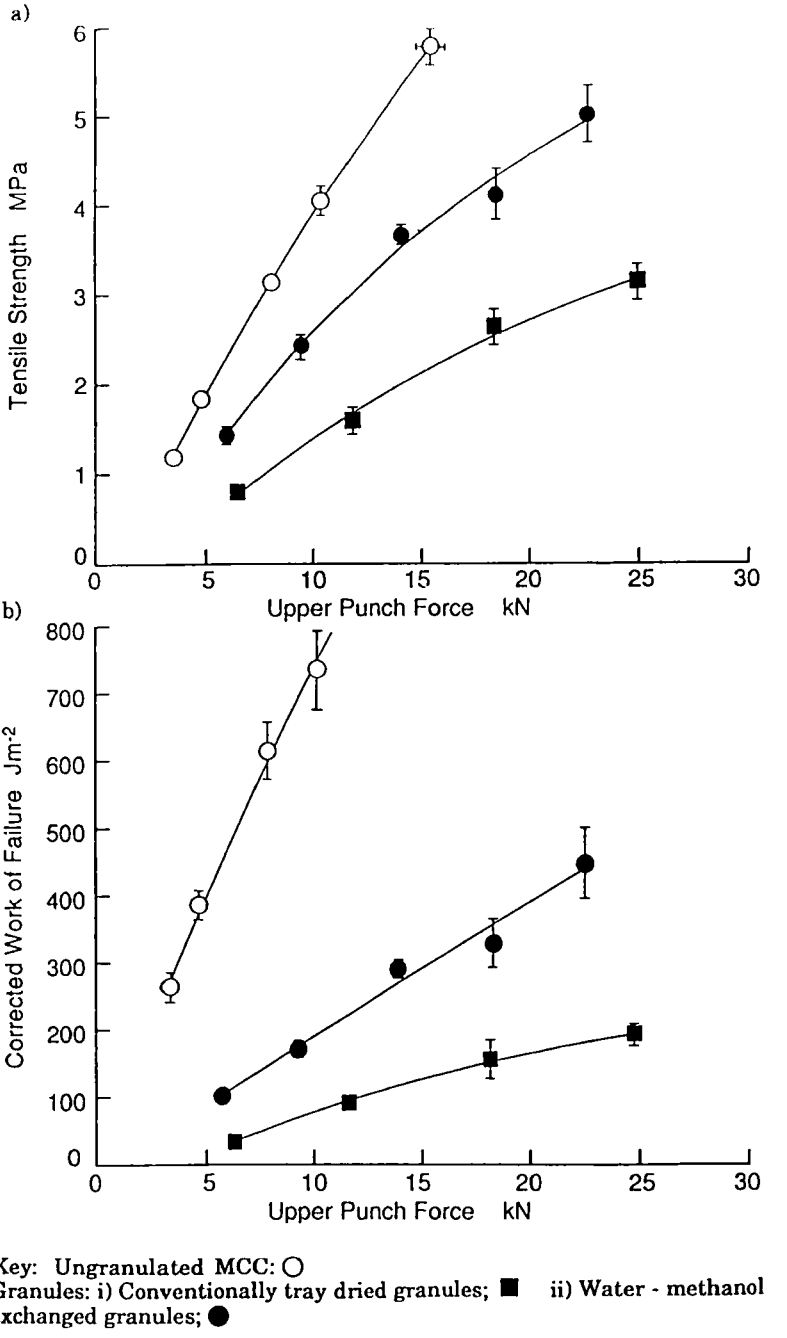
○ Ungranulated MCC.
● Granulation speed; approx. 700 rev min-1 (setting 3), wet massing time; 3 mins., dried immediately following preparation.
▲ Granulation speed; approx. 1000 rev min-1 (setting 5), wet massing time; 3 mins., dried immediately following preparation.
◆ Granulation speed; approx. 1450 rev min-1 (setting 8), wet massing time; 1.5 mins., dried immediately following preparation.
■ Granulation speed; approx. 1450 rev min-1 (setting 8), wet massing time; 3 mins., dried immediately following preparation.
▼ Granulation speed; approx. 1000 rev min-1 (setting 5), wet massing time; 3 mins., stored 20 hours before drying.

Figure 21. Relationship between (a) tensile strength, and (b) corrected work of failure, and compaction force for tablets produced from granules prepared using different wet massing conditions.



Key: Ungranulated MCC: ○
Granules: i) Microwave - vacuum dried ('high' process type); ▲ ii) Freeze dried; ● iii) Fluidised bed dried; ▼ iv) Tray dried until 'just dry'; ■ v) Vacuum dried; ◆

Figure 22. Relationship between (a) tensile strength, and (b) corrected work of failure, and compaction force for tablets produced from granules dried using various techniques.



Key: Ungranulated MCC: ○
Granules: i) Conventionally tray dried granules; ■ ii) Water - methanol exchanged granules; ●

Figure 23. Relationship between (a) tensile strength, and (b) corrected work of failure, and compaction force for tablets produced using aqueous granulation compared with those prepared using a water-methanol granulation.

The data gives a clear indication that in order to conserve maximum compressibility, the exposure of MCC to higher concentrations of water should be avoided. Additionally, there should be benefit in minimizing exposure times.

(ii) The compactibility of MCC can be conserved by judicious selection of process conditions in order to further minimize the exposure of MCC to water. It has been found that:

- Reduction of granulation time (fig 21)
- Reduction of granulation speed (fig 21)
- Drying using a fluidized bed drying method [52] (fig 22)
- Selection of a microwave vacuum drying method also helps to conserve the disintegration characteristics of MCC tablets (table 3)
- Substitution of alcohol for water in the granulating fluid (fig 23)

SUMMARY

Since the first excipients were described for use in Direct Compression Technology and Multi-Operation Processing, advances have been made in characterization, modification and conservation of excipient properties.

Current research is focused on providing a better understanding of the relationship between fundamental particle properties and tablet compressibility, with the aims of enabling further improvements in excipients to continue, so as to provide increased broad-spectrum functionality and reduced process sensitivity.

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