University of Szeged

Faculty of Pharmacy

Education program: Pharmaceutical Technology

Head: Prof. Dr. Piroska Révész

Department of Pharmaceutical Technology

Supervisor: Prof. Dr. Piroska Révész DSc

Orsolya Jójárt-Laczkovich

Amorphization of a crystalline active agent with the aim of pharmaceutical technological formulation

Final Exam Committee:

Head: Prof. emer. Dr. István Erős DSc, SZTE Department of Pharmaceutical Technology

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1 INTRODUCTION

The two forms of solids are the crystalline form and the amorphous form. Solid materials are usually processed in their crystalline form, but application of the amorphous form is increasing. Glassy materials are used in many industrial fields glassy materials are used such as the plastics industry, the textile industry, the food industry, and for the production of semiconductors, ceramics and optical glasses, and naturally in the pharmaceutical industry.

In pharmaceutical formulations, most drug materials are processed in their crystalline form. This is a thermodynamically stable state that exhibits both short-range and long-range order. Unlike a crystalline solid, an amorphous solid has no long-range order of molecular packing, so the molecules are conformationally flexible. 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.

What are the most important advantages of the application of the amorphous drugs? Amorphous forms of APIs have many useful properties. Among the most important ones are a higher dissolution rate and a sometimes higher water solubility relative to that of the crystalline form as there is no lattice energy, which is a thermodynamic barrier to dissolution.

It must be mentioned that there are disadvantages to the use of this form. Amorphous solids generally have lower stability than the corresponding crystals because of the higher energy level. Crystallization inhibitors therefore have to be used in most cases in amorphous pharmaceutical technological formulations. A wide range of auxiliary agents are available to stabilize this form and to prepare a suitable glassy dosage form.

The pharmaceutical industry is highly interested in amorphous formulations because amorphization techniques are very innovative, thanks to the advances in the analytical methods. The detection of amorphous forms is currently a widely investigated field of pharmaceutical technology, as concern both deliberate amorphization and when an unwanted glassy form appears spontaneously during formulation or storage.

The most important review articles connected with amorphous materials in pharmaceutical technology, discussed preparation methods, characterization techniques and possibilities for the stabilization of glassy drugs. From a Hungarian aspect, our team first reported the advantages of amorphization in 2003 and used different methods in the industrial research and development work.

2 AIMS

The primary aim of this study was to establish the literature background of pharmaceutical amorphization. We wanted to know what methods are available to produce this special solid form, and how amorphous materials can be investigated and characterized with different analytical techniques.

The secondary aim was to investigate clopidogrel hydrogensulfate (CLP) as model drug from the aspect of pharmaceutical amorphization. The steps of this work were as follows:

- Characterization of the glassy property of CLP: determination of the investigation methods that can be used to classify CLP according to its glass formability (a poor or a good glass-former).
- Choice of a preparation method which results in pure amorphous CLP without use of an auxiliary agent.
- Investigation of the stability of pure amorphous CLP because of its tendency to undergo recrystallization during storage.
- Identification of a suitable recrystallization inhibitor and determination of its amount which can stabilize the amorphous form of CLP.
- Use of the amorphized product in a scaling-up process.
- Development of tablets as final dosage form that is appropriately stable as concern the recrystallization of CLP.
- Devising a protocol of amorphization in general, as a practical consideration.

It should be mentioned that the experimental part of this thesis was carried out in 2002-2004. In that period, the pharmaceutical industry was greatly in the amorphization of APIs. The amorphous form remains important nowadays but the approach has changed appreciably. Deliberate amorphization is still of great interest industrially, but in the scientific field, a new issue has arisen and has been subject to considerable development. This is when an amorphous form arises spontaneously during the pharmaceutical formulation or during storage. This can give rise to different properties which may cause problems in the processing technology or in the application of drugs.

3 MATERIALS AND METHODS

3.1 Materials

In this study, the crystalline API which was subjected to amorphization was CLP (clopidogrel bisulfate), a potent oral antiplatelet agent often used in the treatment of coronary artery disease, peripheral vascular disease and cerebrovascular disease as Plavix® (an original drug product). Many generic products containing this active agent are currently on the market with in Hungary. The chemical formula of CLP is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and the molecular mass is 419.9. Chemically, it is classed among the thiophenes, and its systematic IUPAC name is methyl (+)-(*S*)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate. The chemichal structure is to be seen in **Figure 1**. Six different polymorphic forms and an amorphous form of the drug have been identified, but only forms I and II are used in pharmaceutical formulations.

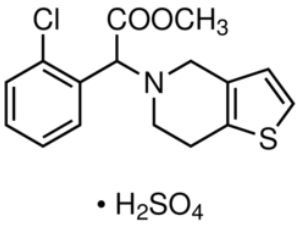

FIGURE 1: The chemical structure of CLP

Table I details the solvents and additives applied and their producers.

Table I: Applied solvents and additives

Type of additives	Materials	Producer
Solvents	Ethanol 96% v/v	Merck, Hungary
	Methanol	
	Acetone	Reanal, Hungary
Crystallization inhibitors	Aerosil 200 (colloidal SiO_2)	Nippon Aerosil Co., Japan
	Syloid 72 FP (porous SiO_2)	Grace, Hungary
	Kaolin	Merck, Hungary
	Mannitol	
	Microcrystalline cellulose (MCC) (Avicel PH 101)	FMC Corporation, Europe
	Poly(vinyl pyrrolidone) (PVP K25) (PVP, Kollidon® 25	BASF, Germany
	Cross-linked PVP (Crospovidone, Kollidon® CL-M, PVP K CL-M)	
	Methylcellulose	(Ph. Eur.)
Auxiliary agents of tablet making	Microcrystalline cellulose (MCC) (Avicel PH 101), as filler	FMC Corporation, Europe
	Cross-linked PVP (PVP Polypl. XL 10) (Polyplasdone® XL 10, *N*-vinyl-2-pyrrolidone polymer), as disintegrant	I.S.P. Technologies Inc., Germany
	Magnesium stearate, as lubricant	Hungaropharma, Hungary

3.2 Methods

3.2.1 Preparation of pure amorphous CLP

Amorphous samples were made with the use of ethanol 96% v/v or methanol. 1.00 g CLP was dissolved in 10.00 g ethanol or 4.00 g methanol with the aid of a magnetic stirrer (Velp® Scientifica, Europe) for 5 minutes at room temperature. The solvent was evaporated by two methods: with blown room temperature air or under vacuum (Binder, Germany). 1.00 g CLP was treated with 20.00 g acetone with magnetic mixing for 15 minutes at room temperature and the solvent was then evaporated off in vacuum (Binder, Germany). After drying, samples were pulverized in a porcelain mortar with a pestle. In the following steps, we used the sample which was prepared with ethanol and dried with room temperature air as amorphous reference sample.

3.2.2 Selection of a crystallization inhibitor

Different masses of CLP were dissolved in different amounts of ethanol 96% v/v. The resulting solutions were mixed with different crystallization inhibitors in a porcelain mortar, leading to the formation of a solution or a suspension or a gel. 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 1:9; 3:7; 1:1; 7:3 and 9:1 with the aim of finding the best active API:auxiliary agent ratio.

3.2.3 Amorphization in scaling-up processes

Sample 1: 28.0 g of CLP was dissolved in 160.0 g of ethanol 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 ethanol 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 vapourized onto the surface of 40.0 g of a MCC bed in a pan (Dragex-1, Jørgen).

3.2.4 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 (**Table II**). 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).

TABLE II: Composition for 1000 tablets

	Substances	**Mass**
Internal phase	CLP	100.00 g
	Aerosil 200	42.86 g
	MCC	243.14 g
External phase	Polyplasdone XL 10	12.00 g
	Magnesium stearate	2.00 g

3.2.5 Differential scanning calorimetry (DSC)

For characterization of the amorphous form, DSC was used (a Mettler-Toledo DSC 821 instrument). Approximately 4.80-5.20 mg of sample was placed into an aluminium pan, which was then sealed and scanned from 25 ºC to 200 ºC at 5 ºC/min under an argon gas flow at 100-150 ml/min. The instrument was calibrated with the use of indium.

3.2.6 X-ray powder diffraction (XRPD)

XRPD was performed with an X-ray Diffractometer Miniflex II (Rigaku, Tokyo, Japan), where the tube anode was copper with $K\alpha$=1.5405 Å. The pattern was collected at a tube voltage of 30 kV and a tube current of 15 mA in step scan mode (4°min^{-1}). The instrument was calibrated with silicon.

3.2.7 FT-IR analysis

To demonstrate, that no degradation occurred during preparation, and for the chemical stability testing of samples, we used an FT-IR apparatus, Avatar 330 FT-IR spectrometer (Thermo Nicolet, USA). The sample, with a CLP content of 0.5 mg, was mixed with 150 mg of dry KBr 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}.

The presence of H-bonding in the samples was confirmed by FT-IR analysis in the solid and in the liquid phase. Dichloromethane was applied as solvent for the preparation of

solutions. In the liquid phase, the concentrations were 0.1000 g, 0.0500 g, 0.0250 g or 0.0125 g in 10 cm^3. IR spectra were recorded 4000 and 400 cm^{-1} on a FT-IR spectrometer (Bio-Rad Digilab Division FTS-65A/869, USA) between. The spectrometer was equipped with a DTGS detector for the measurements on solid samples. Solutions were investigated in a KBr liquid cell of 0.1 mm in thickness. The spectral resolution was 4 cm^{-1} and 128 scans were averaged.

3.2.8 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.

3.2.9 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 ºC with 60±5% RH, and accelerated testing at 40±2 ºC with 75±5% RH. Under both conditions, samples were stored in open and in closed containers; the duration of storage was 4 weeks.

4 RESULTS

4.1 Measurement of T_g

T_g is one of the most important parameters for amorphous materials. The expected temperature interval in which T_g can lie is approximately 2/3 to 4/5 of T_m (in Kelvin). The T_m of crystalline CLP is 177.4 ºC (450.6 K). Accordingly, the expected interval of glass transition is 27.2-87.3 ºC (300.4-360.4 K).

A DSC curve reveals all structural changes accompanied by enthalpy changes. In the curve, T_g is usually indicated by a step, a dislocation from the baseline. For CLP, however, T_g could not be detected during the first heating run T_g, but during the second heating T_g appeared in the curve. When double heating was carried out with two samples with ethanol, the endothermic step in the DSC curve was detected in the same interval. This temperature interval, 82-110 ºC (355-383 K) can be defined as the glass transition of CLP. The midpoints of these changes were 89.4 ºC (362.6 K) and 88.5 ºC (361.6 K), with a mean of 88.9 ºC (362.1 K). Thus, for the calculations, this mean value (88.9 ºC = 362.1 K) was applied as T_g. For CLP, therefore the quotient T_g/T_m is 0.80, and accordingly CLP can be classified as a good glass-former.

4.2 Confirmation of amorphous form

Prepared samples were measured primarily by DSC. With this method, characterization of the amorphous form is possible quickly. The starting material and 5 prepared samples were tested at first by DSC. The crystalline CLP melted 177.4 ºC (450.6 K). The sample which was treated with acetone remained in the crystalline phase. The samples prepared in ethanol or methanol was transformed to the amorphous form both on drying through blowing with room-temperature air and under vacuum. The characteristic melting point disappeared completely from the DSC curves, which were virtually straight lines without any enthalpy changes; no T_g could be detected. Samples were also tested by XRPD measurement. Diffractograms are to be seen in **Figure 2**; for clarity, the diffractograms are displaced along the y axis. This investigation supported the DSC results throughout. Figure 2 shows that the products prepared with ethanol or methanol, independently of the drying procedure, were converted to the amorphous form, because the peaks disappeared from the diffractograms, and the spectra became smooth. The sample treated with acetone remained in the crystalline phase, and the diffractogram of this preparation was the same as that of the

crystalline starting material. To confirm that no degradation had occurred in the prepared samples, FT-IR analysis was performed. The amorphous and crystalline materials furnished the same spectra. Samples prepared with ethanol or methanol transformed to the amorphous form. The objective of ICH Q3C guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. ICH Q3C classifies ethanol into the less dangerous Class 3, while methanol is classified into the more dangerous Class 2. Accordingly, we recomended the application of ethanol for the amorphization of CLP.

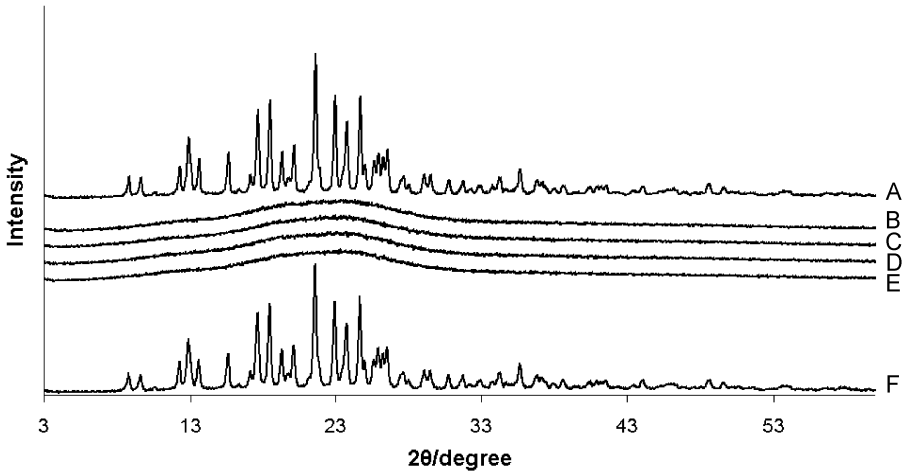

FIGURE 2: CLP samples measured by XRPD. **A**: Crystalline form, **B**: sample prepared with ethanol, dried with room-temperature air, **C**: sample prepared with ethanol, dried under vacuum, **D**: sample prepared with methanol, dried with room-temperature air, **E**: sample prepared with methanol, dried under vacuum, **F**: sample treated with acetone, dried under vacuum.

4.3 Preliminary stability testing

In the case of amorphous materials, stability problems can occur because of the higher energy level. The possibility of recrystallization is very realistic. The amorphous CLP was subjected to preliminary stability testing. A sample prepared with ethanol was stored in a closed glass container at 23±2 ºC and 55±5 RH. It was observed that crystal growth started after 30 days (**Figure 3**). The crystallinity of the sample increased for approximately 76 days and the crystal growth then stopped.

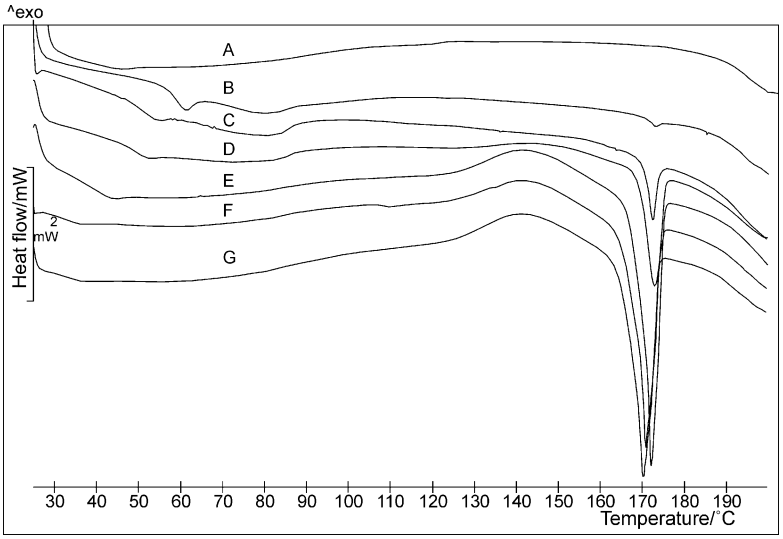

FIGURE 3: Preliminary stability testing: A: Fresh sample; B: sample stored for 30 days; C: sample stored for 34 days; D: sample stored for 45 days; E: sample stored for 76 days; F: sample stored for 96 days; G: sample stored for 109 days.

4.4 Selection of a crystallization inhibitor

Because of the fast recrystallization, the stability of CLP must be increased through the use of a crystallization inhibitor, which is the auxiliary agent in the tablet composition.

DSC curves of the reference CLP (crystalline and amorphous) and samples containing CLP can be seen in **Figure 4**. The thermogram of crystalline CLP exhibited a sharp endothermic peak at 177.4 ºC, corresponding to the melting point of CLP. The scan of the amorphized reference CLP (made with ethanol) did not contain any characteristic peak, of course. The other samples were made with a CLP:auxiliary agent ratio of 7:3. The samples containing PVP K25 or PVP K CL-M and CLP in amorphous form, underwent a colour change because of incompatibility between the components. With ethanol as solvent, Aerosil 200 resulted in perfectly amorphous CLP. After the evaporation of the ethanol, the large surface of SiO_2 fixes the CLP and protects it against crystal growth, because of the interaction between CLP and SiO_2. This interaction presumably involves H-bonding with the surface silanol groups on the SiO_2. These results led us to choose Aerosil 200 as crystallization inhibitor for the scaling-up process. The following step in this work was to find the optimum CLP:Aerosil 200 ratio. Five different compositions were tested with this aim. A CLP:SiO_2 ratio of 7:3 was chosen for tablet formulation.

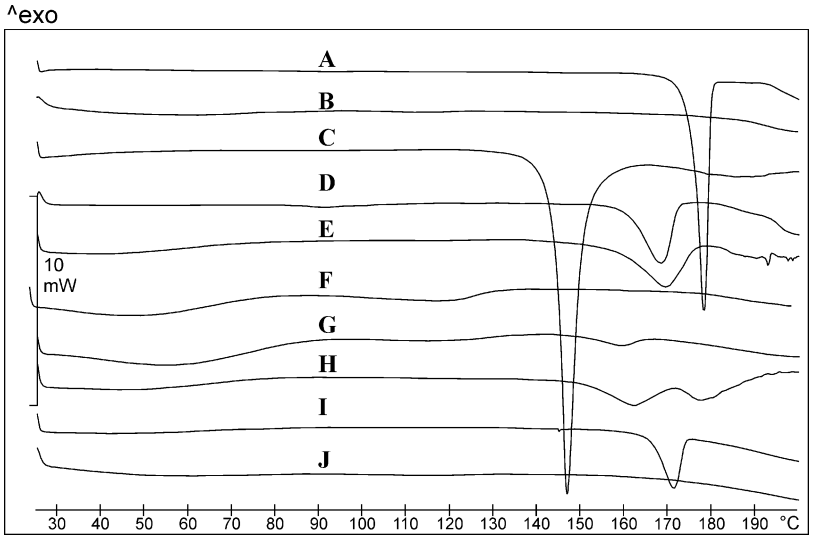

FIGURE 4: Effects of crystallization inhibitors on the crystallinity of CLP. DSC curves of reference materials and samples made with different crystallization inhibitors. **A**: Crystalline reference sample, **B**: amorphous reference sample, **C**: sample with mannitol, **D**: sample with kaolin, **E**: 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.

4.5 Amorphization in scaling-up processes

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*, an alcoholic solution of CLP was vapourized onto the surface of a mixture of MCC and Aerosil 200. 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 ethanol (96% v/v) and vapourized onto a MCC bed. The yield of this preparation method was 85.2%, clearly indicating that the processing of Aerosil 200 in the liquid phase is more advantageous. The DSC scans of both samples and a physical mixture 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 confirm the chemical bonding, we measured *Sample 2* at different concentrations in solution (**Figure 5**). In the interval 1100-1000 cm^{-1}, spectrum **A** reveals extensive association. On dilution of the sample, this association progressively breaks down (spectra **B**, **C**, **D** and **E**). These results confirm the presence of H-bonding in the solid *Sample 2*.

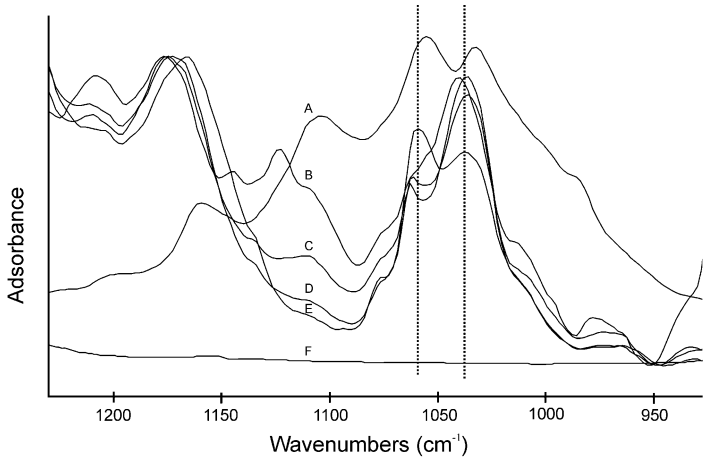

FIGURE 5: FT-IR analysis of *Sample 2* at different concentrations in solutions containing dichloromethane. **A**: Solid *Sample 2*, **B**: 0.1000 g sample in 10 cm^3 of solution, **C**: 0.0500 g sample in 10 cm^3 of solution, **D**: 0.0250 g sample in 10 cm^3 of solution, **E**: 0.0125 g sample in 10 cm^3 of solution, **F**: dichloromethane.

4.6 Preparation and investigation of tablets

The amorphization procedure applied for *Sample 2* was used to make 1000 tablets. 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 slight enthalpy changes detected in the curve indicate that this sample may contain a little crystalline phase. This sample was stored at 40 ºC and 75% RH in an open container for 4 weeks. Curves of other samples do not reveal any crystalline phase in the system. The XRPD investigations resulted in constant data. The fingerprint of CLP did not appear in the diffractogram. 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. We measured physical parameters of the fresh and stored tablets. These results are in harmony with the fact that amorphous materials are hygroscopic. In these changes, the presence of Polyplasdone XL 10, as superdisintegrant, also plays an important part.

5 PRACTICAL ASPECTS

The amorphization of CLP as a model API was studied, tablets containing amorphous CLP were produced, and the stability of the product was tested. On the basis of our study, the following approaches can be suggested for the preparation of different solid dosage forms with amorphized API. There are two different methods for the preparation of amorphous products. **Figure 6** outlines the general differences between these two procedures. The second way can be defined as 'in-process' amorphization, because the classical technological formulation process is combined with amorphization of the API.

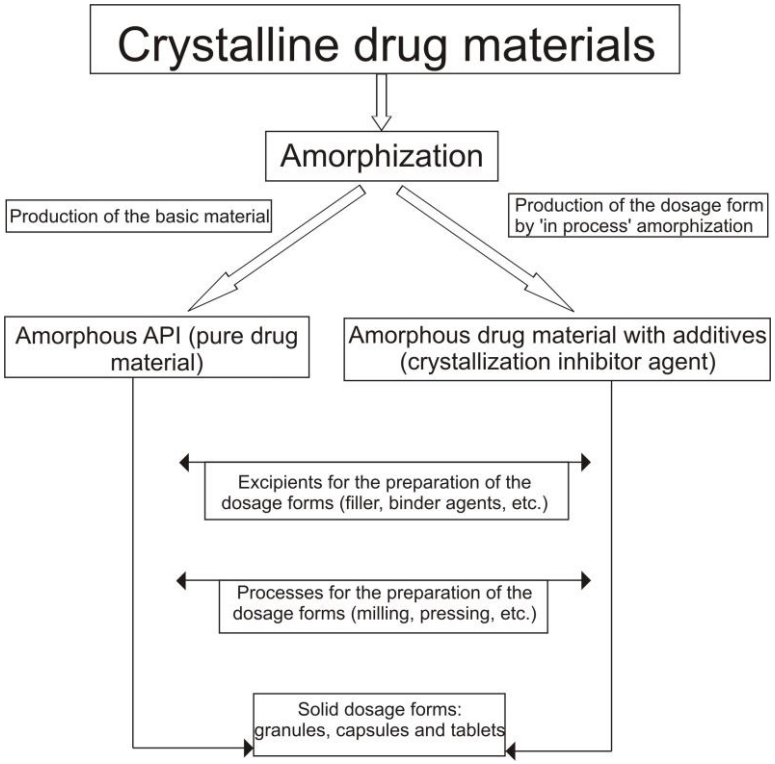

FIGURE 6: Two ways to produce a solid form of an amorphized API

In the light of our results, the following amorphization protocol was developed (**Figure 7**):

- 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 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.

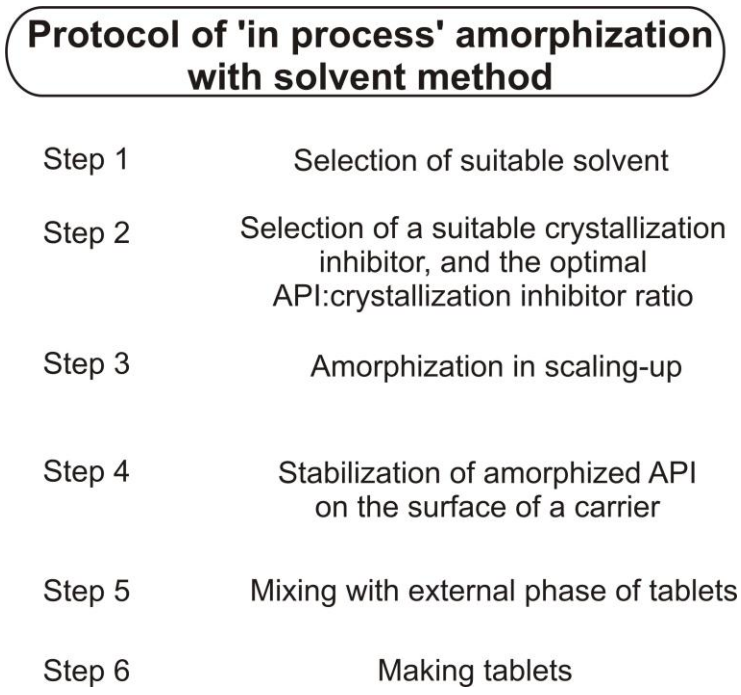

FIGURE 7: Protocol of 'in-process' amorphization.

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