Process-Induced Phase Transformation of Indomethacin during the Melt Granulation process on Hot Melt Extruder

Purpose:

As an emerging platform for granulation, the twin-screw extrusion has various advantages over other techniques as it's a continuous and solvent-free process and has higher efficiency in mixing and temperature control. However, confidence must still be gained regarding whether and how the processing stresses (thermal and shear stresses) affect the drug properties. In our study, the possible solid form changes during the granulation processes of a metastable form Indomethacin (IMC) were monitored and controlled by evaluating the effect of various forms and intensities of stresses which are experienced by the drug. Possible transitions in response to these are identified and model based design spaces are developed in order to control the final dosage form performance.

Methods:

For preparation of the metastable form of IMC, a solvent-evaporation method on RotaVapor was used. 30 gram of γ-IMC was completely dissolved in 450 mL of ethanol at 50°C. The ethanol was then removed from the solution in RotaVapor at a temperature of 50°C and drug were recrystallized into the α form. The collected α-IMC was then collected and dried overnight in a vacuum oven under room temperature. After drying, the drug was screened through #30 sieve to get rid of lumps and then blended with PEG3350 (4:1 w/w) using V-blender at 20 RPM for 20 mins. Approximately 15 gram of the blend was loaded into hot melt extruder (co-rotating twin-screw HME) for melt granulation. During the continuous process on HME, there are two stages for forming granules corresponding to different functioning zones on the barrel. The first stage is heating, melting and mixing, second stage is cooling and consolidating the granules. Therefore, the first two heating zones on HME were kept at various temperatures higher than (or equal to) 60°C in order to melt the binder PEG3350. The last cooling zone was maintained at 40°C for forming the granules before extruding the product out of the screws. The screw speed and feeder speed were maintained at 150 and 25 RPM, respectively. Three different sets of screws (with different screw size D_o/D_I, length and offset angles of kneading blocks) have been used which will apply different shearing stresses onto the processing materials. After collecting sufficient granules (approximately 8 grams), the HME chamber was opened and samples at each temperature controlling zone were also collected and kept in desiccator for later analysis together with granules. X-ray powder diffraction, DSC and in-situ fiber optic dissolution testing system were used to characterize the IMC polymorphs and granules. A Multivariate Curve Resolution-Alternating Least Squares approach was developed in *R* to extract the real reference components from the X-ray diffraction patterns of the extrudate samples. A full pattern fitting method in Microsoft Excel was used with the real/extracted reference patterns to quantify the solid forms of IMC before, during and after the granulation process.

Results:

α-IMC prepared from solvent evaporation method was characterized using DSC and XRPD. The melting point of α-IMC was 154.1°C compared to 160.2°C for the γ-IMC. X-ray powder diffraction patterns agreed well with the calculated powder patterns obtained from Cambridge Structural Database for both forms [CCDC refcode: INDMET01 and INDMET02]. Calibration curves were developed on XRPD with standard physical mixtures using PDXL software and were used to determine the relative quantities of amorphous, α-form and γ-form IMC in the samples. During heating stage, by increasing the heating temperature or changing the screw sets to the one with larger free volumes and stronger kneading elements, the phase changes will occur starting from amorphization/disorder to polymorphic transition

from the metastable form to the stable form. However, while cooling the trapped amorphous IMC was observed to be recrystallized to the metastable form. By quantifying the relative concentration of each component in the extrudate samples using the full pattern fitting method, the extent of transition was calculated and plotted with varying processing stresses and a model-based design space was developed for controlling the melt granulation process on HME.

Conclusion:

During the manufacturing and manipulation of small molecule organic crystals, different techniques do not always impart the same levels of stress due to the inherent tolerance of the equipment and its components and the intentional variation of processing parameters. By varying the batch processes, different (intensity and duration of) stresses may be introduced and can be controlled and different transformation mechanisms will be enabled. By reconciliation of this and the time scale (thermodynamics) of the structure changes (i.e. polymorphic transitions, amorphization/crystallization, hydration/dehydration), possible polymorphic transitions, i.e., the metastable state IMC to its stable form or vice versa can be anticipated and controlled. The various processes parameters selected in our studies successfully created a range of conditions that allow the control of such transformations. This work demonstrates that a platform can be developed by varying the critical process parameters and monitoring the responses of the substance to facilitate control of the solid form of an API in final drug product.