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The improved compaction properties of mannitol after a moisture-induced polymorphic transition

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Abstract

We have previously shown that by exposing one form of mannitol to high relative humidity, a moisture-induced polymorphic transition of mannitol with a concurrent change in particle morphology occurs [Int. J. Pharm. 247 (2002) 69]. In this paper, we propose that if these changes occur during a wet-granulation procedure, it may be possible to make bring about an in situ size-reduction of mannitol with compaction property enhancement. Powder X-ray diffraction and scanning electron microscopy confirmed that a polymorphic transition (the δ form forming the β form) had occurred on wet-granulation, and that a concomitant morphology change resulted in an agglomerate consisting of filament-like fine primary crystals (δ-granule). The aim of present study was to evaluate the compression properties of this agglomerate. The compact compressed with δ-granules possessed a tensile strength 1.5 times higher than other mannitol samples. Heckel analysis indicated that the mannitol compression process proceeded by deformation without fragmentation and was thus particle size dependent. The δ-granule showed enhanced plastic deformability, due to its unique particle structure. Because the intrinsic compression properties of the polymorphs were similar, the primary particle size and specific surface area of mannitol were indicated to be the major contributing factors for the improved compaction behaviour, rather than the polymorphic transition. When using the δ-granule as an excipient for a tablet formulation containing a high amount of phenylpropanolamine hydrochloride (PPA) as a poorly compactable model drug, excellent tablets could be prepared without capping, whereas conventional mannitol produced capped tablets.

Keywords: Mannitol polymorphs; Polymorphic transition; Compaction; Compression; Plastic deformation; Polymorphism

1. Introduction

Tablets are the most commonly used oral solid dosage form with advantages for both the formulator and patient. It is well known that changes in the pharmaceutical properties of drugs and excipients are often induced during pharmaceutical processing and formulation procedures, and that such property changes affect compression characteristics. The characterisation and monitoring of such changes is becoming increasingly important to regulatory bodies. However, through the modification of these properties (York, 1983), including particle size, specific surface area (McKenna and McCafferty, 1982; Morishima et al., 1994), crystallinity, polymorph (Summers et al., 1977; Ibrahim et al., 1977; Suihko et al., 2001), and crystal habit (Staniforth et al., 1981; Kawashima et al., 1982; Marshall and York, 1991; Garekani et al.,

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1999, 2000; Martino et al., 2001), it is possible to improve compression properties.

Mannitol is a commonly used non-hygroscopic tabletting excipient with application in both direct compression and wet-granulation methods (Kibbe, 2000). In an attempt to improve the tabletting properties of mannitol, fused mannitol has been employed (Kanig, 1964). Improved compaction was noted which was attributed to a decrease in mannitol crystallinity resulting from a rapid solidification. However, with storage, a gradual increase in the crystallinity of mannitol caused this benefit to diminish.

Mannitol has several solid-state modifications and the compression properties of polymorphs of mannitol were analysed and reported by Debord et al. (1987) and Burger et al. (2000). Burger et al. concluded that δ form of mannitol should have the best tabletting behaviour due to lower elastic recovery and lower die-wall friction, as compared with the other polymorphs. They noted that compression alone produced no indication of a polymorphic transition.

Generally, where crystals can be finely ground to increase the number of binding sites, better compaction results. However, in the case of mannitol, merely grinding it into a fine powder increases die-wall friction on compression, and also causes increased risk of problems on handling such as high dust levels and poor fluidity. Granular and spray dried forms of mannitol are available on the market to improve both compressibility and fluidity, however, to obtain these products multiple complex procedures are required.

We have previously shown that by exposing one form of mannitol to high relative humidity, a moisture-induced polymorphic transition of mannitol with a concurrent change in particle morphology occurs (Yoshinari et al., 2002). The change in morphology on conversion of δ form to β form of mannitol involved size-reduction to yield aggregates of filament-like fine crystalline particles. In this paper we propose that if these changes occur during a wet-granulation procedure, it may be possible to make bring about an in situ size-reduction of mannitol with compaction property enhancement. The aims of the present study were thus to evaluate the compression properties of the δ form of mannitol after wet granulation and drying and to optimise the process.

2. Materials and methods

2.1. Materials

The polymorphs of mannitol were classified and follow the nomenclature of Walter-Lévy (1968). The β form of mannitol (β-crystal) was the commercial product provided from Merck (Darmstadt, Germany) without further purification. The δ form of mannitol (δ-crystal) was obtained by recrystallisation from dilute aqueous acetone solution at below 0 °C (Yoshinari et al., 2002). A sieved fraction of β-crystal and δ-crystal were used to achieve approximate equivalent particle size. The mean particle sizes were 22.9 and 28.1 μm, respectively. Phenylpropanolamine hydrochloride (PPA) was used as a model drug, which has poor compaction properties, and was purchased from Alps Pharmaceutical (Gifu, Japan). The other chemicals were of reagent grade.

2.2. Wet granulation of mannitol alone

The granulation was carried out using a mortar and pestle. β-Crystal and δ-crystal were kneaded with purified water at concentrations of 5, 10, 15 and 25% (w/w). Samples were then stored under ambient conditions for known times (0, 2, 3, 4 and 72 h) before vacuum drying. The specific surface area of the dried samples was measured by BET method (Flow Sorb 2300, Micrometritics, Norcross, GE) at three levels of % nitrogen (5, 10 and 30% v/v) mixed with helium.

2.3. Static compaction procedure

A compaction procedure was performed using the compaction test apparatus (Autograph AG1 5 kN, Shimadzu, Kyoto, Japan), fitted with a 10.0 mm diameter flat face punch. The die wall was cleaned with acetone and pre-lubricated with magnesium stearate before each compression. Four hundred milligrams of samples were hand filled into the die. Compression and decompression was operated at 10 mm/min and the volume changes against compression force were recorded. The compaction behaviour of various samples of mannitol was evaluated by means of tensile strength measurements of the compacts. The compact tensile strength (Ts) was calculated by the following

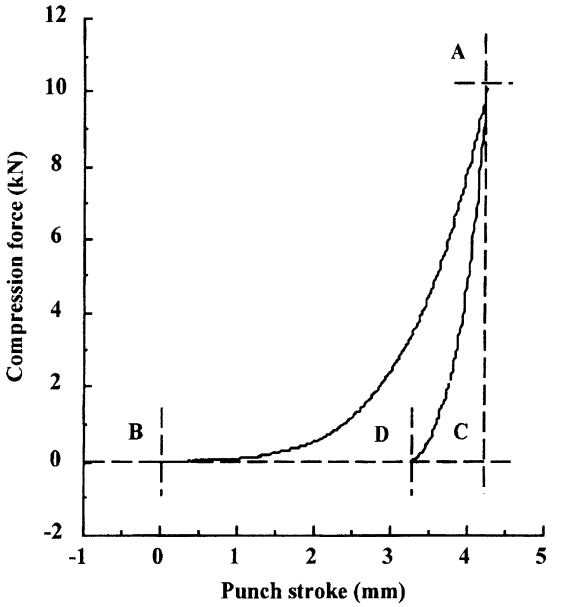

Fig. 1. Representative curve of punch stroke against compression force for δ-crystal obtained at compression speed of 10 mm/min.

equation (Fell and Newton, 1970):

$$\mathrm{Ts} = \frac{2F}{\pi DT}$$

where F is the compact hardness (N), D and T are the diameter and thickness of the compacts (m), respectively.

2.4. Measurement of elastic and plastic energy

The typical punch stroke against upper punch force curve was illustrated in Fig. 1, where B is punch stroke when punch force is zero, C is punch stroke when punch force is maximum (A), D is punch stroke after decompression when punch force is zero again. The area of ABC shows the gross energy, and the area of ABD and ADC is plastic energy and elastic energy, respectively. These areas were calculated for the samples compacted.

2.5. Heckel analysis of compaction data

The thickness of the compact during the single compaction event was plotted as a function of the compression pressure applied by upper punch. The obtained data was analysed by following equation (Heckel, 1961a,b).

$$\ln\left(\frac{1}{1-D}\right) = kP + A$$

where D is the relative density, the ratio of compact density, at an applied pressure P, to true density of powder, and k and A are constants. Value of k and A were obtained from liner portion of the plot, over a range of compression pressures from 20 to 50 MPa. The reciprocal of k is the yield pressure, and the total densification of powder bed after particle rearrangement, D_A, was calculated from the extrapolated intercept on axis (A) and D_0 is the initial densification after filling of die, and D_B is calculated by subtracting D_0 from D_A.

2.6. Tabletting by rotary press machine

2.6.1. Direct compression system

δ-Crystal or β-crystal was granulated with purified water in an agitation granulator (Vertical granulator-10, Powrex, Osaka, Japan). The wet masses were dried at 40 °C for 16 h in vacuum, and were sieved with a screen mill (screen size: 1.5 mm diameter, Power mill, Showa Kagaku Kikai, Osaka, Japan). The sieved granules were mixed with PPA and magnesium stearate using a diffusion mixer (Tumbler mixer, Showa Kagaku Kikai). The mixed granules were then subjected to the tabletting procedure outlined below. The obtained tablets were named Tablet-D(δ) and Tablet-D(β), respectively and the target composition formula was mannitol 709.2 g, PPA 78.8 g, magnesium stearate 12.0 g.

2.6.2. Wet-granulation system

To the same composition as in Section 2.6.1., δ-crystal or β-crystal and PPA were mixed, and granulated with purified water in agitation granulator (Vertical granulator-10). The wet masses were dried at 40 °C for 16 h in vacuum, and were sieved with a screen mill (screen size: 1.5 mm diameter, Power mill). The sieved granules were mixed with magnesium stearate by diffusion mixer (Tumbler mixer). The mixed granules were subjected to the tabletting procedure outlined below. The obtained tablets were named Tablet-W(δ) and Tablet-W(β), respectively.

2.6.3. Tabletting procedure

Tabletting was carried out using a rotary press machine (Correct 19K, Kikusui, Kyoto, Japan), fitted with 8.0 mm diameter flat face punches. Nineteen tablets, each 180 mg, at one revolution were prepared at a rotary speed of 30 rpm.

2.7. Analytical method

2.7.1. Scanning electron microscope

Electron micrographs of samples were obtained using a S-2300 (Hitachi, Tokyo, Japan) scanning electron microscope (SEM). The specimens were mounted on a metal stub with double-sided adhesive tapes and coated with gold under vacuum using ion sputter (E101, Hitachi, Tokyo, Japan) prior to observation. The operating conditions of scanning electron microscopy are followed: acceleration voltage: 25 kV, emission current: 80–100 μA, working distance: 20 mm.

2.8. Powder X-ray diffraction

A RINT 1100 (Rigaku, Tokyo, Japan) X-ray diffractometer was used to obtain powder X-ray diffraction patterns, which was equipped with Cu Kα source operating at a tube load of 40 kV and 40 mA. The divergence slit size was 0.6 mm, the receiving slit 0.3 mm. Data were collected between 3 and 40° of 2θ in a step mode using a step size of 0.6° of 2θ.

3. Results and discussion

3.1. Compaction properties

δ-Crystal or β-crystal was vacuum dried immediately after kneading in the mortar with purified water (25% w/w against mannitol weight), and named δ-granule and β-granule, respectively. Powder X-ray diffraction patterns of the obtained samples were compared, as shown in Fig. 2. The data confirm that a polymorphic conversion had occurred with the δ form forming the β form during the wet-granulation procedure. Powder X-ray diffraction data indicated that no polymorphic change had occurred on formation of β-granule. From the scanning electron micrograph presented in Fig. 3 it can be seen that the δ-granules possess a morphology which is very different to the original crystals prior to granulation. δ-Granules clearly consist of aggregates of many small primary crystals. By granulation, the specific surface area increased from 0.4 m^2/g (δ-crystal) to 3.4 m^2/g (δ-granule). We have previously shown that

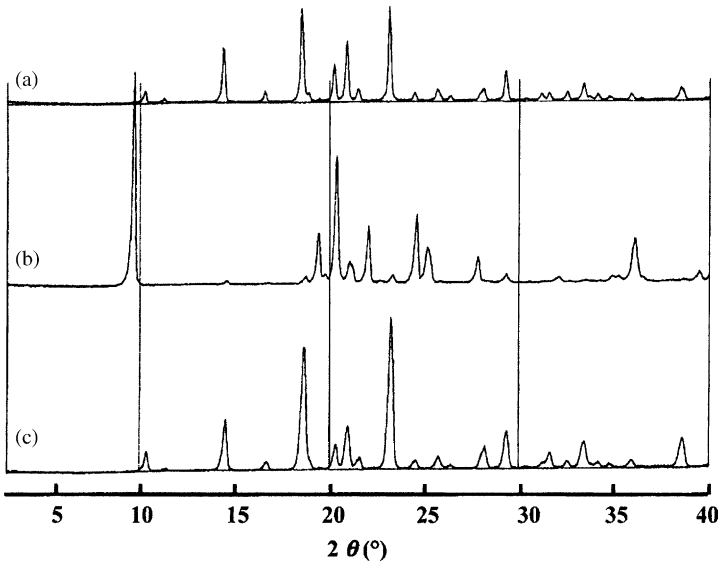

Fig. 2. Powder X-ray diffraction patterns of mannitol: (a) δ-crystal of mannitol after granulation and vacuum drying, (b) δ-crystal before granulation and (c) β-crystal.

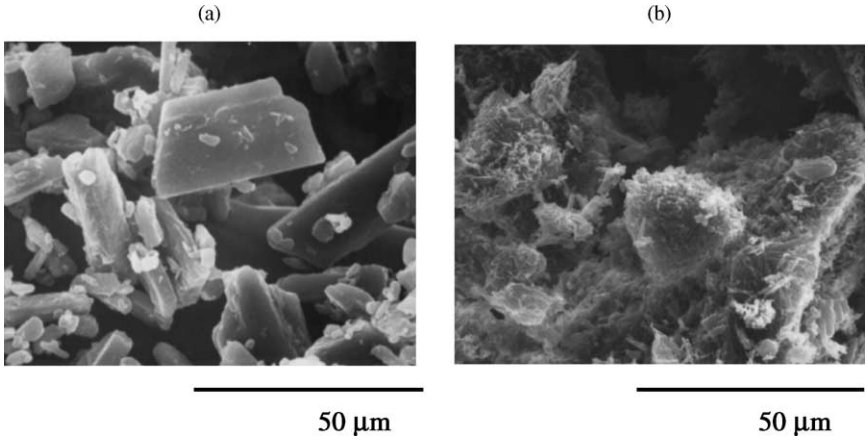

Fig. 3. Scanning electron micrographs of δ-crystal: (a) before and (b) after granulation.

water vapour at high relative humidity (97% RH) is sufficient to bring about this polymorphic transition with a consequent increase in surface area (Yoshinari et al., 2002).

The compaction properties of the native polymorphic forms and of their granulates were assessed using a single punch instrument and the tensile strength of compacts compressed at different compression pressures were recorded. From the data presented in Fig. 4, it can be seen that under static compression conditions, the tensile strength of all samples increased with increased compression pressure. Burger et al. (2000) reported that the crystalline δ form of mannitol should possess superior compaction properties compared to

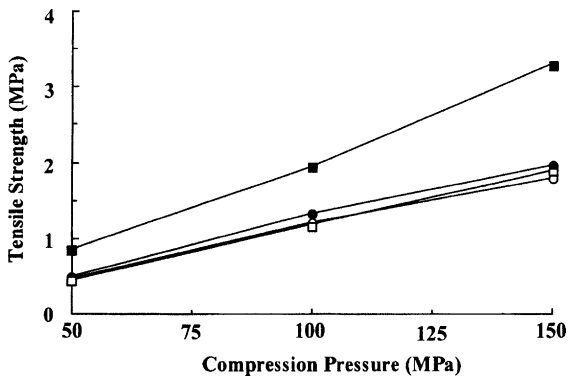

Fig. 4. Tensile strength of various mannitol samples after slow compression speed (10 mm/min): (○) β-crystal, (□) δ-crystal, (●) β-granule, (■) δ-granule.

the β form. The results from the current study indicate that there is no significant difference between δ-crystal and β-crystal regarding the tensile strength of their compacts. It is possible that other factors such as compression velocity or crystal habit or other micromeritic properties affects compaction in addition to the crystal structure (polymorphic) difference. When comparing the tensile strength of resultant compacts prepared from either β-crystal or β-granule, no significant difference was observed. However, granulation may provide benefits such as improved ease of die filling and the avoidance of entrapped air, particularly during the production of tablets on a rotary press. On the other hand, the tensile strength of the compact compressed with δ-granule was 1.5 times higher than any other sample for the range of compression pressures tested. We have shown that δ-granule is made up of aggregates of small primary particles of the β form of mannitol. Furthermore, the results show that the compact properties of similarly sized crystals of β and δ forms have near equivalent tensile strength. It follows that the increase in the tensile strength of compacts prepared from δ-granule must be due to other factors, and not due to the crystal polymorph or a mere granulation effect (Leuenberger, 1982; Alderborn et al., 1987).

3.2. Compressibility

The relative volume changes during the early stage (0–100 MPa) of the compression event were recorded

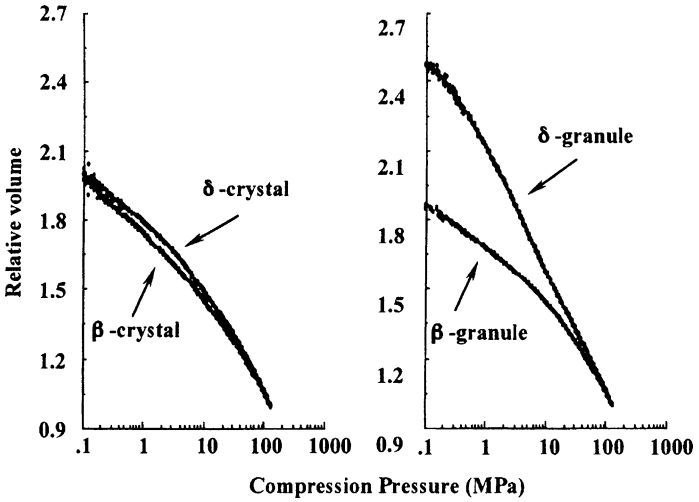

Fig. 5. Relationship between relative volume and compression pressure of mannitol samples.

for each of the samples and the results shown in Fig. 5. In the case of δ-granule, the dramatic difference observed was attributed to the unique particle structure and the consolidation process of its primary particles. The relationship between relative density and compaction pressure during the compression procedure was analysed using the Heckel equation and the plots of this analysis for the four samples are shown in Fig. 6 and the obtained Heckel parameters are shown in Table 1. Hersey and Rees (1971) classified the profiles of Heckel plots according to two types. A type 1 relation is obtained for a powder that exhibits different initial bulk densities, depending on factors such as particle size. Densification occurs under pressure due to particle slippage or rearrangement, and subsequently by plastic deformation mainly. The two stages are represented by the initial curved portion followed by the parallel straight lines. For a type 2 materials, however, in which consolidation largely occurs by fragmentation, the initial structure

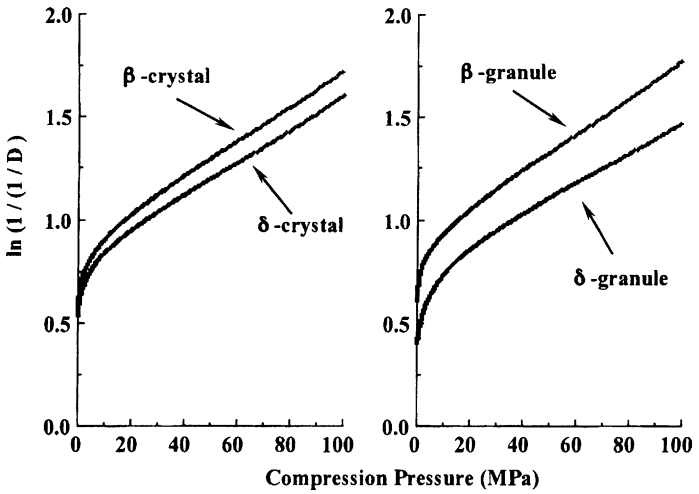

Fig. 6. Heckel plots for the mannitol samples.

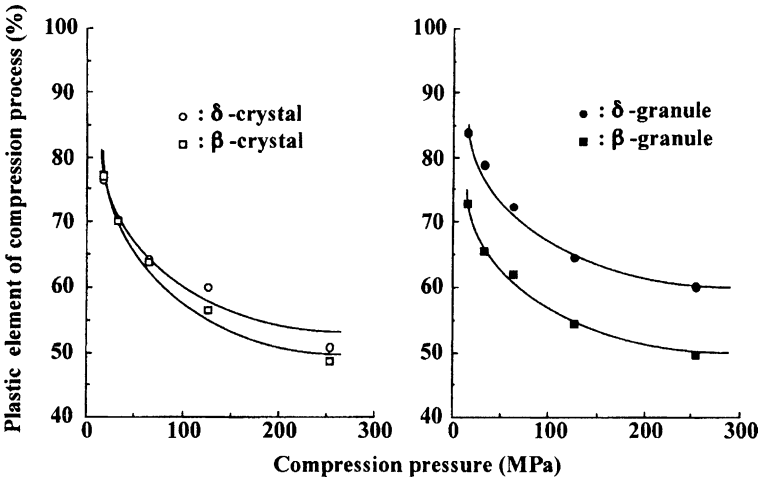

Fig. 7. Relationship between plastic energy during compression process and compression pressure of the mannitol samples.

Table 1
Heckel parameters of the mannitol samples

Sample	Yield pressure (MPa)	D_A	D_0	D_B
β-Crystal	62.1	0.642	0.497	0.145
δ-Crystal	66.0	0.623	0.485	0.138
β-Granule	62.1	0.646	0.518	0.128
δ-Granule	61.0	0.589	0.402	0.187

is progressively destroyed, so that above a certain pressure, coincident linear relations are obtained for all particle size fractions (Duberg and Nyström, 1982).

The results shown in Fig. 6 suggest that the Heckel plots of mannitol samples are typical of type 1 materials. This finding was further supported in that the yield pressures were approximately the same (Table 1). Therefore, like sodium chloride, mannitol compaction mainly proceeded by deformation without fragmentation of the primary particles and was thus sensitive to the primary particle size of the powder. McKenna and McCafferty (1982) and Morishima et al. (1994) reported that for such materials the tensile strength of compacts increases as the particle size decreases. The smaller crystals have more contact points between them, so even if the porosity of the compact

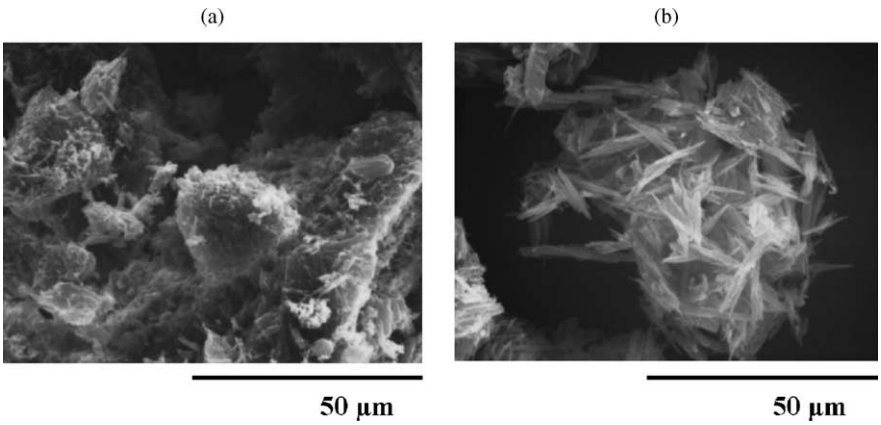

Fig. 8. Scanning electron micrographs showing the effect of drying rate on the primary crystal size after transition: (a) after drying (40 °C, 16 h), (b) after ambient storage for 5 days.

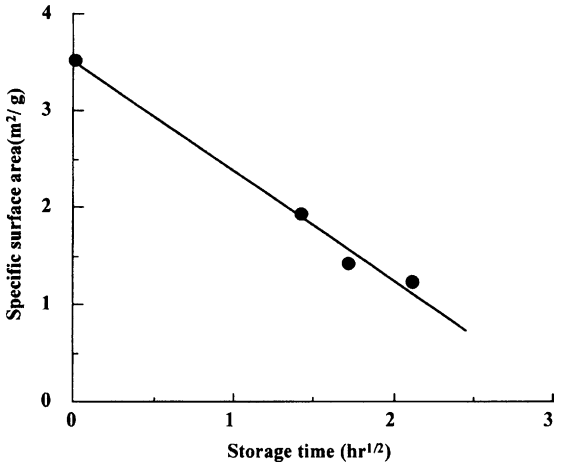

Fig. 9. Effect of storage time prior to vacuum drying on the specific surface area of the resultant granules.

is the same, smaller crystals can be compacted more firmly than larger crystals. Therefore, one of the possible reasons for the better compaction properties of δ-granule was its small primary crystal size. In order to further elucidate the deformation characteristics of the mannitol samples, the percentage plastic energy, the ratio of plastic energy against gross compression energy, was calculated (Fig. 7). The results indicate that δ-crystal was slightly superior regarding plastic energy (%) compared with β-crystal. This finding is consistent with the general rule of thumb that the metastable form has better plastic deformation characteristics than a stable form; the δ form of mannitol being the metastable form under these conditions. However, because of the small free energy difference between the two polymorphic forms, it seems that only a minor difference was detected in our studies. In the case of the granulates, the plastic energy (%) of δ-granule was the highest of all the samples tested and led to the conclusion that the superior compressibility of δ-granule was due in part to the better plastic deformation characteristics, which were once again attributed to its unique particle structure.

3.3. Effect of treatment conditions

The effect of storage time on the resultant specific surface area of the granules was evaluated using δ-crystal with purified water (25% w/w of the mannitol weight). The effect of the drying conditions on the morphological character of the product was evaluated using SEM. The SEM images shown in Fig. 8, clearly indicate that the drying process has a strong influence on the resultant surface area, in that the primary particle size is relatively large when slow drying is employed, such as leaving the granules under ambient conditions, and that the primary particle size of granules is decreased when relatively fast vacuum drying

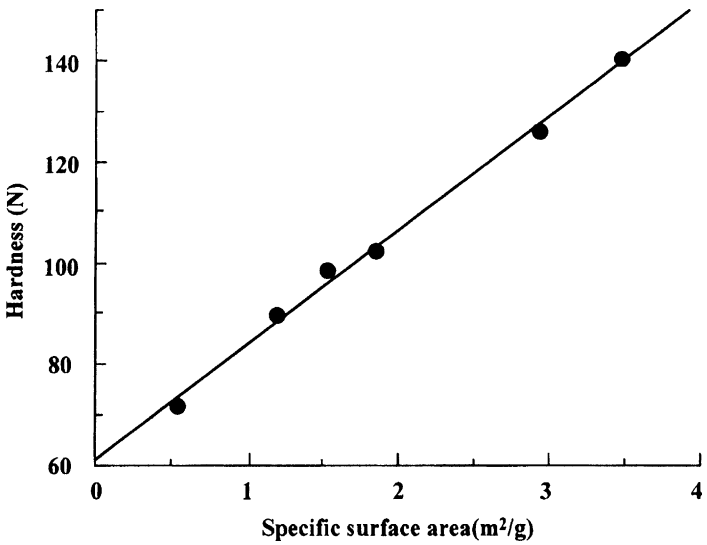

Fig. 10. Relationship between tablet hardness and pre-compression specific surface area of mannitol samples.

is used. A possible explanation of this phenomenon could be that during fast drying greater numbers of seed crystals of the β form are generated at the surface of the converting δ form. On slow drying, mannitol crystal growth in residual water was expected to be significant, and gave rise to larger primary particles. This mechanism is consistent with the finding of a linear relationship between the specific surface area of the resultant granules and the storage time of δ-granules after kneading, but before the commencement of vacuum drying (Fig. 9). Thus, the longer the time of contact with moisture before the commencement of drying, the lower the surface area and the greater the particle size. The increase in surface area had a beneficial effect upon compact properties as shown by the good correlation between the specific surface area and compact hardness after compression in a single punch instrument (Fig. 10). We conclude that for mannitol the particle size and specific surface area are likely to be the major contributing factors towards improved compaction behaviour, independent of which polymorphic form is employed.

The effect of varying the amount of water used in the granulation step on the homogeneity of the granules was evaluated using SEM. With an increase in the amount of added water, the SEM images in Fig. 11 show that a greater percentage of the δ-crystals transform to the more needle like β form. On the other hand, the primary crystal size of the resultant β particles is increased when water levels higher than 15% w/w were employed. For these reasons, for optimisation, it is important to consider the balance between product homogeneity and ease of drying when identifying a suitable mass of water.

3.4. Evaluation of tabletting properties by rotary press machine

Compact hardness and disintegration times, obtained from the direct compaction process (Section 2.6.1) are shown in Fig. 12. The data reveal that it was difficult to impart to Tablet-D(β) enough hardness for robust pharmaceutical handling. This is clear in that the hardness of Tablet-D(β) was still below 20 N even

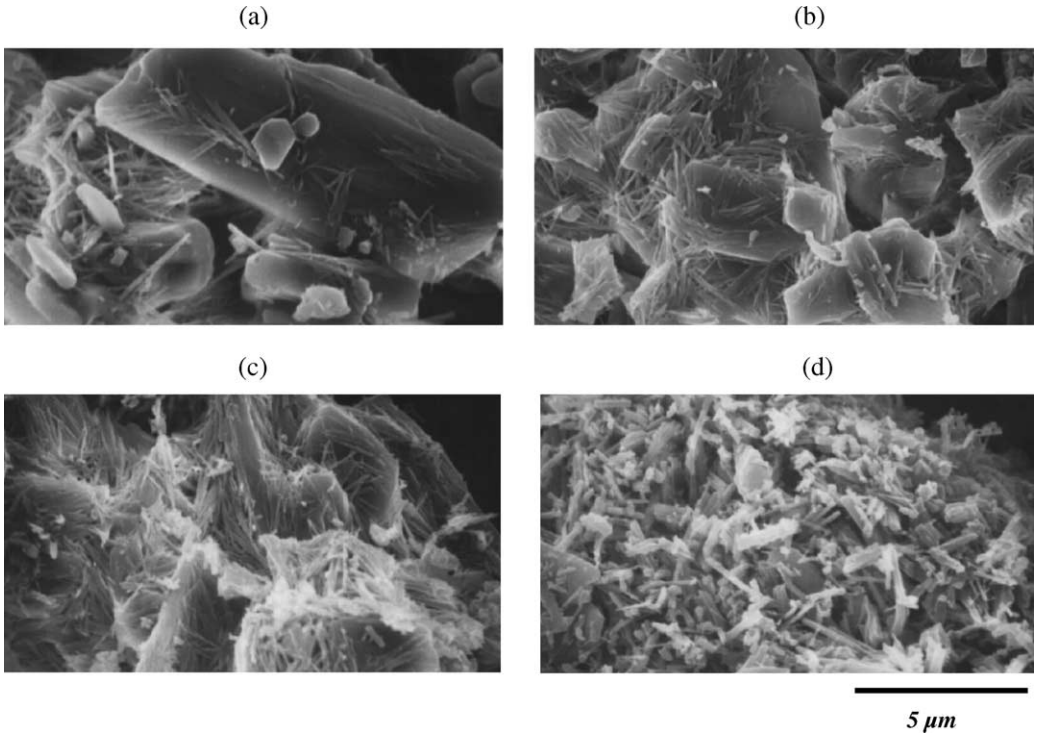

Fig. 11. Scanning electron micrographs of mannitol granules obtained after treating δ-crystal with various ratio of water: (a) 5% w/w, (b) 10% w/w, (c) 15% w/w and (d) 25% w/w.

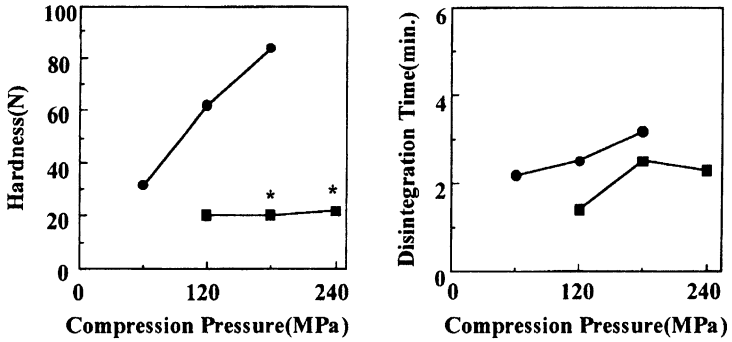

Fig. 12. Comparison of compact hardness and disintegration time between Tablet-D(δ) (●) and Tablet-D(β) (■). (*) Capping.

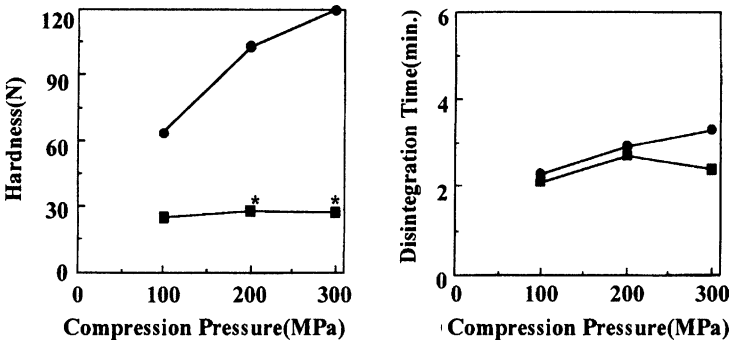

Fig. 13. Comparison of hardness and disintegration time between Tablet-W(δ) (●) and Tablet-W(β) (■). (*) Capping.

at a compression pressure 120 MPa. Additionally "capping" was observed when greater compression pressures were used. On the other hand, Tablet-D(δ) tablets possessed sufficient tablet hardness at as low a pressure of 60 MPa to facilitate ease of handling. This batch also displayed a linear increase of hardness with increase in compression pressure. Sugimori et al. (1990) analysed the "capping phenomenon" and concluded that "capping" was a destruction phenomenon caused by the residual die-wall pressure when the compact was ejected. They also suggested that it was important to decrease the elastic energy of the compaction process in order to impart enough compact strength at low compaction forces to overcome this destructive event and to avoid "capping" since the residual die-wall pressure increased with increased elastic energy of the compaction process. In agreement with this finding, it can be concluded that it is possible to decrease the elastic energy and to increase compact strength by using wet granulation of δ-crystal to produce an excipient. Disintegration time is also an important tablet property. Despite the fact that a relatively high tablet hardness was obtained in the case of Tablet-D(δ), the disintegration time increased only slightly as a function of compression pressure. When granulation of mannitol and PPA was simultaneously performed (wet-granulation process detailed in Section 2.6.2) similar results were obtained (Fig. 13). Capping was evident for Tablet-W(β) with resultant low tablet hardness. However, compacts Tablet-W(δ) were relatively hard yet disintegrated quickly and did not cap.

4. Conclusion

It is possible to improve the compaction and compression properties of mannitol by utilising a polymorphic transition induced by moisture on granulation. This improvement arose from the improved

morphology of the transformed crystals, which were shown to be aggregates of fine crystalline primary particles. This unique structure brought about a decrease in the elastic deformation and increase in particle binding sites in the compact and produced harder compacts with and without the presence of a model drug. These findings indicate that the wet granulated δ-crystal has potential as a direct compression/roller compaction excipient.

Acknowledgements

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