DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(9-11), 1533-1546 (1987)

# STUDY OF DIFFERENT CRYSTALLINE FORMS OF MANNITOL : COMPARATIVE BEHAVIOUR UNDER COMPRESSION

**B. Debord, C. Lefebvre, A.M. Guyot-Hermann**
Laboratoire de Pharmacie Galénique et Biopharmacie
Faculté de Pharmacie de Lille, France

**J. Hubert, R. Bouché**
Laboratoire d'Analyse des Médicaments
Université Catholique de Louvain, Belgique

**J.C. Guyot**
Laboratoire de Pharmacotechnie Industrielle
Faculté de Pharmacie de Lille, France

## ABSTRACT

Mannitol is an excipient commonly used in pharmaceutical formulation. Several polymorphic forms have been described but there are only few reports in past literature about their crystalline structures and about their differential properties.

The aim of this work is to prepare and to study the different polymorphic forms. An investigation of commercialized products is then carried out.

The melting points and the water contents are determined and the crystalline structure is differenciated by powder X Ray diffraction.

Four polymorphic forms have been characterized : the α form and the β form, which have been obtained in pure state, and the δ form containing the α form as an impurity, and a fourth form which we have not identified at this time.

Among the commercial products, we have characterized : the β form, the α form and the unidentified form.

The compressibility of these different samples has been studied : the α form is the best. This valuable property has been found again in the commercial α product.

The particle shape seems also to have a great influence upon the compressibility properties. For the same particle size, the granulated powder has a better behaviour than native crystals powders.

Lastly, the possible polymorphic transitions under compression stress during tabletting process has been studied : no transition has been observed.

## INTRODUCTION

Mannitol is a polyol isomer of the sorbitol. It is to be found in some vegetables exudates but the usual commercial product is prepared by catalytic reduction of different oses (Sucrose - D Glucose - D Mannose - D Fructose). It is often obtained with its isomer, the Sorbitol from which it must be isolated. Consequently, manufacturers of Mannitol, often produce Sorbitol as well.

Mannitol is a white powder with a sweet taste, easily soluble in water. According to different authors, its melting point varies from 165°C to 170°C.

It is commonly used in the pharmaceutical formulation of tablets or granulated powders for oral use. Its very low hygroscopicity is an obvious advantage over Sorbitol.

In addition, as with Sorbitol, its metabolism does not induce considerably the increase in blood glucose content, which allows its use in the formulation of medicines for diabetics.

After working on Sorbitol, we were led to study Mannitol more particularly because of its wide utilisation in the pharmaceutical industry and because of its non hygroscopicity.

### Particle habit and crystalline forms

The habit of native crystals of Mannitol is needle-shaped but, often, in the commercial products, the needles are more or less ground.

On the market, we can also find Mannitol as a granulated powder for direct compression.

Moreover, several polymorphic crystalline forms have been reported in the literature :

Rye and Sorum reported, in 1952, three forms : the α, β and γ forms (1).

In 1968, several publications in different countries pointed out a new interest for Mannitol : Kim, Jeffrey and Rosenstein (2) have obtained accidentally a new form, the K form, from an attempted crystallisation of a Mannitol - boric acid complexe. They study its crystalline structure by comparing it to the β form. According to these authors, the K form could be identical to the γ form of Rye et Sorum. Berman, Jeffrey and Rosenstein (3) compiled all the literature on the problem at this time and carried out a very careful study of the crystalline structure of the α' and β forms of D-Mannitol. All the lattice parameters are given in their article.

In the practical field, Walter Levy gives most accurate indications for the preparation of the α, β and δ pure forms. (4). The lattice parameters of these polymorphs are given as well as the I.R. spectra.

According to this author, the γ form has never been found again.

Lastly, Jones and Lee have identified the same α, β and δ forms by fusion and examination under the microscope between crossed polarizers. (5).

## EXPERIMENTAL

The aim of this work was :

- to prepare the different pure crystalline forms of Mannitol,
- to study these polymorphs : their identification, their physico chemical properties, their behaviour under compression,
- to study some commercial products.

## MATERIALS

1. We have tried to prepare the three nativ forms (α, β and δ forms) according to Walter Levy's indications ( 4), the principle of this preparation was a fractionated crystallisation due to the gradient of evaporation at 25°C of 10 ml of Mannitol aqueous solutions in watch glasses (diameter : 10 cm).

According to the various concentrations of solutions we can isolate several forms :

| Solutions concentration | Zone of watch glass | Isolated form |
|---|---|---|
| 1.2 M | Periphery | α form |
| 1.2 M | Centre | β form |
| 0.4 M | Intermediate zone | δ form |

Crystals were gathered up with tweezers under the microscope and collected in stoppered flasks.

The X Ray diffraction patterns of these three forms differ one from another but they are corresponding to those which have been described by Walter Levy.

Yet, the δ form has never been isolated in the pure state. We have always obtained a mixture of the δ form and the α form.

In addition, by evaporation of a solution of Mannitol (0.4M) in watch glasses at 100°C, we got an other polymorph which we have not identified. This new form is perhaps the γ form. Its X Ray diffraction pattern was quite different of these of the α, β and δ forms. We are still working on this subject. To simplify the text, we named this unknown form : the U form.

2. Four commercial products from different origins : $S_1$ $S_2$ $S_3$ $S_4$.

3. Two samples of granulated crystalline powder of the α and β native forms :

The powders of native crystals (α or β form) were moistened by spraying distilled water and then were passed through a 1 mm sieve.

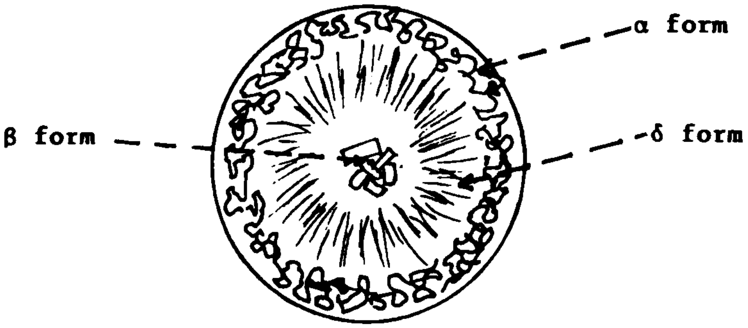

FIGURE 1

Crystallization on a watch glass of the different forms of Mannitol from 0.4 M solution at 20°C.

The granulations were oven dried over 3 hours at 30°C and then over 1 hour at 80°C.

The water content measured by Karl Fischer method was lower than 0.5 %.

## METHODS

### 1. Physical study of the different samples of Mannitol

1.1. X Ray diffraction patterns : Philips PW 1720 Generator equiped with a Guinier Hägg X DC 700 Camera (radiation Cu - K $\alpha_1$, $\lambda$ = 1.5406 Å).

1.2. Melting points : Melting points are determined by using a Mettler FP 52 hot stage. Thermic behaviour will be developed in a later paper.

1.3. Water content : The respective water contents were determined by the Karl Fischer method (direct method).

1.4. Water intake : The different samples were set in controlled relative humidity atmosphere (55 % - 75 % - 86 % R.H.) at 20° C. After a two months storage, the water contents were determined again.

### 2. Behaviour under compression of the different samples of Mannitol

For compression study, the sieve fraction 200 to 400 µm was collected.

The Mannitol samples were directly compressed with a Frogerais OA single punch tablet machine using 1 $cm^2$ area flat punches, the volume of the compression chamber remaining constant (depth : 1cm).

The compression of all the samples were carried out with the same upper punch displacement (0.630 cm).

The compression chamber was filled by hand with 500 mg of each powder sample.

Strain gauges were stuck on the upper and lower punches, connected by means of Weatstone bridges to a computer. This equipment gives us the possibility of noticing for each product the maximum forces $y_1$ and $y_2$ measured on the upper and lower punches during compression.

Before the compression of each tablet the die and the punches were lubricated by the compression of a mixture of Avicel PH 102 with 0.5 % of Magnesium stearate.

The relative humidity of the room atmosphere was kept at 20 %.

The tablets hardness was measured with an Heberlein durometer.

## RESULTS

### 1. Study of the crystalline structure of the different samples of Mannitol

### 1.1. Native crystals prepared by recrystallization

The α and β native crystals, collected on the periphery and in the center of the watch glasses, after evaporation of a solution of Mannitol (0.4 M) at 20° C, were easily identified by their X Ray diffraction patterns, according to the crystallographic parameters of Walter Levy ( 4) and Jones ( 5 ) (Figure 2).

The crystals collected in the intermediate zone were a mixture of the δ and α forms.

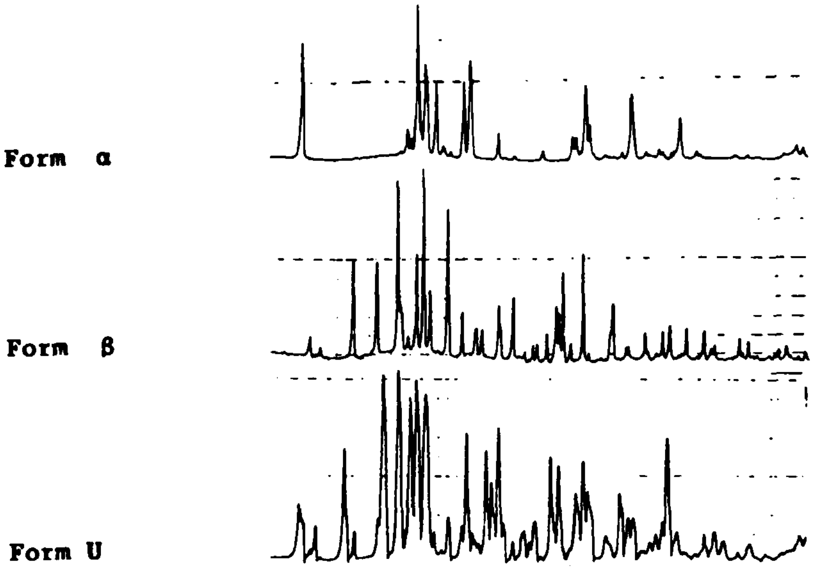

Figure 2
X Ray diffraction patterns of the α, β and U native crystals

The U form, prepared by evaporation at 100° C of a solution of Mannitol (0.4 M) has an X Ray diffraction pattern which is quite different from those of the α, β and δ forms (Figure 2).

### 1.2. Commercial products

By examination of their X Ray diffraction patterns, and comparison with those of the native crystals :

- $S_1$ and $S_2$ were the β form,
- $S_3$ was the U form,
- $S_4$ was the α form.

(Figure 3).

## 2. Water content and hygroscopicity of the different samples of Mannitol

The results of the water content determinations are displayed in table II .

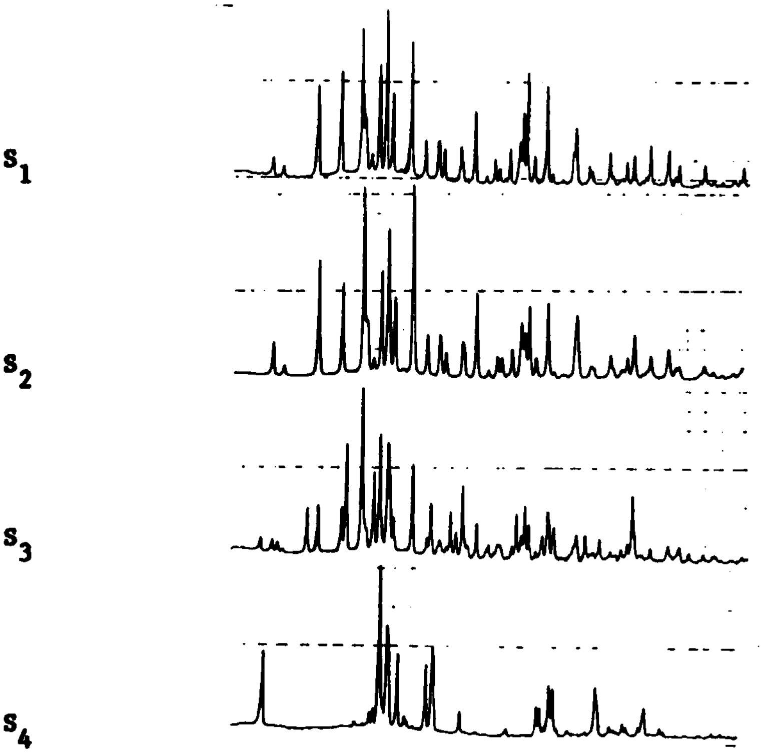

Figure 3

X Ray diffraction patterns of the commercial products : $S_1$ , $S_2$, $S_3$ and $S_4$ .

TABLE II

Water content at 0 time and water uptake of different samples of Mannitol after 2 months storage at different relative humidities

| Sample | 0 time | After 2 months's storage | | |
|---|---|---|---|---|
| Relative humidity | | 55% R.H. | 75% R.H. | 86% R.H. |
| α | 0.90 | 0.47 | 0.59 | 1.10 |
| β | 0.20 | 0.06 | 0.06 | 0.06 |
| $S_1$ (β) | 0.13 | 0.06 | 0.06 | 0.11 |
| $S_2$ (β) | 0.22 | 0.06 | 0.06 | 0.15 |
| $S_3$ (U) | 0.22 | 0.11 | 0.20 | 0.21 |
| $S_4$ (α) | 0.13 | 0.06 | 0.07 | 0.19 |

TABLE III

Comparison of the compression parameters at 50% and 20% of relative humidity : weight = 500 mg
same upper punch displacement (6.3 mm)
$y_1$ = force measured on the upper punch
$y_2$ = force measured on the lower punch
(Results at 20% R.H. are the mean of four tests).

| | R.H. | $y_1$ | $y_2$ | $\frac{y_2}{y_1}$ | Hardness | $y_1$/Hardness |
|---|---|---|---|---|---|---|
| | | KN | KN | | N | N/N |
| α form | 50 % | 14.4 | 7.5 | 0.52 | 25 | 576 |
| | 20 % | 9.3 | 7.5 | 0.81 | 87.5 | 106 |
| β form | 50 % | 11.9 | 6.1 | 0.51 | ≠ 0 | (no tablet) |
| | 20 % | 5.9 | 5.1 | 0.86 | 11.7 | 511 |
| $S_1$ | 50 % | 13.7 | 6.9 | 0.50 | ≠ 0 | (no tablet) |
| | 20 % | 7.6 | 6.4 | 0.84 | 42.6 | 180 |
| $S_2$ | 50 % | 14.9 | 7.6 | 0.51 | 40 | 373 |
| | 20 % | 8.5 | 7.0 | 0.82 | 60.0 | 142 |
| $S_3$ | 50 % | 14.8 | 7.6 | 0.51 | 35 | 423 |
| | 20 % | 8.6 | 7.2 | 0.83 | 53.5 | 162 |
| $S_4$ | 50 % | 15.2 | 7.6 | 0.50 | 35 | 434 |
| | 20 % | 9.0 | 7.6 | 0.84 | 60.0 | 150 |

As can be seen, Mannitol is not an hygroscopic excipient. The α form has the greatest water content, nevertheless it remains low.

## 3. Compression study

### 3.1. Effect of the relative humidity of the surrounding atmosphere

Compression studies have been realised formerly at 50% R.H./ 20°C. They are now performed at 20% R.H./20°C. Results were extremely different (table III).

The $y_1$/hardness ratio is indicative of the compressibility of the powder : the lower this ratio is, the better is the compressibility.

At 50% R.H., tabletting was very difficult, the force transmission ($y_2/y_1$) was very bad and we have observed a marked capping.

On the other hand, at 20% R.H., the results are more satisfactory.

It is interesting to notice the very important effect of the relative humidity on the behaviour of a non hygroscopic substance under compression.

All the other tests were carried out at 20% of relative humidity.

## 3.2. Result of the compression study of the different samples of Mannitol at 20% R.H. (20°C)

### 3.2.1. Parameters of compression

All the results are displayed in table IV. They are generaly the mean of four essais carried out during the same day at 20% of relative humidity and 20°C.

The variation coefficients of the measures were :

1.8 to 4.2 % for $y_1$ and $y_2$
4.2 to 12.7% for the hardness.

From one day to another, the results were almost the same.

The better compressibility of the α native form can be seen, as well as the very bad compressibility of the β native form. The results obtained with commercial products $S_1$ (β form) and $S_4$ (α form) range in the same order.

The granulation of β form ($S_2$) seems to be favourable.

On the other hand, this observation is not so clear for the U form.

### 3.2.2. Behaviour of the crystalline structure under compression

For all the samples studied we did not detect any polymorphic transition under the compression. This conclusion was drawn from

## TABLE IV

Compression parameters of the different samples of Mannitol
- same particle size (sieve fraction 200 - 400 µm)
- same tablet weight = 500 mg
- 20% R.H. 20°C
- same upper punch displacement in the die

(These results are the mean of four tests)

| Crystal-line form | Particle aspect under the microscope | $y_1$ KN | $y_2$ KN | $\frac{y_2}{y_1}$ | Hardness N | $y_1$/Hardness N/N |
|---|---|---|---|---|---|---|
| Native crystals | | | | | | |
| α | elongated opaque tomahawk | 9.3 | 7.5 | 0.81 | 87.5 | 106 |
| β | transparent fragments of needles | 5.9 | 5.1 | 0.86 | 11.7 | 511 |
| Impure δ (α + δ) | rectangular masses of fine needles | 8.3 | 7.0 | 0.84 | 42.5 | 195 |
| U | rectangular ± opaque fragments | 10.2 | 8.6 | 0.84 | 65.0 | 157 |
| Commercial products | | | | | | |
| $S_1$ (β) | ground needles | 7.6 | 6.4 | 0.84 | 42.5 | 180 |
| $S_2$ β | granulated powder (rounded grains) | 8.5 | 7.0 | 0.82 | 60.0 | 142 |
| $S_3$ U | | 8.6 | 7.2 | 0.83 | 53.5 | 162 |
| $S_4$ α | rectangular opaque fragments | 9.0 | 7.6 | 0.84 | 60.0 | 150 |

TABLE V

Comparison of the behaviour under compression of different external morphology of the same polymorphic forms of Mannitol

| | $y_1$ KN | Hardness N | $y_1$/Hardness N/N |
|---|---|---|---|
| α native crystals | 9.3 | 87.5 | 106 |
| $S_4$ (α) | 9.0 | 60.0 | 150 |
| Granulated powder of $S_4$ (α) | 9.7 | 109 | 89 |
| β native crystals | 5.9 | 11.7 | 511 |
| $S_1$ (commercial β) | 7.6 | 42.5 | 180 |
| $S_2$ (commercial granulated powder of β) | 8.5 | 60.0 | 142 |
| Granulated powder of $S_1$ (β) | 8.5 | 53.1 | 160 |
| U native crystals | 10.2 | 65.0 | 157 |
| $S_3$ (commercial granulated powder of U form) | 8.6 | 53.5 | 162 |

the examination of the X Ray diffraction pattern of the samples before and after compression.

### 3.3. Influence of the particle shape

As it can be observed in the table IV, the external morphology of the particles seems to have an influence on their behaviour under compression.

For a more complete study, we granulated the $S_1$ and $S_4$ samples as described in the previous part "Methods" and we studied the compressibility properties of these granulated samples (table V).

On the other hand U native crystals form and $S_3$ commercial product (U form) may be compared.

As it is well known, it can be observed that granulated powders generaly have a better compressibility than native crystals.

Moreover, it can be noticed that the granulation process can influence the compression properties ; the commercial granulated powder $S_2$ (β form) is better than our β native granulated powder.

The particles of the commercial product ($S_2$) are rounded grains which are probably prepared by fusion and recrystallization (6). Our β native granulated powder, which is obtained by wet granulation, is constituted by agglomerates of little fine crystals.

The difference between the β native form and the β samples $S_1$ may be attributed to the external morphology of the particles : the β native particles are transparent and they have a very smooth surface.

The crystals of the β sample $S_1$ are less transparent than those of the β native form, with a much more irregular surface. Their rate of order in the crystal structure is lower than that of the β native crystals. According to the "Activation Theory" of Hüttenrauch (7) it is normal that they have a better compressibility.

On the other hand, some fine particles remain stuck on the 200-400 µm particle. They can help towards better compression.

Finally, it is very interesting to notice that the granulated α native form has the best behaviour under compression, but it has not been found by us on the market.

## CONCLUSION

In this work, we have pointed out that several polymorphic forms of Mannitol may be found on the market. Their behaviour under compression is different. It seems that the wet granulation of α Mannitol gives a very good excipient for direct compression.

## ACKNOWLEDGEMENTS

The authors thank very much the manufacturers who have accepted to send them different samples of Mannitol and Madame Grimmelpont for her very kind help for the English translation.

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