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Summary of Ph.D. thesis

CRYSTAL HABIT OPTIMIZATION BY MEANS OF IMPINGING JET CRYSTALLIZATION METHOD

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1. INTRODUCTION

During the past decades the number of poorly water-soluble drug candidates has increased extraordinarily in pharmaceutical research and development. According to recent evaluations, approximately 75 % of the new candidates belong to BCS Class II (low solubility-high permeability) and Class IV (low solubility-low permeability) categories. In order to overcome the major obstacles that these drug substances possess, such as poor solubility, low dissolution and oral bioavailability, new approaches and possibilities should be taken into consideration. Many of these technologies have already been examined and aimed to be used in pharmaceutical industry, for example particle size reduction, micronization, cyclodextrin complexation, co-crystallization, solid dispersion preparation, solid lipid nanoparticles, polymeric micelles, freeze-dried liposomes, the use of different salt forms, additives, co-solvents, or solubilizing agents, just to name a few.

As the majority of APIs and excipients can be produced by crystallization, significant progress is also essential in the control of crystallization processes to refine attributes of the crystalline product. Namely, different crystallization techniques could result in agglomerated particles, unstable polymorphic forms, poor flow, needle like crystals, or the product could contain impurities which can decrease stability and efficacy. Therefore, already in the early phase of development, the choice of the most appropriate crystallization method and the optimization of crystallization parameters are crucial to achieve a high quality product.

Crystallization methods that are commonly used in the pharmaceutical industry include cooling, antisolvent and precipitation processes. However, with these techniques the particle size can be reduced only within certain limits. New methods are therefore sought to decrease the particle size of APIs with high percentage yield and good reproducibility, such as the use of impinging jet crystallization and the application of multiple inlet vortex mixers. Most of these crystallization processes are performed in batches, but because of the productivity and batch-to-batch variability problems, continuous technologies gain increasing attention. However, not every batch process has been suitable for continuous crystallization thus far, but only a continuous mode would offer potential economic advantages as well as high product efficiency.

2. AIMS

In pharmaceutical technology great efforts have been made to develop cost-effective, time-saving particle size reduction techniques which are suitable for the production of uniform crystalline products and can be built into the process of the manufacturing of pharmaceutical formulations.

The main focus of this thesis is on the development of a robust and fast crystallization technique which can result in high quality crystalline product with proper physico-chemical properties besides high productivity and stability. Process intensification and optimization of operating conditions using batch technology have been accomplished, as well as the conversion of the parameters to continuous mode. The goal is to achieve significant particle size reduction, narrow particle size distribution, optimal crystal shape and stable polymorphic form in the case of a model material and a poorly water-soluble drug. Furthermore, the crystal habit modification effect of different crystallization methods is investigated and compared with each other.

The main steps in the experiments were as follows:

A Investigation of particle size reduction efficacy by impinging jet antisolvent crystallization method with self-developed impinging jet device and comparison of the effect on crystal habit with conventional crystallization methods in the case of a model material, glycine.

B Optimization of crystal habit by adjusting operating conditions with innovative solutions based on factorial design during impinging jet crystallization.

C Determination of particle size reduction effect of impinging jet method in the case of poorly water-soluble drug, cilostazol with the use of a full factorial design.

D Development of continuous crystallization method using the self-equipped impinging jet unit with both a model material and a poorly water-soluble drug.

3. MATERIALS AND METHODS

3.1. Materials

Glycine was purchased from VWR International Ltd., Debrecen, Hungary. Cilostazol was generously provided by Egis Pharmaceuticals Plc., Budapest, Hungary. All of the applied solvents were of analytical grade.

3.2. Methods

3.2.1. Crystallization methods

3.2.1.1. Conventional crystallization methods

Conventional crystallization methods were implemented in a 250-mL flat-bottomed, double-walled crystallization reactor with constant room temperature provided by the Julabo F32 (Julabo GmbH, Seelbach, Germany) cryothermostat controlled by the Julabo EasyTemp 2.3e software with and without the use of high power ultrasound (US) device (Hielscher UP 200S Ultrasonic Processor, Germany). In the case of the antisolvent system (AS), supersaturation was achieved by exposing the saturated API solution to the antisolvent at room temperature with fast addition. Reverse addition of the solutions was applied in the case of reverse antisolvent crystallization (REV).

3.2.1.2. Impinging jet crystallization

The IJ unit was a self-developed device which arranged in a non-submerged mode (see Figure 1). Two calibrated peristaltic pumps (Rollpump Type 5198, MTA Kutesz, Budapest, Hungary) fed the near-saturated solution of APIs and the antisolvents to the IJ unit at defined temperatures. Crystallization experiments were carried out in a 250-mL round-bottomed, double-walled Schmizo crystallization reactor (Schmizo AG, Oftringen, Switzerland) equipped with an IKA Eurostar digital overhead stirrer (IKA-Werke GmbH & Co., Staufen, Germany) and an Anker-type mixer with constant stirring speed. Temperatures were adjusted with a Thermo Haake P5/C10 (Thermo Haake, Karlsruhe, Germany) thermostat and a Julabo F32 (Julabo GmbH, Seelbach, Germany) cryothermostat controlled by the Julabo EasyTemp 2.3e software. The crystallized products were filtered in a porcelain filter and were washed with antisolvent, to minimize the quantity of residual solvent. After 24 hours of vacuum drying at 40 °C, the products were stored in closed containers under normal conditions.

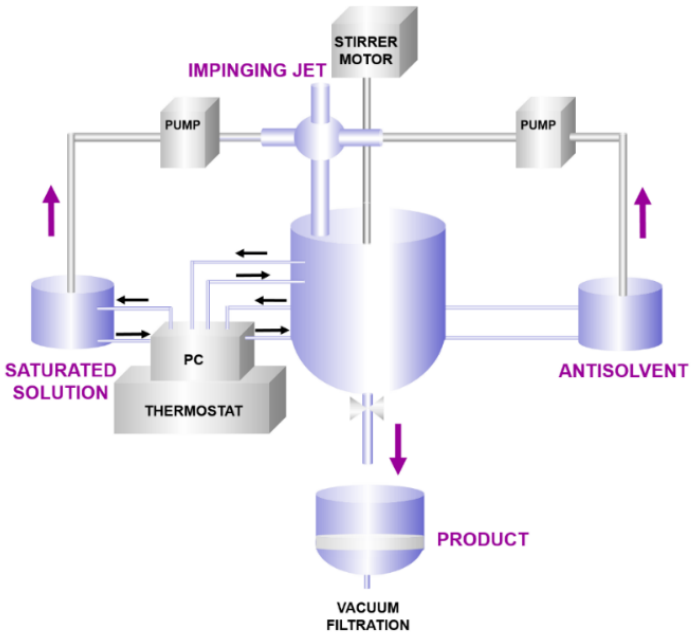

Figure 1 *Self-developed experimental apparatus of impinging jet crystallization.*

3.2.1.3. Continuous crystallization

During the continuous experiments the self-equipped IJ mixer was applied in non-submerged mode in a double-walled crystallization reactor and the continuous mixing was achieved by an IKA Eurostar digital overhead stirrer equipped with an Anker-type mixer with constant stirring speed. Constant temperatures of both of the API solution and the antisolvent were set by Thermo Haake P5/C10 thermostat and Julabo F32 cryothermostat controlled by Julabo EasyTemp 2.3e software. The solutions were dosed in high volume by two calibrated peristaltic pumps. Ongoing filtration was implemented of the crystallized product with porcelain filters without post-mixing. Fractions were separated from the crystallized product at given intervals in order to investigate the physico-chemical properties of the crystals in the pipeline. After 24 hours of vacuum drying at 40 °C, the products were stored in closed containers under ambient conditions.

3.2.2. Determination of solubility

The solubility of glycine and cilostazol was determined by using gravimetric method in pure water, EtOH, MeOH, DMSO, DMF, acetone and in mixtures of different volume ratios of solvents at ambient temperature. The effect of different concentrations of additives (NaCl and KCl) to solubility was also evaluated.

3.2.3. Product characterization

3.2.3.1. Determination of crystal morphology

Light microscopy

The crystal shape of the crystallized products was analysed using the Leica Image Processing and Analysis System (Leica Q500MC; Leica Cambridge Ltd., Cambridge, UK). Approximately 1000 particles per sample were measured and the roundness value was evaluated of high priority.

Scanning electron microscopy (SEM)

The morphology of the crystallized products was investigated by SEM (Hitachi S-4700, 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 applying a gold-palladium coating.

Particle size distribution (PSD) analysis

PSD was determined by a Malvern Mastersizer 2000 laser diffraction analyser (Malvern Instruments Ltd., Malvern, UK) in dry method with a Scirocco dry powder feeder, using air as the dispersion agent in the case of Gly samples. CIL was investigated with wet analysis using the Hydro S dispersion unit.

3.2.3.2. Identification of polymorphism

Crystal structures were identified by X-ray powder diffractometry (XRPD), the experiments were performed with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). The diffraction patterns of the crystallized samples were compared with those of the structures available in the Cambridge Structural Database (CSD, Cambridge Crystallographic Data Centre, Cambridge, UK).

A Mettler Toledo differential scanning calorimetry (DSC) 821^e thermal analysis system, equipped with the STAR^e software version 9.30 (Mettler-Toledo AG, Greifensee, Switzerland) was applied for the determination of polymorphic forms of the samples.

3.2.3.3. Flowability properties

The device was generously provided by Gedeon Richter Plc., Budapest, Hungary for our research work. A Brookfield Powder Flow Tester (PFT230, Brookfield Engineering Labs, Inc., Middleboro, USA) equipped with Powder Flow Pro software (Powder Flow Pro V1.3 Build 23, Brookfield Engineering Labs, Inc., Middleboro, USA) was used to measure the Gly samples with the running of standard Flow Function Test.

3.2.3.4. Determination of wettability by contact angle measurement

Contact angle measurements were conducted under ambient conditions with a DataPhysics Contact Angle System OCA 20 (DataPhysics Instruments, Filderstadt,

Germany). CIL compacted pastilles were produced with a manual hydraulic press (Specac Ltd., Orpington, UK). The sessile drop method was used to determine the contact angle.

3.2.3.5. Residual solvent quantity

The residual solvent content was analysed by a headspace gas chromatographic (hGC) method using a Varian CP-3800 gas chromatograph (Varian, Walnut Creek, CA, USA) in the case of Gly samples and a Perkin Elmer Clarus Gas Chromatograph with CIL samples.

3.2.3.6. Analysis of residual additive content

Qualitative determination of the additive content

SEM (Hitachi S-4700 cold field emission microscope type II) with Energy dispersive X-ray spectroscopy (EDS, Röntec XFlash energy dispersive X-ray spectrometer, Berlin, Germany) was used to examine the topology, the composition, and the elemental map of the samples.

Quantitative determination of the additive content

Determination of the KCl concentration of the samples was performed by Flame Atomic Absorptions Spectrometry (FAAS). A Perkin Elmer 4100 ZL (Überlingen, Germany) flame atomic absorption spectrometer equipped with a deuterium background correction system and an air-acetylene burner was used for the determination of the potassium content.

3.2.3.7. Investigation of dissolution rate

The dissolution rate of the CIL samples was examined by a Ph. Eur. dissolution apparatus with a modified paddle method (Type PTW II, PharmaTest Apparatebau AG, Hainburg, Germany), using pure CIL powder in 100 mL of simulated gastric fluid at a pH value of 1.2 ± 0.1. After filtration and dilution, the API contents of the samples were determined UV-spectrophotometrically (λ_{SGF} = 260 nm).

3.2.4. Factorial design and statistical analysis

The IJ experiments were implemented by a 3^2 full factorial design to identify the relevant factors which affect the solid state properties of the crystallized product. The following equation describing the interactions of the factors was used to determine the response surface and the relative effects of each factor investigated (b): $y = b_0 + b_1x_1 + b_2x_2 + b_3x_1^2 + b_4x_2^2 + b_5x_1x_2$

Statistica for Windows 12 AGA software (StatSoft Inc., Tulsa, USA) and GraphPad Prism 5 Portable statistical software (GraphPad Software Inc., La Jolla, CA, USA) were used for these calculations.

4. RESULTS AND DISCUSSION

4.1. Glycine particle size reduction

4.1.1. Factorial design

In the case of series A the influence of the linear velocity (1.41; 2.77; 4.06 m s^{-1}) and the post-mixing time (0; 5; 10 min) in three different levels. In series B the influence of the temperature difference (0; 12.5; 25 °C) and the post-mixing time (0; 5; 10 min) were investigated on three operational parameters: roundness, d (0.5) and D [4,3].

4.1.2. Crystal habit of the crystallized products

In series A, 1:1 water:ethanol solvent ratio was applied and remarkable particle size reduction was experienced compared to the initial material. The post-mixing time improved the roundness, but increased the particle size of the product significantly. In series B, the solvent ratio was modified to 1:2 water:ethanol ratio and each individual parameter setting resulted in significantly smaller particles as compared with series A (see Figure 2).

Figure 2 *SEM images of the initial glycine (A); product of series A (B); product of series B (C).*

4.1.3. Polymorphism of the crystallized products

4.1.3.1. XRPD and DSC analysis of the crystallized products

The polymorphism of the initial material and the products was examined with XRPD and compared with the structures in the CSD. It was found that both the initial material and the series A products consisted of the pure stable α-polymorph. In contrast, the series B products contained mostly the less stable β-polymorph, and a small amount of the α-polymorph. DSC studies confirmed the results of the powder X-ray analysis.

4.1.3.2. Determination of the transformation of the polymorphic forms

Transformation of the β-form into the α-polymorph began during storage. A novel XRPD calibration approach was developed for the monitoring of this phenomenon. It was specified that the initial β-form content of the series B samples was between 72 and 96%. After 1 year of storage under normal conditions, the β-form content had decreased to 13–17%. The series

A products did not change during this storage period. It was found that the 1:1 solvent ratio used in the crystallization processes was critical for the formation of the stable polymorphic form.

4.1.4. Residual solvent quantity

Ethanol (used as antisolvent) belongs in the ICH Q3C(R7) Guideline Class 3 group, where the residual solvent concentration is at most 5000 ppm. The residual solvent contents of the crystallized samples were determined by hGC. The maximum residual solvent content of the series A samples was 9 ppm, while the samples in series B contained a maximum 145 ppm of ethanol.

4.1.5. Comparison with conventional crystallization methods

The application of the IJ crystallization technique resulted in significantly smaller particle size as compared with the previously investigated conventional crystallization methods. The largest particles were achieved by conventional cooling crystallization. The REV and AS methods with the application of US were also able to achieve slight reductions in the average particle size of glycine. The IJ technology resulted in a further one order of magnitude reduction in particle size (see Figure 3).

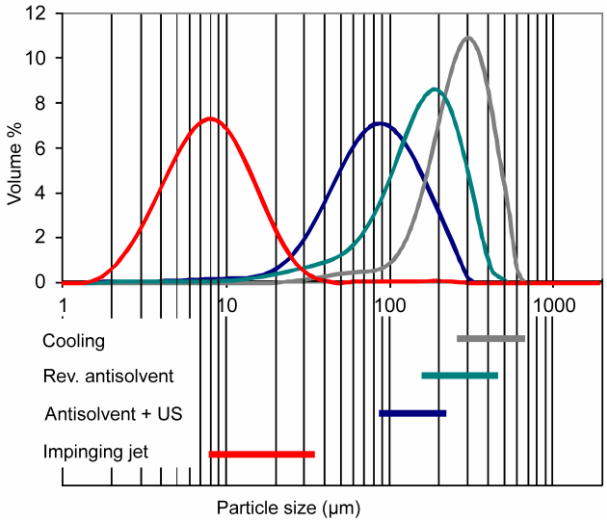

Figure 3 *Particle size distribution and average particle size range produced by different crystallization methods (top: particle size distribution of the product with the smallest average particle size achieved with the given method; bottom: average particle size ranges (d (0.5)) attained with the given method).*

4.2. Optimization of glycine crystal habit with the use of additive

In our initial pilot research, a high concentration (5000-8000 ppm) of KCl resulted in more appropriate morphology in the case of the IJ method. The lower concentration, 2000 ppm approached our final goal mostly. Thus, in series I, the concentration of additive was

decreased, and the concentration range of 1000-2000 ppm of KCl was found to produce the desired effect. In series II, the additive concentration was decreased further with one order of magnitude (100-200 ppm) to find the lowest effective concentration of the additive and to reduce the residual KCl quantity in the products.

4.2.1. *Crystal morphology of IJ products with the use of various concentrations of KCl additive*

In series I the applied concentration of KCl improved the crystal roundness, besides particle size reduction was experienced. An increasing post-mixing time was found to adversely affect these properties. In series II, the additive concentration was decreased sharply. This series of experiments clearly demonstrated that using low concentrations of KCl resulted in even better properties of the crystal habit compared to using higher concentrations of the additive. Even 100 ppm of additive appreciably improved the roundness of the crystals. A KCl concentration of 200 ppm and 0 min of post-mixing time were found to yield the smallest particle size and the most favourable roundness (see Figure 4).

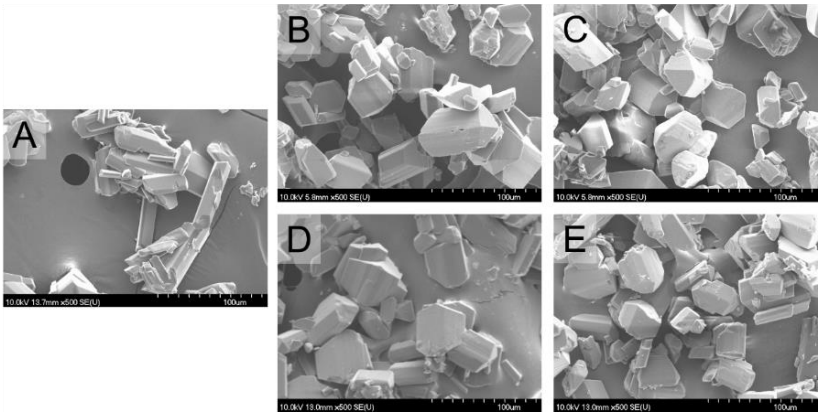

Figure 4 *SEM images of glycine crystals. A: without additive; B: with KCl 1000 ppm; C: with KCl 2000 ppm; D: with KCl 100 ppm; E: with KCl 200 ppm.*

4.2.2. Polymorphism

The polymorphism of the initial material and the products was examined immediately after vacuum drying, by both XRPD and DSC, in parallel. The XRPD diffractograms were compared with the structures available in the CSD. Based on the XRPD analysis, both the initial material and all the products were found to contain only the stable α-polymorph.

The DSC measurements, however, revealed two polymorphs, as this analytical method is more sensitive to the presence of β-glycine. The thermograms of the original glycine and of the products also contained two endothermic peaks at about 251 °C and 254 °C. The first peak corresponds to a small amount of the less stable β-form. The second one is the melting point of the α-form.

4.2.3. Residual solvent content

The residual ethanol content of the samples was analysed by hGC. The ethanol contents of the products of series I and II were between 38 and 80 ppm, which is minimal compared to the maximum value (5000 ppm) defined in the ICH requirements.

4.2.4. Residual potassium content

4.2.4.1. Qualitative analysis of potassium chloride

The arrangement of the residual KCl content within the samples was examined by SEM-EDS. Within the products containing high concentrations (5000 ppm) of the additive, the KCl crystals were found to be arranged separately and individually, as seen in Figure 5.

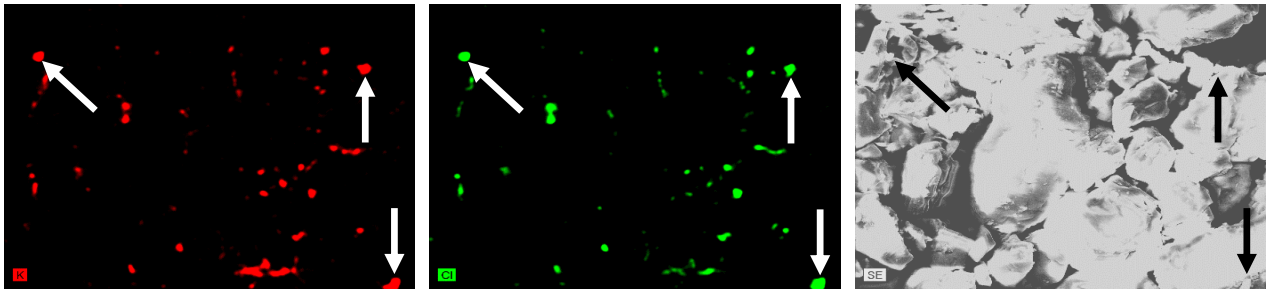

Figure 5 *SEM image and EDS elemental maps of potassium (red spots) and chlorine (green spots) for the arrangement of KCl crystals within the IJ Gly products containing 5000 ppm of additive.*

4.2.4.2. Analysis of residual potassium quantity

The crystal samples produced by using a higher concentration (1000-2000 ppm) of KCl as additive were found to have a residual potassium content of 123-364 ppm. These values were found to be proportional to the length of the post-mixing time. A longer post-mixing time increased the residual potassium content because a higher amount of KCl was allowed to get adsorbed on the surface of the glycine crystals. The products generated in series II contained by one order of magnitude less potassium (22-48 ppm) compared to those produced in series I.

4.3. Poorly water-soluble drug, cilostazol particle size reduction

This is the first study on the application and optimization of the IJ crystallization method in the case of this molecule. In our previous experiments the most influencing crystallization factors were discovered and the process parameters were optimized for our model material, glycine, and these observations were converted to the current experiments and were further devised specifically for the BCS II material, cilostazol.

4.3.1. Crystal morphology

The post-mixing time and the temperature difference between antisolvent and solvent influenced mostly the crystal morphology, therefore cooling crystallization was combined with the antisolvent IJ method. The increase in post-mixing time made the particle size systematically larger, as well as improving percentage yield, but not affecting roundness appreciably. IJ CIL-1; 4 and 7 samples revealed the most appropriate crystal habit. In order to determine the effectiveness of the developed IJ method in the case of CIL, it was compared with the conventionally applied crystallization methods in the pharmaceutical industry, which are also aimed at particle size reduction (see Figure 6).

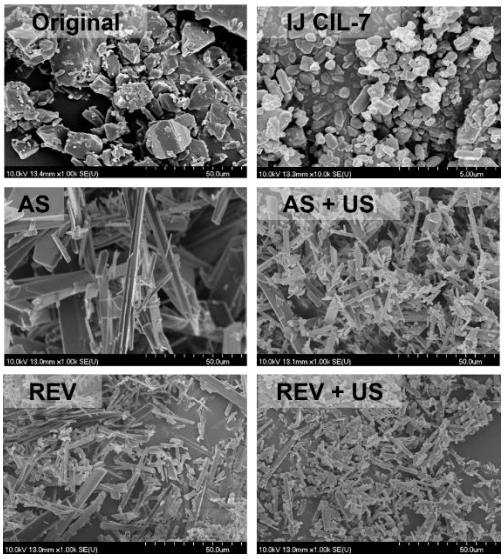

Figure 6 *SEM images of the ground initial CIL crystals (Original), IJ sample with the most appropriate morphology properties (IJ CIL-7) and the products of the different conventional crystallization methods (AS; AS + US; REV; REV+ US).*

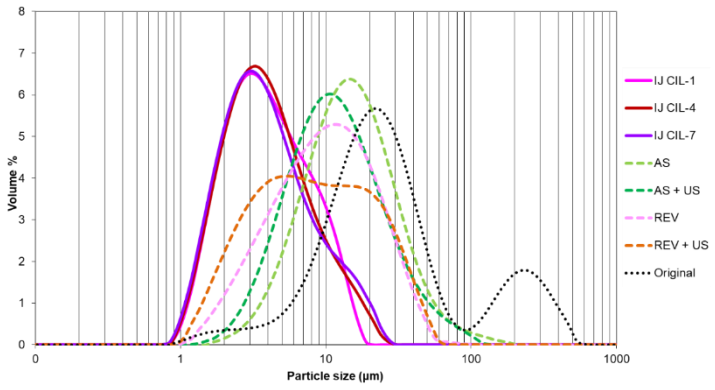

Figure 7 *Comparison of particle size distributions of samples made with different crystallization methods.*

The laser diffraction analysis of all IJ samples revealed monodisperse PSD. The original material and the product of REV combined with US showed polydisperse distribution as can be seen in Figure 7. Overall, based on the results it can be stated that IJ resulted in significantly

smaller average particle size and improved the roundness compared to the initial material and conventional methods, not even with the application of US.

4.3.2. Polymorphism

According to the XRPD and DSC analysis the initial material contains the orthorhombic A polymorph, which is the most stable form at ambient conditions. It was found that all kinds of the crystallization methods resulted in the most stable orthorhombic A form, and any other polymorphic forms were not detected.

4.3.3. Dissolution rate

The dissolution profile of the pure CIL products was accomplished by 120-min-range in vitro studies in SGF without enzymes (pH=2±0.1). At 120 min, the IJ CIL-7 sample with the smallest particle size led to the highest dissolution quantity (see Figure 8). Based on our results, a clear correlation is revealed between the dissolution rate and the particle size; the smaller the particle size, the higher the dissolution rate. If the unique, small particles could remain in the final dosage form as well, the higher dissolved concentration of the API in the initial period of dissolution would improve bioavailability.

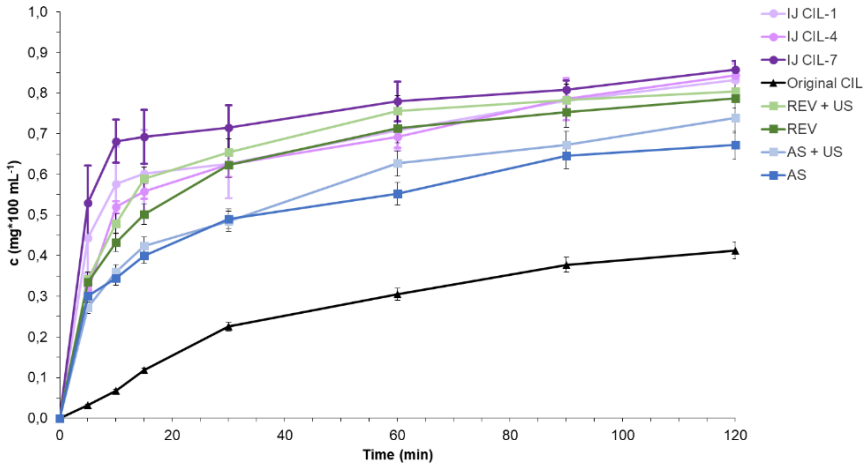

Figure 8 *Dissolution rate of the crystallized CIL products.*

4.4. Development of a continuous crystallization method with glycine

Based on our previous results in the batch processes the optimal parameters were converted to the novel continuous IJ antisolvent crystallization method with the use of glycine, as a model material at first. Moreover, scale-up was also accomplished as the volume of the solutions was 20 times higher than in batch size. In-process-monitoring was achieved with sampling in every minute in order to determine the consistency of the quality, as well as monitoring the key process parameters, for instance average particle size and roundness during the whole process.

4.4.1. Crystal habit and PSD

The crystal morphology was not changed remarkably when the first and the last samples were compared with each other (see Figure 9). The continuous mode resulted in small, bipyramidal shaped crystals with smooth surface. Based on micrometric data the average particle size (d (0.5) = 25.899 µm-34.313 µm) altered with low SD (2.54) and CV (0.08). This indicates the small variation between the process start and end points, and confirms the visual observations by SEM images.

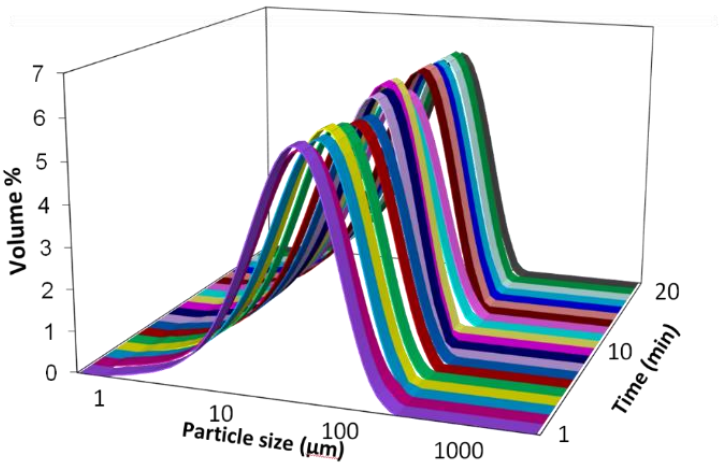

Figure 9 *Particle size distribution of the crystallized products by continuous IJ method.*

4.4.2. Flowability

Powder flow tester results demonstrate that the initial material is a free flowing powder as it was expected from the large isodimensional shape of the particles, and both the batch and the continuous IJ products with the use of additives are mostly easy flowing, and their flowability properties are comparable. The use of these products could be suitable for further tableting procedures.

4.4.3. Polymorphism

According to the XRPD results, all of the samples remained in the same crystal structure, the most common α-glycine, which is identical with the polymorphic form of the initial material. However, the more sensitive DSC revealed the presence of unstable β-form in addition to the stable α-form in the IJ samples.

4.5. Development of IJ continuous crystallization method with cilostazol

After a successful implementation of IJ batch parameters for the novel IJ continuous method in the case of a model material, Gly, the poorly water-soluble drug, CIL was also tested with the application of the method. The previously optimized crystallization parameters for CIL (IJ CIL-7 factors) were selected for our scaled-up, continuous experiments.

4.5.1. Crystal morphology

Based on PSD analysis, all of the samples revealed monodisperse distribution from the beginning until the last samples in the end of one process. In Figure 10 the d (0.5) results were summarized. Compared to the batch process the percentage yield did not increase, it was between 80.19-86.52 %.

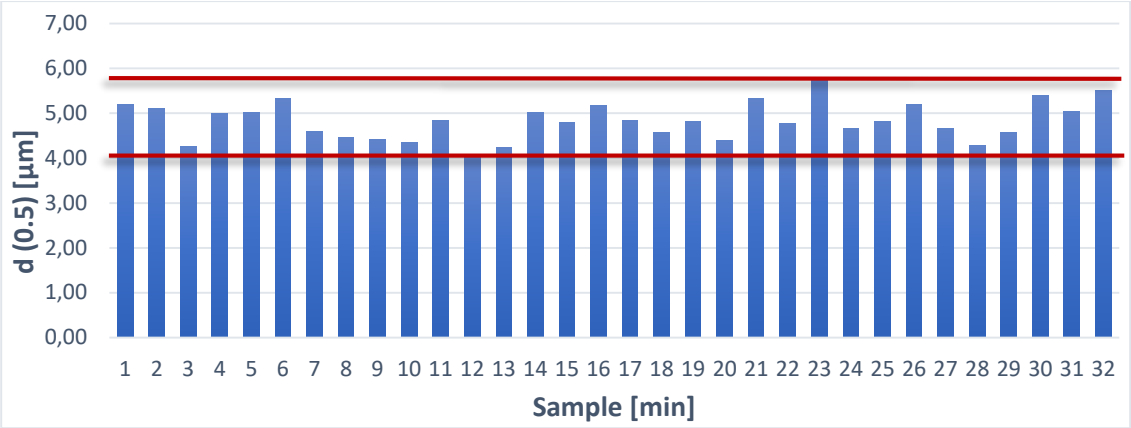

Figure 10 *Average particle size (d (0.5) of the CIL samples made by the IJ continuous method during the whole process.*

4.5.2. Polymorphism

Based on XRPD and DSC results the consistency of the CIL crystal structure through the process can be established, as neither on the diffractograms nor on the thermograms can alterations be observed.

4.5.3. Dissolution rate

It can be stated that the dissolution profile was similar to the batch process results in all of the continuous IJ products and the difference between them was also negligible (see Figure 11), since the average particle size of the samples varied in a narrow range.

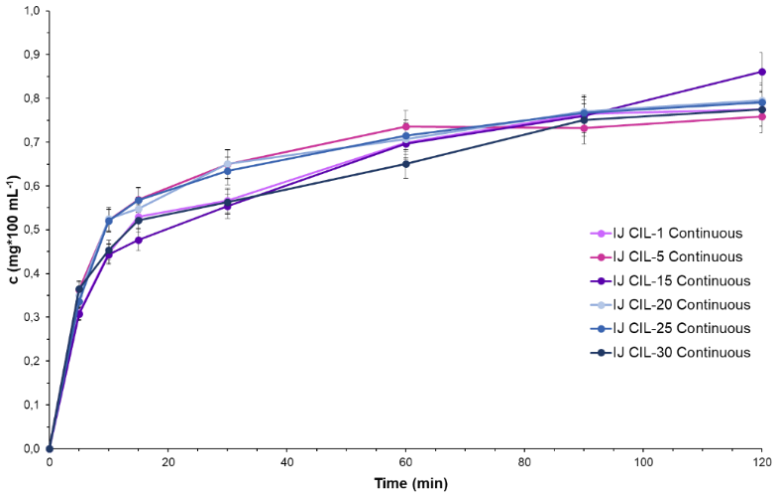

Figure 11 *Dissolution rate of the continuous IJ method products with the sampling of different period of time.*

5. SUMMARY AND CONCLUSIONS

In this study the efficiency of the self-developed impinging jet crystallization method was investigated regarding its crystal habit modification effect in the case of a model material and in the case of a poorly water-soluble drug. The critical process parameters were optimized for both a batch and a continuous mode in order to achieve a stable and uniform crystalline product.

New approaches and practical relevance of the current research work:

A The self-developed impinging jet device proved to be an effective, fast and reproducible tool for particle size reduction of a model material, glycine. The process influencing factors were ascertained by means of a full factorial design.

- A novel X-ray powder diffractometry calibration approach was developed for the monitoring of the polymorph transformation in the case of β-glycine, which has not been reported previously.
- Our impinging jet method resulted in one order of magnitude smaller average particle size compared to the generally applied conventional crystallization methods which methods can reduce the particle size only within certain limits.
- The developed impinging jet crystallization technique enables the production of a stable polymorphic form with a low residual solvent quantity.

B This is the first description of combining the impinging jet crystallization method with the application of different concentrations of potassium chloride as an additive to modify the crystal habit of glycine particles.

- Crystal roundness was successfully improved with even low (100-200 ppm) KCl additive concentration.
- The distinct arrangement of the additive was determined in the final product and its residual quantity was adjusted to an optimal level.
- The critical operational parameters of crystallization were optimized for the desired crystal morphology with suitable flowability and low residual solvent quantity.

C The developed impinging jet method enabled us to reduce the particle size of a poorly water-soluble drug, cilostazol and ensure the quality of the final product, reproducibly.

- Significant improvement of the crystal habit of cilostazol was achieved by a combined impinging jet and cooling crystallization method.
- The critical process parameters were determined by a full factorial design, which were the post-mixing time and the temperature.
- Crystal morphology and dissolution rate were improved remarkably compared to the conventional crystallization methods.

D The batch process was successfully converted to a novel continuous impinging jet crystallization method not only with the use of a model material, glycine, but also in the case of a poorly water-soluble drug, cilostazol.

- The developed continuous method is simple and effective to improve the process efficiency, decrease the process time, but maintain the quality of the final product.
- Scale-up was achieved with an improved percentage yield compared to the batch method.
- During the process the operating parameters were optimized for the actual drug substance, furthermore the key process parameters, for instance particle size, particle size distribution and roundness were monitored, and the results revealed the consistency and robustness of the method.

Overall, it can be concluded that the developed batch and the streamlined continuous methods enable the production of a crystalline material with improved rheological properties, and this material could be applied directly in the tableting processes without further modifications, and the crystallization approach could be built into the manufacturing line of pharmaceutical formulations without large investments. The comparison of the different conventional crystallization methods revealed their particle size reduction capacity, and the results can ease the decision on which method is suitable for attaining the desired particle size range. The observations about the crucial process parameters can serve as a basis for the crystal habit optimization of other poorly water-soluble substances as well.

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6. **Tímea Tari**, Zoltán Aigner: Additívek alkalmazása impinging jet kristályosítási eljárás során.
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