OUTPUT 4	Stability- enhanced hot-melt extruded co-amorphous solid dispersion (TRL4)
Project specific objective	1) Innovative pharmaceutical formulations and technologies
Output description	Stability- enhanced hot-melt extruded co-amorphous solid dispersion.The delivered products will be ready to use in pharmaceutical applications. Prototypes and comprehensive data bases on their physico-chemical key properties and optimized processing parameters will be available.
Project Output Target	1
Expected project specific result (s)	1 new optimized formulation (expected gain 75% in stability) using a large range of different preparation and characterization techniques in line with the current regulatory guidelines. Formulations will benefit from scale-up evaluation and pre-clinical trials. The developed product will increase the competitiveness of SMEs. 1 Patent is targeted.
Partner responsible	PP4 (Ghent University)
Other Partners involved	LP 12 (University of Lille)

Summary of the objectives, activities and achievements obtained during the project

Activities

Amorphous solid dispersions are an efficient way to improve the solubility of poorly water soluble drugs in order to achieve sufficient blood level of the drug and obtain a therapeutic effect. However, amorphous materials are intrinsically unstable. The objective of this study was to improve the stability of hot-melt extruded amorphous solid dispersions at several levels (i.e. during preparation of the solid dispersions and during processing of the solid dispersion into a specific dosage form). Therefore, poorly water soluble drugs were combined with different types of polymers. Research has been conducted by 2 PhD students at PP4 and LP12.

The **achievements** can be categorised into:

1) **Knowledge: Created/Increased skill and capacities**

Via the project knowledge has been gained about the processing of hot-melt extruded solid dispersions into a stable solid dosage form (tablet), taking the physico-chemical properties of the drug and polymer into account to optimize the process settings. A strategy was also devised to miniaturize the manufacturing process of solid dosage forms containing amorphous solid dispersions, an interesting approach when during early product development only limited quantities of a novel drug compound are available. An ingenious protocol was defined to improve the dissolution rate of poorly water soluble drugs in the polymer matrix of an amorphous solid dispersion, ensuring a greater efficacy of the drug upon administration to the patient.

2) **Socio-Economic: Increased business activities/capacities (new products, processes, services, techniques)**

The achievements obtained during the project were disseminated at international scientific meetings to representatives of the pharmaceutical and biopharmaceutical industry. This – in combination with the published scientific reports – ensures that the project results will be implemented during the formulation and processing of amorphous solid dispersions by (bio)pharmaceutical companies.

1) Description of the scientific and technological achievements

A) New strategies to increase our understanding about the processing of solid dispersions into pharmaceutical dosage forms.

Strategies have been explored to increase our understanding about the processing of solid dispersions into pharmaceutical dosage forms. When implemented by the pharmaceutical industry the knowledge gained (which takes into account the physicochemical properties of the solid dispersions) will improve the efficacy of manufacturing solid dosage forms from solid dispersions into a stable and accurate dosage form which can be easily administered to the patient.

In a first part, a polymer-drug combination (using Soluplus® as polymer and Celecoxib as poorly soluble drug) was selected and subjected to a Quality-by-Design (QbD) approach to thoroughly understand how process (barrel temperature, screw speed, throughput) and formulation (drug load) parameters can influence the critical quality attributes of extrudates and tablets prepared from these amorphous solid dispersions. Since the concept of continuous processing is gaining momentum in pharmaceutical manufacturing, a thorough understanding on how process and formulation parameters can impact the critical quality attributes (CQA) of the end product is more than ever required. This study was designed to screen the influence of process parameters and drug load during hot-melt extrusion on both extrudate properties and tableting behaviour of an amorphous solid dispersion formulation using a QbD approach. A full factorial experimental design with 19 experiments was used to evaluate the effect of several process variables (barrel temperature: 160–200 °C, screw speed: 50–200 rpm, throughput: 0.2-0.5 kg/h) and drug load (0–20%) as formulation parameter on the hot-melt extrusion (HME) process, extrudate and tablet quality of Soluplus® (SOL)-Celecoxib (CEL) amorphous solid dispersions.

Although the torque values strongly varied in function of the experimental parameters, none of them exceeded 55% of the maximum torque tolerated by the extruder. Torque was mainly influenced by barrel temperature and drug load since both factors impact the melt viscosity of the formulation. Higher barrel temperatures reduced the melt viscosity of the formulation and therefore less energy input was required to rotate the screws at a predefined screw speed. The latter also occurred when adding CEL to the formulation, since the API can act as a plasticizer when solubilized in the polymer matrix, yielding lower torque values. These findings were confirmed by analysing rheological data of SOL-CEL formulations.

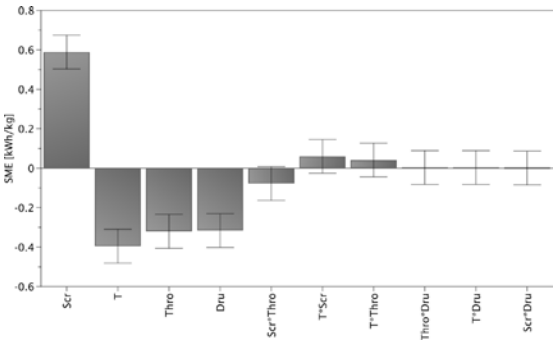

Figure 1: Effect plot of SME including 95% confidence intervals for screw speed (Scr), barrel temperature (T), throughput (Thr) and drug load (Dru) with their interactions (*) as factors.

Increasing the screw rotational speed during HME contributed significantly to higher specific mechanical energy (SME) levels, indicating that more mechanical energy is transferred to the material under such conditions. Factors that reduced the torque such as higher barrel temperatures and drug load resulted in lower SME-levels caused by a drop in matrix viscosity under such conditions. When more material is fed into the barrel at fixed settings, the same amount of energy must be transferred to a larger amount of material, thereby reducing SME values (Figure 1). For the experiments including CEL as model drug, changing the process parameters during HME had no impact on the solid dispersion type. Glassy solutions were obtained at every condition, indicating the suitability of SOL as polymeric carrier for CEL solid dispersions.

Higher drug loads reduced the glass transition temperature (Tg) of the resulting extrudates, as CEL acted as plasticizer, while the process parameters had no significant impact on solid state properties of the glassy solutions. Similar conclusion was drawn after analysis of the particle size distribution (PSD) of the milled extrudates: d50 and d90 values increased for extrudates containing higher drug load. Due to the drop in Tg, the material was less brittle during milling at room temperature compared to extrudates without CEL. However, these differences had no impact on the flow properties of the milled formulations, enabling further downstream processing such as (continuous) feeding of a rotary tablet press during tableting. Significant impact of drug load and barrel temperature was detected on the moisture content of the milled extrudates. When formulating glassy solutions with high drug loads, the moisture content decreased significantly when higher extrusion temperatures were used. As the adsorption of water in dense glassy particles occurs mainly at the surface (via weak interactions) due to the absence of pores penetrable to water, the level of densification during HME might be influenced by the extrusion temperature at higher drug loads, as smaller amorphous clusters or a more extensive molecular dispersion are created at elevated extrusion temperatures. Density of the extrudates was indeed higher with increasing drug loads and therefore this could explain the observed impact of extrusion temperature on the moisture content at higher drug loads. Although the effects in this study were relatively small (e.g. maximal deviation of 0.4%) and the impact of moisture content was not reflected in the tableting behavior of the formulations, it is an important observation since these effects could be more pronounced for other formulations. In general, it could be concluded that drug load had the most significant impact on the extrudates properties, indicating that the HME process was very robust.

In order to quantify the concentration of CEL in the extrudates, offline Raman spectroscopy was applied on powders of the formulations containing API. MDSC and XRD measurements confirmed the absence of crystalline CEL in each formulation, indicating the formation of glassy solutions. The concentration variations were clearly visible in the collected Raman spectra which is reflected in the PCA scores plot of the collected spectra (Figure 2). The two principle components covered nearly all spectral variation, where the first principal component (PC1) accounted for 96% of the total variation. It was confirmed from the scores plot that PC1 captured the spectral variation caused by differences in API-polymer concentration since a clear distinction can be made between the Raman spectra of the calibration set. A PLS model was developed which allowed prediction of the CEL concentration in the extrudate powders of the DOE-formulations by regressing the off-line collected spectra (X) of the calibration set versus the known CEL concentrations (Y). Two PLS components were sufficient since the goodness of prediction of the model (Q2= 0.996) did not significantly increase when adding extra components. The predictive performance of the PLS model was validated by projecting the Raman spectra of a validation set onto the model in order to predict the corresponding CEL concentrations. This resulted in a root mean square error of prediction (RMSEP) of 1.84%. For each validation concentration level, accuracy was evaluated by calculating the trueness and precision. A good precision of the method was noticed as the accuracy of all validated concentrations remained within the acceptance limits of 10%. The latter PLS model enabled quantification of CEL (%) in the extrudate powders of correlating experiments of the experimental design. None of the experiments in the DOE resulted in

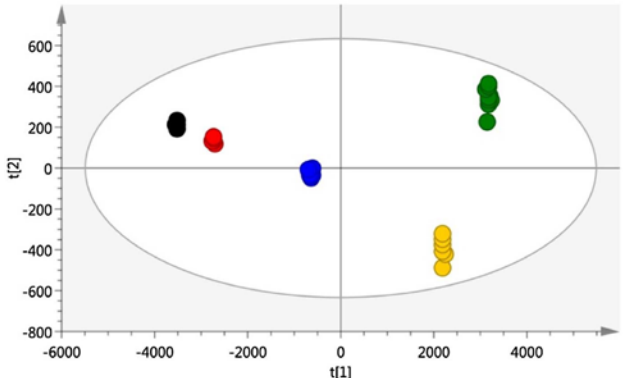

Figure 2: PC1 versus PC2 scores plot of the calibration set for milled extrudates containing 5% CEL (black), 10% CEL (red), 20% CEL (blue), 30% CEL (yellow) and 40% CEL (green).

extrudates with a CEL content deviating > 3% of the label claim, taking into account the RMSEP.

Tabletability was clearly affected by the drug load, while changing the process parameters had no significant impact on this tablet property. Tablets manufactured from extrudates formulated with CEL yielded significantly higher tensile strengths. Additionally, the shape of the curves was influenced by the formulation parameter as the tabletability of formulations without drug was independent of the compaction pressure, while CEL- containing formulations showed an inflection point prior to reaching the 'plateau' phase at higher main compaction pressures. The latter indicated that changes in the mechanical properties of these formulations had occurred, which resulted in tablets of higher tensile strength. Some of the provided energy during compaction can be stored by materials as elastic energy, which is linked to the elastic recovery during decompression thereby causing disruption of some of the previously formed interparticulate bondings. The drug load was inversely correlated with the magnitude of the out-of-die recovery. Low values of the latter are preferred, since the phenomenon was linked to modifications in the compact during the decompression phase and possible issues during coating.

The compaction properties plasticity factor (PF) and in-die elastic recovery (IER), calculated from the recorded energy plots during a compression cycle, represent the contribution to the tablet tensile strength of plastic deformation and elastic behavior, respectively. Drug load had a significant impact on the plastic deformation of the formulation, with higher PF at increasing drug loads, while IER was unaffected by this formulation parameter. Formulation of glassy solutions with increasing CEL content yielded higher Py and Db values, highlighting a more fragmentary behavior of these formulations which contributed to their higher tablet tensile strengths.

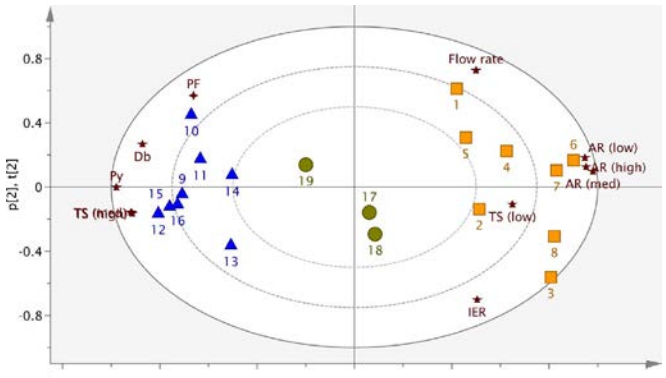

Figure 3: PC1 vs. PC2 bi-plot of the determined compaction and flow properties for formulations of experiments containing 20% CEL (blue triangles), formulations of experiments without drug load (orange boxes) and centerpoints containing 10% CEL (green circles) for which the number represents the corresponding experiment number in the experimental design. The loadings (red star shape) represent the fragmentation factor (Db), the heckel value (Py), the plasticity factor (PF) and the anti-correlated in-die elastic recovery (IER), tablet tensile strength (TS) and out-of-die elastic recovery (AR) for three compaction pressures (low, medium, high) and the flow rate of the powder formulations.

The influence of the design variables on the tableting behavior was summarized using principle component analysis (PCA) where different compaction properties and mechanical properties were included in order to classify formulations of the different experiments according to the contributions of these individual properties. The two principal components in the PCA accounted for 82.5% of the total variance in the ataset, the first principal component (PC1) comprising 68.5% of the variance. When analysing the PCA bi-plot (Figure 3) along PC1, the prominent influence of the formulation parameter drug load stands out with a cluster of the 20% CEL formulations having low PC1 values (blue triangles), formulations without drug having high PC1 values (orange boxes) and the centerpoint formulations with 10% CEL having intermediate values (green circles). The loadings indicated that PC1 (i.e. the direction of the x-axis) differentiated between formulations which experienced more fragmentation and plastic deformation and therefore yielded tablets of higher tensile strength (left of the origin), while it was anti-correlated with the out-of-die elastic recovery (right of the origin). PC2 (i.e. the direction of the y-axis) captured the flow properties of the powders and the IER which was anti-correlated to the PF.

A QbD approach for HME/tableting was successfully implemented in this research study to evaluate the influence of process parameters and drug load during HME on both extrudate properties and tableting behaviour of an

amorphous solid dispersion formulation. Modulation of the torque was possible by adjustment of the barrel temperature and drug load. Additional variations in screw speed and throughput led to different SME-levels, which represent the input of mechanical energy into the material during HME. Drug load had the most significant impact on the extrudate properties with minimal influence of the process variables. Similar results were obtained when evaluating the tableting behaviour of the formulations with a prominent influence of the formulation parameter (i.e. drug load) on the compaction and mechanical properties and no effect of varying HME process parameters. Increasing drug loads resulted in compacts with higher tensile strength since the volume reduction mechanisms changed towards more fragmentary behaviour combined with more plastic deformation and less out-of-die elastic recovery. A PLS model was developed and validated for Raman spectroscopy data which allowed off-line CEL quantification in the extrudates. This research emphasized that HME is a robust process throughout the experimental design space for obtaining amorphous glassy solutions and tablets of such formulations since only minimal impact was detected of the process parameters on the extrudate and tablet properties. However, the quality of extrudates and tablets can be optimized by adjusting specific formulations parameters (e.g. drug load).

In a second part the manufacturing process was miniaturized in order to reduce the amount of solid dispersion needed for manufacturing while maintaining the quality of the end product. An emerging need is to use feed frame designs which enable studies on fully-mounted industrial-scale rotary tablet presses (hence investigating all the factors which might influence the die-filling step) without consuming large quantities of bulk material. This research paper intended to respond to this demand by designing modified feed frames which are based on similar principles as the conventional one, but with a strongly reduced volume. The aim of this study was to understand the impact of two types of miniaturized R&D-feeders (equipped with different paddle designs) on the die-filling step of a rotary tablet press and to elucidate their relevance for downscaling studies.

With the current transformation of the pharmaceutical industry towards continuous manufacturing, there is an inherent need to embrace this concept already during the early stages of drug formulation. Therefore, this research paper investigated the feasibility of using miniaturized forced feeders on a high-speed rotary tablet press with the intention of downscaling the tableting process. Forced feeders with a reduced volume (up to 46% compared to the conventional two-compartment forced feeder) were designed by either sealing one compartment (i.e. R&D1) or lowering of the compartment height (i.e. R&D2). These feed frame designs were thoroughly analysed in combination with two paddle types over a wide range of process-settings (i.e. tableting speed, paddle speed, direction of paddle rotation, overfill-level). A poorly flowing model powder was deliberately selected as challenging formulation.

The volume R&D1 feed frame was reduced by sealing the second compartment of the conventional feed frame. This design implied that the conventional powder flow pattern in a two-compartment forced feeder was altered. Figure 4 presents the predicted changes in weight variability due to interaction of the investigated DOE factors. Plot A describes the interaction of direction of rotation of the paddles with their design on the die-filling variability. Interestingly, a positive effect of rotating the paddle wheels counterclockwise was noticed for both paddle designs. This phenomenon is due to an increased contribution of forced feeding by the paddles when the powder is transported in the opposite direction of the passing dies. When rotating in the default clockwise direction, the powder moves in the same direction as the dies and hence a greater contribution of gravimetric feeding, which is more challenging for poorly flowing formulations, is expected. This beneficial effect of counterclockwise rotation was more pronounced for the curved paddle design (i.e. paddle type A) as indicated by the steeper decrease in RSD tablet weight (TW).

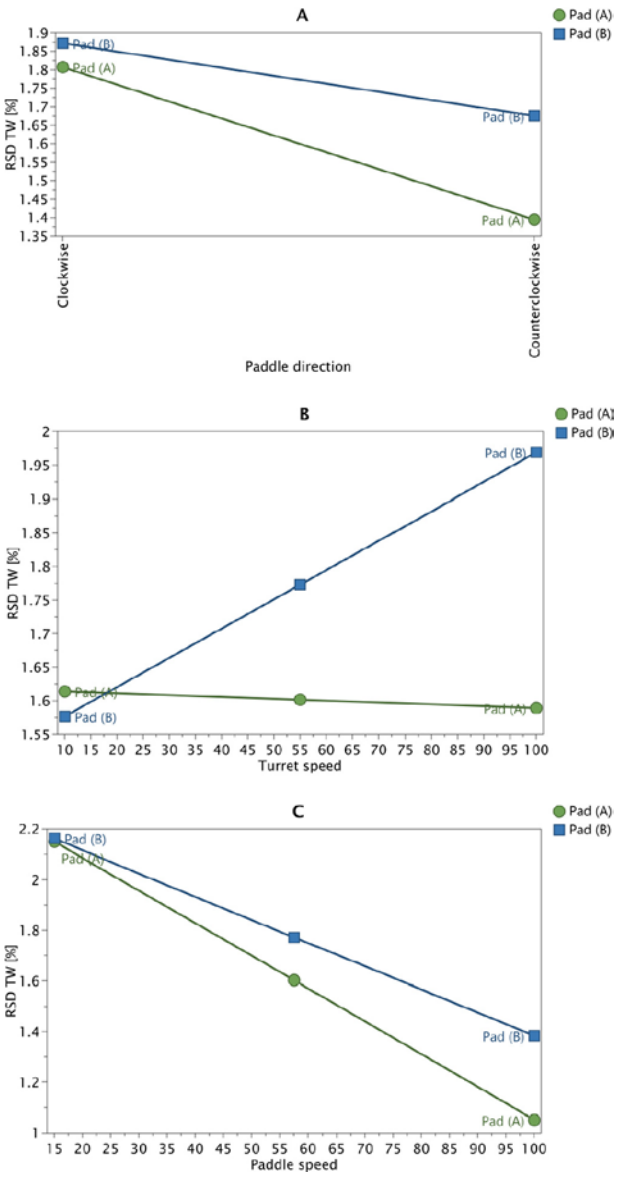

Figure 4: Predicted changes in TW variability due to interaction of paddle design (Paddle A and B) with direction of rotation (A), turret speed (B) and paddle speed (C) in feed frame R&D1.

Powder distribution between the paddles altered significantly with the direction of paddle rotation when using the curved paddle design. Due to the radial curvature, the impacting forces push the powder mainly towards the edges when rotating in counterclockwise direction. In contrast, the curvature would enable a more homogenous powder distribution along the length of the paddle when rotated at the default clockwise direction. The main impact of these effects on the die-filling will be experienced at the 'edges' of the die-slit as these regions can only be covered by powder accumulated at the end of each paddle. Therefore, with the amount of powder at this paddle region being significantly higher when rotating the curved paddles in counterclockwise direction, both zones 1 and 2 are covered by powder, reducing the risk of die-filling variability compared to the default direction of rotation. Using a straight paddle design (paddle type B) the powder distribution was less affected by the direction of rotation.

Plot B and C in Fig. 2 display the change in die-filling variability for paddle type in function of turret speed and paddle speed, respectively. A higher turret speed increased the variability when applying the straight paddle design (i.e. type B), while the curved design (i.e. type A) guaranteed a robust die-filling uniformity over a wide range of tableting speeds. The behaviour of both paddle designs in function of paddle speed was similar with respect to the die-filling variability. For feed frame R&D1, increasing the paddle speed was beneficial for the die-filling uniformity since the dies experienced more paddle passings at a similar tableting speed. To summarize, the tableting process using a R&D1 feed frame can be optimized by rotating the paddle wheel at high speed in counterclockwise direction. Due to its robustness on die-filling at varying turret speed, radial curved cuboid paddles are preferred over the straight design.

The design of R&D2 feed frame strongly resembled a conventional two-compartment forced feeder, having two paddle wheels which rotate in the default direction to prevent powder stream obstruction at the transit zone between both compartments. A reduction in volume was achieved by lowering the height of both compartments, the paddle height as well as the top plate thickness were also adapted to maintain equal gap widths between paddles and feed frame plates. An overview of the impact of process settings and paddle design on the product and process responses for this feed frame is given by the PCA bi-plot in Figure 5. The model contains two principal components (PC) which accounted for 91.7% variance in the dataset with PC1 and PC2 comprising 70% and 21.7%, respectively. The loadings on the biplot represent the investigated responses of the experimental design, while the scores represent the DOE-runs with their specific combination of factors. The clustering of the loadings was similar

as in a conventional feed frame. Increasing the tableting speed was the main source of variability for die-filling and generally resulted in lower mean tablet weights and higher tablet weight variability, based on the reduced filling time that each die experiences at higher tableting speed since it is exposed for a shorter time to the powder bed. Especially at high tableting speed, it is important to optimize the die-filling step by adapting other process settings. For example, an increase in paddle speed resulted in a decrease of the random die-filling variability for runs performed at high turret speed. Due to the effect of the paddle speed, two clusters 1 (i.e. runs at low paddle speed) and 2 (i.e. similar runs a high paddle speed) could be differentiated in Figure 5 among the runs left from the origin in PC1-direction. This was the case for both investigated paddle designs. At higher paddle speed, more paddle passes are available during the short exposure time of the dies (i.e. high turret speed). Moreover, a similar effect of paddle speed on the die-filling was noticed for straight paddles at low tableting speed, comparing run 5 (performed at low paddle speed) and run 7 (performed at high paddle speed) within cluster 3. This highlighted the importance of paddle speed when using this type of feed frame, especially since the volume of powder transported by the paddles is reduced in this miniaturized forced feeder. Therefore, presenting more powder to the dies can be achieved by increasing the paddle speed. A large cluster (4) of good quality runs (i.e. low die-filling variability and high mean TW) was distinguished at the right side of the origin in PC1-direction, showing the centerpoints in the design and most runs at lower turret speed.

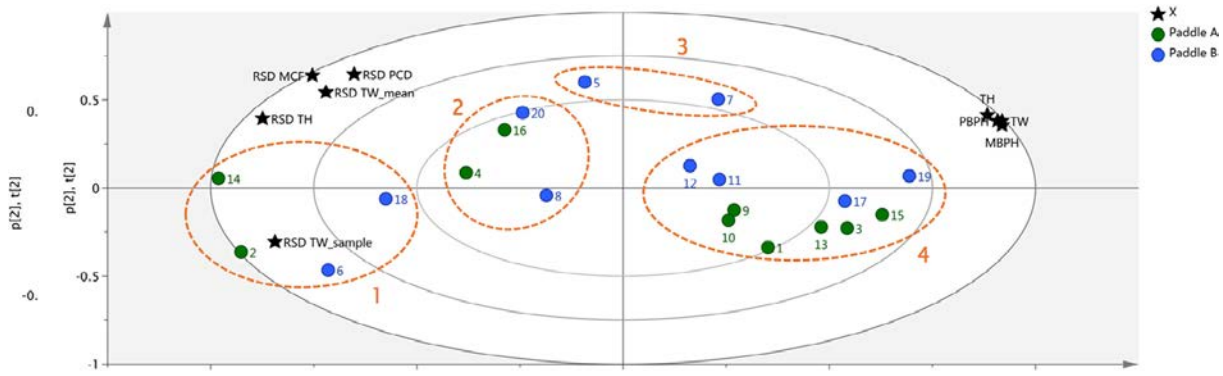

Figure 5: PC1 vs. PC2 bi-plot combining the loadings (DOE-responses, black stars) with the scores (circles, colours in function of paddle design; see legend) where the numbers represent the corresponding experimental run at the specific process settings using feed frame R&D2. Clusters of scores are indicated and numbered by dashed ellipses.

For all experiments performed on each feed frame, the dimensions and fill-depth of the dies were unchanged in contrast to the reduced R&D feed frame volumes. Hence, a comparable volume of powder can be removed by each die at similar experimental settings. However, as the total powder volume inside the R&D feed frames is different for each forced feeder, it is likely that the average residence time (ART) and the number of paddle passes on the powder bed during its residence in the feed frame (Npp) will change in function of the investigated feed frame. Table 4 presents an overview of these responses for the CP-settings of each R&D feed frame in comparison to the conventional feed frame. The ART in both R&D feed frames was significantly reduced. For R&D2 feed frame, ART was reduced at a similar scale (i.e. 32%) as the volume reduction of this feed frame compared to the conventional frame. The same reduction was detected for the number of paddle passes which are indicative of the shear induced on the powder bed during the residence time in the feed frame. In contrast, the magnitude of reduction of these responses for the R&D1 feed frame was different compared to the volume reduction (i.e. 46%) of the miniaturized feed frame. This was linked to the modified powder flow pattern in this miniaturized feeder. A strong reduction (i.e. 77–78%) in shear induced by the paddles was noticed, indicating that the use of this feed frame might be useful for formulations which are prone to segregation or overlubrication. However, the use of a one-compartment feed

frame will be less comparable to the die-filling step in a conventional two-compartment forced feeder. Analysis of this dataset suggested to use the second R&D feed frame (R&D2) in a downscaling study from the conventional feed frame since it bears good similarity in terms of flow pattern and scalability of ART and shear induced by the paddles.

An experimental design was constructed which enabled to compare the effect of paddle design and process settings between the conventional and the miniaturized two-compartment forced feeder. The distribution for both TW and RSD TW responses were relatively similar for both investigated feed frames, with turret speed being an important process parameter regarding TW and TW variability. Furthermore, the impact on the die-filling step of changing turret speed, paddle design, paddle speed and overfill level must be similar in both investigated feed frames when it is intended to use the miniaturized version for representative experiments consuming less material (i.e. downscaling). Interaction plots were analysed to compare both feed frames, as presented by Fig. 6. It is important to focus on the slope of the interaction plots, since the absolute values were expected to differ between the feed frames as no change in fill depth was applied when shifting from the conventional feed frame to the miniaturized version. However, the slope of the plots inherently resulted from the impact of process settings and paddle design on the powder bed inside the investigated feed frame. Switching from curved paddles to the straight paddles induced more die-filling variability in both feed frame. This has been linked to the efficiency of powder transport, which occurred in a comparable manner for both feed frames. A negative impact of higher turret speeds on the die-filling uniformity was observed using both feed frames. However, the slopes of both plots are very similar, indicating that it is relevant to use the R&D2 feed frame to investigate the impact of changing tableting speed on the die filling of a formulation, while consuming considerably less material. Moreover, the R&D2 feed frame allows to acquire valuable knowledge on how the die-filling step can be fine-tuned by changing the speed of the feeding paddle wheel since a similar increase of RSD TW was detected at higher paddle speed in both designs of the forced feeder.

In this work, the performance of two miniaturized forced feeders used during high-speed tableting of a poorly flowing formulation was assesses and it was elucidated for each R&D feed frame how the die-filling step was influenced by both design and process settings. Analysis of R&D1 feed frame, where the volume was reduced by sealing one compartment, revealed a positive effect on die-filling when rotating the paddle wheels in counterclockwise direction and when a curved paddle design was used. Moreover, the number of paddle passages through the powder bed was strongly reduced when using R&D1 feed frame, indicating that this design might be superior for formulations which are shear-sensitive (i.e. reduced risk for segregation or overlubrication). However, in order to gain more knowledge regarding the die-filling behaviour of a conventional two-compartment forced feeder while consuming less material, the R&D2 feed frame bears more potential for being predictive towards the impact of paddle design, tableting speed and paddle speed on the die-filling uniformity in a larger two-compartment forced feeder. Furthermore, the use of this miniaturized feed frame for downscaling studies on a high-speed rotary tablet press could be further encouraged due its ease of handling.

B) Mastering the physical stability of amorphous molecular alloys to optimize drug efficacy

Solubility[1-3] and physical stability[4-8] are two essential properties of a drug. A good solubility is required to get a good bioavailability of the drug and a good physical stability is required to get a reasonable shelf life time. Of course, the most stable physical form of a drug is the crystalline form because it has the lowest free enthalpy[1]. However, the crystalline form is also generally the less soluble. The best solubility is on the contrary provided by the amorphous form which is in a much higher free enthalpy level[9,10]. However, amorphous materials are intrinsically unstable, and return unavoidably toward their crystalline state more or less rapidly and lose their improved solubility. It thus appears clearly that solubility and physical stability are antagonist properties which seem difficult to reconcile. And this problem is all the more crucial that the new drug molecules are more and more complex and thus less and less soluble[3]. There is thus an increasing necessity to formulate drugs in the amorphous state in order to increase their solubility. And this requires to find formulation protocols which are able to stabilize this amorphous state[11-14].

A possible way to stabilize a drug in an amorphous state is to make a molecular dispersion of this drug into an amorphous polymer[12,15-18]. In such a system, the amorphous character of the drug is guaranteed as long as the concentration of the drug into the polymer remains below the solubility limit of the drug into the polymer. It is thus essential to determine the solubility line of the mixture to optimize the formulation and to define the maximum drug that can be loaded into the polymer without a risk of recrystallization. However, this line is very difficult to determine[19-22]. The difficulty mainly comes from the very high viscosity of polymers which slows the dissolution processes and makes the equilibrium saturated state very difficult to reach in practice. That's why the determination of solubility curve is so difficult and very time consuming.

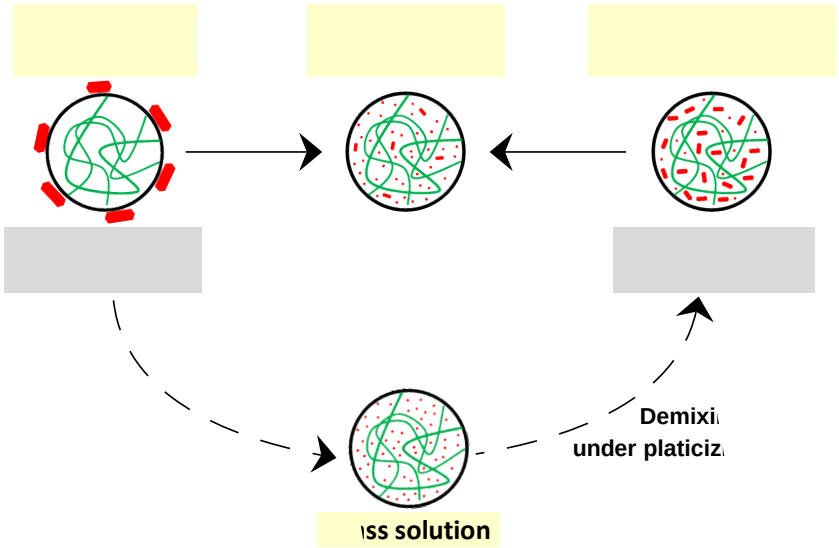

Figure 1 : Schematic pointing out the advantage of MCD over PM to reach faster the equilibrium saturated state of a drug/polymer mixture. The bottom part shows how to convert PM into MCD using milling and annealing under a plasticizing atmosphere. Green lines symbolize the polymer. Red dots and red blocs symbolize respectively molecules and crystallites of drug.

In this thesis, we have developed an ingenious protocol to strongly improve the dissolution rate of drugs into polymer, directly in the solid state. This protocol required to disperse the drug into the polymer, both at the molecular level and in the form of a myriad of small crystallites giving rise to what is called: a molecular/crystalline dispersion (MCD). The dissolution of the drug into the polymer was found to be much faster in the MCD than in the equivalent physical mixture (PM). This is due, in particular, to the fine dispersion of the crystallites inside the polymer matrix that increases both the interface drug/polymer and the number of diffusion centers of the drug. This also shortens strongly the average diffusion length required for the drug molecules to invade homogeneously a polymer grain. Moreover, the plasticizing effect of the molecular dispersion is expected to also increase the dissolution rate by increasing the molecular mobility in the polymer matrix. In practice, MCD were produced by combining high energy milling stage and annealing stage under plasticizing atmosphere as illustrated in figure 1. The milling stage is used to co-amorphize the drug / polymer system in order to get an homogeneous amorphous glass solution in a reasonable time. The glass solution is then annealed under a plasticizing atmosphere (ethanol, methanol, acetone…) to induce a deep recrystallization of the molecularly dispersed drug. The system is then dried to remove the plasticizer and obtain a very fine dispersion of drug crystallites into a polymer matrix slightly plasticized by remaining drug molecules. Such a microstructure strongly increases the dissolution rate of crystallites so that the equilibrium solubility at a given temperature can be easily reached upon annealing. The drug concentration in the polymer at saturation is then determined by measuring the glass transition temperature of the remaining glass solution and by using the Gordon Taylor curve of the mixture as a calibration curve.

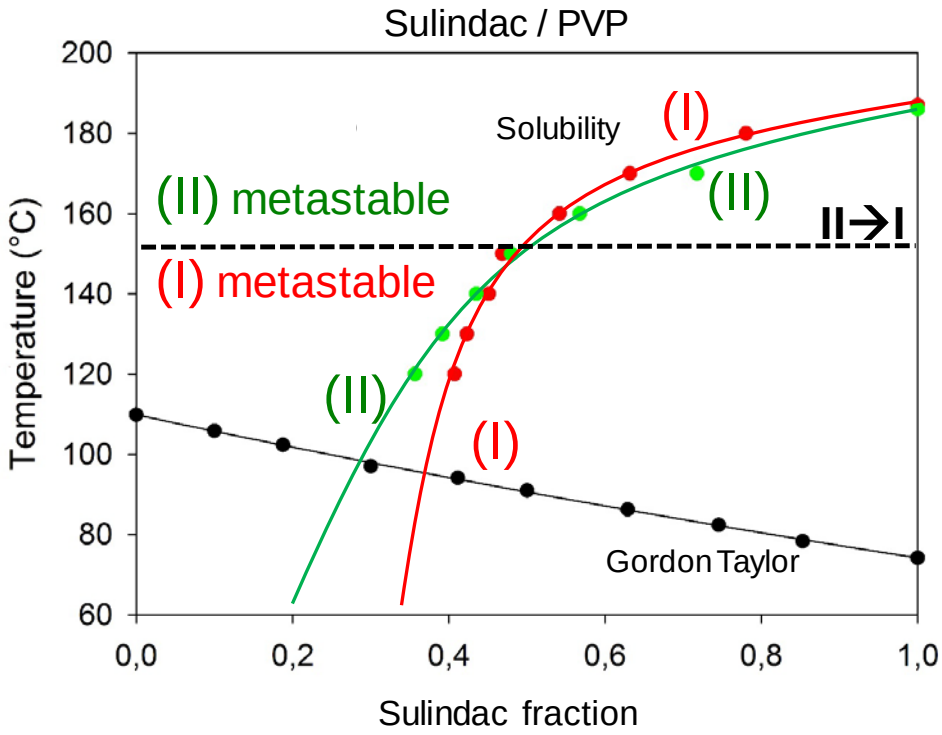

Figure 2 : State diagram of sulindac / PVP binary mixtures
In black: Gordon Taylor plot (Tg(X_{sul})) of sulindac/PVP glass solution. The full circles correspond to experimental Tg values derived from the DSC scans of figure 4. The solid line represents the best fit of the Gordon Taylor[23] law to the data.In red and in green: Solubility curves of form I and form II of sulindac into PVP as a function of temperature. The full circles correspond to experimental data. Solid lines are guides for eyes

The above protocol, and its effect on the dissolution rate, were deeply investigated in the case of the dissolution of sulindac ($C_{20}H_{17}FO_3S$) into PVP (polyvinylpyrrolidon). Sulindac is a nonsteroidal anti-inflammatory agent which can form three crystalline polymorphs. Moreover, we took advantage of both the higher dissolution rate and the possibility to orient the recrystallization toward a specific polymorphic form during the plasticizing annealing stage, to determine the solubility line of both form I and form II of sulindac into PVP. It is the first time that the solubility lines of two different polymorphic forms of a given drug into a polymer was determined[24]. The corresponding state diagram is reported in figure 2.

The above protocol was also used to determine the solubility lines of forms 1 and 2 of paracetamol into PVP. The corresponding state diagram is reported in figure 3. Moreover, we have shown that the fraction of active ingredient dissolved in PVP can also be determined by low frequency Raman spectroscopy. This possibility, combined with the efficiency of the dissolution of the crystalline fraction of DMC in the polymer, enabled us to determine the solubility curve of paracetamol in PVP, in real time, during a single temperature ramp. This direct measurement is much faster and more accurate than scanning the equilibrium saturated states to determine the Tg of the glassy mixture at saturation. Moreover, it does not require the prior determination of the Gordon Taylor curve. It should be noted that the two independent methods developed in the thesis lead to identical solubility curves which reinforces their validity.

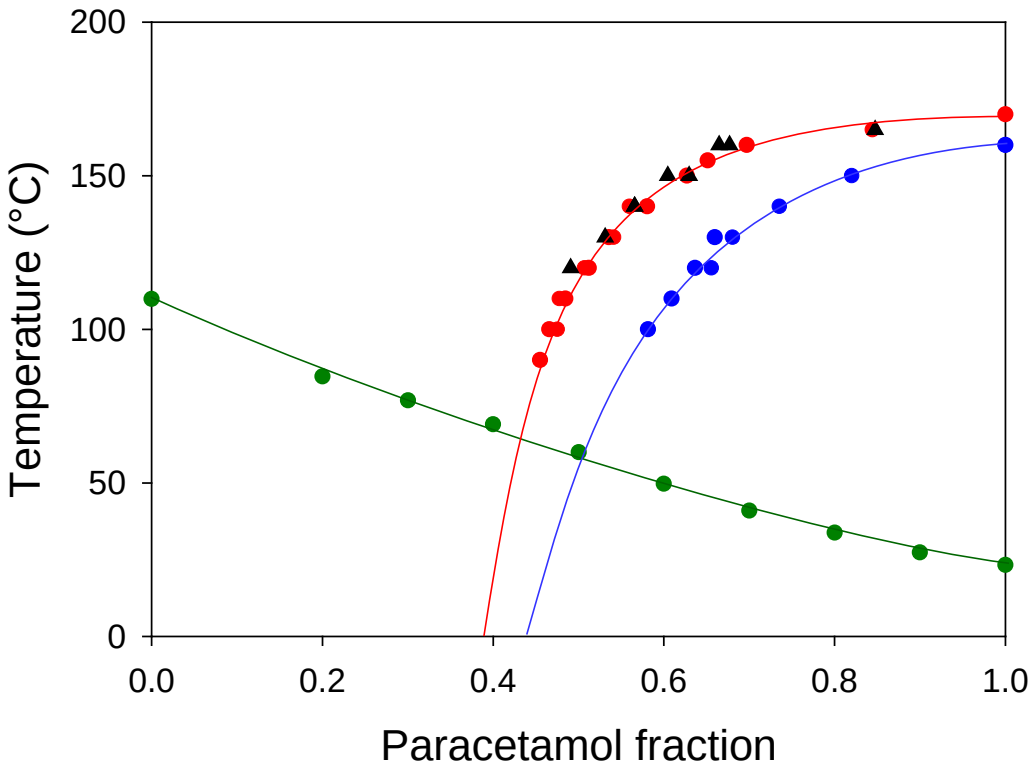

Figure 3 : State diagram of paracetamol / PVP binary mixtures. In green: Gordon Taylor plot ($Tg(X_{para})$) of paracetamol/PVP glass solutions. The full circles correspond to experimental Tg values while the solid line represents the best fit of the Gordon Taylor[23] law to the data. In red and in blue: Solubility curves of form I and form II of paracetamol into PVP as a function of temperature. The full circles correspond to experimental data derived from DSC experiments while triangles derived from real time Raman measurements recorded upon heating a DMC. Solid lines are guides for eyes.

In the margin of these studies, we have shown how high energy milling processes can be used to investigate deeply the polymorphism of drugs. It was shown, in particular that the introduction of defects in crystals through a slight milling can trigger polymorphic transformations which are not detected in non-milled materials. This makes possible the direct observation of polymorphic transformations and the determination of the relative stability of polymorphic forms. As an example, figure 4 shows a heating DSC scan of sulindac form 2 recorded after a slight milling. It shows an endotherm at 160°C corresponding to the polymorphic transformation 2 → 1 which is not detected in the absence of milling. This indicates that forms 1 and 2 are enentiotropically related, in coherence with the crossing of their solubility line at 160°C (figure 2).

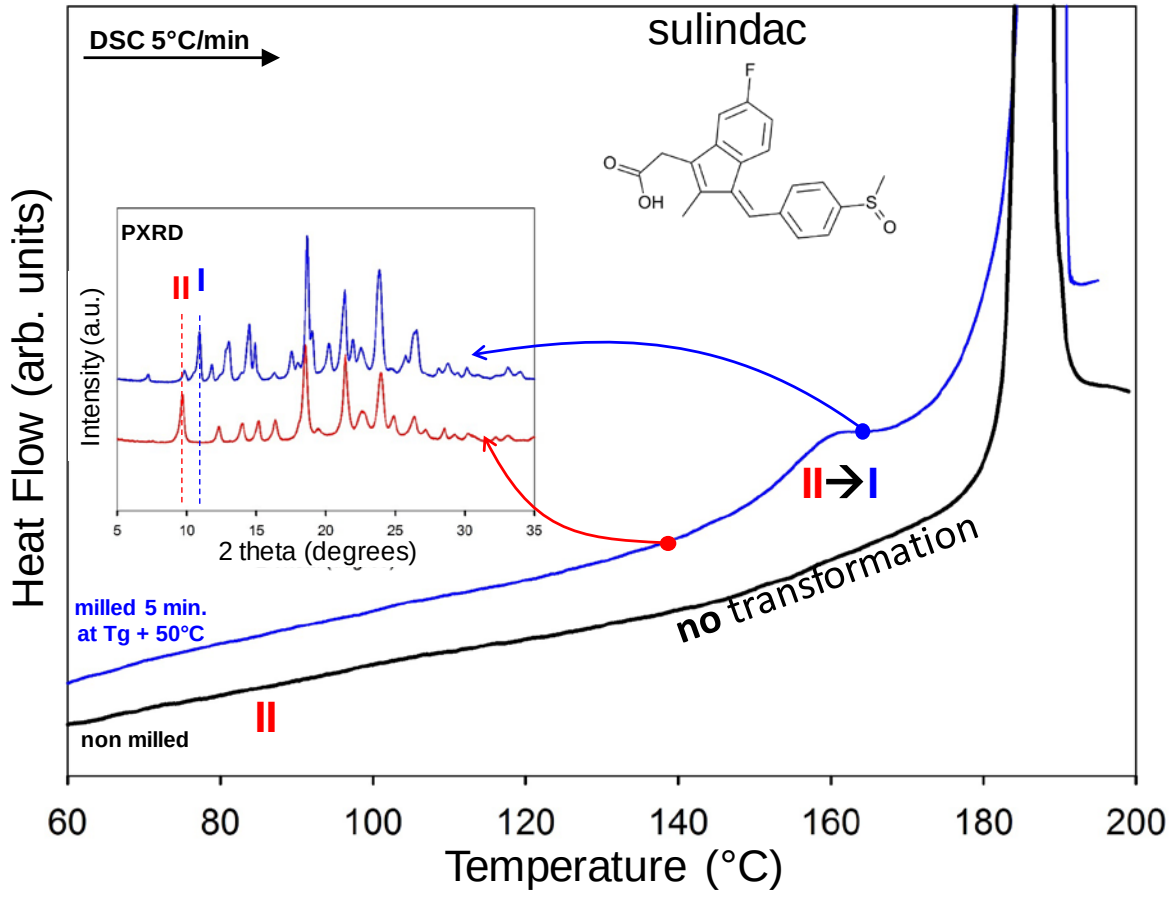

Figure 4 : DSC heating scans (5°C/min) of sulindac (form II) recorded before (black) and after (blue) a 5 minutesmilling at 130°C. Insert: X-ray diffraction patterns of sulindac milled for 5 minutes at 130°C, recorded at 140°C and 165°C i.e. above and below the endotherm occurring at 160°C in the milled material.

The mechanism of dissolution of active ingredients in polymers was also investigated in details. In particular, we have been able to understand the origin of the structuration of the endotherm which often characterizes the dissolution of a drug into in a polymer during the heating of a physical mixture. This structuration reveals a certain complexity of the phenomenon. The investigations were conducted by MDSC (Modulated temperature DSC) which has the advantage of being able to distinguish reversible phenomena of non-reversible phenomena. The analysis of the results clearly indicates that the structuration of the heat flow reflects the specific trajectory of the system in its solubility diagram. It shows that the dissolution results from the combination of a non-equilibrium process which makes it possible to reach the solubility curve, followed by an equilibrium process which makes it possible to follow this solubility curve upon heating. This study thus shows the great interest of MDSC with to analyze in detail the

process of dissolution of an active ingredient into a polymer. In addition, in the case of sulindac / PVP mixtures, we were able to characterize, indirectly, the temporal evolution of plasticized polymer zones as well as the evolution of their drug concentration during an isothermal dissolution process. This characterization has been possible by analyzing the evolution of glass transitions associated with different amorphous zones developing or disappearing during the isothermal dissolution. It shows in particular the progressive disappearance of the Cp jump characteristic of the glass transition of the pure polymer and the concomitant development of a Cp jump characteristic of the glass transition of PVP saturated by sulindac. These antagonistic evolutions indicate that the sulindac molecules diffuse into the PVP by ensuring a concentration corresponding to the saturation in the invaded zones. This mode of dissolution is shown schematically in Figure 6-VI.

All of this work resulted in three publications[24-26]

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2) Description of the results obtained for the output in term of specific results category and specific result type

Specific results category And Specific result type	Description of the specific results
Knowledge - Created/Increased skill and capacities 1 new optimized formulation (expected gain 75% in stability) using a large range of different preparation and characterization techniques in line with the current regulatory guidelines. Formulations will benefit from scale-up evaluation and pre-clinical trials.	Knowledge to improve the manufacturing of solid dosage forms containing solid dispersions, based on the physico-chemical characterisation of the solid dispersions using a variety of techniques. Knowledge to optimize the processing of solid dosage forms containing solid dispersions using limited amounts of material (i.e. material-sparing strategies during development when only limited amounts of material are available. This allows to fasten the development process of the formulation, bringing the product faster to the market. Knowledge to master the physical stability of amorphous molecular alloys to optimize drug efficacy. Reports targeting both academic and industrial partners: • Increasing pharmaceutical process understanding for twin-screw extrusion and tablet manufacturing (PhD thesis Wouter Grymonpré, 2018) • Increasing pharmaceutical process understanding for twin-screw extrusion and tablet manufacturing (PhD thesis Wouter Grymonpré, 2018) • Mastering the physical stability of amorphous molecular alloys to optimize drug efficacy (PhD thesis Mansour Latreche 2019) • In-line monitoring of compaction properties on a rotary tablet press during tablet manufacturing of hot-melt extruded amorphous solid dispersions (Grymonpré et al., Int. J. Pharm., 517, 2017, 348-358) • Downstream processing from hot-melt extrusion towards tablets: a quality by design approach (Grymonpré et al., Int. J. Pharm., 531, 2017, 235-245) • Optimizing feed frame design and tableting process parameters to increase die-filling uniformity on a high-speed tablet press (Grymonpré et al., Int. J. Pharm., 548, 2018, 54-61) • Downscaling of the tableting process: feasibility of miniaturized forced feeders on a high-speed rotary tablet press (Grymonpré et al., Int. J. Pharm., 550, 2018, 477-485) • Using milling to explore physical states: The amorphous and polymorphic forms of sulindac (Latreche et al., Journal of Pharmaceutical Sciences, 108, 2019,2635-2642) • Polymorphism versus devitrification mechanism: low-wavenumber Raman investigations in sulindac (Latreche et al., International Journal of Pharmaceutics, 567, 2019, 118476) • Interest of molecular/crystalline dispersions for the determination of solubility curves of drugs into polymers (Latreche et al, Journal of

	Pharmaceutical Sciences, 570, 2019, 118626) A second PhD thesis is scheduled for Q2 2020, while 2 additional papers are in preparation. The work has also been presented at different scientific meetings: • Pharmaceutical Solid State Research Cluster (Copenhagen, Denmark, 7/2016) • European Conference on Pharmaceutics (Krakow, Poland, 4/2017) • Compaction Simulation Forum (Ghent, Belgium, 6/2017) • JRS Tableting Symposium (Rosenberg, Germany, 10/2017) • AIChE Annual Meeting (Minneapolis, USA, 11/2017) • World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (Granada, Spain, 3/2018) • Pharmaceutical Solid State Research Cluster (Leuven, Belgium, 9/2018) • European Conference on Pharmaceutics (Bologna, Italy, 4/2019) • Pharmaceutical Solid State Research Cluster (Dusseldorf, Germany, 9/2019) • 1st International Conference on Contemporary Pharmacy Challenges (Wisla, Poland, 9/2018) • Invited Seminar at Astra Zeneca (Göteborg, Sweden, 10/2018)
Socio-Economic Increased business activity /capacity (new products, processes, services, techniques)	When presenting the research work at the international meetings the results have been discussed with numerous representatives from academic institutions and pharmaceutical companies. This (in combination with the publically accessible research papers) ensures that the project results can be implemented by interested parties (i.e. pharmaceutical companies). The results obtained regarding the improvement of the manufacturing efficiency did not allow to file a patent application. As a result specific technology transfer is not possible. However, pharmaceutical companies have access to the findings of the project via scientific literature and can implement this in their manufacturing process. It is however likely that this will not be disclosed to us.

List of documents enclosed as annex

Images	
Reports and high impact publications	- 3 articles of W. Grymonpré in International Journal of Pharmaceutics - 3 articles of M. Latrèche in International Journal of Pharmaceutics - W .Grymonpré Thesis
Communications in European and/ or international events	
Patent prior art search & patent preparation	
Patent	
Official letters from company(ies)	
…	…