University of Szeged

Faculty of Pharmacy

Department of Pharmaceutical Technology

Head: Prof. Dr. Habil. Piroska Szabó-Révész DSc

PhD thesis

THE STUDY OF PHYSICO-CHEMICAL PROPERTIES OF CRYSTALLINE AND AMORPHOUS MATERIALS

By

Ágota Gombás

Pharmacist

Supervisor:

Prof. Dr. Habil. Piroska Szabó-Révész DSc

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LIST OF ORIGINAL PUBLICATIONS

I. **Gombás Á.,** Szabóné Révész P., Erős I., Olvadékkristályosítás és olvadékból történő konfekcionálás, *Gyógyszerészet* 45 (2001) 299-304.

II. **Gombás, Á.,** P. Szabó-Révész, M. Kata, G. Regdon jr., I. Erős, Quantitative determination of crystallinity of α-lactose monohydrate by DSC, *J. Therm. Anal. Cal.*, 68 (2002) 503-510.

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III. **Gombás, Á.,** I. Antal, P. Szabó-Révész, S. Marton, I. Erős, Quantitative determination of crystallinity of α-lactose monohydrate by Near Infrared Spectroscopy, *Int. J. Pharm*. 256 (2003) 25-32.

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IV. **Gombás, Á.,** P. Szabó-Révész, G. Regdon jr., I. Erős, Study of thermal behaviour of sugar alcohols, *J. Therm. Anal. Cal*., 73 (2003) 615-621.

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ABSTRACTS

V. **Gombás, Á.,** P. Szabó-Révész, M. Hasznos-Nezdei, K. Pintye-Hódi, I. Erős, Study of interaction between sorbitol and citric acid by thermoanalytical methods, 6th European Congress of Pharmaceutical Sciences (EUFEPS), Budapest, 2000.

VI. **Gombás Á.,** Szabóné Révész P., Szabó S., Antal I., Erős I., Tejcukor kristályossági fokának kvantitatív meghatározása, Műszaki Kémiai Napok, Veszprém, 2001.

VII. **Gombás, Á.**, P. Szabó-Révész, I. Antal, S. Marton, I. Erős, Quantitative determination of crystallinity of alpha-lactose monohydrate by near infrared spectroscopy (NIRS), 4th Central European Symposium on Pharmaceutical Technology, Bécs, 2001.

VIII. Szabóné Révész P., **Gombás Á.**, Antal I., Erős I., A kristályossági fok meghatározásának összehasonlító vizsgálata, XIV. Országos Gyógyszertechnológiai Konferencia, Hévíz, 2002.

ABBREVIATIONS

A	[-]	particle or the nucleus
A	[s^{-1} m^{-3}]	pre-exponential constant
A_T	[m^2]	surface of all the crystals
$c_{B,cr}$	[wt.%]	concentration of the component to be removed in the crystal layer
$c_{B,m}$	[wt.%]	concentration of the component measured in the remaining melt
Δc^g	[wt.%]	concentration change
DSC	[-]	Differential Scanning Calorimetry
ESR	[-]	Electron Spin Resonance
ΔG	[J]	free energy
ΔG_S	[J]	change in surface free energy
ΔG_V	[J]	change in volume free energy
H	[J/g]	enthalpy
ΔH_m	[J/g]	enthalpy of melting
IR	[-]	Infrared Spectroscopy
J	[s^{-1} m^{-3}]	rate of nucleus formation
k	[$1{,}3805 \cdot 10^{-23}$ J K^{-1}]	Boltzmann constant
k_1	[$s^{-1}m^{-3}$]	rate constant of particle aggregation
k_2	[$s^{-1}m^{-3}$]	rate constant of nucleus disintegration
k_{eff}	[-]	effective distribution coefficient
k_G	[m/s]	rate constant of crystal growth
MLR	[-]	Multiple Linear Regression
NIRS	[-]	Near Infrared Spectroscopy
NMR	[-]	Nuclear Magnetic Resonance
r	[mm]	particle size
R	[m/s]	rate of crystal growth
R^2	[-]	regression coefficient
r_{crit}	[mm]	critical particle size
RS	[-]	Raman Spectroscopy
SSNMR	[-]	Solid-State Nuclear Magnetic Resonance

T	[K, ºC]	temperature
t	[s]	time
T_{cr}	[ºC]	temperature of crystallization
T_g	[ºC]	glass transition
T_m	[ºC]	melting point
W	[g]	mass of the crystals
XRPD	[-]	X-ray powder diffraction
Y	[%]	crystallinity
$\Delta\mu_c$	[J/mol]	chemical potential of the crystallizing material in the solid phase
$\Delta\mu_L$	[J/mol]	chemical potential of the crystallizing material in the solution or melt
σ	[J/m^2]	specific surface free energy

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1. Introduction

A major part of modern pharmaceutical research is constituted by formulating a base material of high purity with reproducible physical, chemical and biological properties. The majority of solid organic and inorganic materials occur in a crystalline form in nature, and the same is true for materials produced synthetically. A crystalline material is characterised by a regular, well-definable crystalline structure in which the molecules form a three-dimensional structure.

However, under certain circumstances materials can appear in an amorphous form, too. One possibility for this is when a partially or entirely amorphous form arises during the formulation of materials. The most common such technological procedures can be classified into four groups:

1. condensation from a vapour state
2. supercooling of the melt
3. mechanical activation of a crystalline material. e.g. milling, pressing of a crystalline material
4. rapid precipitation from solution, e.g. freeze drying or spray drying

In pharmacy, amorphous character is general in the case of polymer molecules used as auxiliary materials or in the case of peptides and proteins of a great molecular mass and with a therapeutic effect, but is may also occur with smaller organic and inorganic molecules.

The regular three-dimensional lattice typical of crystalline materials is absent from amorphous materials, only short-range order can be seen in them. Among others, this explains why the amorphous form differs from the crystalline form in terms of certain thermodynamic properties, such as melting point, vapour pressure or solubility; therefore it is essential to know these properties in order to understand and to quantify spontaneous changes occurring during the storage or handling of materials.

2. Aims

The aims of my research can be summarized as follows:

⇒ The aim of my thesis was to investigate the crystalline and amorphous nature of materials, and as part of this to review particularly the properties of amorphous character, its features which are important from the pharmaceutical aspect, its occurrence and importance in certain fields of pharmacy such as pharmaceutical technology, pharmacology and biopharmacy.

⇒ Another aim was to summarize the methods suitable for studying crystalline and amorphous structures, to review their possibilities of application, their advantages and disadvantages.

⇒ One of the aims of my experimental work was to work out a reliable method which can be used for the quantitative measurement of the degree of crystallinity of materials. α-lactose monohydrate was chosen as the model material for this.

- The task was to prepare an amorphous form from this material and also to work out the procedure for this. This was realized with crystallization from a solution, with spray drying.
- Crystalline-amorphous material mixtures of different proportions were needed for the examinations, so another task was to work out how to produce them. Physical mixtures were prepared for this purpose.
- Finally, an analytical method had to be chosen and the investigation parameters had to be set for the quantitative measurement of the degree of crystallinity. Our aim was to perform this measurement with an instrument which is used in a relatively wide range. Moreover, the procedure had to satisfy "modern" requirements such as environmental protection and cost effectiveness, too.

⇒ A further aim of the experimental work was to study melt technology and its pharmaceutical applicability. This technology includes procedures which are advantageous in several respects, yet their use is not widespread enough.

- We had to model thermal processes occurring in melt technology and by means of this to study the thermal behaviour of the materials chosen. This is all the more important because the thermal treatment of materials is performed not only in melt technology but they are exposed to heat effect in the course of other technological procedures as well, e.g. during spray drying, the preparation of solid solutions or even tablet pressing. Therefore it is very important to know the thermal behaviour of materials as it can help us to predict what changes base materials may go through during various technological processes.
- Sugar alcohols (mannitol, sorbitol) were chosen as model materials for the work. The aim of the examinations was to determine in what form these materials can be used in melt technology. The thermal properties of pure mannitol, sorbitol and their mixtures were investigated. Furthermore, it was examined what effect prior melting and solidification had on these materials and on their processibility.

Remark

When the aims of the present work were set in the years of 1999-2002, they were timely and novel. It was also in that period that the investigations were performed and the results were obtained, some of which were original and unprecedented in the given topic, which is confirmed by the citation index since then.

The thesis was written in 2007. In the period which has passed since then there has been increased interest in the quantitative determination of the degree of crystallinity, its importance has grown. Accordingly, several new publications have appeared presenting newer and more modern results, some of which use or refer to the results of the present thesis.

Thus the aim of the thesis is to summarize the results of the work performed between 1999 and 2002. However, for the sake of completeness, the thesis is supplemented with a separate chapter at the end, outlining the most important new results in this topic since then.

3. Literature survey

3.1. Crystallization in general

Crystallization is one of the oldest and most important procedures of chemical industry [1]. The essence of the process is to transform one or more materials from solution, melt or gas phase into a crystalline state. The purpose of the procedure can be to obtain a crystalline phase, to separate a material mixture, to concentrate a solution, to prepare a high-purity crystalline material or to obtain a pure solvent. Its importance is clearly shown by crystallization being one of the major steps of preparing several chemical products, for example medicines, foods, agricultural chemicals, pigments, dyes or proteins. This field is of a multidisciplinary nature, it is connected to many other fields such as physical-chemistry, chemical, materials and biological sciences, and it can also be applied in rapidly developing fields like biotechnology, processing of minerals, waste treatment, etc.

Several crystallization procedures are known, these can be classified basically into two large groups [2, 3]. Crystallization form *solution* or from *melt* is distinguished according to the initial material. Technically, it is difficult to draw a sharp line between the two, as in the case of two- or multi-component systems the terms solution and melt can be used as synonyms. Essentially, every solution can be considered to be a melt because they solidify when cooled to a temperature low enough. At the same time melts behave similarly to solutions over their melting point. Melts are generally materials of liquid state which solidify when cooled to room temperature. A governing definition could be that crystallization from solution is the case when heat transport is negligible compared to material transport, while in every other case the term crystallization from melt applies [4].

Crystallization is a component enrichment operation based on the different distribution of a given component between the phases [5]. The initial phase can be gas, solution, melt or solid. The transition taking place during the process needs a driving force, which can be the termination of equilibrium achieved by supersaturation. This can be realized with a temperature change, solvent extraction, or by adding a displacing agent or a reaction partner. In this state the chemical potential of the two phases differ, this provides the driving force ($\Delta\mu$).

$$\Delta\mu=\Delta\mu_c-\Delta\mu_L, \quad (1)$$

where $\Delta\mu_c$ is the chemical potential of the crystallizing material in the solid phase, while $\Delta\mu_L$ in the solution or melt.

Crystallization takes place if $\Delta\mu < 0$.

3.1.1. Crystallization from solution

The solubility curve of a solid substance (**Figure 1**) clearly shows that the solution is stable saturated along the saturation curve, stable undersaturated below it and supersaturated over it; this supersaturation is the condition of crystallization [6]. Two zones can be distinguished here, a metastable zone and an unstable zone. Spontaneous nucleation takes place in the unstable zone, while in the metastable zone, despite supersaturation, independent nucleation is unlikely to occur in the absence of a solid material, here only the further increase of the already existing crystals can be observed, the driving force of which is supersaturation. Thus this zone is very important from practical aspects as it is here that crystallization can be controlled. Its width depends on the system, on contaminants in it and on the cooling rate, it is usually determined experimentally [7, 8].

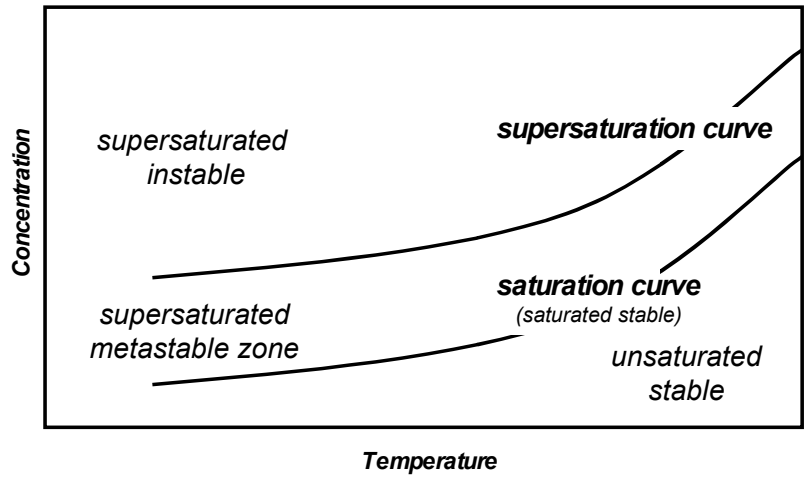


Figure 1 Solubility curve of solid material

The two major steps of crystallization are nucleation and crystal growth, by means of which the system tries to reach thermodynamic equilibrium.

Nucleation

Homogeneous nucleation takes place if there are no foreign particles or own crystals in a supersaturated solution or melt, while the presence of foreign materials facilitates crystallization, in which case *heterogeneous nucleation* occurs. *Primary nucleation* is the term used if nucleation occurs in the absence of own crystals under metastable supersaturation; on the other hand, if the system has low supersaturation, nuclei appear only in the presence of own crystals or seed crystals added, this is called *secondary nucleation* [9].

The crystal nucleus is a short-lived molecular aggregate, which is formed by the elementary particles being aggregated. If local supersaturation is lower in the solution or if the particles collide in an unfortunate manner, the aggregate will disintegrate. However, where local supersaturation is higher, the aggregates will form molecular chains. These are not stable formations, either, they may disintegrate, but with fortunate collisions several chains can form a molecular layer on which crystal growth will start.

Nucleation occurs according to the following:

$$A_1+A=A_2 \tag{2}$$

$$A_2+A=A_3 \tag{3}$$

$$A_n+A<\frac{k_1}{k_2}>A_{n+1} \tag{4}$$

where A is the particle or the nucleus, k_1 is the rate constant of particle aggregation, and k_2 denotes the rate constant of nucleus disintegration.

The kinetics of nucleation can be described by the rate of nucleus formation (J), which is influenced by the change in the surface free energy of the particle (ΔG) [5].

$$J=A\exp(-\Delta G/kT), \tag{5}$$

where A is the so-called pre-exponential constant, k is the Boltzmann constant and T is the temperature.

The change of free energy (ΔG) can be described with the following relationship:

$$\Delta G=\Delta G_S+\Delta G_V, \tag{6}$$

where ΔG_S denotes the change in surface free energy and ΔG_V is the change in volume free energy.

The latter two parameters (ΔG_S, ΔG_V) can be determined as follows:

$$\Delta G_S = 4\pi r^2 \sigma \quad (7)$$

$$\Delta G_V = (4/3)\pi r^3 \Delta G_v, \quad (8)$$

$$\text{thus } \Delta G = 4\pi r^2 \sigma + (4/3)\pi r^3 \Delta G_v, \quad (9)$$

where σ is the specific surface free energy and r is the particle size.

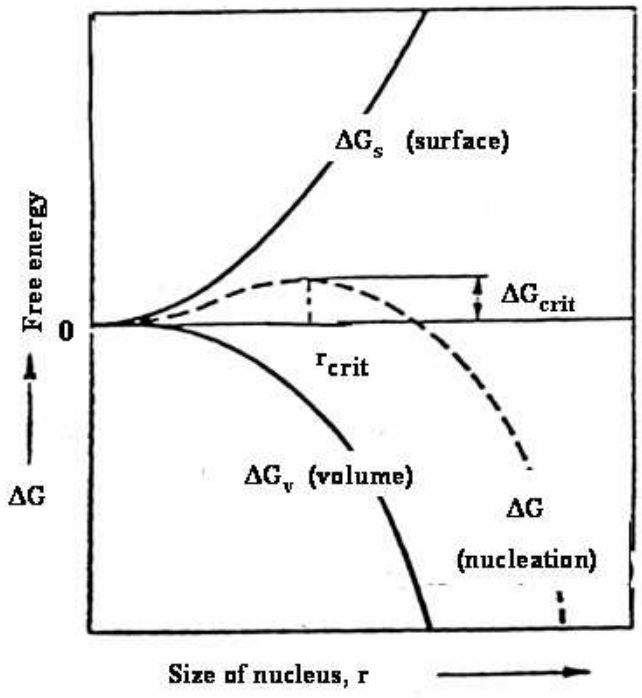


Figure 2 Energy diagram of nucleation

The curve showing the energy of nucleation as a function of particle size (**Figure 2**) reveals that ΔG_S is a positive quantity the value of which is proportional to the second power of particle size, while ΔG_V is a negative value proportional to the third power of particle size. The vector sum of the two curves is the ΔG curve, and the particle size belonging to its maximum value is called critical particle size (r_{crit}). Here, irrespective of whether crystal separation starts or the particle re-dissolves, energy will develop in the process, and the local supersaturation conditions will determine in which direction the process takes place.

Crystal growth

Nucleation is followed by crystal growth, which also means the arrangement of the molecules into a regular crystal lattice [9]. In the course of this the building elements flow onto the surface by means of diffusion or convection and are then built in into the crystal lattice. The rate of crystal growth (R) can be described with the following relationship:

$$R=(1/A_T)\cdot(dW/dt)=k_G\cdot\Delta c^g , \qquad (10)$$

where A_T denotes the surface of all the crystals present in the system, W is the mass of the crystals, t is the time, k_G is the rate constant and Δc^g is the concentration change.

The rate constant of crystal growth (k_G) depends on the temperature, on the size of the crystal nuclei, on the hydrodynamic pressure and on the presence of impurities.

3.1.2. Crystallization from melt

Melt crystallization is one of the numerous crystallization procedures, it is modern and offers advantages in many respects [10].

Melt crystallization is a technique used mainly for *separation* and *purification*, based on the different melting points of the components. In addition to the crystallization procedure in the conventional sense – which means the melting of the solid material and the formation of a crystal aggregate – it is an excellent method, for example, to produce organic materials of great purity, to separate isomers, to separate oils and fats, to manufacture base materials in pharmaceutical industry, to concentrate liquid foods, to purify problematic industrial sewage or to desalinate salt water [11]. Thus this procedure offers an extensive range of application possibilities, and in spite of its advantages, it is still not used widely enough in industry [12].

Energetically it is more advantageous than other methods of separation as it is performed at a low temperature, thus the phase transition enthalpy is also lower, and this is also beneficial in the case of heat-sensitive materials. As no solvent is used there is no residual waste-water either, which is extremely useful in respect of environmental protection. The procedure is of high selectivity, with proper settings a product of almost 100% purity can be obtained from a eutectic mixture [13].

In terms of kinetics, it is simpler than crystallization from solution because it involves only a slight extent of nucleation and secondary nucleation does not take place at all. In this case

primary heterogeneous nucleation, that is nucleation induced by a foreign particle, takes place. The process is controlled by heat transport.

A further advantage is that 70% of organic materials have a melting point between 0-200°C, and 80% of them form a eutectic or a quasi-eutectic mixture. Actually, this property makes them suitable for separation with melt crystallization [14].

Melt crystallization can be performed as *layer crystallization* or *suspension crystallization* [15]. In the course of the former one the crystals separate on a cooled layer in a compact manner, while in the latter procedure they are suspended in the cooled melt. The advantage of layer crystallization is that a liquid-solid phase separation takes place at the same time, thus mechanical separation is no longer needed. Both types have continuous or fractional and static or dynamic versions depending on whether the melt to be crystallized is static or in motion [16].

In melt crystallization the initial binary system is a homogeneous melt in which the component in excess is considered to be the main component, while the one with a low concentration is the contaminant. Depending on the aim, separation is based on the selective liquid-solid phase transition of one of the components. The heat of phase transition is the melting point, which coincides with the solidification point. In an ideal case the system shows considerable eutectic behaviour (**Figure 3**).

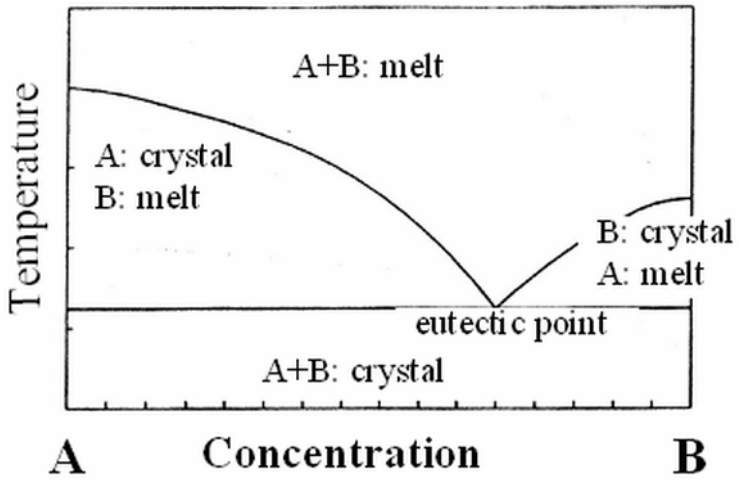


Figure 3 Phase diagram of a two-component eutectic mixture

Kinetically, two processes can be distinguished again, nucleation and crystal growth. In suspension crystallization the crystals can grow in all the three directions, but in the case of

layer crystallization the surface and the neighbouring growing crystals limit growth, and while the free crystal can grow continuously, a crystal in the layer is often enclosed by the neighbouring, rapidly growing crystals and thus it stops growing. In the case of layer crystallization the term layer growth is more appropriate than crystal growth. Nucleation in layer crystallization can be negligible under certain conditions. Here the process can be described as follows: first, irregularly distributed crystals are formed on the layer, then with the formation of more and more crystals a coherent layer is formed, which grows continuously [17]. During layer growth the remaining melt may be enclosed in the layer, thus the layer is composed of the actual crystal layer, the inclusions and the remaining melt adhering to the layer; the latter one covers the surface and may also solidify on it. Therefore additional procedures such as washing and so-called sweating are necessary after crystallization [18]. During washing the crystal aggregate is contacted with a washing solution which removes surface contaminations and inclusions, while sweating means that the inclusions and the melt adhering to the surface are removed with direct heating [19, 20]. The actual separation effect can be expressed with the effective distribution coefficient (k_{eff}), which is the concentration of the component to be removed in the crystal layer ($c_{B,cr}$) divided by the concentration of the component measured in the remaining melt ($c_{B,m}$).

$$k_{eff} = \frac{c_{B,cr}}{c_{B,m}} \tag{11}$$

Ideally, its value is 0, that is the concentration measured in the crystal layer is 0, while if the value of k_{eff} =1, separation did not take place.

3.1.3. Melt technology

In several fields of industry dealing with the production, use or further processing of materials the shape, surface, size and particle size distribution of the particles are very important material properties. Their importance in terms of drug formulation lies in the fact that these macromorphological properties influence, for example, the space filling, flow properties or surface treatment (coating) of a material, through which its tablettability, encapsulation capacity or bioavailability are influenced considerably.

Several methods are known to exist for producing particles of a given shape or size including, for instance, various milling procedures or agglomeration, but melt technology also gives a possibility for this, starting from the melt [21, 22]. The method involves the aimed

solidification of the melt, which means that particles of a given size and shape are produced from the initial melt. This procedure is also known in literature as pelleting or granulation. The liquid melt is a frequent end product of chemical reactions, in this case this method results in a product which can be handled and stored easily, in other cases the aim is to obtain a shape suitable for further processing [23-25].

One possibility provided by melt technology is droplet formation, which results in products of uniform shape, quality and stability [26, 27]. The essence of the procedure is that droplets are formed from the melt with the use of an instrument, then they are solidified with cooling [28, 29]. Cooling can be carried out both directly and indirectly. If direct cooling is applied, the melted material is in direct contact with the liquid cooling medium, but occasionally it may be a problem that the cooling liquid has to be removed from the system subsequently or that the shape of the end product may be influenced by the physical parameters, e.g. viscosity, of the medium. This problem can be eliminated with indirect cooling as the material is crystallized on a cooling surface cooled from below. Particles of various shapes can be obtained with this method, from pellets to spherical particles, the size of which can range from a few millimetres to a few centimetres [30]. Even rectangular or pillow-shaped particles can be produced by using or supplementing the instrument.

The method described can be used excellently during the production of certain pharmaceutical base materials which are required to have a uniform form, surface and size. This procedure makes the further processing of active ingredients and auxiliary materials simpler and cheaper (direct pressing, encapsulation). For instance, active ingredient particles produced in this way can be surface-treated or coated directly, and thus the effect can be modified according to the aim desired. On the other hand, this method gives the possibility to prepare matrices, when the matrix product can be prepared directly from the melt of the mixture of the active ingredient and the excipient. By choosing the proper composition the release of the active ingredient from the matrix and thus its bioavailability can be influenced.

3.2. Characteristics of the amorphous structure

Although there are many ways for producing a partially or completely amorphous material, the supercooling of the melt is mentioned the most commonly in literature when preparing glassy systems. **Figure 4** illustrates the basic difference between formulating a

crystalline and an amorphous material, the enthalpy of the solid material can be seen in relation to temperature [31].

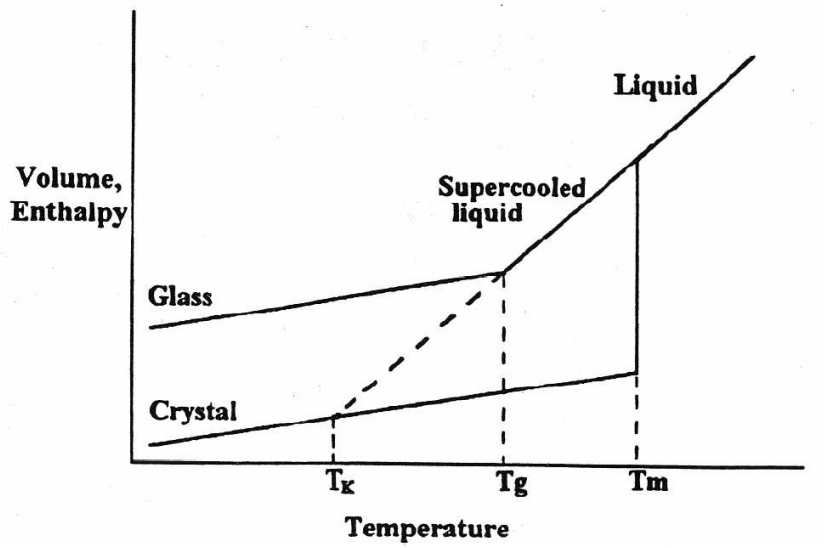


Figure 4 Schematic representation of enthalpy (or specific volume) in relation to temperature

A crystalline material has a low enthalpy value at a low temperature, and it changes with temperature slightly and uniformly until the melting point of the material is reached (T_m). Upon reaching the melting point, the material starts to melt. The temperature does not increase any more with further heat transfer, the energy transferred is used for melting until the material is completely melted. This is called latent melting heat. The heat capacity of a melted material is higher than that of a crystalline one, which means that it absorbs more heat with a smaller temperature rise, this is shown by the changed slope of the line in the figure. Thus two things happen when a crystalline material melts: a certain quantity of heat is absorbed, this is latent melting heat, and the heat capacity of the material changes. These processes are called first-order phase transitions. When starting from a liquid state, if the temperature is decreased until the melting point, transition to the crystalline phase will occur; this means a thermodynamically stable state below T_m, in contrast with the non-crystalline state. The exothermal crystallization process leads to the sudden contraction of the system, which in turn results in the decrease of specific volume. Thus enthalpy (H) and specific volume (V) decrease at the temperature of the melting point.

When an amorphous material is heated, the temperature also increases continuously until a characteristic value. This is called glass transition temperature (T_g), at which T does not stop increasing, therefore there is no latent heat. The temperature continues to rise although

not to the same extent, as the heat capacity of the material increases after glass transition. These transitions, during which heat capacity changes but there is no latent heat, are called second-order phase transitions.

During the rapid cooling of the melt the value of H follows the equilibrium curve typical of the liquid, then a supercooled liquid is formed by cooling the system below T_m, which is an amorphous state with a structure typical of liquids but with much higher viscosity. Upon further cooling, when the value of T_g is reached, the material vitrifies in a liquid state, the bonds between the molecules are similar to a liquid state, but the translational and rotational motions among them decrease considerably while vibratory movements are intensified. When a glassy material is formed, the cooling rate is too fast for crystallization to take place, or crystallization fails to occur because of the shape or size of the molecules, which is common e.g. in the case of proteins.

The properties of a glassy material at temperature T_g differ from the properties of the equilibrium supercooled liquid, the glassy material is characterized by a non-equilibrium state with a higher enthalpy value. The consequences of higher internal energy include changed thermodynamic properties, better solubility, higher vapour pressure and greater molecular mobility as compared to the crystalline state. Amorphous systems have a greater chemical reactivity, and as follows from **Figure 4**, they are liable to crystallize spontaneously thereby aiming to reach a thermodynamically more stable state with lower internal energy [32].

3.2.1. Occurrence and importance of amorphous character in pharmacy

The pharmaceutical importance of the above-mentioned characteristics of amorphous structure lies in the fact that higher internal energy and together with this greater specific volume may lead to increased solubility and bioavailability, at the same time the amorphous material may change back spontaneously into crystalline form during storage or certain technological operations, particularly due to the effect of higher temperature or relative humidity [33, 34]. As, compared to crystalline materials, the molecules of amorphous materials are in a metastable state thermodynamically, the potential for crystallization is always present in the material during storage or handling. Such crystallization is probably in the background of phenomena like e. g. the post-hardening (ageing) of tablets after pressing [35], the structural collapse of lyophilized products [36] or the particle aggregation of powders intended for dry inhalation [37].

During pharmaceutical research, factors which may influence processibility, stability, bioavailability and therapeutic effect have to be considered when choosing active ingredients and auxiliary materials used in the composition of a solid dosage form.

Similarly to other solid materials, pharmaceutical base materials are rare to occur in a completely crystalline or completely amorphous form, therefore it is essential to know how a partially crystalline or amorphous system can be expected to behave. The simultaneous presence of the two thermodynamically different parts in the same material can result in a characteristic, well-measurable heterogeneity in a material, or in the random variation of the properties of the material from sample to sample. The presence of one phase in the other can be the starting point for spontaneous phase transitions such as e. g. crystallization [38]. If the relationship between the two phases is even more direct, their properties will not be independent from each other, either. For instance, in the case of solid dispersions, if a crystalline material is dispersed in an amorphous embedding material, this will change the T_g value of the amorphous phase measured previously [39].

In the field of pharmacy, amorphous materials are encountered basically in two cases. One is when the presence of the amorphous part in the material is intentional in order to make the most of its individual physical and chemical properties and thus to improve the biopharmaceutical or other characteristics of the product. For example, if an amorphous mixture is prepared from a poorly water-soluble crystalline material with an auxiliary material of high water-solubility, this will bring favourable consequences as solubility, and thus bioavailability, will be increased [40].

The other possibility is that our material is a crystalline one and a certain quantity of amorphous form is produced accidentally during certain procedures (e.g. milling, lyophilization, granulation, drying), which has the potential to change the physical and chemical properties of the material [41, 42].

In the course of drug formulation several auxiliary materials are used in a completely or partially amorphous state, for example microcrystalline cellulose, starch or sugar esters, and there are also auxiliary materials which are produced specifically in an amorphous form in order to achieve better properties, this is exemplified by spray dried lactose.

3.2.2. Amorphous character and physical properties

There are several examples in the field of pharmaceutical technology when the amorphous character of a material influences major physical parameters [43]. The effect of the degree of crystallinity of cellulose on tablettability was examined. The results showed that cellulose of a lower degree of crystallinity resulted in tablets of lower strength than cellulose of a higher degree of crystallinity did [44]. Further research revealed that there was no direct proportion between the two parameters, but microcrystalline cellulose with a degree of crystallinity of 53-82% proved to have better pressing properties than the material containing a crystalline part of 26-49% [45].

3.2.3. Amorphous character and chemical stability

In many cases chemical stability depends on the amorphous or crystalline character of the materials [46].

The examination of cefoxitin-sodium revealed that temperature-dependent decomposition increased considerably in the case of the amorphous form [47].

The amorphous form of the sodium and potassium salt of penicillin G prepared with evaporation from solution is less stable chemically than the crystalline form. Crystalline potassium-penicillin resists dry heat for several hours without considerable decomposition. The activity of the amorphous form shows a major decrease under the same conditions [48].

3.2.4. Amorphous character and bioavailability

It is well-known that the rate of release determines bioavailability in the case of oral drug preparations in which drug release is the first step of absorption [49]. The rate of dissolution of the crystalline and amorphous forms of indomethacin in water and in a water-ethanol mixture was investigated. The results showed that the dissolution of the amorphous material was faster in both cases [50].

Efficiency depends on the degree of crystallinity in the case of insulin, too. When insulin is reacted with zinc chloride, an insoluble complex is formed, and it can precipitate in an amorphous or crystalline form, depending on the pH value. The suspension containing an amorphous insulin-zinc complex has a rapid effect, is absorbed easily, the effect has a rapid

onset and lasts for a short time. On the other hand, the insulin-zinc suspension containing a crystalline complex is absorbed very slowly and has a long-lasting effect. The therapeutic preparation is formulated from a suspension which contains a complex of 7 crystalline and 3 amorphous parts, thus a medium-term effect can be achieved. A further difference between the two forms is particle size. Fast-acting insulin contains small particles, while slow-acting insulin has large ones, which is another example for absorption and bioavailability being determined by the amorphous or crystalline nature of the product and by the concomitant change of particle size [51].

The differences between crystalline and amorphous forms were investigated for novobiocin, too. Tablets and capsules were formulated by using the sodium salt of novobiocin, which is active upon oral administration but is chemically unstable in solution. On the other hand, the insoluble forms of novobiocin acid are chemically stable. Crystalline novobiocin acid is absorbed to a smaller extent and it does not reach a therapeutically efficient blood level when administered orally. In contrast with this, its amorphous form is absorbed easily and is active therapeutically. This difference in bioavailability is due to the different water-solubility of the two forms. At 25°C the amorphous form dissolves in 0.1n HCl 10 times better than the crystalline form, and this difference in solubility is manifested in absorption from the gastrointestinal tract, too. However, amorphous novobiocin is gradually crystallized in an aqueous medium, which leads to reduced absorption and finally to the entire loss of the therapeutic effect. Additives suppressing crystallization have to be used in order to prevent this. Methyl-cellulose, PVP, sodium alginate, propylene glycol alginate, etc. are suitable for this purpose [52].

3.3. Investigation methods for determining amorphous and crystalline states

The basis of the analytical methods suitable for studying the crystalline-amorphous transition is that several physical properties of the material such as density, viscosity, heat capacity, X-ray diffraction or diffusion properties change during transition. Therefore methods which measure these material properties either directly or indirectly can be used for detecting the presence of the amorphous material, and some of them are also suitable for the quantitative measurement of the amorphous content of a partially crystalline material, that is the degree of crystallinity.

3.3.1. Diffraction procedures

Unlike crystalline materials, amorphous materials do not have a well-defined three-dimensional molecular structure. The consequence of the disordered internal structure is that electromagnetic radiation is diffracted irregularly or scattered diffusely by the molecules, as compared to crystalline materials. Thus diffraction techniques are the most authentic analytical procedures for studying the molecular structure of a material or for the quantitative measurement of the degree of order. Among them, the most widespread method is X-ray diffraction, which will be discussed in more detail later.

3.3.2. Methods for volume measurement

Another parameter which can describe an amorphous material is its volume. Because of the irregular arrangement of the molecules, specific volume is greater while density is lower in amorphous materials than in crystalline structures, thus the so-called "free volume" is greater (**Figure 4**). The use of a gas-displacement pycnometer for the determination of the amorphous content of a partially crystalline drug material was described, the accuracy of the measurement was ±10% [42]. A liquid-displacement pycnometer was used to determine the crystallinity of certain starches [53], and it was also applied for the quantitative measurement of a small degree of disorder in crystalline drugs [54].
However, given the difficulty to determine the small volume and density difference between crystalline and amorphous states precisely and the time-consuming nature of these methods, they have not become widespread in practice for studying the amorphous state.

3.3.3. Viscosity measurement

One of the characteristic properties of the amorphous state is viscosity, the value of which is $<10^{12}$ Pa·s over the glass transition temperature and $>10^{12}$ Pa·s below it. The methods which can be used for determination are very special, therefore they are applied only in specially-equipped research laboratories [55].

3.3.4. Spectroscopic methods

Various spectroscopic methods can be used successfully for studying the amorphous structure on account of their excellent structure resolution power. Such procedures are e.g. the following: nuclear magnetic resonance (*NMR*) [56], solid state nuclear magnetic resonance (*SSNMR*) [57], Raman spectroscopy [58], infrared spectroscopy (*IR*), electron spin resonance (*ESR*) [59, 60], which can be used efficiently to determine the glass transition temperature or to detect the % amorphous content [61-63]. Not only simple powders or solutions but finished dosage forms, too, can be examined with these non-destructive methods.

3.3.5. Thermal methods

Methods of thermal analytics are also widely used for the investigation of the amorphous state [64, 65], they can be employed to determine the glass transition temperature or the major thermodynamic parameters of the amorphous state like heat capacity or enthalpy change.

Thermal analysis includes procedures which measure some of the physical-chemical properties of the sample as a function of temperature. They have several application possibilities in pharmaceutical industry [66-69]. They are used, for example, for identification, for the description of active and inactive components, for routine analysis, for quality control and for stability examinations [70].

3.3.6. Methods based on moisture sorption

Amorphous and crystalline materials also differ considerably with respect to moisture sorption [41]. A crystalline material is capable of *adsorbing* a small amount of moisture on its surface, or it forms a "solvate" with a larger quantity. On the other hand, an amorphous material is capable of *absorbing* a large quantity of moisture, even 100% of its mass. This property can be measured with the following methods: water vapour sorption, gravimetric methods (vacuum microbalance, saturated salt solution) and certain volume measurement and potentiometric methods [71-73].

It is clear from the previous chapters that there are several reliable and precise methods for the examination and description of amorphous drug materials, including not only initial base materials but also the finished dosage form. The most typical difference between these procedures is to what extent they can be used for the quantitative measurement of order or disorder in a partially amorphous system, or for monitoring the molecular-level changes in a wide temperature range.

4. Materials and methods

4.1. Materials

4.1.1. Lactose

Alpha-lactose monohydrate was chosen as the model material because it is well known that its crystalline and amorphous forms, as auxiliary materials, influence the production and stability 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). The particle size was in the range of 50–280 μm. In order to prepare totally amorphous lactose crystalline alpha-lactose monohydrate was dissolved in water at a ratio 1:10 to obtain a solution for spray drying. 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, inlet and outlet temperature: 175°C and 80°C. The crystallinity of the SD lactose is considered as 0%. The average particle diameter of SD lactose was 5–30 μm. The resulting amorphous particles were kept in a glass vial and stored in a desiccator at 30% relative humidity (*RH*) and room temperature (50-60% RH is the critical RH for crystallization of amorphous lactose) [74].

Physical mixtures of amorphous and crystalline lactose were prepared to achieve 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95 and 100% crystalline content by weight. The components were weighed to a total amount of 25 g and were mixed in a Turbula mixer (Turbula WAB, System Schatz, Switzerland) with 10 g of 2 mm glass beads. The powder mixture was stored at 30% RH and room temperature up to the analysis.

4.1.2. Sugar alcohols

Sugar alcohols such as mannitol and sorbitol are widely used in the pharmaceutical and food industry. They have the sweetness of sugars but they have a lower caloric value, they are not cariogenic and they are suitable for diabetics.

Mannitol has a strong tendency to crystallize, nonetheless exists in fully or partially amorphous state in certain formulations. Because of its low chemical reactivity and low hygroscopicity, it is used in tablet formulation as filling and binding material in a direct compression of suckable, chewable and effervescent tablets. In food industry they are used for the production of sweets and chewing gums. The modern use of spray-dried mannitol is the stabilization of proteins in aerosols. It is also frequently used as auxiliary material in spray- and freeze drying.

Sorbitol is the stereoisomer of mannitol, it is easily compressible but its disadvantage is its high hygroscopicity.

Both materials can be used for the preparation of solid dispersions, in order to increase the dissolution rate of poorly water soluble drugs and to amorphize materials with a propensity for polymorphism. In the preparation of solid dispersion systems the drugs can be mixed in melted excipients and after solidification this is suitable for further processing. Sorbitol and mannitol are suitable for this purpose because they are very stable to heat and melt without decomposition.

β-*D*-mannitol (Ph.Eur.4) and *D*-sorbitol (Ph.Eur.4) were used for the study. The particle size of both materials was in the range of 0.16-0.32 mm. At first, physical mixtures were prepared to achieve 0, 10, 30, 50, 70, 90 and 100% sorbitol content by mass. The components were weighed and then mixed in a Turbula mixer (Turbula WAB, System Schatz, Switzerland) for 10 min. The prepared mixtures were divided into two parts. The first portion was processed hereafter as a physical mixture, the second portion was melted and then the solidified melt was used for further studies. During melting, the mixtures were heated in a furnace up to 170ºC and then cooled at room temperature. The solidified by cooling materials were pulverized and sieved (0.16-0.32 mm). During the preparation and storage of the mixtures <55% relative humidity was ensured because of the strong plasticizing effect of water.

A Korsch EKO eccentric tablet machine (Emil Korsch Mashinenfabrik, Berlin, Germany) was applied for tablet forming. The compression tools were single, flat punches 10 mm in

diameter, furnished with strain gauges. The rate of compression was 30 tablets/min with a pressure forces 2, 4 and 6 kN, at room temperature of 24ºC and relative humidity of 45%. The mass of tablets was 0.20 g.

4.2. Methods

4.2.1. X-ray powder diffraction (XRPD)

XRPD is the traditional and at the same time one of the most reliable procedures for studying crystalline structure. The basis of this examination is that the monochromatic unidirectional X-ray collides with the atom, from the electron shell of which one or several electrons are displaced. Upon returning to their original path, these electrons emit their energy gain in the form of X-ray radiation. The atoms in a crystalline material are arranged in a regular crystal lattice, the individual radiations emitted by them are accumulated at certain points of the space according to the laws of interference, and this makes the examination of the crystalline structure possible. Powdered crystalline materials have a characteristic X-ray diffraction picture, which consists of peaks of a certain position and with varying intensity. In contrast with crystalline materials, the induced atoms of the amorphous material are arranged irregularly, therefore the emitted radiation is diffused and thus cannot be measured.

Thus X-ray diffraction can be used to determine the structure of the crystalline material, to identify the crystal modifications of a given material, to determine the various crystal forms of the same material or the relative quantity of the components in a mixture containing various crystalline materials. There are references in literature about the application of the traditional X-ray diffraction method for determining a minimum quantity of 5% of a non-crystalline component in a material [42], and also about the monitoring of phase transitions or for the quantification of a crystalline material embedded in an amorphous auxiliary material [75].

However, it must be noted that diffraction techniques are capable of identifying molecular order; disorder – which is indicative of the amorphous structure – is only an accompanying phenomenon, so these methods are suitable for confirming the presence of the amorphous structure but not for studying it.

4.2.2. Near Infrared Spectroscopy (NIRS)

The method of near infrared spectroscopy (NIRS) was first used widely in agricultural and food industrial research, e.g. for determining the moisture, protein and starch content of grain or for detecting the components of various foods. Its pharmaceutical use came only later, and the range of its application possibilities is continuously widening today [76].

This method has several advantages over other analytical procedures. The sample does not need preparation so it can be measured directly, the measurement takes only a short time so a great number of samples can be measured. The samples can even be measured in their original packagings if fibre optics is used. Several characteristic parameters can be determined simultaneously from one measurement, the examination does not destroy the material so it can be subjected to further investigations. No chemicals are needed for the examination, so it is environment friendly and cost-effective.

Near infrared spectroscopy is an analytical procedure based on the interaction between the sample and near infrared radiation. Near infrared radiation encompasses the 700-2500 nm range of the electromagnetic spectrum. During radiation, the vibrational and rotational states of the molecules are induced while some of the photons are *absorbed*, some are *transmitted* and pass through the sample, and some are *reflected* from the surface of the sample. The energy changes of the sample components are indicated by the spectrum, for which the intensity of the reflected or transmitted light is used. The spectrum shows the reflectance or absorbance calculated from it (*log 1/R*) as a function of wavelength. The spectrum of a sample is the result of the light absorption of the bonds between certain molecules (-CH, -NH, -OH, -SH) at different wavelengths, arising as the vector sum of fundamental vibrations, overtones and their combination.

NIRS can be used for qualitative and quantitative determinations in various fields of pharmacy. Both the physical and chemical properties of a sample can be determined with this method, and it can also be used for identification, qualification or occasionally quantification. Identification is carried out on the basis of spectrum libraries, qualification gives to what extent a given property of the sample differs from the former one, while in the case of quantification a sample series has to be prepared in which the quantity of the component to be measured is varied while keeping the other quantities the same.

The identification and qualification of base materials is an extremely important field of application [77, 78]. Literature references were found, for example, about the investigation of the structure of cellulose [79], about the monitoring of the re-crystallization of amorphous

lactose [80] or about the determination of the type of polyvinyl pirrolidone [81]. Particle size can also be determined with NIRS. The basis of the method is that reflectance increases with the decrease of the average particle size of the pure sample [82, 83].

In-process examinations include certain technological processes, for example fermentation, mixing or drying, which can be monitored with the help of NIRS and their efficiency can be controlled [84, 85], but it is also possible to control production processes on-line [86]. Moisture determination is such a possibility, it is based on the fact that the OH bond in water shows a characteristic absorption in the range of 1900-2000 nm. Several physical and chemical properties of water can be determined with NIRS, such as density, refractive index, dielectric constant, surface tension or ionization constant [87]. NIRS has been applied to investigate the water content of freeze-dried products, the residual moisture of lyophilized sugar in a sealed glass vessel or the moisture content of organic solvents [88]. This method can be used for checking homogeneity in the case of powder mixtures [89] or for investigating the stability of base materials [90]. Decomposition processes can be monitored, the investigation of the decomposition products of intact aspirin tablets with NIRS has been described [91].

The NIRS technique also has an important role *in the investigation of finished products*. Several references were found in which NIRS was used for the investigation of the active ingredient of tablets and capsules (lovastatin, simvastatin, enalapril) [92-94]. In the case of tablets NIRS can also be used for the examination of the uniformity of the active ingredient, the measurement can be performed even through the PVC blister [95]. The applicability of NIRS for the determination of the hardness of tablets was also confirmed [96, 97]. It gives the possibility to identify and to qualify tablets [98, 99], to determine their active ingredient content [100, 101], or to measure the thickness of the film coat [102] and by means of this even to predict drug release [103]. Moreover, this method can also be used for the measurement of transdermal preparations [104] or for the investigation of ointments, e.g. for the determination of their active ingredient content [105]. The moisture content of lyophilized injections through a glass vial [106, 107] and the moisture content of gelatine capsules and proteins were also measured [108, 109].

4.2.3. Differential Scanning Calorimetry (DSC)

In the DSC apparatus the sample and the reference material – which is a thermally inactive material – are in a common, thermally isolated space. The sample is heated or cooled by the furnace according to a controlled temperature program. The two thermocouples are switched on opposite each other, thus no current flows through ΔT galvanometer until the temperatures of the sample and of the inert material are the same. If some transformation accompanied by heat absorption or heat release starts in the sample, the temperature increase stops or is accelerated. Meanwhile, the temperature of the inert material continuously and steadily rises, which leads to a temperature difference between the two materials, ΔT galvanometer deviates. During the DSC measurement the amount of energy used for the equalization of this temperature difference is measured, thus the energy change or energy transition of various thermal processes becomes measurable [110]. The measurement results are plotted and evaluated with a calorigram, from which both qualitative and quantitative data can be read. The shape of the peak indicates the quality, impurity of the material, and the area under the curve is proportional to the energy amount used for equalizing the temperature difference.

The DSC method can be used both in qualitative and quantitative examinations. The processes of crystallization, modification change, polymorphic transitions, melting, evaporation and decomposition can be investigated qualitatively [111, 112]. A quantitative aim can be to determine enthalpy, specific heat or degree of crystallinity, or to examine the degree of impurity. Melting, desolvation, dehydration, reduction reactions and decomposition processes are processes which result in characteristic endothermic peaks in the DSC curves. Exothermic peaks are seen when the processes of crystallization, re-crystallization or oxidation are investigated [113].

4.3. Examination parameters

X-Ray Powder Diffraction (XRPD)

XRPD profiles were taken with an X-ray powder diffractometer (Philips PW 1050/70 PW 1710). The measurement conditions were as follows: radiation source: Cu Kα, scan speed (2θ): 0.035, step size (2θ): 0.035, time per step (s): 1.0.

Near Infrared Spectroscopy (NIRS)

The diffusion reflectance was measured by a Hitachi U-3501 UV/VIS/NIR spectrophotometer (Hitachi Ltd., Japan) equipped with integrating sphere (*d*=60 mm) and PbS detector. Solid samples were placed into the 5-mm layered sample holder of the instrument and the diffuse reflectance spectra were recorded in the 200–2600 nm wavelength range.

Differential Scanning Calorimetry (DSC)

DSC studies were performed using a DSC 821^e(Mettler-Toledo GmbH, Switzerland). The instrument was calibrated using indium.

In the case of lactose samples, samples of approximately 4 to 4.5 mg were weighed into non-hermetically sealed aluminium pans. The samples were heated from 20 to 240°C at a heating rate of 5°C min^{-1}.

In the case of sugar alcohols, samples of 15-20 mg were heated in a hermetically sealed aluminium pan. At first the samples were heated from 25ºC to 200ºC at a heating rate of 3.5°C min^{-1}. Then the samples were cooled in liquid nitrogen, subsequently the mixtures were reheated from -20ºC to 200ºC at the rate of 3.5°C min^{-1}.

Study of tablets

The tablets were stored in sealed glass containers at room temperature of 20±2ºC and 50±5% relative humidity. The crushing strength was investigated with Heberlein apparatus (Flisa, Le Locle, Switzerland). The crushing strength was determined one day (24 h) after formulation because of the texture change (elastic recovery).

5. Results

5.1. Lactose

5.1.1. X-Ray powder diffraction

It was confirmed with X-ray diffraction that the initial α-lactose monohydrate sample was a 100% crystalline material.

The profile of the crystalline form (**Figure 5**) had specific diffraction peaks at 12.39-12.53°; 16.2-16.38°; 19.12° and 19.59°. At these 2 theta (2θ) values the greatest relative intensity values can be measured.

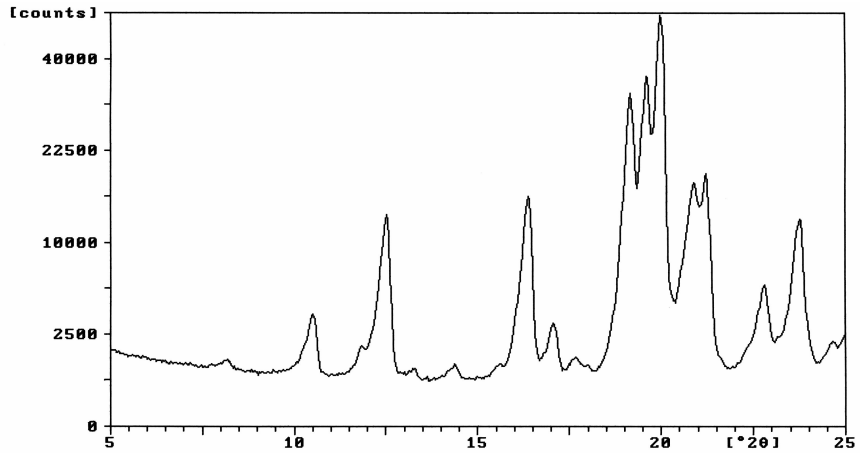


Figure 5 X-ray diffractogram of the crystalline α-lactose monohydrate

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 of the individual components diffraction is in proportion to the quantity of the components in mixture. So quantification is possible [114]. The intensity values were read from the diffractograms of the mixtures at the chosen 2θ values of the 100% crystalline sample (**Table I**).

Table I Intensity values at chosen 2θ values

Concentration of crystalline part (%)	Intensity			
	2 theta (2θ) values (^{o})			
	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

Analysis was performed on these data sets by Multiple Linear Regression (*MLR*). The dependent variable is the crystallinity and the independent variables are the intensity values at chosen 2θ values. The confidential interval was 95% (α=0.05).

From this calculation a calibration equation was achieved:

$$Y = 0.3626 + a_1 \cdot x_1 + a_2 \cdot x_2 + a_3 \cdot x_3 + a_4 \cdot x_4, \qquad (12)$$

where Y is the crystallinity (%), 0.3626 denotes the intercept, a represents the regression coefficients (**Table II**), x denotes the intensity.

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

2 theta (^{o})	Regression coefficient (a_1-a_4)
12.39-12.53	0.007536
16.2-16.38	0.01496
19.12	-0.00878
19.59	0.008496

On the basis of this equation the predicted crystallinity can be obtained. **Figure 6** shows the relation between the actual and predicted crystallinity.

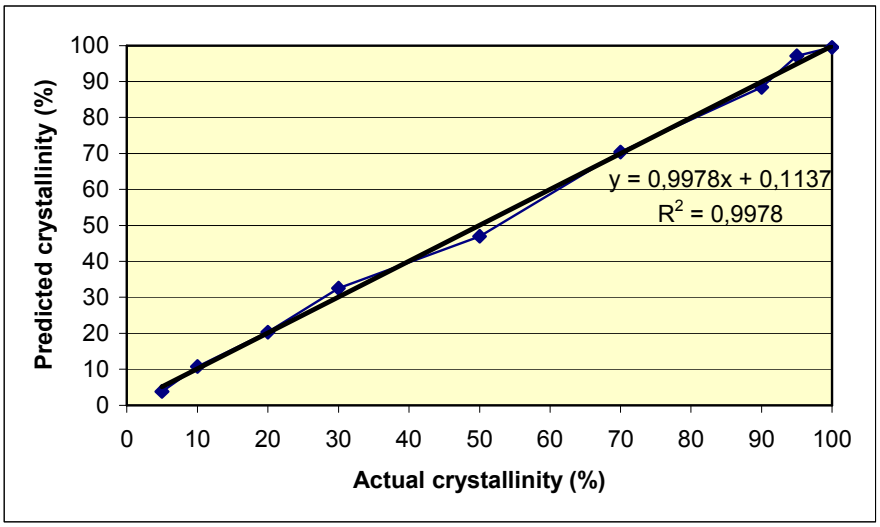


Figure 6 Relation between predicted and actual crystallinity of physical mixtures of crystalline and amorphous lactose, determined by conventional X-ray powder diffraction

The slope of the line is 0.9978, the intercept is 0.1137 and the correlation coefficient (R^2) is 0.9978.

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

5.1.2. Near Infrared Spectroscopy

Three spectra of each sample were collected and subsequently averaged to produce a single spectrum used for further analysis. The measured reflectance data were transformed into log(*1/R*) in order to convert reflectance to absorbance.

Comparison of the crystalline and amorphous lactose results in a different absorbance spectrum (**Figure 7**), where increased hydrogen bonding shifts OH bands to higher wavelengths (first overtone from 1480 to 1550 nm, second overtone from 1000 to 1060 nm). Apart from different intensities observed in the UV range at 290 and 360 nm,

absorbance values of the crystalline form were also lower at the characteristic wavelengths of OH combination band (~2100 nm) and CH absorption bands at about 1200 nm (second overtone), 1400 nm (combination), and 1760 nm (first overtone).

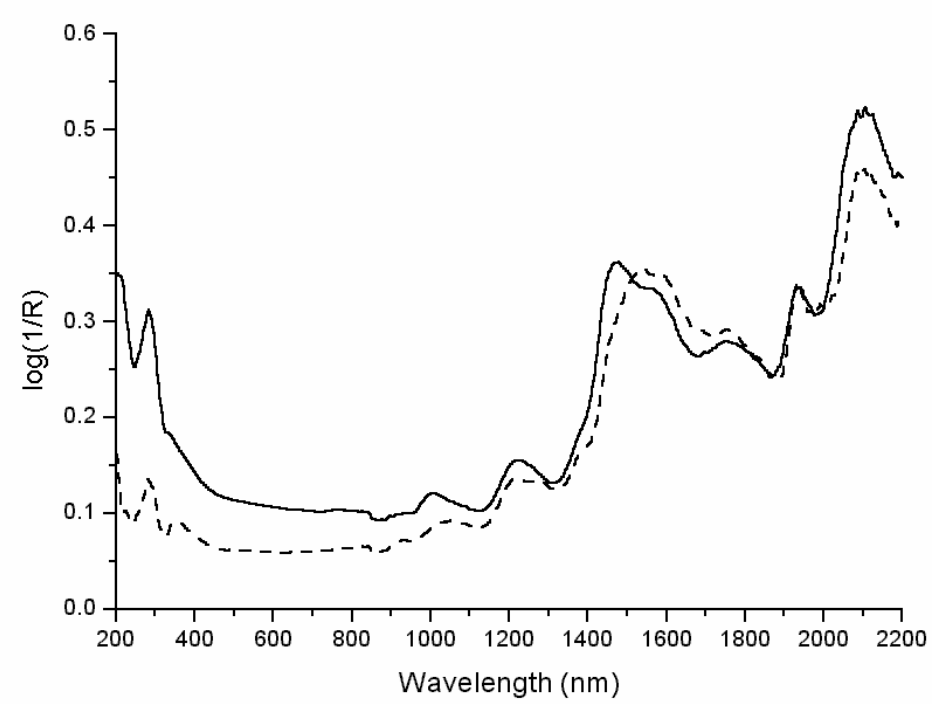


Figure 7 Absorbance [*log(1/R)*] spectrum of amorphous and crystalline lactose sample (*solid*: amorphous, *dashed*: crystalline)

Quantification of crystallinity was performed using second-derivative spectra (**Figure 8**) in order to minimize the well-known effects of particle size and variable scattering of NIR radiation. In addition, the second-derivative spectrum has the benefit of normalizing the baseline (exclusion of the upward baseline shift) and sharpening spectra features.

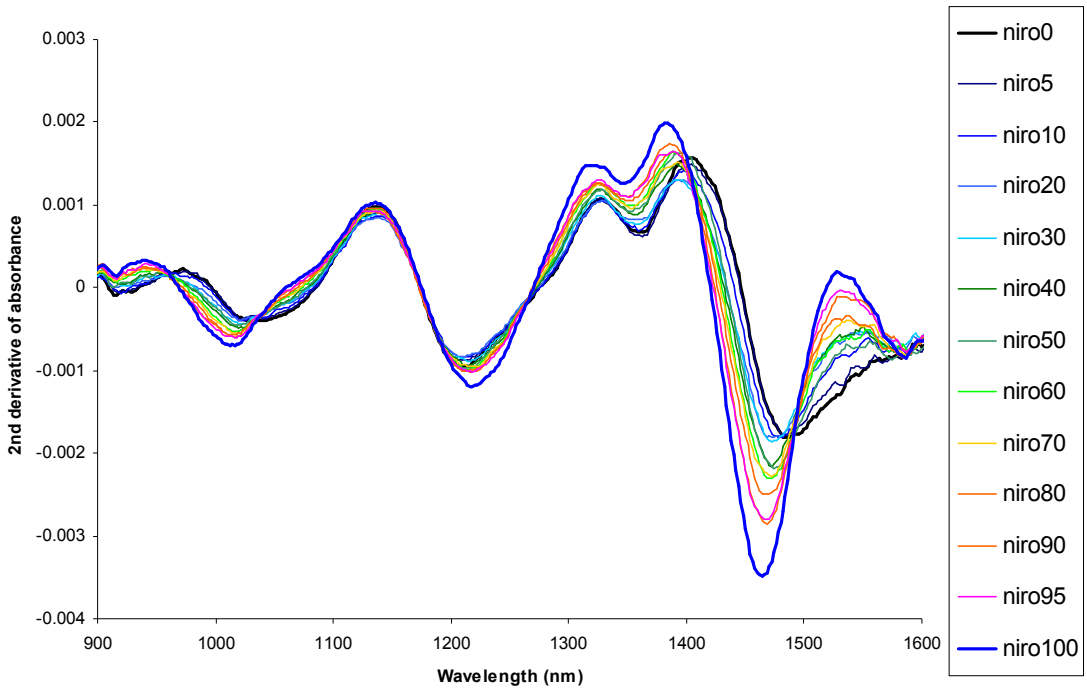


Figure 8 Second derivative spectra of absorbance spectra of mixtures

Using the second-derivative values, MLR was performed at different wavelengths (**Table III**). The wavelengths were chosen on the basis of distinct differences of the spectra. The dependent variable is the crystallinity and the independent variables are the second-derivative values of absorbance values. The confidence interval was set at 95% (α=0.05). The following calibration equation was constructed:

$$Y = 257.62 + a_1x_1 + a_2x_2 + \ldots a_{11}x_{11}, \quad (13)$$

where Y denotes the crystallinity, the value 257.62 represents the intercept, a_{1-11} denotes the regression coefficients (**Table III**), x_{1-11} represent the second-derivative values of absorbance spectra at the characteristic wavelengths.

Table III Regression coefficients of equation (13) determined by Near Infrared Spectroscopy

Wavelength (nm)	Regression coefficient (a_1-a_{11})
298	63.35
386	-1136.86
916	6364.18
1016	-1955.00
1216	-3318.20
1360	-1982.80
1484	1820.77
1534	-44023.55
1536	45880.45
1946	-1442.98
2090	-979.23

In the case of an unknown sample, after taking the spectrum, the degree of crystallinity (%) of the sample can be obtained if the second derivatives of the absorbance values are substituted into the equation. **Figure 9** shows the relation between the actual and predicted crystallinity determined by NIRS.

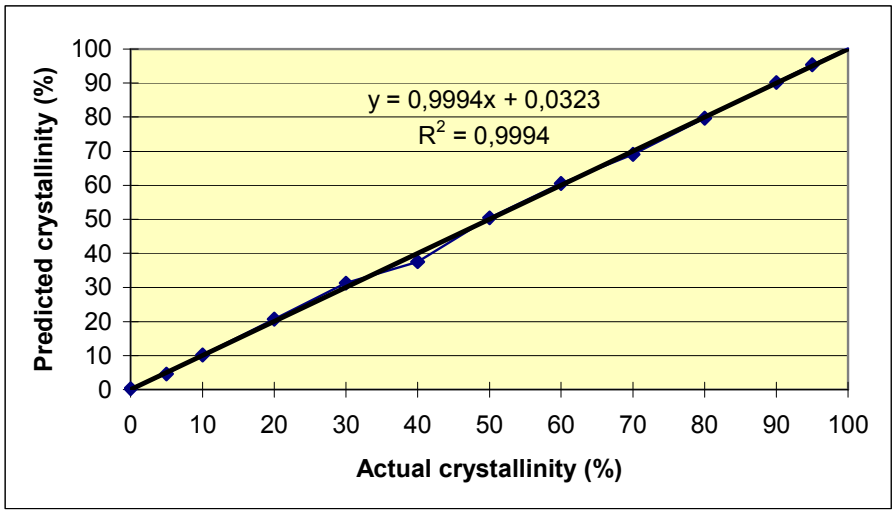


Figure 9 Relation between predicted and actual crystallinity of physical mixtures of crystalline and amorphous lactose, determined by Near Infrared Spectroscopy

The value of the correlation coefficient of the determination (R^2=*0.9994*) shows a close correlation. Thus, NIR spectroscopy is an appropriate method for the quantitative evaluation of crystallinity of pharmaceutical products.

5.1.3. Differential Scanning Calorimetry

The DSC measurements of the samples were recorded. The DSC curve for 100% amorphous lactose is shown in **Figure 10.**

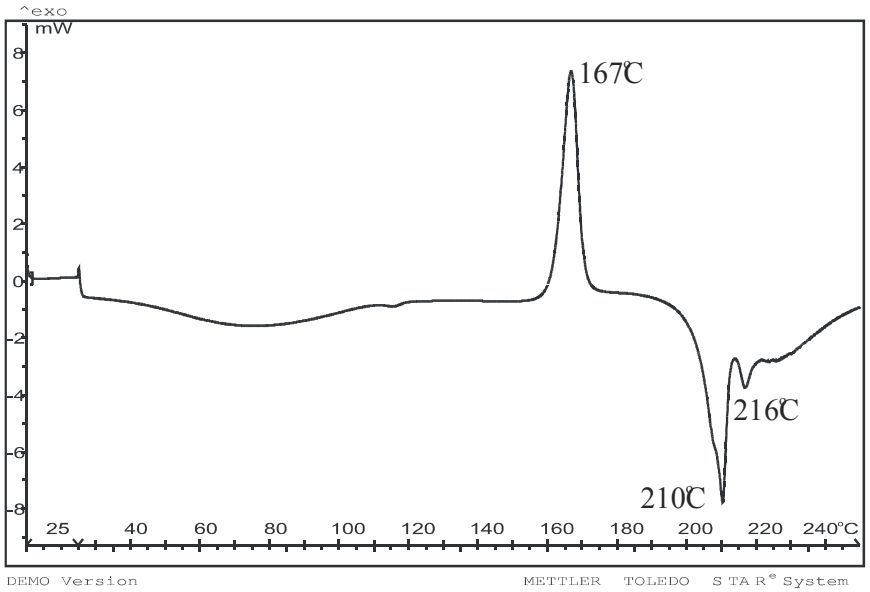


Figure 10 DSC curve for 100% amorphous lactose

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°C 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.

In case of the 100% crystalline sample the DSC diagram has an endothermic peak at 144°C, which represents the loss of crystalline water. This is proven by thermogravimetric analysis, where the sample loses 4.34% water in the range of 130-160°C. The endothermic peak is followed by two melts of α and β forms at 213°C and 224°C (**Figure 11**).

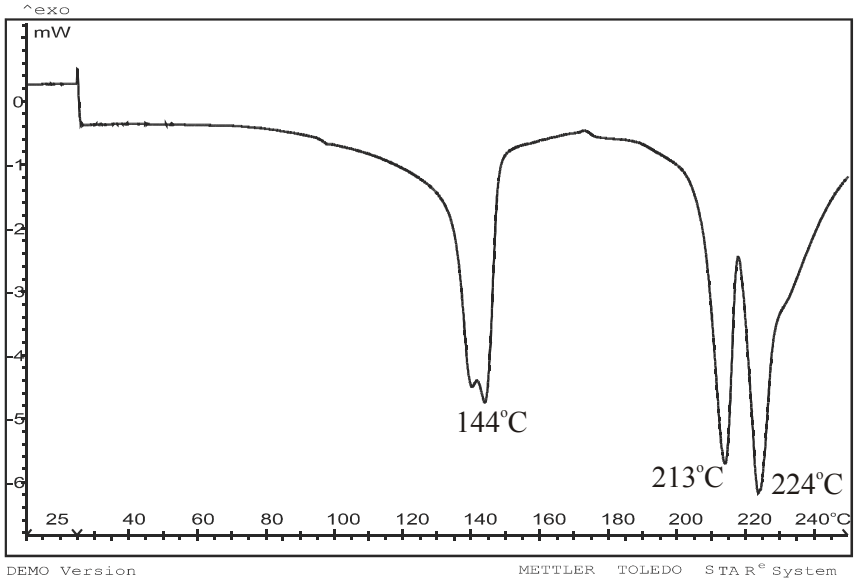


Figure 11 DSC curve for 100% crystalline α-lactose monohydrate

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.

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 (**Figure 12**).

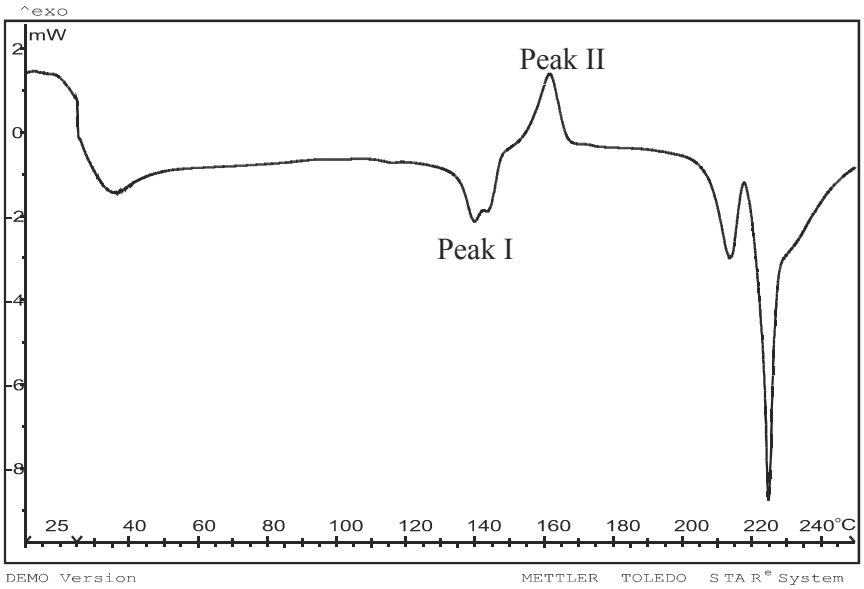


Figure 12 DSC curve of the sample with 50% amorphous part. (*Peak I*: endothermic peak typical for the crystalline form, *Peak II*: exothermic peak typical for the amorphous form)

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 for quantitative evaluation.

20-100% 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 IV** shows the energy values of the exothermic peak typical for crystallization in the mixtures with different proportions.

Table IV Transition energy values of the mixtures with different crystallinity

Degree of crystallinity (%)	**Transition energy (J/g)**
0	112.15
5	99.31
10	95.64
20	78.3
30	55.93
50	39.45
60	33.73
70	28.97
80	14.01

The regression analysis of these values generates the following calibration equation:

$$y = 87.241\text{-}0.825\,x, \tag{14}$$

where y: degree of crystallinity (%), x: transition energy ($J\,g^{-1}$), *87.241*:intercept, *0.825*; slope. The 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 13** shows the predicted crystallinity (determined by regression analysis) as a function of 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 the 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.

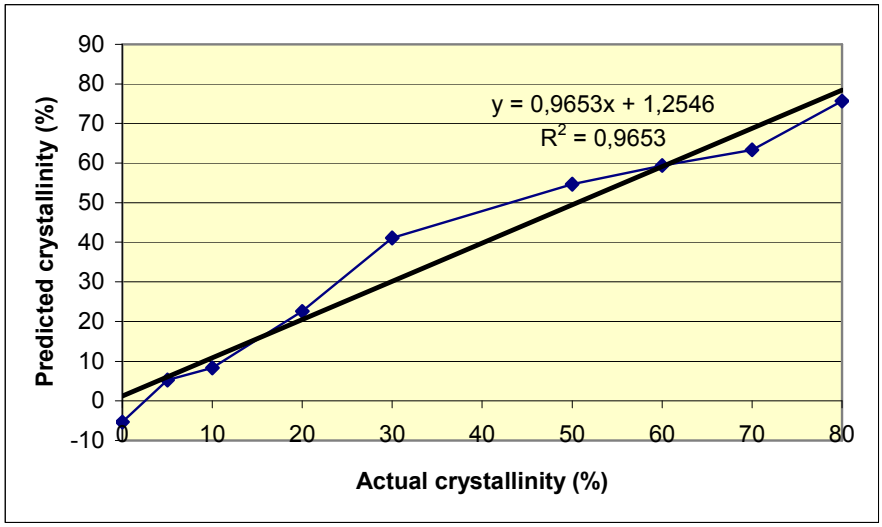


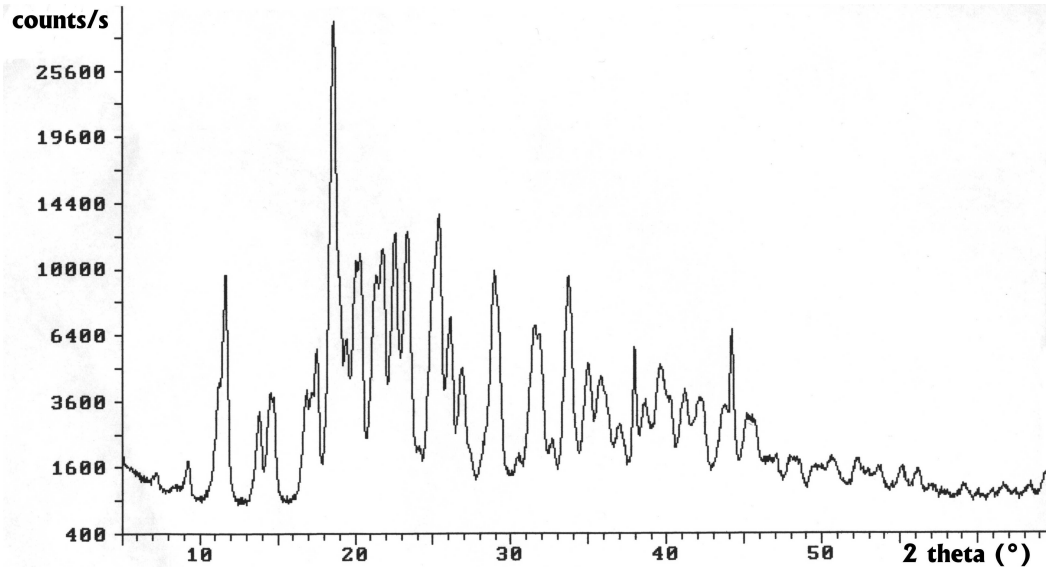
Figure 13 Relation between predicted and actual crystallinity of physical mixtures of crystalline and amorphous lactose, determined by DSC

5.2. Sugar alcohols

5.2.1. Thermal behaviour of pure sorbitol and mannitol

On the first DSC scan pure sorbitol melted at 96.8ºC, and by cooling it cannot be recrystallized from its melt. If vitrified systematically, this leads to an amorphous state, which can be proved by X-ray powder diffraction (**Figure 14**). On the second DSC scan at -2.3ºC glass transition (*T*g) was observed (**Table V**).

a)



b)

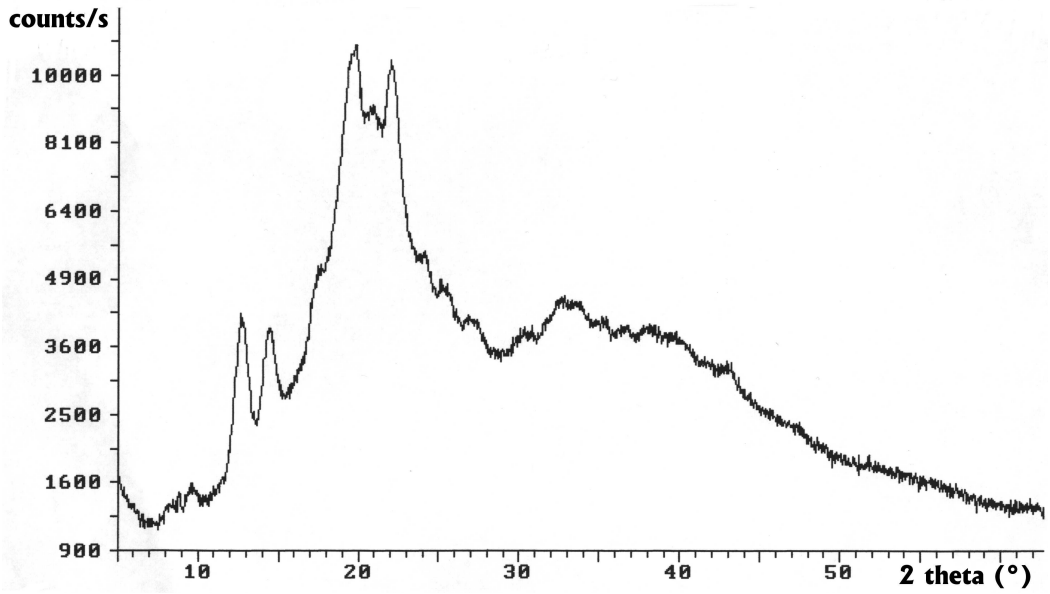
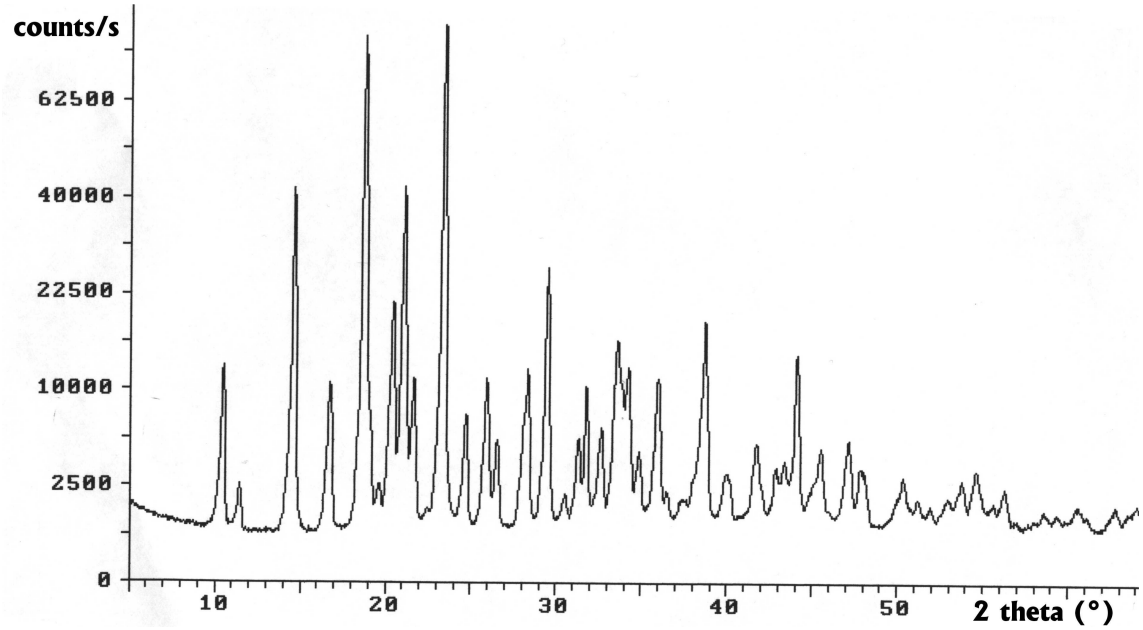


Figure 14 X-ray powder diffractograms of pure sorbitol (*a*) and sorbitol cooled after melting (*b*)

The starting mannitol was β-*D*-mannitol, observed by XRPD, which melted at 165ºC on the first heating. The melt crystallized during cooling as α-*D*-mannitol, therefore polymorph

transition took place (**Figure 15**). In case of mannitol no glass transition was observed on the second DSC scan (**Table V**).

a)



b)

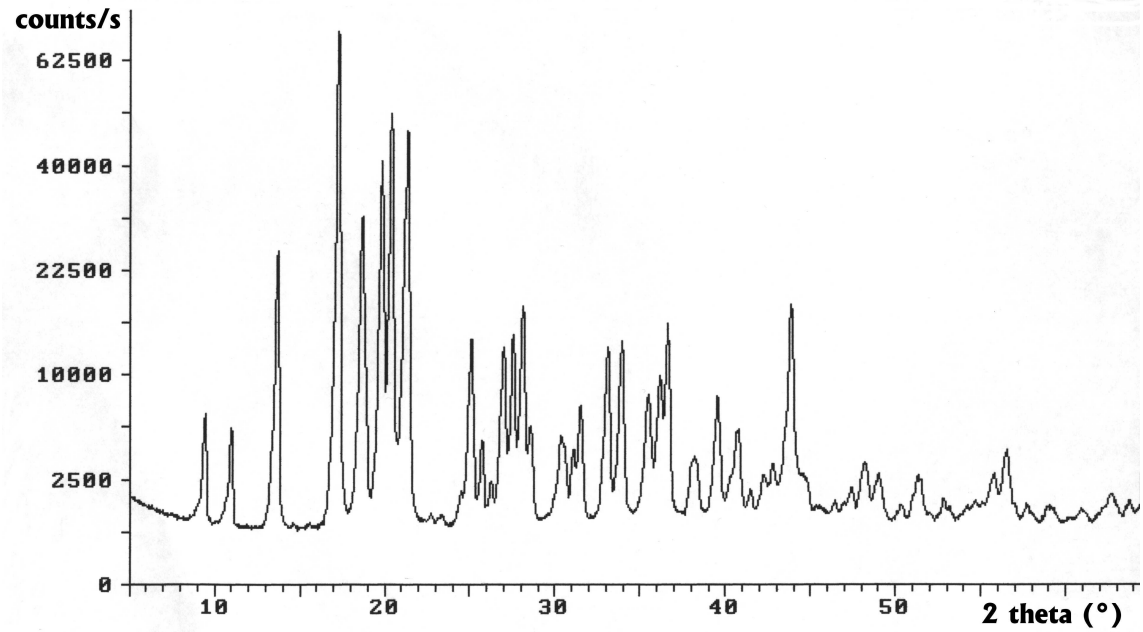


Figure 15 X-ray powder diffractograms of pure mannitol (*a*) and mannitol cooled after melting (*b*)

Table V Characteristic thermal parameters of sorbitol and mannitol

	T_m (ºC)	ΔH_m(J/g)	T_g (ºC)
sorbitol	96.8	217	-2.3
mannitol	165	338	-

It can be stated that neither pure mannitol nor pure sorbitol is suitable for hot melt technology. Because of mannitol's high melting temperature, it cannot be used in case of materials which decompose at this temperature. Sorbitol's vitrified state after melting is difficult to handle during further processing. Our additional aim was to eliminate these problems with mixing the two sugar alcohols.

5.2.2. Thermal behaviour of the different sorbitol and mannitol mixtures

During the examination of the mixtures, the decrease in the melting temperature of mannitol was observed when the ratio of sorbitol was increased in the mixture, because mannitol dissolves in sorbitol melt (**Figure 16**). On the other hand, the melting point of sorbitol was only slightly affected by the presence of mannitol with a higher melting point. The eutectic temperature was detected at 93.6ºC.

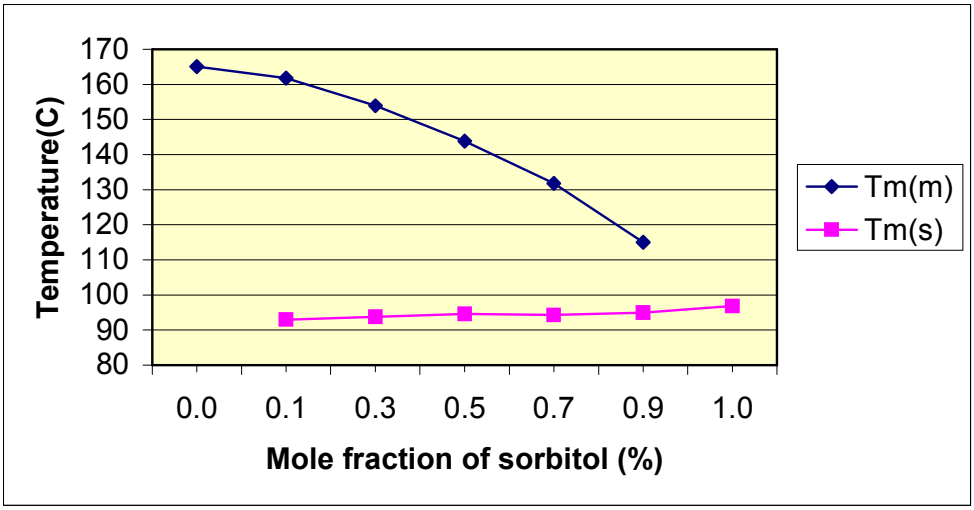
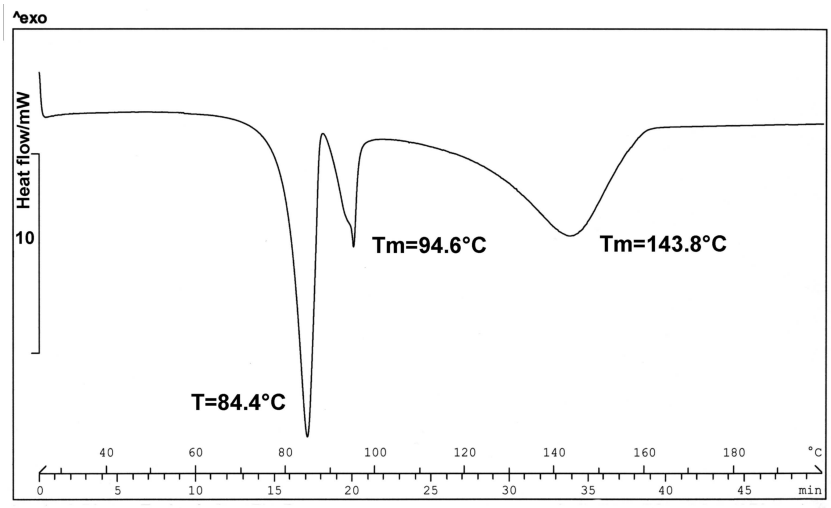


Figure 16 The melting temperature (*Tm*) of sorbitol (*s*) and mannitol (*m*) in relation to mole fraction of sorbitol in the mixtures

In case of the 50% mannitol and 50% sorbitol mixture, the melting of sorbitol and mannitol was observed in the form of two endothermic peaks (94.6ºC and 143.8ºC). The endothermic peak at 84.4ºC was not characterized. During the second DSC scan glass transition was detected at 4.9ºC, this was followed by crystallization exotherm of mannitol at 59.8ºC and melting endotherm of mannitol at 142.8ºC (**Figure 17**).

a)



b)

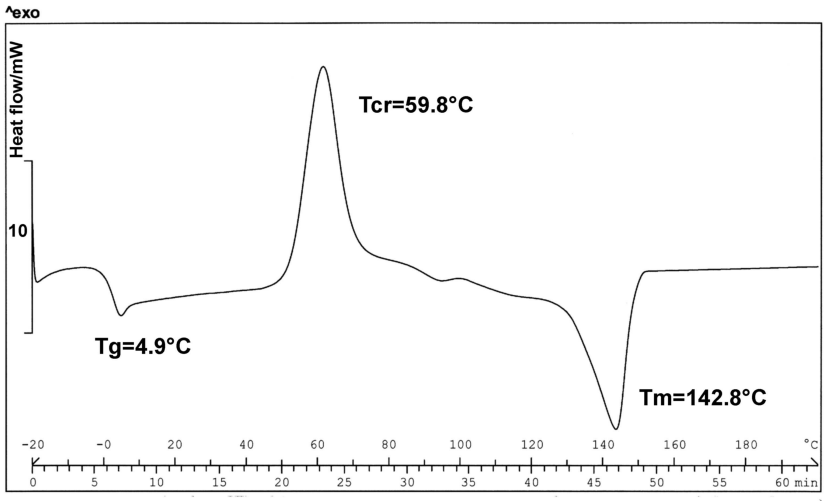


Figure 17 DSC curve of the mixture with 50% mannitol+50% sorbitol (*a*: first scan and *b*: second scan)

When the ratio of sorbitol was lower than 30%, no glass transition was detected on the second DSC scan. When the sorbitol content was above 90%, only glass transition was detected (**Table VI**).

Table VI Thermal parameters of sorbitol and mannitol mixtures during the second heating

Sorbitol content (%)	T_g (ºC)	T_{cr} (ºC)	T_m (ºC)
0	-	-	165
10	-	-	161.5
30	-	52.2	154
50	4.91	59.8	142.8
70	1.96	81.2	131.8
90	-1.39	-	-
100	-2.3	-	-

It can be stated that the vitrification of sorbitol cannot be avoided with the addition of mannitol. However much mannitol is mixed with sorbitol, the crystallization of sorbitol cannot be achieved. When the high melting point of mannitol is the problem during processing, this can be improved with the addition of sorbitol. The melting point of mannitol decreases when mixed with sorbitol as seen in **Figure 16**. A further question is whether these mixtures are technologically suitable for further processing.

5.2.3. Results of tablet study

In the case of tablets prepared from physical mixtures, the crushing strength increased with the increase of the sorbitol ratio at all three pressure forces (**Table VII**).

The melted and solidified mixtures were pressed with the same method as the simple physical mixtures. In the case of melted mannitol, tablets could not be pressed with pressure forces 2 and 4 kN because the tablets broke easily and disintegrated. With the other mixtures all three pressure forces could be used. The crushing strength of the tablets prepared from melted mixtures increased with the increase of pressure forces and also with the increase of the sorbitol ratio. The tablets formulated from the solidified melt of pure sorbitol were the strongest.

The comparison of physical mixtures and melted/solidified samples with the same component ratio shows that, when the sorbitol content was lower than 50%, tablets of physical mixtures were stronger, and when the sorbitol content was above or equal to 50%, the tablets of melted mixtures had higher crushing strength values (**Table VII**).

Table VII Crushing strength of tablets (*N*) at different pressure forces

Sorbitol (%)	**2 kN**		**4 kN**		**6 kN**	
	physical mixture	**melted mixture**	**physical mixture**	**melted mixture**	**physical mixture**	**melted mixture**
0	31.6	-	38	-	51.2	22.4
10	39.6	18	43.6	26	52.8	40
30	47.2	26	60	55.3	74.8	66
50	50.6	62	62	90.7	75.2	114.6
70	76.8	163.3	109.6	176	114.4	177.3
90	122	192.6	162.4	195.3	171.6	197.3
100	126	198.7	166	>200	179.6	>200

6. Summary

Nowadays a great variety of base materials is processed in pharmaceutical research, increasingly diverse dosage forms appear the formulation of which necessitates new technologies, and the relevant requirements are stricter and stricter. The quality of initial materials and finished dosage forms is gaining in importance, and new aspects like cost-effectiveness and environment protection come to the foreground during procession.

Amorphous materials are increasingly common during the production of dosage forms, either as an initial material or as a finished product specifically produced in this form, or possibly as a non-desirable form occurring in the course of operations. This makes it necessary to know more about the crystalline or amorphous character of the materials, to quantify the degree of crystallinity. Moreover, one should study the procedures which can help us to produce crystalline and amorphous materials such as crystallization procedures from solution and from melt, spray drying, etc, and also the technological procedures during which these properties can be expected to change. Besides, it may also be important to have more thorough knowledge about operations (see melt technology) which can offer many possibilities in respect of pharmaceutical production but are not utilized widely enough yet.
In order to achieve the above aims, analytical methods have to be developed which are suitable for monitoring the changes arising during thermal processes on the one hand, and for qualifying base materials, intermediate and finished products on the other hand. There is great demand for the quantitative determination of the degree of crystallinity as quickly, simply and precisely as possible.

The results of my research could be summarized as follows:

$\Rightarrow$ In the case of lactose, it was proved with X-ray diffraction that the initial material was really 100% crystalline α-lactose monohydrate, and also that a 100% amorphous product could really be formulated by its spray drying, with the parameters developed by us. The examination of the mixture samples confirmed that the samples obtained with the proper physical mixture of the initial crystalline and amorphous materials represented the various degrees of crystallinity well.

The X-ray diffraction examinations confirmed the fact already known from literature that this method is very reliable in the quantitative determination of the degree of crystallinity. For this reason, it was expedient to choose this method as a starting method and to compare the other two procedures with it.

The results of our NIRS examinations revealed that this method is also suitable for determining the degree of crystallinity with proper accuracy. **Figure 18** shows the values of the degree of crystallinity predicted with the NIRS method as a function of the values estimated with X-ray diffraction.

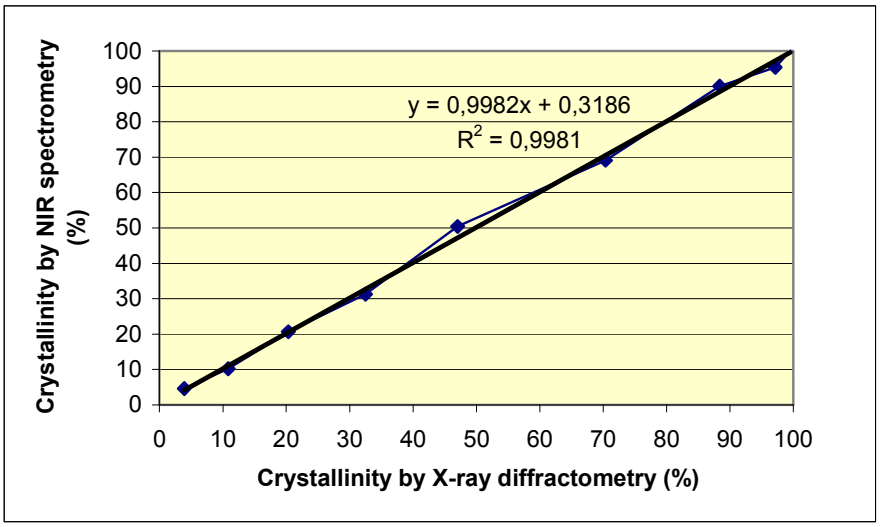


Figure 18 Relationship between the values of the degree of crystallinity determined with the NIRS and XRPD methods

On the basis of this, NIRS can definitely be recommended for the quantitative determination of the degree of crystallinity of α-lactose monohydrate.

It was confirmed with DSC examinations that the procedure can be used excellently for studying the crystalline-amorphous transition, important thermodynamic parameters of the sample can be given with its use.

In the quantitative determination it can actually be considered to be a semi-quantitative method as only minimum 20% of amorphous content could be detected with certainty.

However, the advantage of DSC is that great amorphous content not detectable with X-ray diffraction can also be identified quantitatively.

In the case of lactose, the presence of the amorphous form in the sample influences compressibility. This parameter is important as lactose is widely used as an auxiliary material in tablet formulation. With respect to compressibility, it is ideal if the product contains more than 30% of amorphous part. DSC can be used to determine this, and there are several other cases where its accuracy suffices. As the DSC method is commonly used for other examinations in pharmaceutical industry, the determination of the degree of crystallinity can add to its range of application.

$\Rightarrow$ The examinations with the chosen sugar alcohols, sorbitol and mannitol, were mainly aimed at determining in what form these materials can be used in melt technology and also at studying their thermal behaviour.

It was proved during the investigations that the use of D-mannitol or D-sorbitol alone is disadvantageous in melt technology. It is true for both materials that they do not decompose at their melting point, which in itself would make them suitable for the preparation of solid dispersions. However, the use of mannitol is limited by its high melting point and also by its polymorhic transition after melting (β-D-mannitol$\rightarrow$ α-D-mannitol). Moreover, after sorbitol is melted, it is vitrified in a gel-like form (T_g= -2.3°C) so its handling is very difficult or even impossible during further processing.

We tried to eliminate these problems by mixing the two materials. It can be concluded from the research that the glass transition of sorbitol after melting cannot be avoided and the crystallization of the material cannot be achieved with the addition of mannitol. The high melting point of mannitol can be decreased by adding sorbitol. Thus its original melting point of 165°C can even be lowered to 115°C. However, in this case the mix shows glass transition characteristic of pure sorbitol, so it is not advantageous in respect of further processing. A similar situation arises in the case of a eutectic mixture (melting point: 93.6°C) containing 1.8% mannitol and 98.2% sorbitol.

When the thermoanalytical data were compared with the crushing strength studies performed, the mixture of 30% mannitol and 70% sorbitol was found to be the best. The melting point of this sample was 131.8°C. After melting and solidification, we could press tablets with the greatest crushing strength from this sample.

The sample preparation we used was a good model for the material changes occurring during melt technology, and it could be monitored and described well with the chosen method (DSC).

A good possibility in processing base materials is offered by the preparation of solid solutions or dispersions, when the active ingredient is dispersed in the melt of the excipients, and after solidification it becomes suitable for further processing. Thus, for example, the solubility of poorly soluble active ingredients can be enhanced or materials with a propensity for polymorphism can be amorphized.

However, neither mannitol nor sorbitol is suitable for this in itself, the desired thermal properties could be achieved and the requirements expected during further processing could be met only by combining the two materials in proper proportions.

In sum, the investigations performed drew attention to the fact that although melt technology can be applied in pharmacy, the procedure has its limitations and should be used with great care.

7. Supplement

Since the results of the thesis and the related publications have appeared, research in the fields concerned has developed dynamically and much progress has been made both in terms of the methods applied and their measurement accuracy. In the following I would like to summarize the most important achievements.

Several new methods were tried for the description of crystalline and amorphous lactose and for the determination of the degree of crystallinity, and their applicability was confirmed. These include Raman spectroscopic method [115] and the solid state NMR (SSNMR) method [116] which proved to be good and accurate methods for quantification.

The accuracy of determining the crystalline or amorphous part of lactose with NIRS and XRPD methods was reduced below 1% [117].

Organic dynamic vapour sorption was described as a new method for determining a low amorphous content [118].

The applicability of DSC for quantifying small amounts of amorphous content in materials was examined in new research. One possibility for this is to heat the sample over T_g thereby inducing spontaneous re-crystallization, which appears as an exothermic peak on the thermogram. The area under this peak is proportional to the amorphous content of the material [119].

At the same time it was found that in the case of lactose the traditional DSC method for quantification should be applied with caution, because in a partially amorphous sample not only the re-crystallization of the amorphous part takes place but also the simultaneous dehydration of the hydrate form. The re-crystallized products of partially and entirely amorphous lactose samples differ from each other: that of the entirely amorphous sample also contains crystalline anhydrate, while the re-crystallized partially amorphous sample will be a monohydrate.
Because of all these, it is difficult to evaluate the traditional DSC curve in such cases as it is exactly the process of re-crystallization which is examined and analysed by it. For this reason the methods of modulated temperature DSC (*MTDSC*), high speed DSC (*hyper DSC*) and StepScan DSC (*SS-DSC*) were used, which measure C_p (specific heat capacity) at temperature T_g. The value of this is proportional to the amorphous content. These are novel methods in the field of pharmacy, their use gives 1% or smaller measurement accuracy, which is better than the measurement accuracy achievable with the traditional DSC method [120].

A new method was also developed for the preparation of lactose samples of different amorphous content. For this purpose precisely measured quantities of 100% crystalline and 100% amorphous products were mixed in different proportions both in previous studies and in the present work. In this case the mass proportion of the crystalline and the amorphous parts gave the amorphous content of the sample, supposing that the crystalline and amorphous phases were of the same density. However, this is considered to be an erroneous supposition by new research. Moreover, it was found that physical mixing results in a product in which the crystalline and amorphous parts are separated as separate phases in different particles. These samples do not model the real situation in which the two phases are in a much more direct relationship within a particle. Therefore it is better to produce spray dried lactose from an ethanol-water solution or suspension, in the course of which products with different amorphous content are made depending on the ethanol/water proportion [120, 121].

Recently there has been increased demand for producing base materials, especially Active Pharmaceutical Ingredients (*API*), with exactly defined and well-reproducible properties. In order to do so, fast, reliable and relevant methods are needed to monitor production processes and to perfect our knowledge about them. Such methods also hold great importance for PAT (Process Analytical Technologies), which are coming into the foreground of attention.

Based on research in this area NIR proved to be one possible method for this purpose, it has several advantages which can make it one of the most reliable on-line or in-line examination methods.
NIR supplemented with fibre optics was used for the investigation of polymorphic changes or amorphous-crystalline changes of state observed during the crystallization of APIs [122]. The research was aimed at improving the safety, productivity and reproducibility of the crystallization of APIs. The real-time data obtained in this way are used for monitoring, optimizing and controlling the process.

An in situ X-ray diffraction technique was developed for the examination of crystallization processes. This procedure, supplemented – if necessary – with ex situ Scanning Electron Microscopy and chromatography, proved to be suitable for studying the phase compositions and structure changes occurring during crystallization.
This method was used to investigate the crystallization of lactose in humid space during spray drying [123], to study the crystallization of spray dried lactose/protein mixtures in humid space [124], and to investigate the crystallization of freeze dried lactose/salt mixtures in humid space, which are widely used in pharmaceutical technology as filling materials in tablets and capsules or as carriers in dry powder inhalation [125].

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