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**Crystallinity changes of organic materials in pharmaceutical
technology**

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1. Introduction

Investigation of the crystal structures of pharmaceutical materials is a continuously increasing interest. The variety of the order of molecules in the unit cell of an active pharmaceutical ingredient (API) can result differences in dissolution rate, wettability, solubility or bioavailability.

Amorphous or glassy materials are in the solid phase, but unlike crystalline ones they lack long-range order. Their lattice energy is at a minimum level, they will not have a characteristic melting point (T_m), but they respond to heating from low temperature by softening at a specific point, which is called the glass transition temperature (T_g). Below T_g amorphous materials are generally brittle and rigid, while above it they are rubbery or viscous. The amorphous form will always be thermodynamically unstable and will tend to recrystallize, as demonstrated many times.

Amorphous form can appear many ways: the material can be amorphized deliberately or it can accidentally be converted into an amorphous form by a pharmaceutical technique. Three basic ways have been developed to amorphize the APIs: solvent methods, hot-melt techniques, and milling. Attention has nowadays started to turn to cases, when the amorphous form is not a particular aim, but is a result of one of the techniques used during the formulation. For that methods are made for prediction of the amorphization or glass-forming properties of any given material. Most authors calculate with the ratio of T_g and T_m . Kerč & Srčić, (1995) classified poor glass-formers as those with $\frac{T_g}{T_m} < 0.7$; while for good glass-formers is $\frac{T_g}{T_m} > 0.7$.

When the aim is the preparation of amorphous solid, suitable excipients can be extremely helpful. Also excipients used in pharmaceutical technology has a high effect on amorphization of a material, when it is not a desired goal.

The methods for the investigation of amorphous materials are based on the various physical and physical-chemical properties: as they can differ in appearance, molecular structure, intra-molecular interactions and hygroscopicity, they can be investigated with a broad number of devices (XRPD, Thermal analysis methods, vibrational spectroscopy, nuclear magnetic resonance etc.)

2. Aims

In present study, our primary aim was to investigate the changes in crystallinity of selected materials, which differ in many aspects, especially in glass-forming properties. To achieve this, we compiled the following steps:

- 1) to establish the literature background of investigation methods which are suitable to follow changes in crystallinity of organic materials with small molecular weights,
- 2) to find an easy and rapid method, that is able to predict the glass-forming properties of given materials,
- 3) to select an excipient pair, which are similar chemically, but differ in crystal structure; which are relatively inexpensive, widely used in pharmaceuticals and have different glass-forming properties. Mannitol and sorbitol turned out to possess these properties,
- 4) to characterize the change in crystallinity of MX without any excipient and also with polymers (PEG, PVP) using different investigation methods,
- 5) to characterize the amorphization tendency of CLP by co-grinding with an inorganic silicon dioxide (Aerosil 200).

3. Materials and Methods

3.1. Finding the model materials

To choose the most suitable model materials for our study 30 possible materials, commonly used in pharmaceuticals were investigated. Melting points (T_m), glass transition (T_g) and their ratio were measured with DSC equipment.

Heating was first applied up to slightly over the melting point. This determined the T_m . After the whole amount of the sample had melted it was cooled down to below the T_g as fast as the device allowed (approximately 45 °C/sec), measurement was then repeated. If the crystalline form of the material emerged, it was considered as poor glass-former. If the amorphous form appeared, the ratio T_g/T_m was calculated and the glass-forming properties were concluded on this basis. For further investigations, we chose materials from the groups of poor and good glass-formers. Two similar sugar-alcohols with dissimilar glass-forming properties were also chosen.

3.2. Mannitol and sorbitol

We first investigated the crystallinity changes of β -D-mannitol and D-sorbitol. Both are widely used in pharmaceuticals as sweeteners, bulking agents or moisture stabilizers (Kim et al., 1998; Maury et al., 2005). Both are stable and inert compounds, properties which make them a good choice as excipients during tableting, freeze-drying, capsulizing, granulating or grinding.

3.3. Meloxicam

Pure crystalline meloxicam (MX) (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-benzothiazine-3-carboxamide-1,1-dioxide) was purchased from EGIS Ltd. Budapest, Hungary.

MX is a non-steroidal anti-inflammatory drug that is mainly applied in therapy as an anti-inflammatory and strong analgetic agent. MX is practically insoluble in water, while it displays a relatively high permeability through cell membranes. It was chosen as model compound because it is capable of hydrogen-bond to other materials.

3.4. Clopidogrel bisulphate

Pure polymorphic form II clopidogrel bisulphate (CLP) (methyl (+)-(*S*)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(*4H*)-acetate sulphate) was obtained from EGIS Ltd., Budapest, Hungary.

CLP is an oral antiplatelet drug, which is often used in the treatment of coronary artery disease, peripheral vascular disease and cerebrovascular disease. The amorphous and polymorphic forms of CLP has been prepared and described in the literature.

3.5. Additives

Polyvinylpyrrolidone (PVP C30, with a molecular weight of 58,000), obtained from BASF (Ludwigshafen, Germany) and polyethylene glycol (PEG 6,000) from Sigma-Aldrich Chemie GmbH, (München, Germany), were used as grinding excipients. Aerosil 200 (colloidal SiO₂, with hydrophilic properties) was purchased from Nippon Aerosil Co., Japan.

4. Methods of sample preparation

Physical mixtures of the crystalline sugar-alcohols (mannitol and sorbitol) and stabilizer polymer additives (PVP C30 and PEG 6,000) were prepared and charged into a hard polyamide mortar. Equal amounts of agate balls were also placed into the chamber. The mass ratio of the mixtures was in all cases 1:1. The grinding processes were carried out with a Fritsch - Pulverisette[®] planetary ball mill. Mixtures were ground at 120 min on 400 rpm. Samples were withdrawn for investigation after 20, 40, 60, 80, 100 and 120 min.

Physical mixtures of MX, as API, and the grinding (stabilizer) polymer (PEG 6 000 or PVP C30) were prepared and charged into the stainless steel jar of a planetary ball mill containing 10 stainless steel balls (Retsch PM 100, Retsch GmbH & Co., Haan, Germany). The mass ratios were based on previous work, so as to give nanoparticles (200-600 nm). For the PVPs, the drug-excipient mass ratio was 1:1, while for the PEGs it was 1:2. Mixtures were

ground for 140 min, samples being withdrawn for investigation after 20, 40, 60, 80, 100, 120 and 140 min. During the grinding process, the temperature of the mortar was measured with an infrared thermometer immediately before sample withdrawal. The temperature of the mortar was not higher than 56 °C throughout milling.

The co-grinding of the mixture of CLP and Aerosil 200 was performed in a planetary ball mill (Retsch PM 100, Retsch GmbH & Co., Germany). The mass ratio of CLP and Aerosil 200 was 7:3. This ratio was based on a previous work by our team (Jóhárt-Laczkovich, 2011). The maximum grinding time was 240 min. Samples were withdrawn for investigation after 15, 30, 45, 60, 90, 120, 150, 180 and 240 min.

5. Methods of investigation

5.1. X-ray powder diffraction (XRPD)

XRPD analysis was performed with Bruker D4 and Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) systems with Cu K λ I radiation ($\lambda = 1.5406 \text{ \AA}$). The samples were scanned at 40 kV and 40 mA from 3° to 40° 2θ , at a scanning speed of 0.05°s⁻¹ and a step size of 0.010°. All manipulations of diffractograms and the calculation of area under curves were performed with DIFFRACTplus EVA software.

In the case of MX samples, we used an internal standard method to avoid the problems caused by the particle size reduction and randomly oriented particles.

5.2. Differential scanning calorimetry (DSC)

DSC data were recorded with a Netzsch STA-409 (Selb, Germany) and a Mettler-Toledo DSC 821e instruments with intercoolers. 4.5-5.5 mg samples were crimped in aluminium pans with two holes and were examined in temperature interval 25-200 °C under an argon gas flow at 100-150 ml min⁻¹, at heating rates of 10 and 20 °C min⁻¹.

5.3. Thermogravimetry (TG)

TG curves were obtained with a TGA/DSC1 (Mettler-Toledo, Switzerland). 4.5-5.5 mg of the samples were crimped in aluminium pans with two holes and were examined in the temperature interval 25-200 °C. Heating rate was 20 °C min⁻¹.

5.4. Fourier transform infrared (FT IR) spectroscopy

FT IR spectra were recorded with a Bio-Rad Digilab Division FTS-65A/896 FT IR spectrometer (Bio-Rad Digilab Division FTS-65A/869, Philadelphia, USA) between 4000 and 400 cm⁻¹, at an optical resolution of 4 cm⁻¹; operating conditions: Harrick's Meridian SplitPea single reflection, diamond, ATR

accessory. Thermo Scientific GRAMS/AI Suite software (Thermo Fisher Scientific Inc., Waltham, USA) was used for the spectral analysis.

For FT IR determinations, the ATR method was chosen, because with this there is no need for sample preparation, such as particle size reduction or KBr tableting, which would expose the samples to further physical stress.

5.5. Scanning electron microscopy (SEM)

The morphology of the MX particles was examined by SEM (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan). A sputter coating apparatus (Bio-Rad SC 502, VG Microtech, Uckfield, UK) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3-13.0 mPa. Briefly, the samples were sputter-coated with gold-palladium under an argon atmosphere, using a gold sputter module in a high-vacuum evaporator and the samples were examined at 10 kV and 10 μ A. MX particle diameter distributions were obtained by analyzing several SEM images with the ImageJ software environment.

6. Results

6.1. Investigation of sugar-alcohols

6.1.1. Determination of crystallinity of mannitol

The DSC measurements indicated that the ratio T_g/T_m (K/K) for pure β -D-mannitol (T_g : 285.75 K T_m : 440.05 K) is lower than 0.7, suggesting that this compound has only a low tendency to exist in amorphous form.

DSC measurements demonstrated that the raw mannitol did not suffer any loss in crystallinity during the grinding process. The mannitol samples made with polymer additives behaved similarly to pure mannitol: the amorphous PVP has no peak in the DSC curve, while the semi-crystalline PEG had a broad melting peak at around 338 K; the mannitol in the mixtures displayed identical melting action to that without polymers.

XRPD measurements were performed on each of the raw materials and samples (Figure 1). Amorphous PVP exhibited a halo with no specific peaks in the diffractogram, while PEG, as a semi-crystalline polymer gave a few broad peaks in the investigated range. Pure mannitol displayed peaks characteristic of the β -D form.

After 120 min of grinding, the same peaks were found in the curve. No shifts were observed, no peaks disappeared and no new peaks appeared. The areas under peaks at 9.5 - $11^\circ 2\theta$; 13.7 - $15.5^\circ 2\theta$ and 17.7 - $19.9^\circ 2\theta$ were calculated for each sample that was withdrawn. This

revealed that, although some peaks decreased to an irrelevant extent, no fundamental change in crystallinity occurred during grinding (Figure 1).

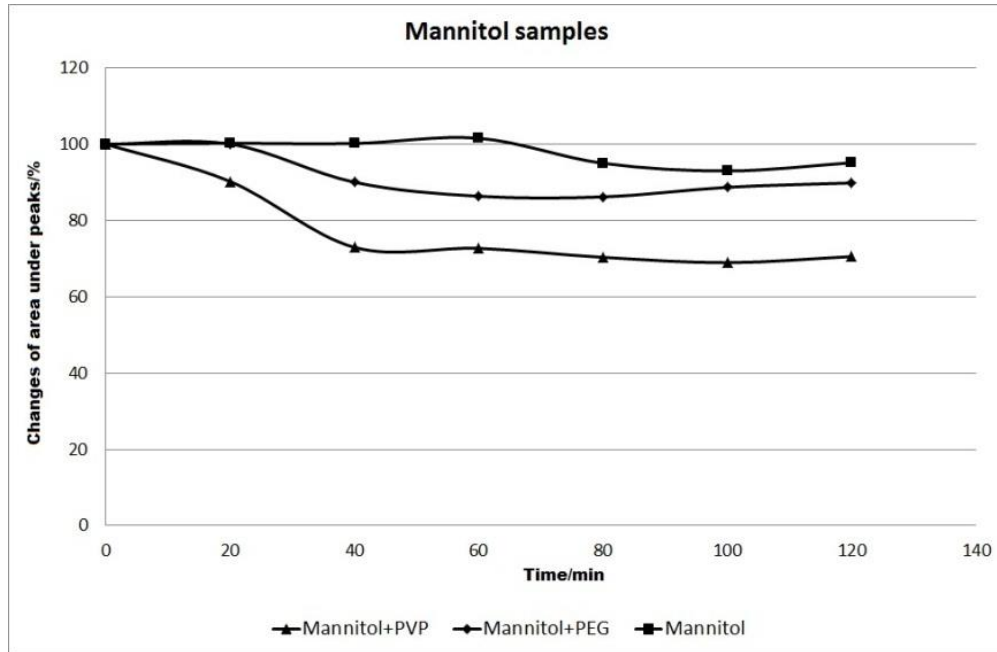


Figure 1 Crystallinity change of mannitol and mannitol ground with polymer additives (PVP and PEG) as a function of the milling time

Same grinding and investigation method was applied in the presence of the polymer additives. The samples containing PEG gave the peaks characteristic of mannitol and the broad peak relating to PEG at around $22-24^\circ 2\theta$. Crystallinity determination (based on the same peaks as utilized in the case of raw mannitol) proved that minor amorphization took place after 40 min of milling. No polymorph transition was observed: no peaks underwent a shift or disappeared and no new peaks were detected. Slightly different behaviour was observed for the samples containing PVP. The peaks were specific for mannitol, but the areas under the curves decreased with increasing grinding duration.

6.1.2. Crystallinity determination of sorbitol

The ratio T_g/T_m (T_g and T_m in K) measured for D-sorbitol was 0.75 (T_g : 273.92 K T_m : 364.55 K), which predicted this material is a good glass-former.

The DSC measurements showed that the sorbitol used was a mixture of the epsilon (T_m : 364.55 K) and gamma (372.05 K) polymorphs. During the grinding process the proportions of the polymorphs changed. The pure material contained a predominance of the epsilon form. The milling led to a decrease in the amount of the epsilon form, while the amount of the gamma polymorph slightly increased (Figure 2). This means that the mechanical energy broke down the

crystal structure of the crystalline epsilon sorbitol. Some of the amorphous material recrystallized due to the mechanical impact.

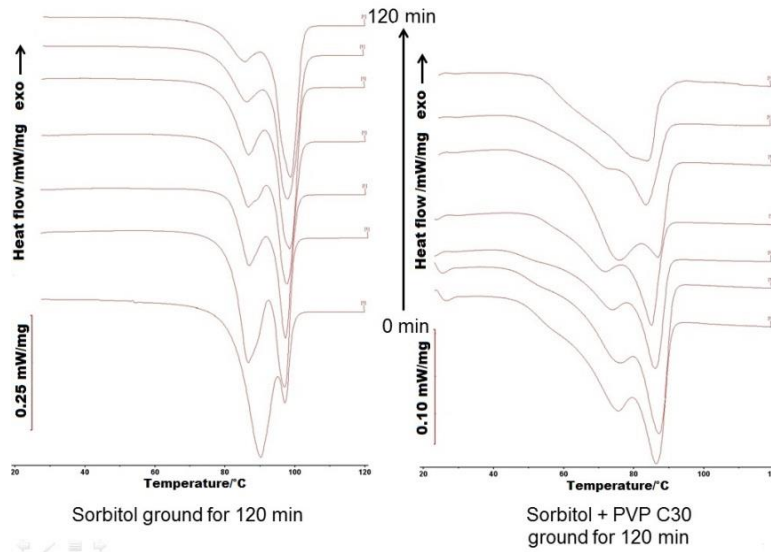


Figure 2 DSC curves of pure sorbitol grinding, and sorbitol ground with PVP C30

A similar phenomenon was observed in the DSC curves of sorbitol co-ground with PVP. The melting point of the sorbitol was lowered by the polymer excipient. Both polymorphs gave characteristic DSC curve. Similarly as when no additive was present, the epsilon polymorph amount decreased during the milling. In this case, the content of gamma polymorph also decreased, as demonstrated by the decrease of the area under the curve. The bulk part of the system lost its well-defined long-range order of the crystal structure.

The DSC investigation of sorbitol samples containing PEG did not show any significant change in crystallinity.

To investigate the change in crystallinity of the co-ground sorbitol and to calculate the extent of amorphization, XRPD method was also carried out on the samples.

The peaks of X-ray diffractograms of pure sorbitol were mostly characteristic of the epsilon form, though the peaks of the gamma form were also present. During the milling process the areas under the peaks relating to the epsilon form noticeably decreased with milling time. In parallel the peaks of the gamma polymorph became slightly larger at a similar rate. A similar polymorph transition took place during the grinding of sorbitol with PVP. During the milling process, the areas under the peaks characteristic of the epsilon form decreased markedly (Figure 3).

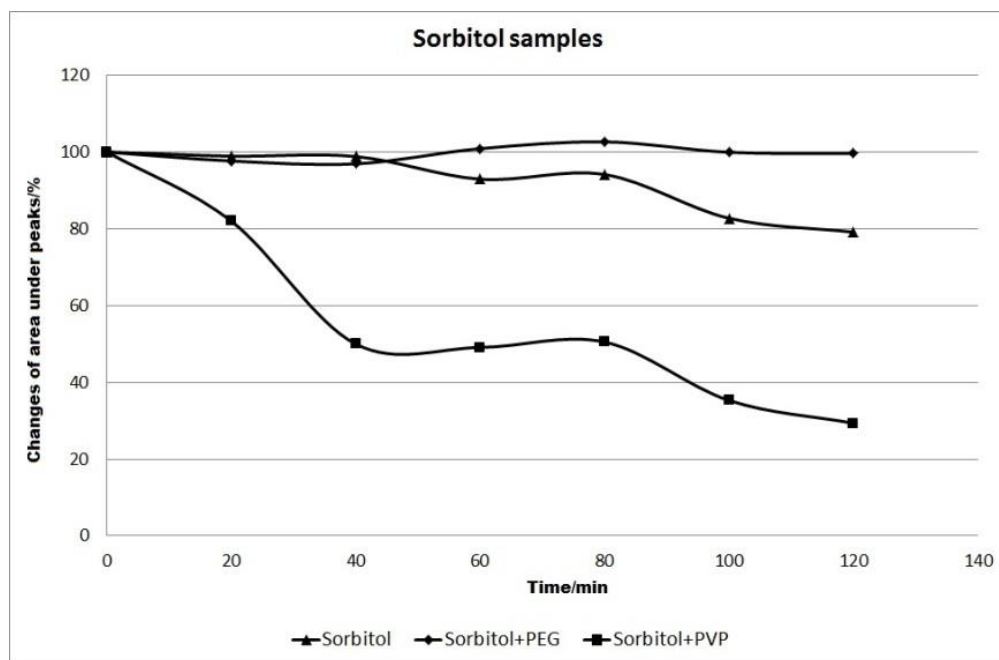


Figure 3 Crystallinity change of sorbitol and sorbitol ground with polymer additives as a function of milling time.

From the areas under the peaks of the epsilon form at $9.5-11^\circ 2\theta$, $23.15-24.53^\circ 2\theta$ and $28.2-29.6^\circ 2\theta$, the degree of reduction in crystallinity was measured. During the first 40 min, the system lost about 50% of its well-defined crystal structure. After 40 min there was an apparent lag phase. At the end of the milling, slightly more than 30% of the sorbitol remained in the epsilon polymorph form. Most of the remaining 70% had lost its well-defined order of molecular packing and a minor part had been transformed into the gamma polymorph.

Only the peak at $11.5-12.1^\circ 2\theta$ is clearly related to the gamma form. All the other peaks were characteristic either of epsilon form or of both polymorphs. This gamma sorbitol peak was used to evaluate the polymorphic transition. All the changes observed are indicative of a constant crystallinity decrease as the milling time becomes longer, some of the sorbitol recrystallizing and changing into the gamma polymorphic form during the process.

The samples containing PEG displayed different behaviour during mechanical activation. The degree of crystallinity changed by around 100% during the overall procedure.

6.2. Investigation of crystallinity changes of meloxicam

MX was selected as model API because it has only a low tendency to occur in amorphous phase: T_g/T_m (K/K) is 0.63. The polymers were PVP and PEG.

Amorphization of MX samples are illustrated in Figure 4, which shows the crystallinity changes based on the areas under the peaks. The samples made with PEG did not undergo any amorphization. The long-range order of molecular packing remained. The diversity of the values may be caused by the variation in particle size, and the orientation of the larger particles. Samples involving the use of PVP as grinding material lost their well-defined molecular conformation. The areas under the peaks decreased on increase of the grinding time. For PVP C30 12.23% of the MX remained in crystalline form at the end of the grinding process.

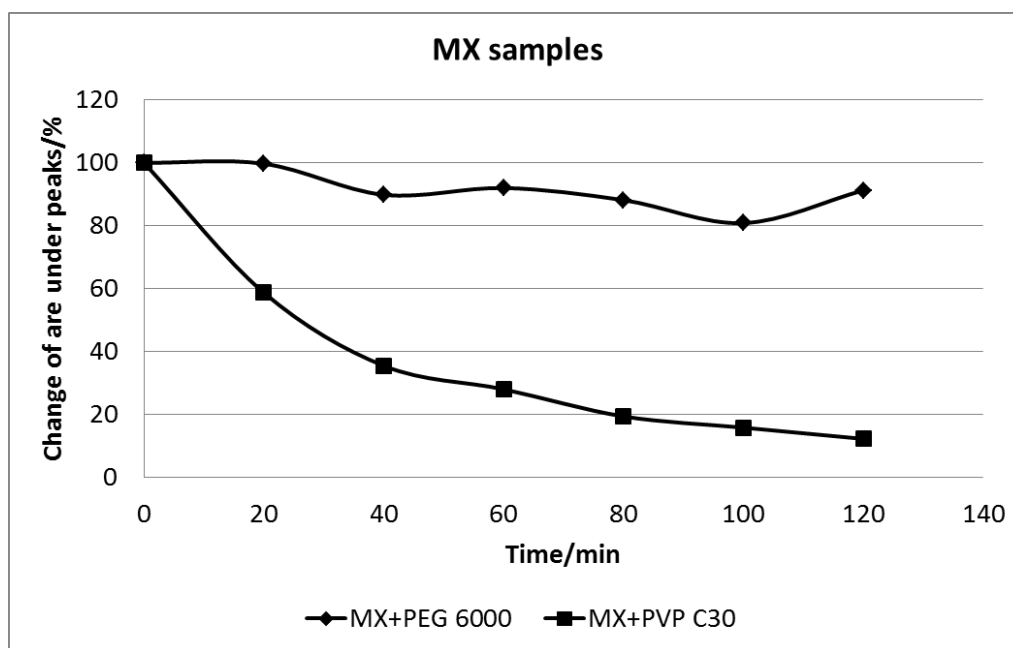


Figure 4 Crystallinity changes of MX mixed with PEG 6000 and PVP C30.

To determine whether any decomposition occurred during the grinding process and to search for any possible bonding between the API and the polymers, FT-IR spectroscopy was carried out. No measurable changes were observed in the case of the products made with the PEGs. No shifts, no changes in band shape and no new bands were detected in the curves.

The samples made with the PVP polymers exhibited several changes in the spectra during the grinding process, most significantly in the interval 3725-2600 cm^{-1} . At 3400-3500 cm^{-1} , the intensity of the associated νOH mode increased with increasing grinding time. A similar increase was observed in the range of CH and NH valence vibrations, between 3000 and 2800 cm^{-1} . The separation of the two ranges is impracticable.

The most significant changes for both excipients are related to the secondary amide group of MX. Increases in intensity can be observed at around 1620 cm^{-1} (νCONH) and between 1550 cm^{-1} and 1530 cm^{-1} (νNH). Further, the intensity relating to a hybrid stretching mode at around 1440 cm^{-1} is increased and a shoulder grows around 1390 cm^{-1} .

All these alterations point to the presence of weak bonding between the carboxyl group of MX and the polymers, which is able to help the molecules to separate from each other and keep them in this (not well-defined) conformation.

Based on SEM photos the PEG is locally melted by the impact and friction of the balls in the mortar. Reduced-sized MX particles can be observed in the melt of the polymer. These particles are in the nano range.

PVPs are amorphous polymers, and did not melt during the milling process. The temperature was locally higher than the T_g of the excipients, so the polymers softened and coated the amorphized MX. These MX particles more or less preserved their contour while they were decreased to the nano level.

6.3. Investigation of crystallinity change of clopidogrel bisulphate

CLP was chosen as a model API, as it has a relatively high melting point, and did not melt in the milling chamber and it has a really high tendency to exist in amorphous form. Its T_g/T_m (K/K) ratio is 0.80. Aerosil 200 was used as carrier because of its amorphous properties.

As thermal analysis techniques are widely used in the characterization of the amorphous form, the intact CLP, Aerosil 200 and the prepared samples were investigated by DSC. The curve of the raw CLP gave a characteristic sharp peak at 181.20 °C, corresponding to the melting point of the material. No other changes were observed on the curve. The Aerosil 200 did not exhibit any thermal signal.

The curves of the samples indicated the endothermic peak of the melting point of CLP in each case, except that at 240 min. The area of the peak decreased with increasing grinding time until it practically disappeared after 240 min of grinding. The peak of the physical mixture was similar to the peak of the raw CLP, but with a smaller area. This indicates the decreasing crystallinity of the CLP, which was finally converted into the amorphous phase. The peaks are shifted slightly to lower temperatures during the grinding while a peak was observed at 80 °C after 120 min of grinding.

The X-ray pattern of the raw CLP exhibits characteristic high-intensity diffraction peaks, which demonstrates the crystalline nature of the unprocessed API.

The typical peaks of the CLP emerged clearly in the diffractograms of the ground products. The intensities of these peaks were lower than those of the peaks for the raw API, corresponding to the concentrations of the materials in the samples. The amorphous Aerosil 200 did not exhibit any further reflection. The intensities of these peaks decreased with increasing grinding time and

practically disappeared after co-grinding for 240 min. The diffractogram of the last sample displayed the amorphous halo. During the co-grinding process, no other polymorphic form of the CLP appeared, no shifting of the peaks occurred, and no any new peaks were observed in the pattern. Quantification of the crystallinity was also made (Figure 5).

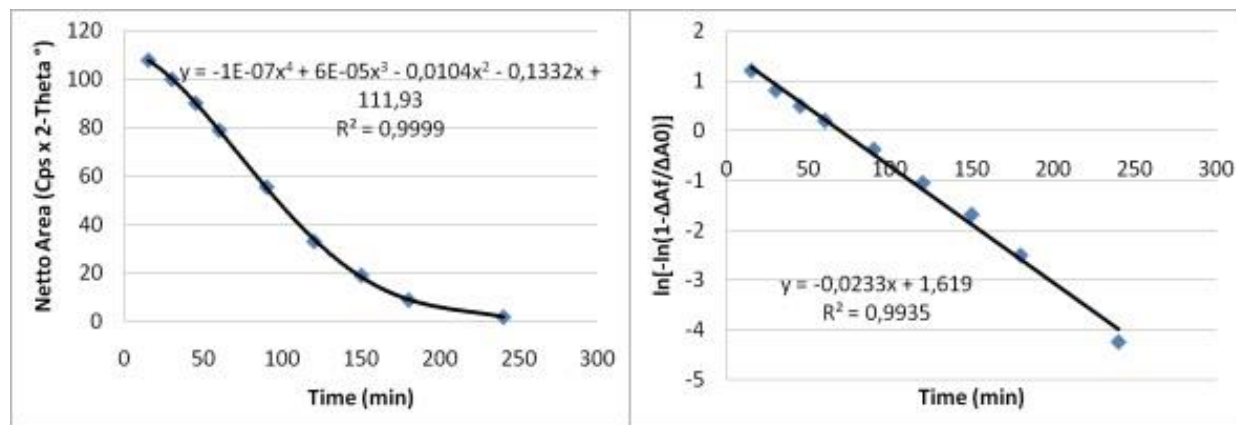


Figure 5 Crystallinity changes during grinding. First function shows the area under the curves decreasing with increasing grinding time; the second function is the linearization of the first.

The curves of the samples ground for more than 120 min demonstrated an endothermic peak at 80 °C. The area under this peak increased and sharpened with increasing grinding time. To identify the source of the peaks, the last sample (ground for 240 min) was investigated by TG and hot-humidity stage XRPD.

The TG curve revealed that the product was thermodynamically stable and a mass decrease of only 3.33% was detected up to the melting point of the CLP. At 80 °C, the determination did not show a salient mass decrease, which means that the peak observed in the DSC pattern did not involve dissolution or solvent evaporation. Neither was any major decrease observed at 100 °C, which means that the sample was sufficiently dry.

The last sample (ground for 240 min) was determined by XRPD, using the hot-humidity chamber. The diffractograms showed an amorphous halo in all three cases, so this peak did not relate to any change in crystallinity.

FT IR spectroscopy is a suitable method for the investigation of interactions between pharmaceutical materials and polymers.

FT IR determination showed that the grinding process caused several small changes in the spectra of the samples. One of the most spectacular changes was seen at 1752 cm^{-1} , the region of the $\nu\text{C}=\text{O}$ valence vibration of CLP. These peaks of the samples ground for more than 120 min expanded, shifted to lower wavenumbers, and slightly increased in intensity with increase of the grinding time.

Another change was observed at 865 cm^{-1} where a band with high intensity started to decrease after 120 min of grinding, while a double peak at 858 cm^{-1} and 838 cm^{-1} fused into one peak with a higher intensity (Figure 6). These changes proportionally followed the changes at 1752 cm^{-1} . The same phenomenon was observed between 1200 cm^{-1} and 1135 cm^{-1} : the peak at 1188 cm^{-1} decrease, while the peak at 1150 cm^{-1} slightly increased parallel after 120 min of co-grinding.

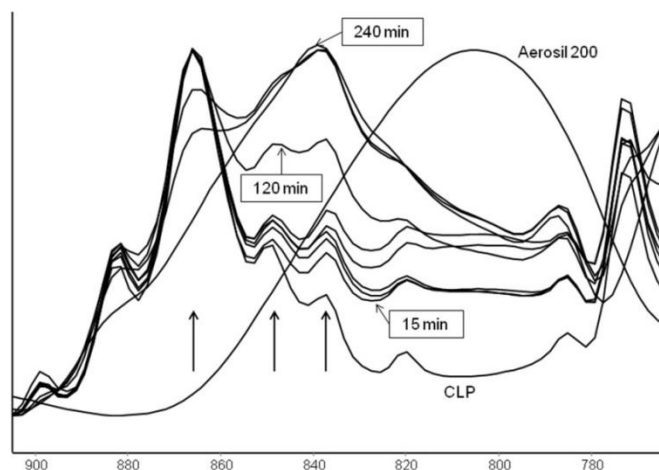


Figure 6 Bands of Aerosil 200, CLP and 9 samples ground for from 15 min to 240 min. The area under the peak at 865 cm^{-1} decreased after 120 min of grinding, while the double peak at 858 cm^{-1} and 838 cm^{-1} fuse into one peak with a higher intensity.

The described changes can refer to the following processes: the CLP first temporarily melts forming a molecularly disperse system. After 120 min of grinding, a weak secondary bond appears between CLP and the silanol groups of the CLP. This bond is strong enough to keep the CLP in amorphous phase. The work of our team (Jójárt-Laczkovich, 2011), demonstrated that this secondary bond is a hydrogen-bond.

7. Summary, novelty and practical relevance

- 1) Our first aim, to establish the literature background of investigation methods which are suitable to follow changes in crystallinity of organic materials with small molecule weights was accomplished: all of the widely used investigation methods were learnt and practiced. Those that were most suitable for our aims were chosen and used.
- 2) An easy and rapid method, which is able to predict the glass-forming properties of given materials were applied: DSC method was carried out, with only a small amount of material and two heatings were needed to determine the glass-forming properties of each material. It was therefore quite simple to choose between the possible substances: two sugar-alcohols, which are

widely used in pharmaceuticals, were selected: although they are chemically equivalent, they have different tendencies to exist in amorphous form. Interesting APIs were investigated: MX, although considered poor glass-former readily occurs in amorphous form, and CLP with its relatively high T_g/T_m ratio needed a long-term grinding with Aerosil to amorphize completely. The method used, which was suitable to decrease the degree of crystallinity of the chosen materials was relatively cheap. Its most important advantage was its repeatability and feasibility.

3) First, two chemically equivalent sugar-alcohols (mannitol and sorbitol) as model materials were subjected to milling both alone and in the presence of polymer excipients (PVP C30 and PEG 6000) to accentuate the differences in behavior of analogous materials. As a poor glass-former, mannitol did not exhibit any decrease in crystallinity when it was milled alone or together with PEG. In the presence of PVP, the crystal structure of mannitol was slightly lost. When ground alone or together with PVP, sorbitol suffered amorphization and it underwent polymorph transformation when co-ground: the initial, mostly epsilon form was transformed continuously into the gamma form, while parallel lost more than 70% of its crystallinity. PEG preserved the well-ordered molecular packing of sorbitol and stabilized the crystal structure so that the sorbitol could not amorphize. It can be concluded that these sugar alcohols, which have the same chemical structure, demonstrated different rates of crystallinity loss.

4) A similar effect of polymers was proved by the grinding of MX: the work demonstrated that the polymers used to reduce the grinding energy during co-grinding to nanoparticles can decrease the crystallinity of MX. These polymers have different abilities to convert the drug into amorphous form. XRPD measurements confirmed that the PEG did not have a significant effect on the crystallinity of MX, while the PVP decreased it drastically. Weak secondary bonding between MX and the PVPs was found by FT IR. The SEM images confirmed the major particle size decrease and the differences in crystal behaviour of the samples made with the different polymers.

5) Raw, crystalline CLP was amorphized by co-grinding. It was found that the crystallinity decreased sigmoidally with increasing co-grinding time. XRPD and DSC examinations confirmed that the product had become totally amorphous after a relatively long time, 240 min of grinding. No polymorphic conversion was observed in the samples. TG proved that no major mass reduction occurred during the procedure. FT-IR changes indicated the formation of a secondary bond between CLP and Aerosil 200, which is able to keep the drug in the amorphous phase.

Finally it can be concluded, that so similar molecules as two chemically equivalent sugar-alcohols can behave completely different on effect of grinding. The study also revealed the possibility of polymorph transition, which can lead to issues in physical appearance, dissolution or stability.

It was proven, that organic APIs, which amorphization inclination were predicted as different, can react similarly to a high energy intake: two material with dissimilar tendency to present in amorphous form exhibited comparable reaction to the co-grinding process.

Important properties of excipients used as co-grinder additives were revealed too. Some of the materials can support amorphization by decreasing the energy devoted to grinding or stabilizing the molded amorphous dispersion. Meanwhile some of them can prevent the API from crystallinity loss by coating the particles and protect their structure from breaking down.

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3. **Csaba Mártha**, Orsolya Jójárt-Laczkovich, Joachim Ulrich, Piroska Szabó-Révész: Investigation of the crystallinity of sugar alcohols co-ground with polymeric excipients. *Journal of Thermal Analysis and Calorimetry* (2013) 115. 2479–2486. (**IF: 2.206**)
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