

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

ARTUR BURGER, JAN-OLAV HENCK, SILVIA HETZ, JUDITH M. ROLLINGER, ANDREA A. WEISSNIGHT, HEMMA STÖTTNER

Institut für Pharmakognosie der Universität Innsbruck, Josef-Moeller-Haus, Innrain 52, A-6020 Innsbruck, Austria

Received 18 March, 1999; accepted 23 December 1999

ABSTRACT: Three modifications of D-mannitol were produced and investigated: mod. I (mp 166.5°C, heat of fusion 53.5 kJ mol⁻¹), mod. II (mp 166°C, heat of fusion 52.1 kJ mol⁻¹), and mod. III (mp incongruent 150–158°C, heat of transition, III to I 0.2 kJ mol⁻¹). The measured densities are 1.490 ± 0.000 g cm⁻³ [95% confidence interval (CI)] for mod. I, 1.468 ± 0.002 g cm⁻³ (95% CI) for mod. II, and 1.499 ± 0.004 g cm⁻³ (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.

Groth¹ already quoted in 1910 that Schabus,² Zepharovich,³ as well as Grailich and Lang,⁴ have described two polymorphic modifications of D-mannitol. He mentioned the lattice parameters of the α - and β -form. The latter is commonly known to be the commercial product. These descriptions were verified by Becker and Rose⁵ in 1923, and they were specified by Marwick⁶ in 1931. Rye and Sorum⁷ presented in 1952 besides form α and β a new form γ . This modification was obtained by rapid cooling of a solution of D-mannitol in ethanol/water 1:1. The α' -form characterized by Mak⁸ in 1963 for the first time is

Correspondence to: A. Burger. (E-mail: Artur.Burger@uibk.ac.at)

Parts of this work were presented at 40th Annual Conference of the APV, Mainz (Germany) 9–12 March 1994. Abstract: *Eur J Pharm Biopharm* 1994;40:21.

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

Journal of Pharmaceutical Sciences, Vol. 89, 457–468 (2000)
© 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association

Table 1. D-mannitol—Review of the Literature

Chronological	Designations and Allocation of the Modifications Worked On							
	α	β	γ	δ	α'	κ	U	D
Groth ¹	α	β						
Becker and Rose ⁵		β						
Marwick ⁶		β						
Rye and Sorum ⁷	α	β	γ					
Mak ⁸					α'			
Berman et al. ⁹	α	β						
Walter-Levy ¹⁰	α	β		δ				
Kim et al. ¹¹			κ			κ		
Jones and Lee ¹²	II	I		III				
Debord et al. ¹³				α			U	
Giron ¹⁴	B	A		C			C	D
Grindley et al. ¹⁵	κ	β	κ	α	δ			
Pitkänen et al. ¹⁶	κ	$\alpha + \beta$		δ				
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.⁹ Walter-Levy¹⁰ also described three modifications of D-mannitol in 1968. Besides the orthorhombic forms α and β , a monoclinic form was investigated for the first time. This modification was called δ -form. Berman et al.⁹ published the X-ray crystal structure of the β -form and Kim et al.¹¹ presented the form κ in the same year. Kim et al. already assumed that their form K is identical with γ -form of Rye and Sorum.⁷ In 1970 Jones and Lee¹² investigated D-mannitol by means of thermomicroscopy.¹² 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.¹³ investigated several commercial products of D-mannitol in 1987. Besides the forms α , β , and δ , 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 γ -form of Rye and Sorum.⁷ In 1990 Giron¹⁴ obtained four forms of D-mannitol, which were named A, B, C, and D. She equated form A to the β -form of Debord et al.,¹³ B to the α -form, C to the U-form and introduced form D as a new modification. In the same year Grindley et al.¹⁵ worked on three modifications of D-mannitol. Their α -form corresponds to the α' -form of Mak⁸ and Berman,⁹ which they equated to the δ -form of Walter-Levy.¹⁰ The β -form corresponds to the β -forms of other authors and as the third modification they inserted κ , which they assumed is equal to the κ form of

Kim et al.,¹¹ to form γ of Rye and Sorum⁷ and the α -form of Walter-Levy.¹⁰ Pitkänen et al.¹⁶ 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.^{17–19} This hydrate can be formed in the process of freeze drying. It converts to anhydrous crystal forms (mod. I and III) on gentle heating.¹⁹

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.^{20,21} 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^{22,23} 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 μ 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⁻¹) 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⁻¹. 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.²⁴

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⁻¹; 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⁻¹ instrument resolution).

X-ray powder diffraction patterns were ob-

tained on a Siemens D-5000 X-ray diffractometer equipped with θ/θ -goniometer (Siemens AG, Karlsruhe, Germany) using monochromatic $\text{CuK}\alpha$ radiation (tube voltage, 40 kV; tube current, 40 mA) from 2 to 40°; 2θ 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. I¹¹ and II⁹ were used to calculate the idealized X-ray powder pattern for a $\text{CuK}\alpha$ radiation with the program *PowderCell for Windows*.²⁵

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⁻¹ 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.²⁶

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

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

heating rate of 20 K min⁻¹. Then the heating rate was reduced to about 0.5 K min⁻¹ 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⁻¹ 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⁻¹ as well as differences in the C-H deformation vibrations between 1400 and 1200 cm⁻¹. The vibrations involving the stretching of the C-O bond (1400 to 1200 cm⁻¹) also show significant shifts for the three crystal forms. Furthermore, differences can be found in the region between 800 and 600 cm⁻¹. IR spectra of the three modifications were also reported by Walter-Levy.¹⁰ The patterns of these spectra are in good agreement with the ones depicted in this article.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.