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**RESEARCH ARTICLE**

# Formulation of tablets containing an 'in-process' amorphized active pharmaceutical ingredient

Orsolya Jójárt-Laczkovich and Piroska Szabó-Révész

*Department of Pharmaceutical Technology, University of Szeged, Szeged, Hungary*

**Abstract**

The aim of this work was a preliminary study of the "in-process" amorphization of clopidogrel hydrogensulfate (CLP) as model drug during the production of tablets as dosage form. A solvent method was used for amorphization and the crystalline phase of CLP was detected by differential scanning calorimetry; the physical parameters of fresh and stored tablets were investigated. For the amorphous form, Aerosil 200 was selected as crystallization inhibitor as the most suitable of eight auxiliary agents. The optimum composition of the product for amorphization in the scaling-up process (100-fold) was 7 parts of CLP to 3 parts of Aerosil 200. In this scaled-up product, the amorphous CLP was fixed on the surface of microcrystalline cellulose. The tablet form further stabilized the amorphous form. Finally, the steps of an "in-process" amorphization are given as a protocol, which can promote stabilization of an amorphized active pharmaceutical ingredient.

**Keywords:** Aerosil 200, amorphous, clopidogrel hydrogensulfate, crystallization inhibitor, 'in-process' amorphization



## Introduction

In pharmaceutical formulations, most drug materials are processed in their crystalline form, which is a thermodynamically stable state that exhibits both short-range and long-range order[1,2]. Unlike a crystalline solid, an amorphous solid has no long-range order of molecular packing, so the molecules are conformationally flexible[3]. The application of an active pharmaceutical ingredient (API) in amorphous form is increasingly common in the development of pharmaceutical solid formulations, with all its risks and benefits[4,5]. The amorphous or glassy form is one of the two solid subphases next to the crystalline form[6]. In pharmaceutical technology, this solid form is well known and widely studied because of its advantageous properties[7,8]. The applications of amorphization can be divided into three groups:

- amorphization of inorganic crystalline materials[9];
- amorphization of organic materials consisting of small molecules (most APIs can be classified in this group)[10]; and
- amorphization of large polymer molecules[11].

The present work is concerned with the second point, using a model API for amorphization.

Amorphization can be applied in pharmaceutical technology for four reasons:

- to increase the dissolution rate and solubility of a poorly water-soluble API[12–15],
- to protect active agents from a polymorphous transformation[16],
- to revise the processability of the corresponding crystalline drug[17], and
- to take out a new patent relating to the amorphous form of a given API (US Patent 6,767,913 B2).

The possibility of amorphization is very important as concerns amorphous formulations, because there are two groups of APIs from the aspect of the glass-forming tendency. Crystalline APIs can be divided into poor (or fragile) glass-formers and good (or strong) glass-formers. There is an empirical formula with which the glass-forming tendency of an API can be predicted. For poor or fragile glass-formers, $T_g/T_m < 0.7$, and for good or strong

*Address for Correspondence*: Dr. Piroska Szabó-Révész, Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, Szeged, 6720 Hungary. Tel.: +36/62–545572. E-mail address: revesz@pharm.u-szeged.hu

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glass-formers, $T_g/T_m > 0.7$, where $T_g$ is the glass transition temperature and $T_m$ is the melting point[18]. If the investigated API can be classified as a good glass-former, its amorphous formulation is possible.

In pharmaceutical formulations, it is necessary to differentiate two possibilities if the chosen API is a good glass-former. The first is when an amorphous form of the API is produced alone, without any auxiliary agents[19,20]. The second is when a composition is made containing both the amorphized API and an auxiliary material(s) as crystallization inhibitor(s). A product made in this way can be a solid dispersion[21] or a solid solution or some other multiple system[22]. Figure 1 outlines general differences between these two ways. The second way can be defined as "in-process" amorphization, because the classical technological formulation process is combined with amorphization of the API. The technologies which are used for making an amorphous form in pharmaceutical technology[23] are a solvent method[10], hot melt technology[24] and a milling process[25].

In this work, clopidogrel hydrogensulfate (clopidogrel bisulfate) (CLP) (methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate)[26] was used as model API for amorphization. This API is a potent oral antiplatelet drug often used in the treatment of peripheral vascular disease, coronary artery disease and cerebrovascular disease. Six different crystalline forms (I–VI) and an amorphous form of CLP are known in the literature. In pharmaceutical technological formulations and in therapy, polymorphs (Ps) I and II have been used to date[27]. Our preliminary investigations indicated that this API is a good glass-former, with $T_g/T_m = 0.80$, but with a considerable tendency to undergo recrystallization[28].

The aim of this work was to study the "in-process" amorphization of CLP during the production of tablets as dosage form. We report here the selection of the crystallization inhibitor, the amorphization of CLP in the scaling-up process and the stabilization of the amorphous form as regards the composition of the tablets. Finally, the steps of an "in-process" amorphization protocol are given which can promote stabilization of an amorphized API.

## Materials

The empirical chemical formula of CLP II (EGIS Company, Hungary) is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ with molecular mass 419.9. Chemically, it is classed among the thiophenes, and its systematic IUPAC name is methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate. The solvent applied was ethyl alcohol 96% v/v (Merck Kft., Hungary). Our previous study showed that this solvent is the most suitable for amorphization of CLP[28]. In this study, we used acetone, methanol and ethanol as solvents. Our results suggested that the samples

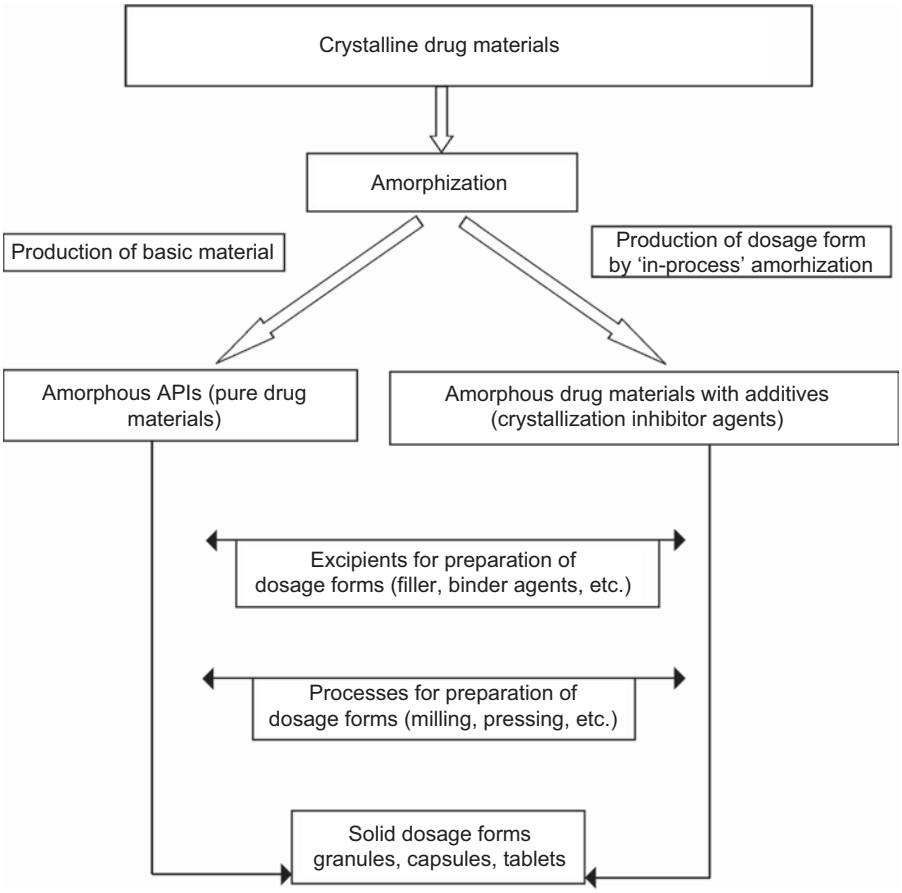


Figure 1. Two ways of making a solid form of an amorphized API.

prepared with ethanol or methanol were transformed to the amorphous form independently of the drying procedure, but the sample treated with acetone remained in the crystalline form. ICH Q3C classifies ethanol into the less dangerous Class 3, while methanol is classified into the more dangerous Class 2[38]. According to these facts, we suggest the application of ethanol for amorphizing of CLP.

As possible crystallization inhibitors, the following excipients were applied: Aerosil 200 (colloidal $SiO_2$, Nippon Aerosil Co., Japan; with hydrophilic properties), Syloid 72 FP (porous $SiO_2$, Grace, Hungary, with hydrophilic properties); kaolin (Merck Kft., Hungary); mannitol (Merck Kft., Hungary); microcrystalline cellulose (MCC) (Avicel PH 101, FMC Corporation, Europe); polyvinylpyrrolidone (PVP K25) (PVP, Kollidon® 25, BASF, Germany); methylcellulose (Ph. Eur.) and cross-linked PVP (Crospovidone, Kollidon® CL-M, BASF, Germany) named PVP K CL-M.

MCC was used as filler in tablet making. Cross-linked PVP (PVP Polypl. XL 10) (Polyplasdone® XL 10, N-vinyl-2-pyrrolidone polymer, I.S.P. Technologies Inc., Germany) was applied as disintegrant, and magnesium stearate (Hungaropharma, Budapest, Hungary) as lubricant agent in the composition of the final tablets.

## Methods

### Preparation of amorphous reference sample

An amorphous reference sample was made by using ethyl alcohol 96% v/v. 1.00 g of CLP was dissolved in 10.00 g of ethyl alcohol with the aid of a magnetic stirrer (Velp® Scientifica, Europe) for 5 min at room temperature. The solvent was evaporated off with blown room-temperature air. After drying, the sample was pulverized with a pestle in a porcelain mortar.

### Selection of crystallization inhibitor

Different masses of CLP were dissolved in different amounts of ethyl alcohol 96% v/v. The resulting solutions were mixed with different crystallization inhibitors in a porcelain mortar, heading to solution or suspension or gel formation. The ratio CLP:crystallization inhibitor was 7:3. The mixtures were then dried with room-temperature air (25°C, 46% relative humidity (RH)). After the most suitable inhibitor had been chosen, it was mixed with CLP in ratios of CLP 1:9; 3:7; 1:1; 7:3 and 9:1 with the aim of finding the best active API/auxiliary agent ratio.

### Amorphization in scaling-up process

*Sample 1*: 28.0 g of CLP was dissolved in 160.0 g of ethyl alcohol 96% v/v with the use of a magnetic mixer for 2 min. 12.0 g of Aerosil 200 and 40.0 g of MCC were mixed with a Turbula mixer (speed: 50 rpm, duration of mixing: 5 min). The solution of CLP was then vaporized onto the surface of the Aerosil 200-MCC mixture bed in a pan (Dragex-1, Jørgen).

*Sample 2*: 28.0 g of CLP was dissolved in 160.0 g of ethyl alcohol 96% v/v with the use of a magnetic mixer for 2 min. 12.0 g of Aerosil 200 was added to the solution of CLP and underwent solvation in 2 min; a gel was made by mixing. This mixture was vaporized onto the surface of 40.0 g of a MCC bed in the same pan.

The parameters (in both cases): pan (Dragex-1 stainless steel equipment), which was furnished with exhauster system for removal of solvent under processing, rotation speed: 25 rpm; pressure of spraying air: 0.1 bar; type of vaporizer: Walther, 1 mm nozzle diameter; drying air temperature: 25°C; RH of drying air: 46%; transportation of liquid: Peripump; speed of transportation: at the beginning of measurement 5 ml/min; at the end of measurement: 1 ml/min (this depends on the speed of drying). This step involves a 28-fold scaling-up. During the process, the loss of powder was very different depending on the place of Aerosil (in powder bed or in alcoholic solution).

### Tablet making

A larger amount of stabilized product was prepared with the production method employed for *Sample 2*. This product was the internal phase of the tablets. The mass of a tablet was 400 mg, containing 100 mg of CLP. The composition for 1000 tablets is given in Table 1. The internal and external phases were mixed with a Turbula mixer (speed: 50 rpm, duration of mixing: 5 min). Tablets were made with a Korsch EKO eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany) (35 tablets/min, punch diameter 12 mm, compression force: 9 ± 1 kN).

### Differential scanning calorimetry

For characterization of the amorphous form, differential scanning calorimetry (DSC) was used (a Mettler-Toledo DSC 821 instrument). Approximately, 4.80–5.20 mg of sample was placed into an aluminum pan which was then sealed and scanned from 25°C to 200°C at 5°C/min under an argon gas flow at 100–150 ml/min.

### FT-IR analysis

Confirming the presence of H-bonding in the samples, we used FT-IR analysis in solid and in liquid phase. Dichloromethane was applied as solvent for preparation of solutions. In liquid phase, concentrations were 0.1000 g/10 $cm^3$, 0.0500 g/10 $cm^3$, 0.0250 g/10 $cm^3$, 0.0125 g/10 $cm^3$. Infrared spectra were recorded on a Furier transform infrared spectrometer (Bio-Rad Digilab Division FTS-65A/869, Philadelphia, PA ) between 4000 and 400 $cm^{-1}$. The spectrometer was equipped with a

Table 1. Composition for 1000 tablets.

| | Substances | Mass |
|---|---|---|
| Internal phase | CLP | 100.00 g |
| | Aerosil 200 | 42.86 g |
| | MCC | 243.14 g |
| External phase | Polypl. XL 10 | 12.00 g |
| | Magnesium stearate | 2.00 g |

DTGS detector for the measurement of solid sample. Solutions were investigated in KBr liquid cell of 0.1 mm thickness. The spectral resolution was 4 $cm^{-1}$ and 128 scans were averaged.

For the chemical stability testing of samples, we used FT-IR apparatus also. The equipment was an Avatar 330 FT-IR spectrometer (Thermo Nicolet, Madison, WI). The sample, with CLP content of 0.5 mg, was mixed with 150 mg of dry κBr in an agate mortar, and the mixture was then compressed into a disc at 10 t. Each disc was scanned 64 times at a resolution of 2 $cm^{-1}$ over the wavenumber region 4000–400 $cm^{-1}$.

### Investigation of tablet parameters

Five parameters of the tablets were investigated: mass, diameter, height (measured with a screw micrometer; Mitutoyo Corporation, Tokyo, Japan), hardness against pressure (Heberlein apparatus, Le Locle, Switzerland) and the time of disintegration (Erweka ZT71, GmbH, Germany). Investigations were made with fresh and with stored tablets.

### Investigation of stability of products

As recommended by international guidelines (ICH Q1A), we stored samples under two different conditions. Long-term testing was performed at 25 ± 2°C with 60 ± 5% RH, and accelerated testing at 40 ± 2°C with 75 ± 5% RH. Under both conditions, samples were stored in open and in closed containers; the duration of storage was 4 weeks.

## Results and discussion

### Selection of crystallization inhibitor

The aim of this investigation was to select a suitable crystallization inhibitor. As mentioned in the Introduction, CLP is a good glass-former. Ethyl alcohol 96% v/v was used as amorphizing solvent for CLP. Amorphous CLP is unstable: its recrystallization starts within a month[28]. The stability of CLP can be increased through the use of a crystallization inhibitor, which is the auxiliary agent in the tablet composition. In this step, different crystallization inhibitors were tested: Aerosil 200, Syloid 72 FP, kaolin, mannitol, MCC, PVP K25, methylcellulose and PVP K CL-M. These auxiliary agents can be classified as crystalline (e.g. mannitol), semicrystalline (e.g. MCC) and amorphous (e.g. Aerosil 200) materials. Their common property is a large specific surface and they undergo physical interactions (secondary bonding) with numerous materials. These properties can prevent the growth of crystals and the development of the long-range order of molecules of APIs.

DSC curves of the reference CLP (crystalline and amorphous) and samples with CLP can be seen in Figure 2. The thermogram of crystalline CLP exhibited a sharp endothermic peak at 177.4°C, corresponding to the melting point of CLP. The scan of the amorphized reference CLP did not contain any characteristic peak, of course. For the sample in which mannitol was present as crystallization inhibitor, the peak occurred at about 146°C, due to the dissolution of CLP in the melted mannitol ($T_m$ for mannitol is 165°C)[29]. The samples with

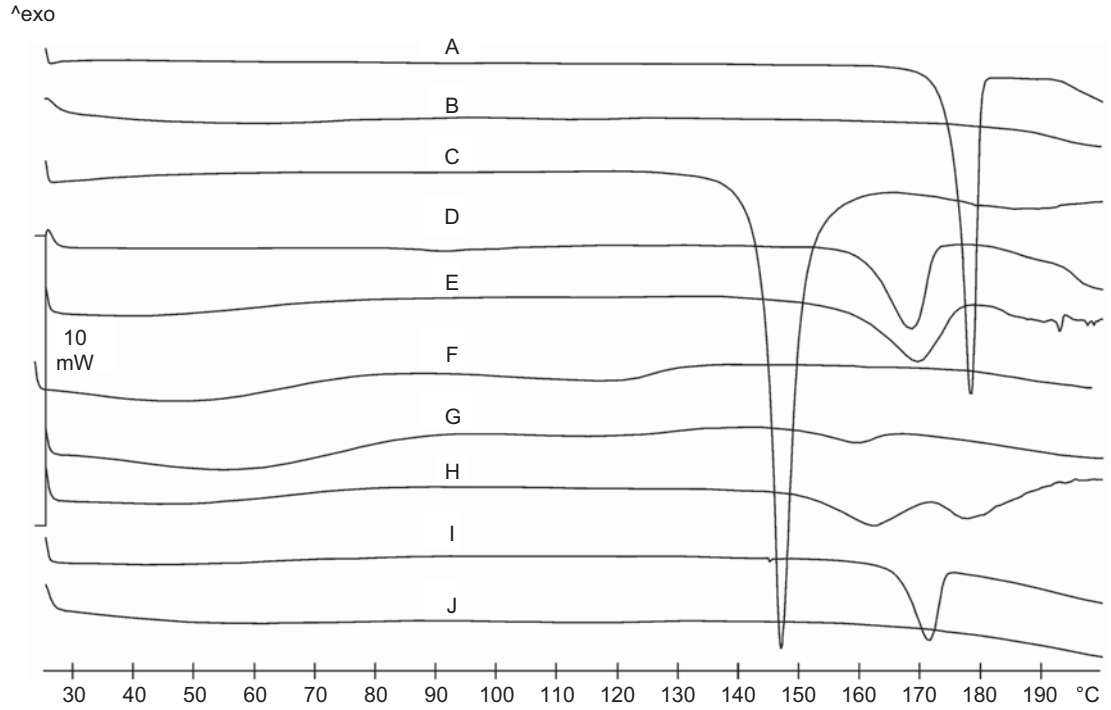


Figure 2. Effects of crystallization inhibitors on crystallinity of CLP. DSC curves of reference materials and samples made with different crystallization inhibitors. **A**: Crystalline reference sample, **B**: amorphous reference sample, **C**: sample with mannitol, **D**: sample with kaolin, **E**: sample with MCC, **F**: sample with PVP K25, **G**: sample with PVP K CL-M, **H**: sample with methylcellulose, **I**: sample with Syloid 72 FP, and **J**: sample with Aerosil 200.

kaolin and MCC exhibited decreased CLP $T_m$ values (168 and 169°C). In this range, these agents do not have melting points. The samples with PVP K25 and PVP K CL-M contained CLP in amorphous form, but suffered a color change because of incompatibility between the components. The curve for the sample made with methylcellulose displayed a double peak effect, at 167.9°C and 177.6°C. This may be an indication of two Ps in this sample. It has been reported that P IV melts at 167.9°C[30] and P II at 177.6°C[31]. Accordingly, this sample contains three different forms of CLP: the amorphous form, and the crystalline forms P IV and P II. Aerosil 200 and Syloid 72 FP differ greatly in applicability as crystallization inhibitors despite both of them consisting of $SiO_2$. With ethyl alcohol as solvent, Aerosil 200 resulted in perfectly amorphous CLP, in contrast with Syloid 72 FP, which amorphized the CLP only partially. This result can be explained as a consequence of the gelling property of Aerosil 200 in ethyl alcohol. After the evaporation of the ethyl alcohol, the large surface of $SiO_2$ fixes the CLP and protects against crystal growth, because of the interaction between CLP and $SiO_2$. This interaction presumably involves H-bonding with the surface silanol groups of $SiO_2$. Such silanol groups are not present on the surface of Syloid 72 FP, which rules out this interaction. This supposition is based on the reported verification of the presence of H-bonding between indomethacin and $SiO_2$ by solid-state nuclear magnetic resonance imaging[32]. These results led us to choose Aerosil 200 as crystallization inhibitor for the scaling-up process. This auxiliary agent is a classical additive in pharmaceutical formulations. In the case of solid forms, it can be used as glidant[33] or coating material[34] in tablet making, as surface modifier (for example, DPI formulations, due to its highly hydrophilic and adsorbing property)[35] and as auxiliary agent in the case of preparation of solid dispersion[36]. It is an amorphous agent itself, and thus the presence of API crystals in samples can be detected unambiguously, e.g. by DSC.

The following step in this work was to find the optimum CLP/Aerosil 200 ratio. Five different compositions were tested with this aim. The DSC curves are presented in Figure 3. Melting is not detected in curves **A**, **B**, **C**, **D** and **E**, and these samples can therefore be regarded as amorphous. Curve **F**, which relates to a CLP:Aerosil 200 ratio of 9:1, indicates $T_m$ at 169.5°C, which means the recrystallization of CLP. Accordingly, this amount of crystallization inhibitor is not sufficient to maintain the active agent in amorphous form. For this reason, a CLP:$SiO_2$ ratio of 7:3 was chosen for tablet formulation.

## Amorphization in scaling-up process

The next step was to stabilize amorphous CLP on the surface of the carrier. In this system, MCC was used as the carrier, which serves as a filler/binder in tablet making. In *Sample 1*, the alcoholic solution of CLP was vaporized onto the surface of the mixture of MCC and Aerosil 200. With this preparation procedure, the powder underwent considerable outflow from the pan (powder effusing or dusting). The yield of the preparation was only 64.8%. For *Sample 2*, only MCC was added to the pan. The mixture of CLP and Aerosil 200 was dissolved in ethyl alcohol (96% v/v) and vaporized onto MCC bed. The yield of this preparation method was 85.2%, clearly indicating

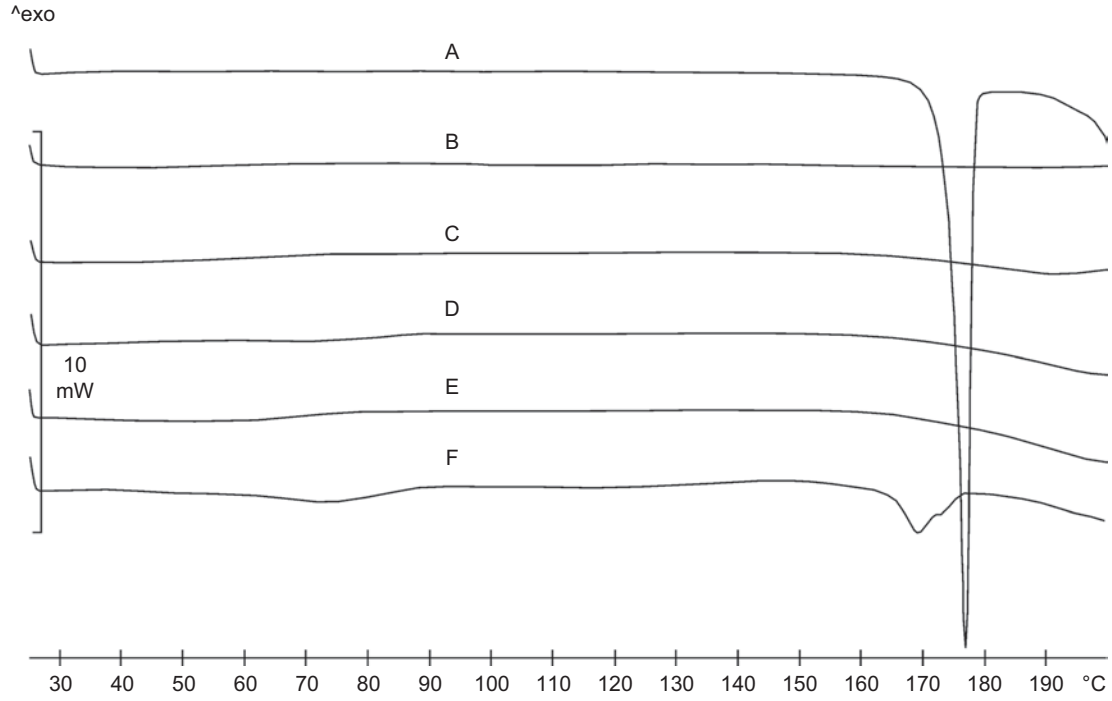


Figure 3. DSC curves of samples containing Aerosil 200. **A**: Reference (crystalline CLP), **B**: CLP:$SiO_2$ = 1:9, **C**: CLP:$SiO_2$ = 3:7, **D**: CLP:$SiO_2$ = 1:1, **E**: CLP:$SiO_2$ = 7:3, **F**: CLP:$SiO_2$ = 9:1

that the processing of Aerosil 200 in the liquid phase is more advantageous. The DSC scans of both samples and a physical mixture (Figure 4) demonstrated that the CLP in both samples was in the amorphous form (in contrast with the situation for the physical mixture) because there was no sign of $T_m$ in the curves.

To verify of H-bonding between silanol groups of Aerosil 200 and CLP molecules, we compared FT-IR spectrums of *Sample 2* and the corresponding physical mixture (see Figure 5). In the interval of 900–600 $cm^{-1}$, spectrum **A** contains vibrations of C structure's deformation. These bands decrease remarkably in spectrum **B**. It refers that the product is in amorphous state. On the other hand, it denotes the presence of a chemical bonding in the product.

To confirm the chemical bond, we measured *Sample 2* in different concentration in solutions (see Figure 6). In the interval of 1100–1000 $cm^{-1}$ spectrum **A** shows wide association. With the dilution of the sample, this association breaks off continually (spectrums **B**, **C**, **D**, **E**). Between 1058 and 1036 $cm^{-1}$, two bands were appeared that characterize $\nu_{AS}$ C-O-C stretching (this marks acetates). The band, at 1058 $cm^{-1}$ shifted to the band, at 1036 $cm^{-1}$ with the dilution. It means that the association breaks off.



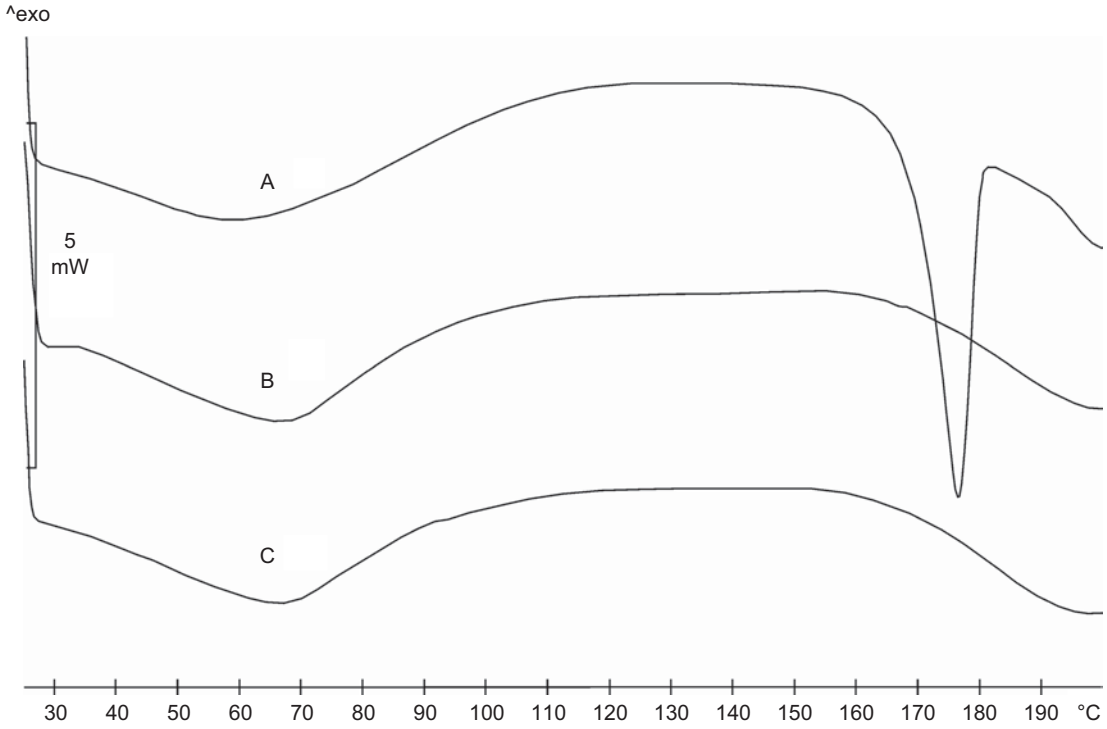


Figure 4. DSC curves of samples. **A**: physical mixture, **B**: *Sample 1*, **C**: *Sample 2*.

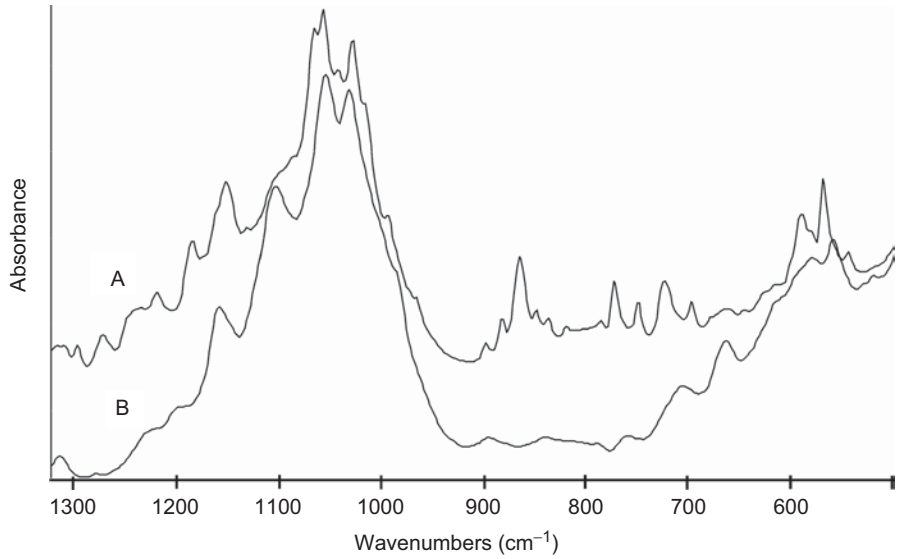


Figure 5. FT-IR analysis of *Sample 2* and the corresponding physical mixture. **A**: physical mixture, **B**: *Sample 2*.

These results justify the presence of H-bonding in the solid *Sample 2*. The different states of samples cause different places of bands. The spectrum **F** shows that dichloromethane has not got sign in this interval.

In the study of the stability of amorphous CLP, *Sample 1* and *Sample 2* were stored for 4 weeks at 25°C and 60% RH. The results revealed that the stored samples remained in the amorphous phase. The findings of accelerated testing showed that when *Sample 1* was stored in either open or closed containers after 4 weeks, it included crystalline material. For *Sample 2*, only the sample stored in an open container included a crystalline phase.

To investigate the chemical stability of *Sample 2*, FT-IR analysis was used. The FT-IR spectrums showed no chemical changes in the samples, which were stored in open and closed containers. All of the peaks are the same in the fresh and in the stored samples (see Figure 7). It can be concluded that the preparation procedure applied for *Sample 2* is better, and this product is more stable than *Sample 1*. In *Sample 2*, the gel structure of the CLP/Aerosil 200/ethyl alcohol system extends the adherence of the CLP/Aerosil 200 system on the surface of MCC. There is an interaction between surface silanol groups of Aerosil 200 and hydroxyl groups of MCC on its surface, which is a hydrogen bonding[37]. This interaction can come into existence easily in liquid phase (*Sample 2*), than in solid phase in the case of a simple mixing (*Sample 1*). For these reasons, the amorphization procedure used for *Sample 2* was applied in tablet making.

### Tablet making and investigation of tablets

The amorphization procedure applied for *Sample 2* was used to make 1000 tablets. This tablet composition (see Table 1) resulted in good flowability and tablettability.

Both fresh and stored tablets were investigated. In the thermoanalytical study, a physical mixture of the tablet components was also investigated because of the presence of the crystalline phase of CLP. The DSC curves are depicted in Figure 8. The slight enthalpy changes detected in curve **E** indicate that this sample may contain a little crystalline phase. This sample was stored at 40°C and 75% RH in an open container. Curves **A**, **B**, **C**, **D** and **F** do not reveal any crystalline phase in the system. A feature of importance for tablet making was that the surface area of the amorphous product decreased, which was another stabilizing step in the formulation.

The physical parameters of the fresh and stored tablets are reported in Table 2. The change in mass of the tablets was greatest for the tablets stored in an open container under accelerated conditions (40°C, 75% RH). As the mass of these tablets increased, the diameter and height also increased. In the other cases, the changes were negligible. The hardness against pressure of the tablets decreased in all cases, most strongly for the tablets stored in open containers. The time of disintegration also decreased in all cases, and again the most considerable changes occurred for the tablets stored in open containers. These results are in harmony with the fact that amorphous materials are hygroscopic. In these changes, the presence of Polyplasdone XL 10, as superdisintegrant, plays an important part also. It may be concluded that it is very important to choose the correct conditions for the formulation and storage of amorphous CLP. These conditions include the use of dry air (low RH) and a closed container.

## Conclusions

The "in-process" amorphization of CLP as model API was studied, tablets containing amorphous CLP were

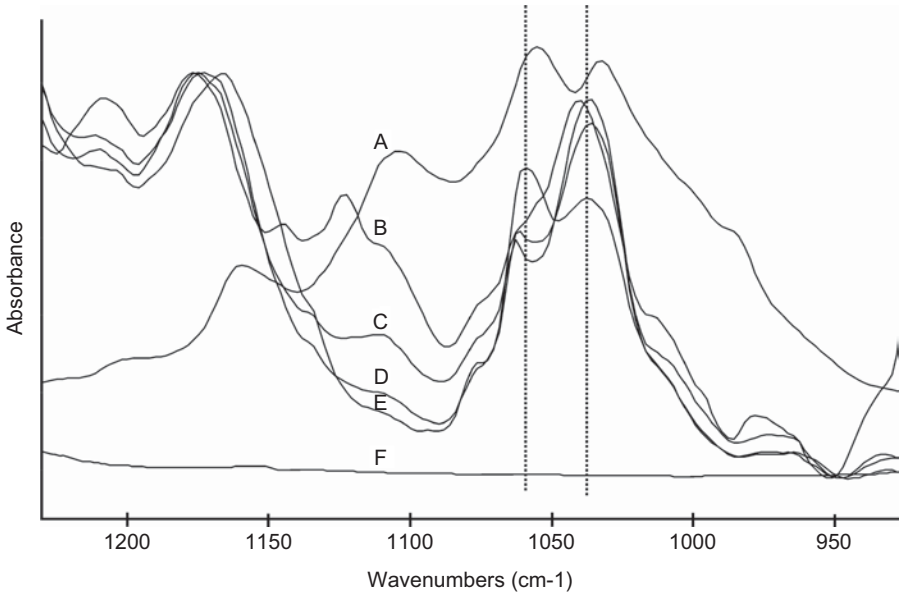


Figure 6. FT-IR analysis of different concentrations of *Sample 2* in solutions containing dichloromethane. **A**: solid *Sample 2*, **B**: 0.1000 g sample in solution of 10 $cm^3$, **C**: 0.0500 g sample in solution of 10 $cm^3$, **D**: 0.0250 g sample in solution of 10 $cm^3$, **E**: 0.0125 g sample in solution of 10 $cm^3$, **F**: dichloromethane.

produced, and the stability of the product was tested. The results suggested the following amorphization protocol (see Figure 9):

- In the first step, a suitable solvent for the API should be selected. In this step, it is very important that the crystalline API should dissolve completely: any crystals remaining in the system can function as seeds and crystallization can start during evaporation of the solvent.
- In the second step, a suitable crystallization inhibitor should be selected and the optimum amount of this auxiliary agent required to maintain the API in amorphous form should be determined. In this step, several crystallization inhibitors should be screened

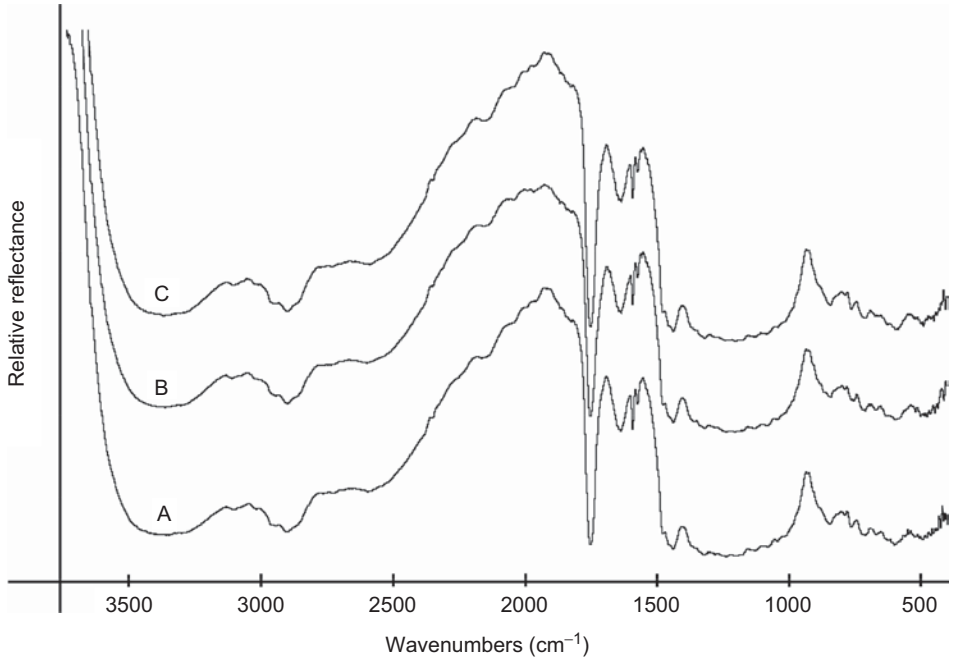


Figure 7. FT-IR investigation of the fresh and stored *Sample 2*. **A**: fresh *Sample 2*, **B**: stored *Sample 2* (40°C, 75% RH, open), **C**: stored *Sample 2* (40°C, 75% RH, closed).

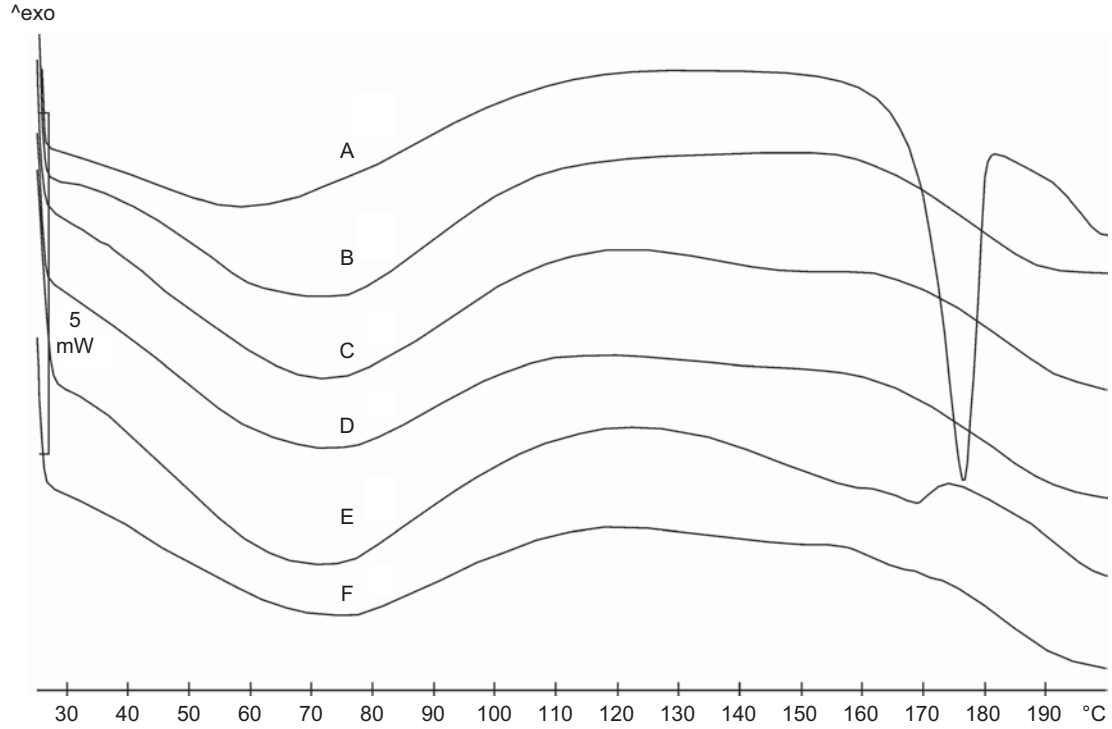


Figure 8. Stability of tablets. **A**: Physical mixture, **B**: fresh product, **C**: stored sample (25°C, 60% RH, open), **D**: stored sample (25°C, 60% RH, closed), **E**: stored sample (40°C, 75% RH, open), **F**: stored sample (40°C, 75% RH, closed).

Table 2. Investigation of tablet parameters.

| Tablets | | Mass (g) | Diameter (mm) | Height (mm) | Hardness against pressure (*N*) | Time of disintegration (s) |
|---|---|---|---|---|---|---|
| Fresh | | 0.4060 (SD ± 0.003) | 12.10 (SD ± 0.060) | 3.50 (SD ± 0.023) | 93.4 (SD ± 2.67) | 86 (SD ± 27) |
| Stored 25°C and 60% RH | Open | 0.4097 (SD ± 0.004) | 12.13 (SD ± 0.050) | 3.55 (SD ± 0.032) | 70.4 (SD ± 3.63) | 30 (SD ± 13) |
| | Closed | 0.4078 (SD ± 0.004) | 12.12 (SD ± 0.054) | 3.51 (SD ± 0.027) | 83.6 (SD ± 3.37) | 54 (SD ± 13) |
| Stored 40°C and 75% RH | Open | 0.4106 (SD ± 0.003) | 12.24 (SD ± 0.038) | 3.69 (SD ± 0.016) | 65.8 (SD ± 2.74) | 6 (SD ± 4) |
| | Closed | 0.4060 (SD ± 0.003) | 12.10 (SD ± 0.009) | 3.53 (SD ± 0.021) | 84.8 (SD ± 3.79) | 79 (SD ± 16) |

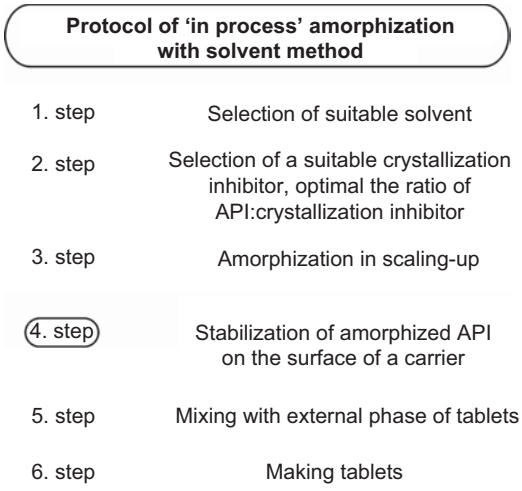


Figure 9. Protocol of 'in-process' amorphization.

and, if possible, the type of interaction between the API and the auxiliary agent should be investigated.

- In the third step, the amorphization process must be scaled up.
- In the fourth step, the amorphized API should be stabilized on the surface of a carrier. This is an important step in this protocol, because the API, the crystallization inhibitor and the carrier act together in this system to result in stable amorphous API during the technological process.
- In the fifth step, the external phase of the tablets should be mixed with the amorphized product. The mixing must be performed very carefully, because mechanical force can induce recrystallization.
- In the sixth step, the tablets should be pressed. Compression can be a further stabilizing step, fixing the amorphous form because of the smaller surface.

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## Declaration of interest

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