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QUANTITATIVE DETERMINATION OF CRYSTALLINITY OF α-LACTOSE MONOHYDRATE BY DSC

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Abstract

In pharmaceutical practice it is important and useful to know the crystallinity of materials and to monitor it during formulation development, production processes and storage. The purpose of this study was to assess the quantitative capability of DSC for determining crystallinity in crystalline/amorphous powder mixtures and to compare the accuracy of the DSC method with that of conventional powder X-ray diffraction. Alpha-lactose monohydrate was chosen as the model material. On the basis of this study it can be concluded, that DSC method can be applied safely for semiquantitative evaluation of the crystallinity of lactose samples consisting of an amorphous content higher than 20%.

Keywords: crystallinity, DSC, lactose, X-ray powder diffraction

Introduction

The majority of solid dosage forms are formulated from crystalline solid bulk materials, which have a symmetrical crystalline structure. This is in general a physically and thermodynamically stable state. Some technological operations, for example: freeze drying, spray drying, rapid cooling of melt, transform crystalline materials to amorphous form; this is a thermodynamically unstable state with higher energy level [1]. The presence of the amorphous form may determine many particle properties, for example: particle size, particle shape, density, chemical stability, water solubility, hygroscopicity, flow properties, compactibility. A material, which is partly amorphous, may have problems regarding stability and hygroscopicity, resulting in transformation to a more stable crystalline form during storage [2]. Above-mentioned physico-chemical properties may determine the processibility of materials and the bioavailability of dosage forms, so it is important and useful to know the crystallinity of materials and to monitor it during formulation development, production processes and storage [3]. For this purpose such analytical methods are necessary, which are rapid and possibly cost effective and environmentally friendly.

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X-ray powder diffraction

X-ray powder diffraction (XRPD) is considered to be a most accurate method for the study of crystalline structure [4, 5]. The method is well suited to studying changes in the crystalline state, but not to changes in the amorphous state. Despite, it is one of the most widely used technique, its use is limited by cost and hazardousness. The limit of detection using XRPD is recognised as being in the range of 5 to 10%, and sometimes particle size reduction is required.

Thermoanalytical methods

Thermoanalytical techniques measure the change in physical or chemical properties of the sample as a function of temperature. There are many possible applications in the pharmaceutical industry, for example: identification, characterization of active and inactive ingredients, routine analysis, qualitative control, stability study [6]. Differential scanning calorimetry (DSC) involves the heating or cooling of a sample and reference and the measurement of the differential heat flow between them with respect to temperature. The change of energy in thermal processes can be measured, so it can be used in the same way for qualitative and quantitative studies [7]. With the help of DSC, crystallization, modification, polymorph transformation, melting, evaporation and decomposition processes can be studied [8, 9]. The value of enthalpy, specific heat, degree of crystallinity, impurity can be determined.

The purpose of this study was to assess the quantitative capability of DSC for determining crystallinity in crystalline/amorphous powder mixtures and to compare the accuracy of the DSC method with that of conventional powder X-ray diffraction.

Experimental

Materials

Alpha-lactose monohydrate was chosen as the model material because it is well known that its crystalline and amorphous forms, as auxiliary material, influence the production and suitability of solid-state dosage forms.

A sample of alpha-lactose monohydrate (Pharmatose DCL 15, DMV International, The Netherlands) was used as the reference material (corresponding to 100% crystalline lactose). Crystalline alpha-lactose monohydrate was dissolved in water in a ratio 1:10 to obtain a solution for spray drying, which resulted in totally amorphous lactose. Spray dried (SD) lactose was prepared using an A/S NIRO Atomizer (Copenhagen, Denmark). The processing conditions were as follows: feed rate: 20 mL min^{-1}, inlet and outlet temperature: 175 and 80°C. The resulting amorphous particles were kept in a glass vial and stored in a desiccator with <50% relative humidity (RH) at room temperature (50–60% RH is the critical RH for crystallization of amorphous lactose).

Physical mixtures of amorphous and crystalline lactose were prepared to give 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95 and 100% crystalline content by mass. The components were weighed to a total amount of 25.00 g and were mixed in a Turbula mixer (Turbula WAB, System Schatz, Switzerland) with 10 g of 20 mm glass beads and then stored at <50% RH at room temperature up to the analysis.

Methods

X-ray diffraction

X-ray powder diffraction profiles were taken with an X-ray diffractometer (Philips PW 1050/70 PW 1710). The measurement conditions were as follows: radiation source: CuK_{α}, scan speed: 0.035 2 theta s^{-1}, step size: 0.035 2 theta s^{-1}, time per step: 1.0 s.

Differential scanning calorimetry

DSC studies were performed using a DSC 821^{e} (Mettler-Toledo GmbH, Switzerland) with samples of approximately 4 to 4.5 mg weighed into non-hermetically sealed aluminium pans. The samples were heated from 20 to 240°C at heating rate of 5°C min^{-1}. The instrument was calibrated using indium.

Results

X-ray diffraction

X-ray diffractograms of the samples with different amorphous content were recorded. The reflections on the diffractograms were presented as peaks, which deviated from the baseline. The area under the peak is proportional to the intensity values of the diffraction. When the curves are symmetrical, the height of the curves can also describe the intensity. On the diffractogram of the mixture, the intensity the individual components diffraction is in proportion to the quantity of the components in mixture. So quantification is possible [10].

Table 1 Intensity values at chosen 2 theta values

Crystallinity/%	Intensity 2 theta values			
	12.39–12.53°	16.2–16.38°	19.12°	19.59°
5	100	132	250	350
10	317	441	1243	1457
20	868	711	1905	2298
30	1516	1319	3869	4115
50	1733	1987	4786	5405
70	3042	3295	7604	7604
90	3886	4599	10120	9278
95	3644	4983	10238	9973
100	3901	5174	11638	11131

The profile of the crystalline form (Fig. 1) had specific diffraction peaks at 12.39–12.53°; 16.2–16.38°; 19.12° and 19.59°. At these 2 theta values the greatest relative intensity values can be measured (Table 1). Analysis was performed on these

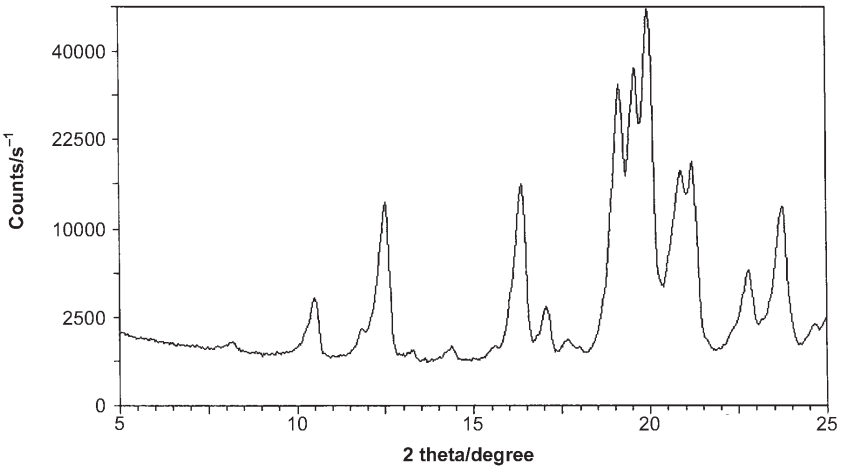

Fig. 1 X-ray diffractogram of the crystalline α-lactose monohydrate

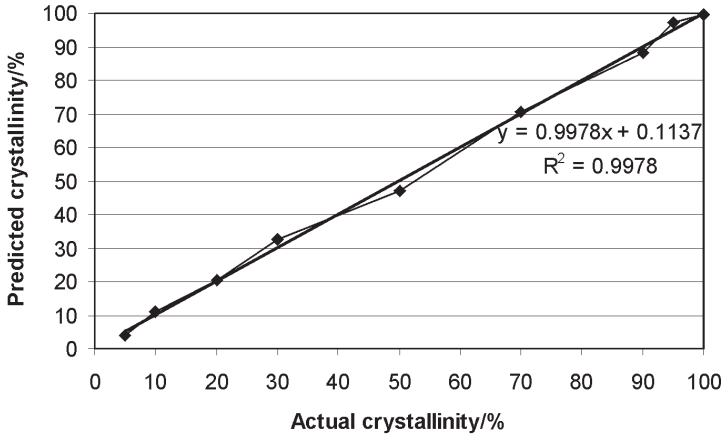

Fig. 2 Relation between predicted and actual crystallinity of physical mixtures of crystalline and amorphous lactose, determined by conventional X-ray powder diffraction

data sets by Multiple Linear Regression (MLR). The dependent variable is the crystallinity and the independent variables are the intensity values at chosen 2 theta values. The confidential interval was 95% (α=0.05). From this calculation a calibration equation was achieved:

$$Y=0.3626+a_1x_1+a_2x_2+a_3x_3+a_4x_4$$

where Y – crystallinity (%), 0.3626 – intercept, a – coefficients (Table 2), x – intensity.

On the basis of this equation the predicted crystallinity can be obtained. Figure 2 shows the relation between the actual and predicted crystallinity. The slope of the line

is 0.9978, the intercept is 0.1137 and the correlation coefficient is 0.9978. Thus, there is close correlation between the two crystallinity values, so XRPD is indeed suitable for determining the crystallinity of the α-lactose monohydrate.

Table 2 Regression coefficients, determined by conventional X-ray powder diffraction

2 theta	Coefficients/a_1–a_4
12.39–12.53°	0.007536
16.20–16.38°	0.014960
19.12°	–0.008780
19.59°	0.008496

Differential scanning calorimetry

DSC measurements of the samples were recorded. DSC curve for the 100% amorphous lactose is shown in Fig. 3. The amorphous form of lactose was identified by the presence of an exothermic peak at 167°C, which represented the transformation of amorphous to crystalline form. It is followed by two endothermic peaks, one at 210 and the other at 216°C. These melting peaks belong to alpha- and beta-lactose respectively. It confirmed the transformation of the amorphous form of lactose to the two types of crystalline form by heating [11].

The 100% crystalline lactose, according to XRPD, contains α and β forms (curve here is not presented). The DSC diagram has an endothermic peak at 144°C, which represents the loss of crystalline water. This is proven by thermogravimetric analysis, where

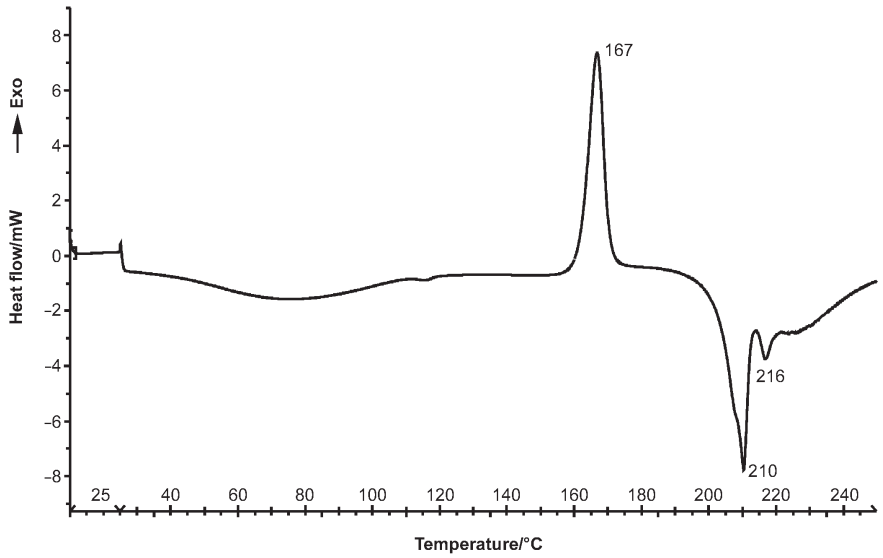

Fig. 3 DSC curve for the 100% amorphous lactose

the sample loses 4.34% water in the range of 130–160°C (curve here is not presented). The endothermic peak is followed by two melts of α and β forms at 213 and 224°C (Fig. 4).

In different mixtures, the ratio of the height and areas under curves of these two peaks varied, but no relation could be proven between crystallinity and these peaks.

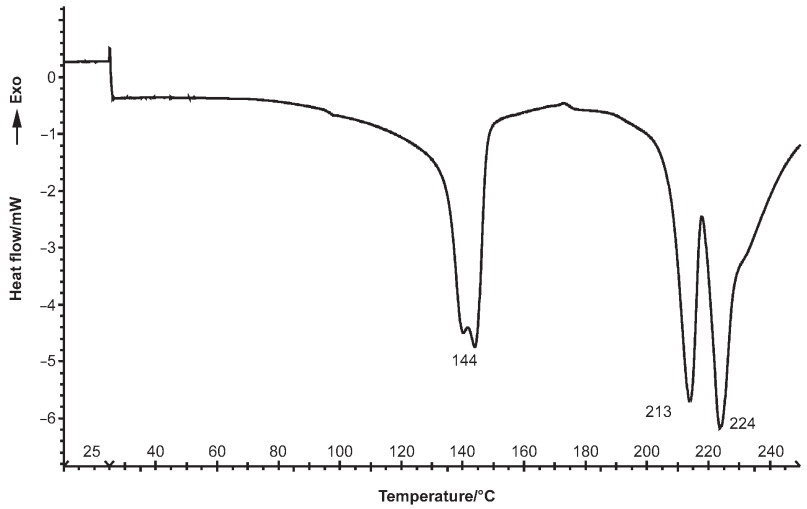

Fig. 4 DSC curve for the 100% crystalline α-lactose monohydrate

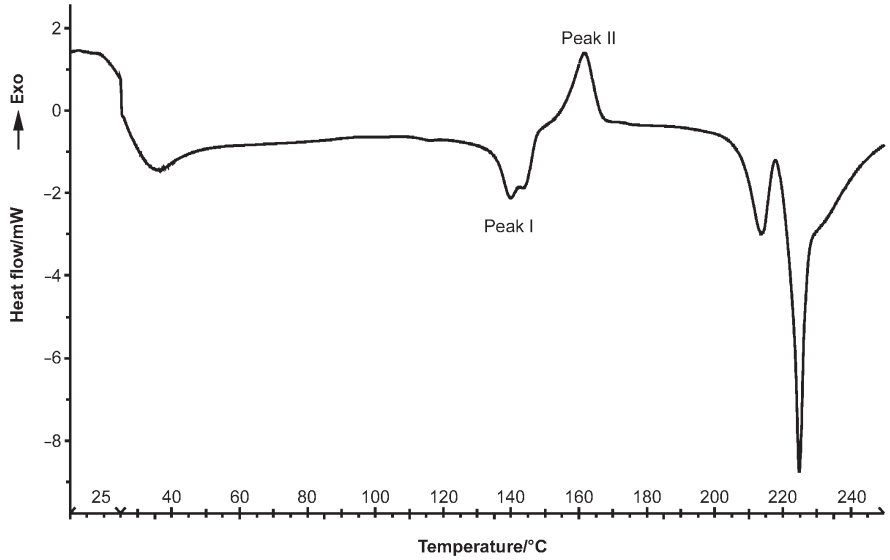

Fig. 5 DSC curve of the sample with 50% amorphous part. (Peak I.: endothermic peak typical for the crystalline form, Peak II.: exothermic peak typical for the amorphous form)

With the increase of amorphous component in the mixtures, the height of the endothermic peak (typical for crystalline form) decreases and the height of the exothermic peak (typical for amorphous form) increases on the DSC diagrams (Fig. 5). Both parameters typical for endothermic and for exothermic processes were studied as a function of degree of crystallinity. On the basis of this, the transition energy values of the amorphous component were used to quantitative evaluation.

Table 3 Transition energy values of the mixtures with different crystallinity

Crystallinity/%	Transition energy/J g^{-1}
0	112.15
5	99.31
10	95.64
20	78.30
30	55.93
50	39.45
60	33.73
70	28.97
80	14.01

At least 20% amorphous content (0 to 80% crystallinity) was possible to be determined by DSC during the measurements. In cases of lower amorphous content, the exothermic peaks were characterless, unsuited for quantitative evaluation. Table 3 shows the energy values of the exothermic peak typical for crystallization in the mixtures with different proportions. Regression analysis of these values generates the following calibration equation:

$$y=87.241–0.825x$$

where y – degree of crystallinity (%), x – transition energy (J g^{-1}), 87.241 – intercept, 0.825 – slope. Value of the regression coefficient (R^2) is 0.9653.

With this equation the crystallinity of an unknown lactose sample can be easily calculated, when the transition energy value is known. Figure 6 shows the predicted crystallinity (determined by regression analysis) as a function of the actual crystallinity.

The correlation (0.9653) is less close than in case of X-ray diffraction studies (0.9978), nevertheless DSC can be applied safely, especially for quantitative evaluation of lactose samples with high amorphous content (0 to 80% crystallinity). However, when the lactose sample contains 80 to 100% crystalline part, X-ray diffraction is recommendable for exact quantitative determination.

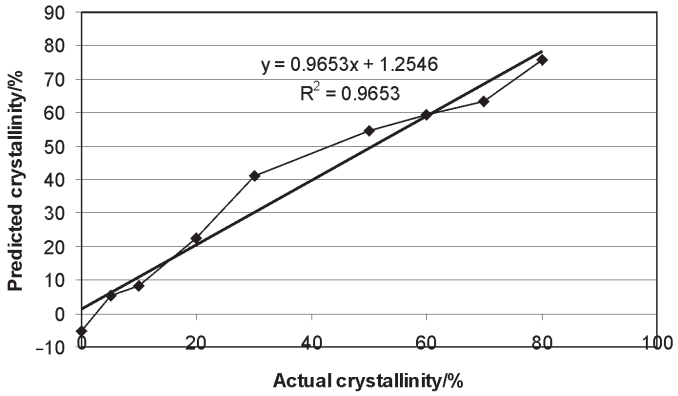

Fig. 6 Relation between predicted and actual crystallinity of physical mixtures of crystallinne and amorphous lactose, determined by DSC

Conclusions

Thus, DSC can be used in semiquantitative determination of the crystallinity of lactose, although it is less precise than X-ray diffraction. The advantage of DSC over X-ray diffraction is that high amorphous content can be detected. In case of lactose, the presence of amorphous form in the material influences the compactibility. This parameter is important, since lactose is widely used as auxiliary material in tablet formulation. From compactibility respect it is ideal, that the product contains more than 30% amorphous part. Consequently, DSC is suitable for the semiquantitative measurement of this amount. This method is widely used in other fields of the pharmaceutical industry, so this employment can expend its application.

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