

# Energy/Temperature Diagram and Compression Behavior of the Polymorphs of D-Mannitol

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**ABSTRACT:** Three modifications of D-mannitol were produced and investigated: mod. I (mp 166.5°C, heat of fusion 53.5 kJ mol<sup>-1</sup>), mod. II (mp 166°C, heat of fusion 52.1 kJ mol<sup>-1</sup>), and mod. III (mp incongruent 150–158°C, heat of transition, III to I 0.2 kJ mol<sup>-1</sup>). The measured densities are 1.490 ± 0.000 g cm<sup>-3</sup> [95% confidence interval (CI)] for mod. I, 1.468 ± 0.002 g cm<sup>-3</sup> (95% CI) for mod. II, and 1.499 ± 0.004 g cm<sup>-3</sup> (95% CI) for mod. III. It was possible to relate the different modifications given in the literature to one of the three pure crystal forms or to mixtures of two or all three modifications. The thermodynamic relationship among the crystal forms is represented in a semi-schematic energy/temperature diagram. From these data we can conclude that mod. III is thermodynamically stable at absolute zero. It is enantiotropically related to mod. I and mod. II. FTIR and Raman spectra, differential scanning calorimetry curves, and X-ray powder patterns of these crystal forms are depicted for doubtless assignment in the future. The water uptake of the three modifications at 92% relative humidity and 25°C is less than 1%. The differences of the heat capacities and the heats of solution between mod. II and III are not significant, whereas mod. I shows small significant differences compared with the other modifications. In addition, compaction studies of these crystal forms were performed by means of an instrumented hydraulic press. The results show that mod. III should have the best tableting behavior under these conditions. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 89: 457–468, 2000

## INTRODUCTION

The acyclic sugar alcohol D-mannitol is an excipient commonly used in the pharmaceutical formulation of tablets or granulated powders for oral use. Several polymorphic forms have been described, but there are still some important questions (e.g., the order of thermodynamic stability of the modifications at ambient conditions). Different names of the crystal forms by several authors have left behind a chaotic picture in the literature

about which physicochemical properties belong to which crystal form. Table 1 gives an overview of the polymorphic modifications of D-mannitol presented in the literature and the assignment to the already known modifications given by the respective authors.

Groth<sup>1</sup> already quoted in 1910 that Schabus,<sup>2</sup> Zepharovich,<sup>3</sup> as well as Grailich and Lang,<sup>4</sup> have described two polymorphic modifications of D-mannitol. He mentioned the lattice parameters of the  $\alpha$ - and  $\beta$ -form. The latter is commonly known to be the commercial product. These descriptions were verified by Becker and Rose<sup>5</sup> in 1923, and they were specified by Marwick<sup>6</sup> in 1931. Rye and Sorum<sup>7</sup> presented in 1952 besides form  $\alpha$  and  $\beta$  a new form  $\gamma$ . This modification was obtained by rapid cooling of a solution of D-mannitol in ethanol/water 1:1. The  $\alpha'$ -form characterized by Mak<sup>8</sup> in 1963 for the first time is

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Dedicated to Prof. Dr. Maria Kuhnert-Brandstätter on the occasion of her birthday.

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**Table 1.** D-mannitol—Review of the Literature

Chronological	Designations and Allocation of the Modifications Worked On							
	$\alpha$	$\beta$	$\gamma$	$\delta$	$\alpha'$	$\kappa$	U	D
Groth <sup>1</sup>	$\alpha$	$\beta$						
Becker and Rose <sup>5</sup>		$\beta$						
Marwick <sup>6</sup>		$\beta$						
Rye and Sorum <sup>7</sup>	$\alpha$	$\beta$	$\gamma$					
Mak <sup>8</sup>					$\alpha'$			
Berman et al. <sup>9</sup>	$\alpha$	$\beta$						
Walter-Levy <sup>10</sup>	$\alpha$	$\beta$		$\delta$				
Kim et al. <sup>11</sup>			$\kappa$			$\kappa$		
Jones and Lee <sup>12</sup>	II	I		III				
Debord et al. <sup>13</sup>				$\alpha$			U	
Giron <sup>14</sup>	B	A		C			C	D
Grindley et al. <sup>15</sup>	$\kappa$	$\beta$	$\kappa$	$\alpha$	$\delta$			
Pitkänen et al. <sup>16</sup>	$\kappa$	$\alpha + \beta$		$\delta$				
Our results	II	I	I + II/III	III	III	I + II/III	I + II + III	I + II

mentioned in a review by Berman et al.<sup>9</sup> Walter-Levy<sup>10</sup> also described three modifications of D-mannitol in 1968. Besides the orthorhombic forms  $\alpha$  and  $\beta$ , a monoclinic form was investigated for the first time. This modification was called  $\delta$ -form. Berman et al.<sup>9</sup> published the X-ray crystal structure of the  $\beta$ -form and Kim et al.<sup>11</sup> presented the form  $\kappa$  in the same year. Kim et al. already assumed that their form K is identical with  $\gamma$ -form of Rye and Sorum.<sup>7</sup> In 1970 Jones and Lee<sup>12</sup> investigated D-mannitol by means of thermomicroscopy.<sup>12</sup> They confirmed the existence of three modifications and designated them according to their stability above room temperature as phase I (stable), phase II, and phase III. Debord et al.<sup>13</sup> investigated several commercial products of D-mannitol in 1987. Besides the forms  $\alpha$ ,  $\beta$ , and  $\delta$ , they crystallized a new modification that they could not assign to one of the known modifications and therefore designated this one as form U (unidentified). Debord et al. supposed that this modification might be the  $\gamma$ -form of Rye and Sorum.<sup>7</sup> In 1990 Giron<sup>14</sup> obtained four forms of D-mannitol, which were named A, B, C, and D. She equated form A to the  $\beta$ -form of Debord et al.,<sup>13</sup> B to the  $\alpha$ -form, C to the U-form and introduced form D as a new modification. In the same year Grindley et al.<sup>15</sup> worked on three modifications of D-mannitol. Their  $\alpha$ -form corresponds to the  $\alpha'$ -form of Mak<sup>8</sup> and Berman,<sup>9</sup> which they equated to the  $\delta$ -form of Walter-Levy.<sup>10</sup> The  $\beta$ -form corresponds to the  $\beta$ -forms of other authors and as the third modification they inserted  $\kappa$ , which they assumed is equal to the  $\kappa$  form of

Kim et al.,<sup>11</sup> to form  $\gamma$  of Rye and Sorum<sup>7</sup> and the  $\alpha$ -form of Walter-Levy.<sup>10</sup> Pitkänen et al.<sup>16</sup> published a thermoanalytical study on several crystal forms of D-mannitol. However, the results presented in this article were not critically discussed and only increase the confusion on the polymorphism of D-mannitol.

The aim of this work is to scrutinize the manifold and often contradictory descriptions of the various polymorphic modifications of D-mannitol given in the literature and to present their thermodynamic relationship by an energy/temperature diagram. Furthermore, compaction studies on the different crystal forms were performed to investigate which modification shows the best properties for direct tableting. It is not the intention of this work to expand these investigations to pseudo-polymorphic forms (e.g., a monohydrate), which was recently described in the literature.<sup>17–19</sup> This hydrate can be formed in the process of freeze drying. It converts to anhydrous crystal forms (mod. I and III) on gentle heating.<sup>19</sup>

## EXPERIMENTAL SECTION

### Materials and Solvents

The studies of D-mannitol [ $C_6H_{14}O_6$ ,  $M_r$  182.2] were carried out using the commercial product (mod. I) provided from Apoka ACM Handelsgesellschaft m.b.H. (Vienna, Austria). The chemical identity of the commercial product was checked by measuring the optical rotation. The substance meets the requirements according to the Euro-

pean Pharmacopoeia. Modification I is also obtained by crystallization from water and ethanol. Modification II is obtained by crystallization from 70% ethanol. D-mannitol, 100 g, is dissolved in 900 g of 70% ethanol and slowly cooled down to 20°C. Afterwards, the solution is kept at 4°C for 12 h. The received crystals are filtered and dried at 40°C.

The reproducible production of mod. III is difficult. The most successful procedure is to cool a hot saturated solution of D-mannitol in water rapidly to 0°C using an ice bath. As soon as crystals appear, this solution must be filtered rapidly. The filtered crystal form is to wash with acetone to displace the water and dry at reduced pressure (~10 mbar). The received crystals are stored in a desiccator. A second route to obtain mod. III is the precipitation of a solution of D-mannitol in water by acetone. As described previously, the received crystals must be dried immediately to prevent the transformation into mod. I. Furthermore, crystals of mod. III can be obtained by freeze-drying.<sup>20,21</sup> For freeze-drying experiments we used a laboratory freeze dryer Lyolab B (Inula, Vienna, Austria) equipped with a mechanical vacuum pump type Alcatel 2004 A (Annecy, France). Aqueous solutions of D-mannitol (about 500 mL, 10% w/v, dissolved in deionized water) were frozen by dropping it into a 1000-mL glass beaker filled with liquid nitrogen, providing a large surface of the frozen solution. Then, the glass beaker was placed directly in the vacuum chamber of the freeze-dryer, which was not precooled because the temperature of the freeze-dryer cannot be controlled by the instrument used. The excess liquid nitrogen ensured the solid state of the mannitol solution until full vacuum was achieved. Thereafter, a vacuum was maintained for 10 days in which a pressure of 0.02 mbar could be reached. The freeze-dried samples produced in this way were stored at 105°C for 2 h to remove residual moisture and to advance crystallinity. This method allows the production of about 50-g scales of mod. III, although small admixtures of mod. I and II (<5%) can sometimes be detected by means of powder X-ray diffraction.

### Optical Rotation

The optical rotation of this solution was measured using a Zeiss circular polariscope 0.01 (Carl Zeiss, Oberkochen, Germany) with a 10-cm polarimeter tube. D-mannitol, 200 g, and sodium tetraborate, 2.6 g, were dissolved together in 25 mL of water at

30°C. According to the European Pharmacopoeia, the amount of rotation has to be between +23 and +25° at a wavelength of 589.3 nm and 20°C.

### Thermoanalytical Methods

*Polarized thermomicroscopy*<sup>22,23</sup> was performed using a Kofler hot stage microscope (Thermovar, Reichert, Vienna, Austria). To prepare a crystal film approximately 2 mg of D-mannitol was heated between a microscope slide and a cover glass using a Kofler hot bench (Reichert, Vienna, Austria). The molten film was quenched to 20°C by use of a metal block.

*Differential scanning calorimetry* (DSC) was carried out with a DSC-7 and Pyris software for Windows NT (Perkin-Elmer, Norwalk, CT) using perforated aluminum sample pans (25  $\mu$ L). Sample masses for quantitative analysis were 1 to 3 ( $\pm$ 0.0005) mg (Ultramicroscales UM3, Mettler, CH-Greifensee, Switzerland). Nitrogen 99.990% (20 mL min<sup>-1</sup>) was used as purge gas. Calibration of the temperature axis was carried out with benzophenone (mp 48.0°C) and caffeine (mp 236.2°C). Enthalpy calibration of the DSC signal was performed with indium 99.999% (Perkin-Elmer, Norwalk, CT). The normal heating rate was 2 or 5 K min<sup>-1</sup>. Specific heat was determined with Perkin Elmer DSC 7 Series/UNIX Thermal Analysis Software using the two curve cp method with sapphire as the reference material. For measurements mannitol modifications were prepared as compacts (diameter, 5 mm; pressure, 4 kN) to achieve greater accuracy than using powders only.<sup>24</sup>

### Spectroscopic and Diffractometric Methods

*FTIR spectra* were recorded with a Bruker IFS 25 FTIR-spectrometer (Bruker Analytische Meßtechnik GmbH, Karlsruhe, Germany). Samples were scanned as potassium bromide pellets (diameter, 13 mm; 1 mg D-mannitol to 270 mg KBr; pressure, 740 MPa) at an instrument resolution of 2 cm<sup>-1</sup>; 50 interferograms were coadded for each spectrum.

*FT-Raman spectra* were recorded with a Bruker RFS 100 FT-Raman spectrometer (Bruker Analytische Meßtechnik GmbH, Karlsruhe, Germany) equipped with a diode-pumped 100 Nd:YAG Laser (1064 nm) as excitation source and a liquid nitrogen-cooled high-sensitivity detector (64 scans at 4 cm<sup>-1</sup> instrument resolution).

X-ray powder diffraction patterns were ob-

tained on a Siemens D-5000 X-ray diffractometer equipped with  $\theta/\theta$ -goniometer (Siemens AG, Karlsruhe, Germany) using monochromatic  $\text{CuK}_\alpha$  radiation (tube voltage, 40 kV; tube current, 40 mA) from 2 to 40°;  $2\theta$  at a rate of  $0.005^\circ 2\theta \text{ s}^{-1}$ . The diffractometer was fitted with a Göbel mirror (entrance slit, 1 mm; exit slit, 0.6 mm) and a scintillation counter (Soller slit; detector slit, 0.1 mm). The single crystal data for mod. I<sup>11</sup> and II<sup>9</sup> were used to calculate the idealized X-ray powder pattern for a  $\text{CuK}_\alpha$  radiation with the program *PowderCell for Windows*.<sup>25</sup>

### Density Measurements

The determination of the powder volumes was carried out by means of an air comparison pycnometer (model 930, Beckman Instruments, Fullerton, CA) at 25°C with sample amounts of ~10 mL and helium as purge gas.

### Solution Calorimetry

The solution calorimetric experiments were performed with a LKB 8700-1 Precision Calorimetry System (LKB-Produkter AB, Bromma, Sweden) equipped with a precision thermostatic water bath, LKB 7600, and a 100-mL glass reaction vessel. The electrical calibration system was checked by chemical calibration with the enthalpy of reaction of TRIS (tris(hydroxymethyl)aminomethane p.a., Merck, Darmstadt, Germany) in 0.1 mol L<sup>-1</sup> HCl at 25°C (N.B.S.-724a:  $-29765 \pm 10 \text{ J mol}^{-1}$ ). The glass ampules (1 mL), plastic-plug stoppers, and the sealing wax for the ampules were purchased from Thermometric AB (Järfälla, Sweden) and used as recommended. Sample mass: ~100 mg  $\pm$  0.1 mg. Temperature change was calculated by graphical extrapolation based on Dickinson's method.<sup>26</sup>

### Powder Compaction Studies

Dry granulation: with a hydraulic labor press PW 10; diameter of matrix, 13 mm; sample weight, 500 to 900 mg. Production of sieve fractions: crushing with mortar and pestle and sieving with ALPINE-Luftstrahlsieb A200 Labortyp (Hosokawa-Alpine, Augsburg, Germany). The sieve fraction of granules between 50 and 100  $\mu\text{m}$  were used for the consolidation. Compacts were prepared using a hydraulic labor press PW 10 equipped with 8-mm matrix diameter flat-faced punches. The sample weight was 150 mg, the

relative humidity was 43%, and the temperature was 24°C. The hydraulic labor press was instrumented as follows: pressure measurements with load cell HBM Typ C9A (Hottinger-Baldwin Meßtechnik, Darmstadt, Germany), displacement with an inductive position transducer HBM W5TK. Pressures applied were 96, 143, 215, and 322 MPa. The thickness of the compacts was measured with a Helios digit-micrometer (Helios, Niedernhall, Germany). The crushing force was measured immediately after compaction and after 7 days with a Schleuniger 2E/205 Tablet Tester (Schleuniger & Co, Switzerland). Tensile strength  $Q$  was calculated using the following equation:

$$Q = \frac{2 \cdot H}{\pi \cdot d \cdot h}$$

where  $H$  is the crushing force;  $d$  is the diameter; and  $h$  is the thickness of the compact.

Crystal form identity before and after compaction was confirmed by FTIR spectroscopy. Enthalpy of fusion, density, solution calorimetry, and heat capacity measurements were performed in triplicate.

## RESULTS AND DISCUSSION

Important physicochemical properties of the three modifications of D-mannitol are given in Table 2.

### Thermomicroscopy

A melt film of D-mannitol quenched on a metal cooling block (20°C) and followed by heating (heating rate, 5 K min<sup>-1</sup>) on the polarizing hot stage microscope leads to gray spherulites of mod. II at 109 to 130°C. The center of these spherulites sometimes contain short varicolored brushes of mod. I. On the other hand, it is possible to find mod. III in the center of the spherulites of mod. II. Modification III crystallizes in fine rays or needles. In the crystal film mod. III transforms into mod. II during heating between 102 and 118°C. To determine the melting difference between mod. I and II, one small crystal of each form was placed next to each other on a microscope slide. After covering the crystals with a cover glass, this preparation was brought to the hot stage microscope and heated to 160°C with a

**Table 2.** D-mannitol—Important Physicochemical Parameters of the Modifications

Modification	I	II	III
Crystal habit	Prismatic rods	Prismatic rods	Needles
Melting point (°C) TM <sup>a</sup>	166.5	166	~155 (incongruent)
Melting point (°C) DSC-onset temperature, 5 K min <sup>-1</sup>	166	166	155 (incongruent)
Enthalpy of fusion (kJ mol <sup>-1</sup> )	53.5 ± 0.4 <sup>b</sup>	52.1 ± 0.9 <sup>b</sup>	53.7 <sup>c</sup>
Entropy of fusion (J mol <sup>-1</sup> K <sup>-1</sup> )	122 ± 0.9 <sup>b</sup>	119 ± 2.1 <sup>b</sup>	125 <sup>d</sup>
Transition into mod I (°C) DSC, 1.5 K min <sup>-1</sup>			130
Enthalpy of transition (kJ mol <sup>-1</sup> )			+0.17 ± 0.01 <sup>b</sup>
Selected FTIR bands (cm <sup>-1</sup> )	1210	1196	1193
	1081	1085	1088
	1019	1020	1025
	959	953	968
	930	927	932
	514	519	522
Selected FT Raman band (cm <sup>-1</sup> )	1232	1258	1251
Density, measured (g cm <sup>-3</sup> )	1.490 ± 0.000 <sup>b</sup>	1.468 ± 0.002 <sup>b</sup>	1.499 ± 0.004 <sup>b</sup>
Density, calculated (g cm <sup>-3</sup> ) <sup>10</sup>	1.489	1.470	1.501
Heat of solution (kJ mol <sup>-1</sup> ) at 25°C	22.3 ± 0.2 <sup>b</sup>	21.5 ± 0.2 <sup>b</sup>	21.7 ± 0.4 <sup>b</sup>
Specific heat (J g <sup>-1</sup> K <sup>-1</sup> ) at 25°C	1.383 ± 0.009 <sup>b</sup>	1.273 ± 0.008 <sup>b</sup>	1.263 ± 0.002 <sup>b</sup>

<sup>a</sup> Thermomicroscopy.<sup>b</sup> 95% CI.<sup>c</sup> calculated by adding the enthalpy of transition to the enthalpy of fusion of mod. I.<sup>d</sup> calculated by adding the entropy of transition to the entropy of fusion of mod. I.

heating rate of 20 K min<sup>-1</sup>. Then the heating rate was reduced to about 0.5 K min<sup>-1</sup> and the melting point of mod. II was observed at 166.0 and of mod. I at 166.°C.

### Differential Scanning Calorimetry

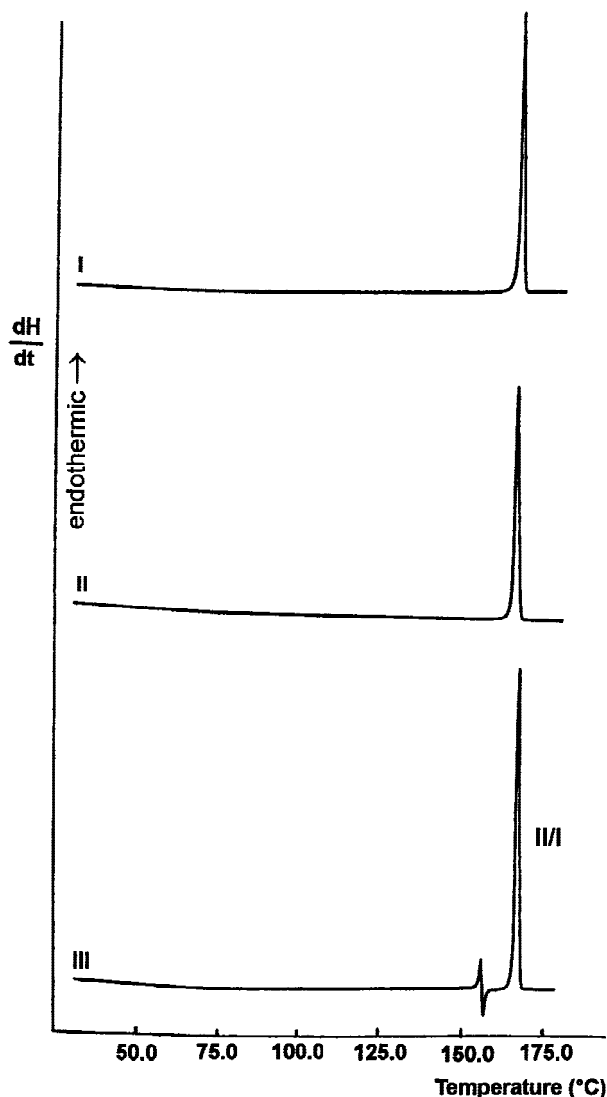
The DSC curves of mod. I and II show one endothermic peak representing the melting of the respective crystal forms (Fig. 1). Modification III (Fig. 1) shows incongruent melting between 150 and 158°C, followed by the solidification of the melt to form mod. I and/or II and the melting of the respective crystal form or mixture. The endothermic transition of mod. III into mod. I was determined by applying a heating rate of 1.5 K min<sup>-1</sup> to a mixture of mod. III and I (ratio 3:1). Thus, the transition of mod. III into mod. I was induced at about 130°C (Fig. 2).

Another endothermic peak often observed during heating of mod. III at about 90°C does not belong to any process of D-mannitol. This effect is caused by almost small admixtures of D-sorbitol and corresponds to the eutectic melting in the binary mixture of mannitol mod. III and sorbitol

mod. I. The sorbitol amount usually contained in commercial mannitol mod. III showed admixtures of about 0.5%, which could be quantified by DSC evaluation of the eutectic heat of fusion.

### FTIR and Raman Spectroscopy

Both the FTIR (Fig. 3) and Raman spectra (Fig. 4) of the three modifications differ considerably, reflecting the different interaction forces between and the different conformational arrangements of the molecules. The FTIR spectra of the modifications show significant differences relating O-H and C-H stretching vibrations in the range between 3700 and 2500 cm<sup>-1</sup> as well as differences in the C-H deformation vibrations between 1400 and 1200 cm<sup>-1</sup>. The vibrations involving the stretching of the C-O bond (1400 to 1200 cm<sup>-1</sup>) also show significant shifts for the three crystal forms. Furthermore, differences can be found in the region between 800 and 600 cm<sup>-1</sup>. IR spectra of the three modifications were also reported by Walter-Levy.<sup>10</sup> The patterns of these spectra are in good agreement with the ones depicted in this article.



**Figure 1.** DSC curves of mod. I, II and III of D-mannitol (heating rate 5 K min<sup>-1</sup>).

The spectral regions between 3000 and 2800 cm<sup>-1</sup> and 1150 and 1100 cm<sup>-1</sup> are suitable to distinguish the three modifications by FT Raman spectroscopy. In addition, mod. I shows a single peak at 876 cm<sup>-1</sup>, which is split and slightly shifted in the spectra of mod. II and III (Fig. 4).

#### X-ray Diffractometry

The three crystal forms can easily be distinguished by their X-ray powder patterns as shown in Figure 5. X-ray single crystal data are available for mod. I and II. The powder patterns of both modifications were calculated from the single crystal structure data as recommended by Bar and Bernstein.<sup>27</sup> The computed diffracto-

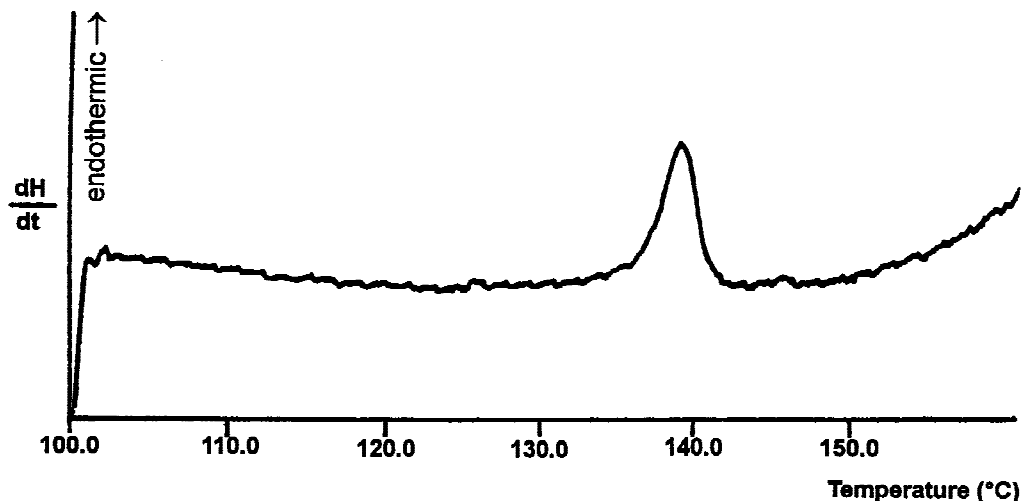
grams for mod. I and II are in agreement with the respective experimentally obtained patterns. Because no atomic coordinates for mod. III have been published yet, we were not able to calculate the respective pattern.

#### Energy/Temperature Diagram

The physicochemical data of the D-mannitol modifications, summarized in Table II, allow an estimation of their thermodynamic relationship and the construction of the semi-schematic energy/temperature diagram (Fig. 6). For a detailed discussion on the construction and interpretation of energy/temperature diagrams in general, reference is made to the literature.<sup>28-32</sup>

The lowest melting crystal form mod. III turned out to be enantiotropically related to mod. I on account of the endothermic transition from mod. III into I according to the heat-of-transition rule. Its enthalpy of transition comes to  $0.17 \pm 0.01$  kJ mol<sup>-1</sup> registered by DSC. The enantiotropic relation between mod. III and II follows by applying the density rule because the density of mod. III is about 2.1% greater than mod. II. Thus, mod. III is the thermodynamically stable crystal form at absolute zero. The only slightly higher density of mod. III in view of mod. I (0.6%) is not suitable to the application of the density rule.<sup>31</sup>

Much more difficult to interpret are the experimental results concerning the energetic relations between mod. I and II. A monotropic relationship is suggested pursuant to the slightly, but significantly, higher enthalpy of fusion of mod. I than mod. II (heat-of-fusion rule). Especially in cases of small differences in the heat of fusion of two modifications, care must be taken in the application of the heat-of-fusion rule according to the divergence of H-isobars toward higher temperatures. This circumstance takes more effect the larger the melting point difference of the involved modifications is. In these cases the difference in the entropies of fusion are more meaningful to distinguish between monotropism and enantiotropism than the difference in the heats of fusion.<sup>31-34</sup> Because the melting points of D-mannitol mod. I and mod. II only differ in 0.5 K, these considerations should not be taken into account comparing the very close values for entropies of fusion (95% CI) of mod. I and II (Table 2). However, the density of mod. I is about 1.5% higher than of mod. II. This is stated as a significant difference<sup>31</sup> for the application of the density rule and suggests a monotropic relationship between mod. I and II.

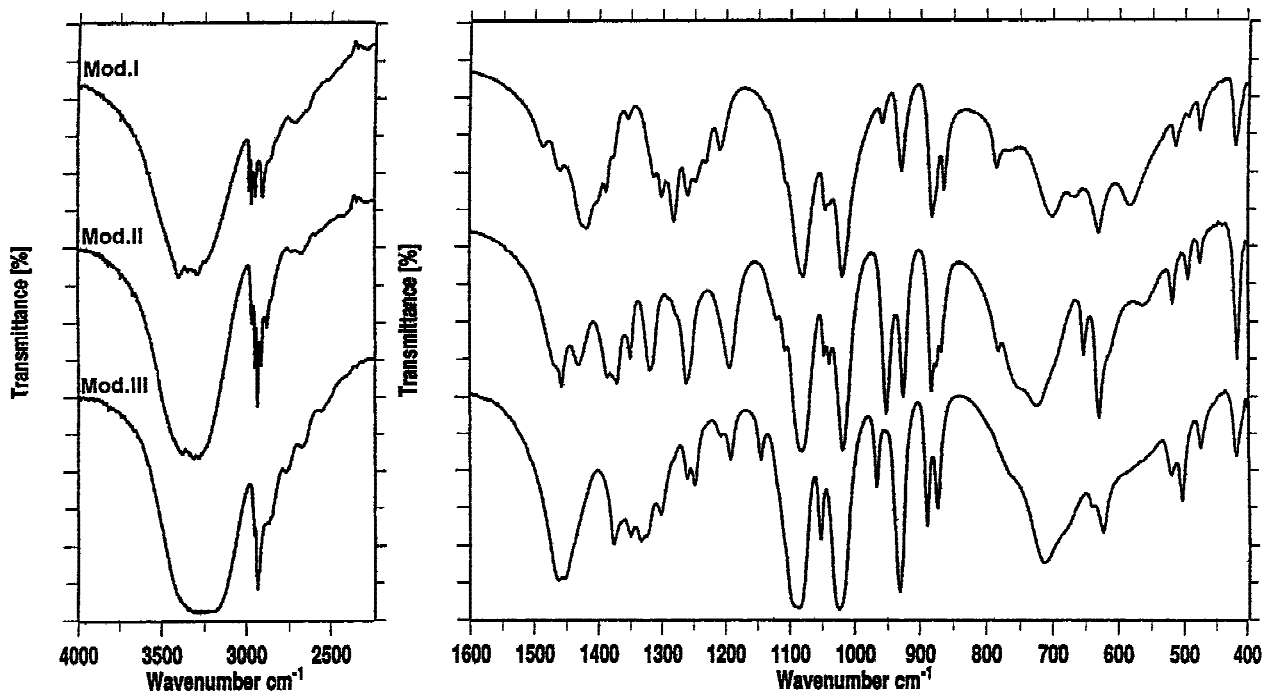


**Figure 2.** DSC curve of a mixture of mod. III and I (ratio 3:1) of D-mannitol (heating rate  $1.5 \text{ K min}^{-1}$ ).

Other physicochemical properties of the modifications like hygroscopicity, heat capacity, heat of solution, and light stability are useful to distinguish whether two modifications are monotropically or enantiotropically related.<sup>30,31</sup> Heat-of-solution experiments and heat capacity measurements were performed with the three modifications. The order of the heats of solution of different modifications gives the enthalpy order. For D-mannitol these heats were determined at  $25^\circ\text{C}$

(Table 2). From the statistical point of view the data only show a significantly higher heat of solution for mod. I (3.7%) in view of mod. II indicating a monotropic relationship between these two crystal forms.

According to the heat-capacity rule,<sup>30,33</sup> a system is enantiotropic if the higher melting polymorph has a higher heat capacity than the lower melting modification at a given temperature. Our results for the determination of the specific heat



**Figure 3.** FTIR spectra of mod. I, II, and III of D-mannitol.

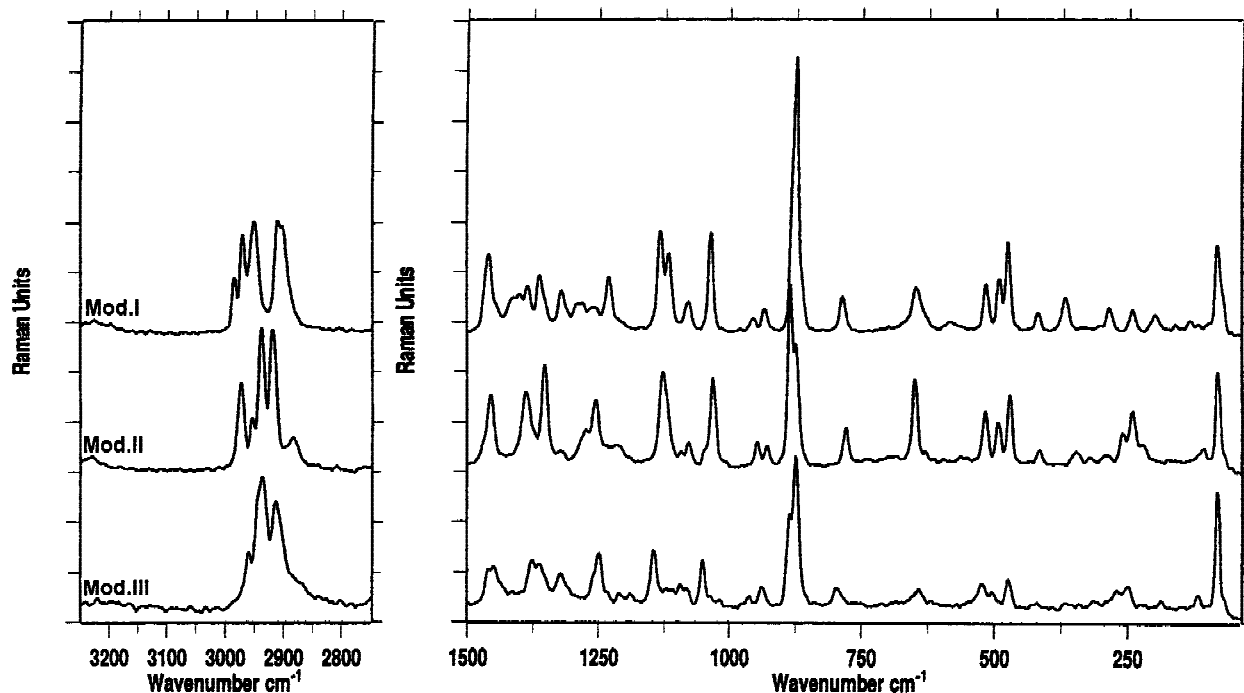


Figure 4. FT Raman spectra of mod. I, II and III of D-mannitol.

of the different crystal forms obtained at 25°C are given in Table 2. Although the data for mod. II and III are not quite significantly different, the enantiotropic relation between III and I, as well as between III and II, is confirmed but not the monotropism between II and I.

By means of the measured physicochemical properties of the three modifications of D-mannitol, the relative curve course of H- and G-isobars of mod. I and III could be explained in the energy/temperature diagram, whereas the energetic relationship between mod. I and II is doubt-

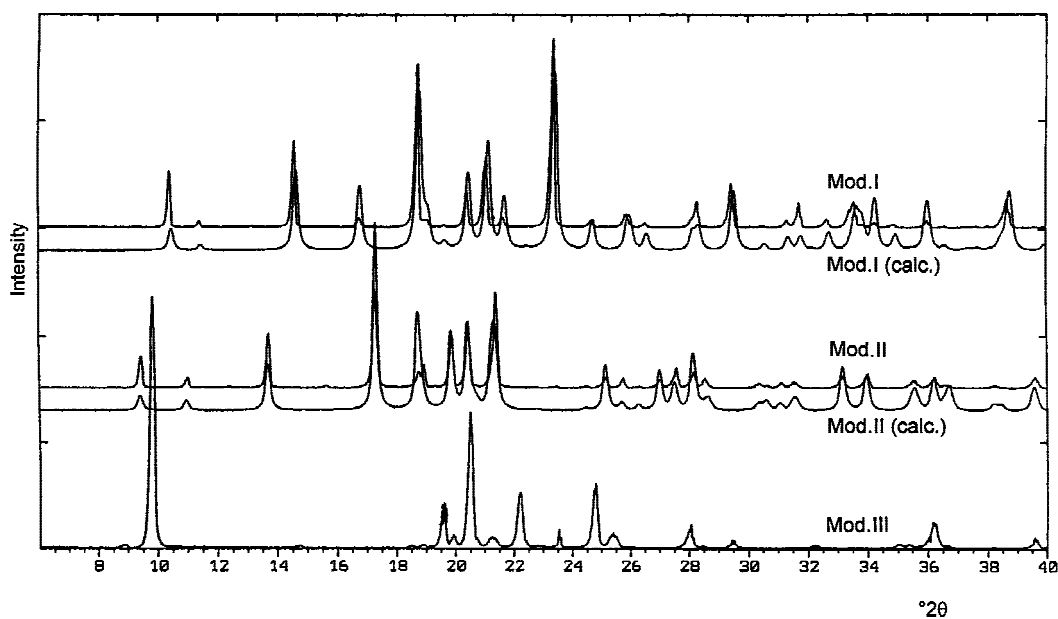
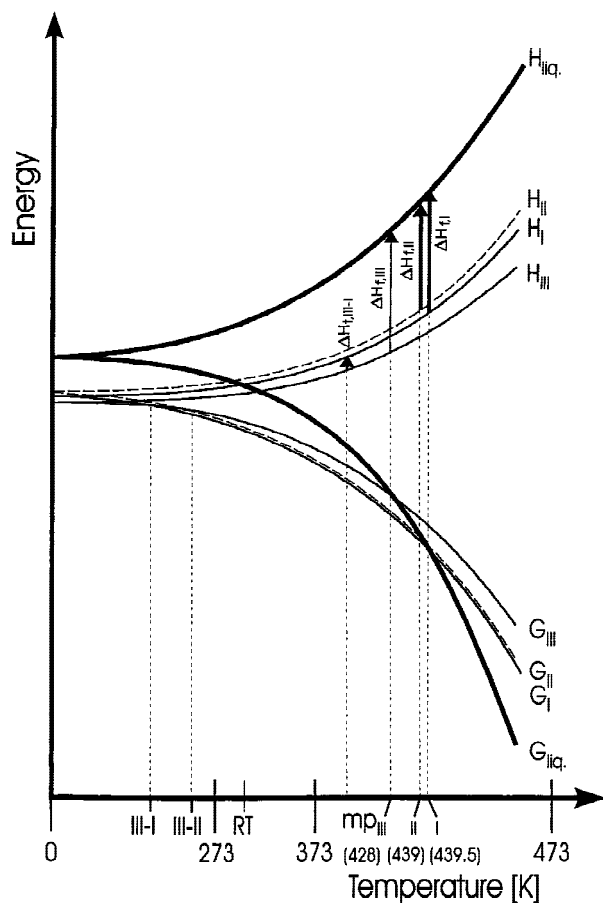


Figure 5. X-ray powder patterns of mod. I, II (also calculated from single-crystal data) and III of D-mannitol.





**Figure 6.** Semi-schematic energy/temperature diagram of the crystalline modifications of D-mannitol and its melt:  $G$ , free energy;  $H$ , enthalpy;  $\Delta H_f$ , enthalpy of fusion;  $\Delta H_t$ , enthalpy of transition; *liq*, melt; *mp*, melting point; *RT*, room temperature; measured enthalpy effects are drawn bold. The  $y$ -axis is without scale and the  $x$ -axis is enlarged against higher temperatures on a logarithmical basis.

ful if a strict standard is applied. Therefore, in Figure 6 the curves of isobars of mod. II are depicted as dotted lines assuming to be monotropically related to mod. I.

But how is the order of thermodynamic stability of the modifications at ambient conditions? Modifications III and II show a reproducible transformation into mod. I at 20°C within 1 day, when a suspension of the modification is stirred (magnetic stirrer) in a solvent (water, ethanol) at fluctuating temperatures between 15 and 25°C. Modification I remains unchanged. Thus, mod. I is the thermodynamically stable modification at ambient conditions and therefore the thermodynamic transition points of the enantiotropic systems must be less than 20°C.

In addition, water sorption experiments were performed on the three modifications. After storage for 3 months in a desiccator at 24°C and 43% relative humidity using potassium carbonate, the crystal forms were sieved (50 to 100  $\mu\text{m}$ ) and afterward exposed to 0%, 75%, and 92% relative humidity at 25°C. The water sorption behavior of the three modifications is similar. The sample mass of the crystal forms increased 0.4 to 0.8% at 75%, as well as 92%, relative humidity within 48 h. The small differences in water uptake cannot be explained by the differences in the crystal lattices of the modifications. However, this behavior can be related to surface effects or differences in the degree of activation of the crystalline products. Care must be taken that only chemically pure mannitol is used for the measurement of water sorption. An admixture of 0.5% sorbitol increases the water uptake by about 1% at 92% relative humidity and 25°C.

The kinetic stability of the modifications is considerable because no transformation of mod. III and II into mod. I occurs during mechanical stress [milling, pressure (0.74 GPa)] or storing for more than 5 years at 25°C if kept dry. Therefore, it was possible to investigate the compaction behavior of the crystal forms.

### Powder Compaction Studies

Because the crystallographic and thermodynamic properties of a polymorphic substance vary within the modifications, their compression behavior and therefore their tabletability can show significant differences.<sup>36–38</sup> Thus, investigations on the compression behavior of different crystal forms of drug substances and excipients are of particular interest. The compression behavior of the three modifications of D-mannitol was studied by evaluation of (i) *compressibility*: compression pressure versus porosity; (ii) *compactibility*: compression pressure versus tensile strength; and (iii) *friction of the compacts*: compression pressure versus ejection force.

*Compressibility* of a material is its ability to be reduced in volume as a result of an applied pressure. The simplest method to compare the compressibility of a set of substances consists in representing the gradual change in compact porosity as a function of any increase in compression pressure. The results obtained for the three modifications of D-mannitol are represented in Figure 7. It can be observed that the compressibility of the three crystal forms is significantly different.

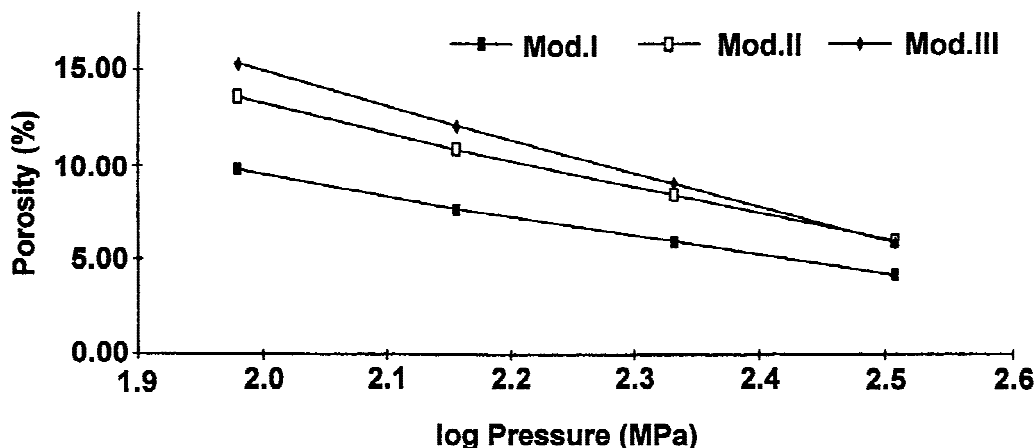


Figure 7. Compactibility of D-mannitol modifications.

Modification III shows the best compressibility followed by mod. II and I. The increase in the compressibility of mod. III and II could be derived from an increase in densification during compression or from a decrease in elastic recovery during decompression.

*Compactibility* is the ability of a material to produce compacts with sufficient strength under the effect of densification. Figure 8 presents the relationship between compression pressure and tensile strength for different D-mannitol modifications. These results strongly suggested that the interparticle bond structure of the three modifications is significantly different. It can also be observed in Figure 8 that, for a similar porosity, the tensile strength of compacts of D-mannitol mod. III is substantially greater than that of the two other crystal forms.

The *friction of the compacts* of the different D-mannitol modifications within the matrix is represented in Figure 9. Modification III shows

the lowest die wall friction followed by mod. II and I. It can be concluded that mod. III contains the best self-lubricating activity within the three crystal forms.

The results of the compaction studies on the crystal forms of D-mannitol show that mod. III exhibits the best consolidation behavior of the three crystal forms. From the compact technologic point of view mod. III is the crystal form of choice because at a given pressure the compacts made of this crystal form show the greatest hardness. Because mod. III needs the lowest compression pressure to form suitable compacts, the attrition of an industrial compactor will be the lowest. Therefore, the use of mod. III is of interest from an economic point of view.

## CONCLUSION

As given in Table 2, only Walter-Levy<sup>10</sup> and Jones and Lee<sup>12</sup> obtained the three pure modifi-

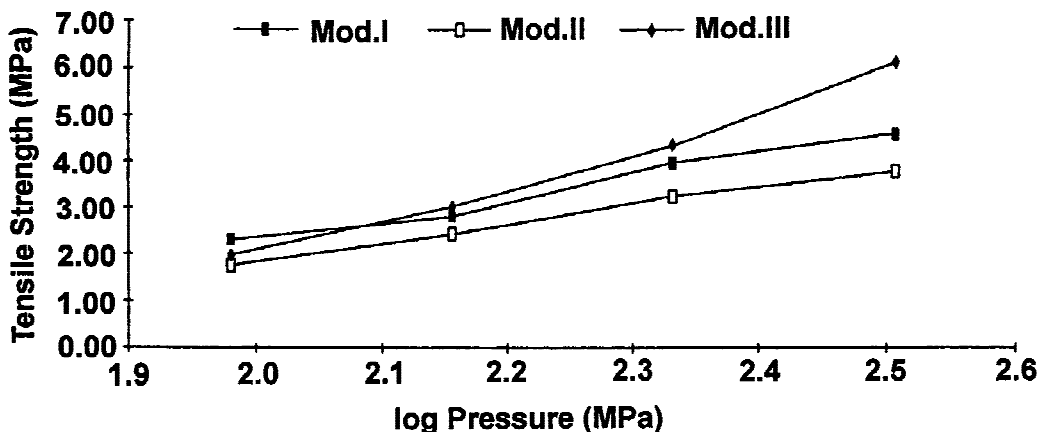


Figure 8. Tableability of D-mannitol modifications.

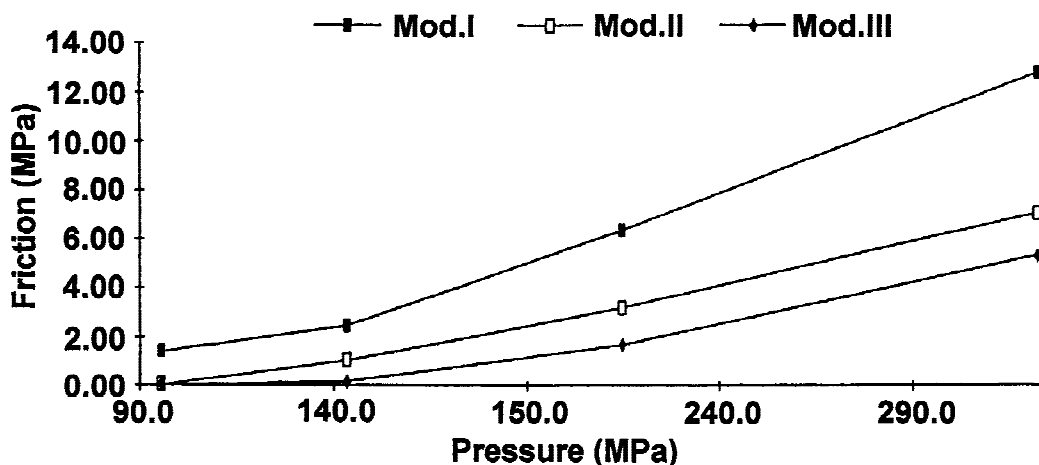


Figure 9. Friction of compacts of D-mannitol modifications within the matrix.

cations of D-mannitol. There they studied crystallographic and optical properties. Grindley et al.<sup>15</sup> measured the solid-state <sup>13</sup>C NMR spectra of the three pure crystal forms and of mixtures of modifications of D-mannitol. In this work a semi-schematic energy/temperature diagram (Fig. 6) was constructed by means of physicochemical data obtained. Therein the thermodynamic relationship between the three modifications of mannitol is explained. Modification III is enantiotropically related to mod. I and II. Only small energetic differences between mod. I and II could be found, which is also manifested in small differences of melting points and heats of fusion as well as in a similar crystal lattice belonging to the same space group (orthorhombic, P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>).<sup>9-11</sup> Obtained data show more evidence for monotropism than enantiotropism, although there was no reliable assignation possible. However, mod. I is the thermodynamic stable crystal form at 20°C and greater.

Besides the thermodynamic properties of the three modifications, we focused on their implications to pharmaceutical technology. Although mod. III of D-mannitol is a thermodynamically unstable crystal form at ambient conditions, it shows significant kinetic stability. This crystal form is durable over a period of at least 5 years at 25°C if kept dry, and even mechanical stress such as grinding or compacting does not cause a transition into the room temperature thermodynamically stable mod. I. Several ways are described in the literature of how to crystallize mod. III exclusively. It seems to be possible to find a routine way to produce this crystal form in macroscopic amounts routinely and to take advantage of its

excellent tableability properties in the production of solid dosage forms containing D-mannitol.

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