Controlling polymorphism of pharmaceutical cocrystals via polymer assisted cocrystallization in continuous processes

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Pharmaceutical cocrystals are the subject of interest in academic and industrial research as they offer better control over physicochemical, mechanical, and pharmacokinetic properties of active pharmaceutical ingredients (API) while their therapeutic activity remains intact. This class of materials, as well as single component pharmaceutical solids, is prone to exhibit the different packing arrangements and molecular conformations within the crystal lattice with the same chemical composition i.e. polymorphism. Hot melt extrusion (HME) is a solvent-free, continuous, and scalable technique which makes it an important candidate for the industrial application in a continuous synthesis of pharmaceutical cocrystals. However, processing APIs and coformers with significant difference in their melting temperatures is limited by the possibility of a lower-melting substrate decomposition. As a consequence, reduction of the conversion to a cocrystal during extrusion may be observed.

In this work we used mechanochemical approach to obtain two pharmaceutical cocrystals known to exist in at least two polymorphic forms: theophylline (TP) with benzamide (BZ) [1] and nicotinamide (NCT) with malonic acid (MA) [2] via matrix assisted cocrystallization (MAC) using hot melt extrusion [3] and polymer assisted grinding (POLAG) [4]. The polymers used in the experiments were polyethylene glycol derivatives of different molecular weight (in range from 200 to 20000), Tween® 20 and 80, Span® 80, Brij® 93 and Poloxamers of different HLB values. The milling procedures were performed using a ball-mill (Fritsch Mini-Mill Pulverisette 23) while hot melt extrusion processing was conducted using a co-rotating twin-screw Process 11 extruder (Thermo Fisher Scientific, Karlsruhe, Germany). Structures of the synthesised products were investigated using X-ray powder diffraction (D2 PHASER, Bruker AXS, Karlsruhe, Germany) and Fourier Transform Infrared Spectroscopy (Nicolet 380, Thermo Scientific, USA) whereas phase transitions were assessed using differential scanning calorimetry (DSC 214 Polyma, Netzsch, Germany).

The physical mixture of TP and BZ is difficult to process in the hot melt extrusion process because of the melting temperature difference (m_{pTP} = 273 °C, m_{pBZ} = 128 °C). In case of processing neat mixture of API and coformer, the barrel temperature of 120 °C was necessary to perform a successful cocrystal extrusion whereas the addition of a polymer matrix allowed to decrease the process temperature to 40 °C. In the formulations of higher polymer concentration, i.e. 30% and more, the extrusion led to TP:BZ (1:1) cocrystal form I occurrence while polymer content below 20% resulted in form II cocrystallization. In contrast both polymorphic forms of TP:BZ (1:1) cocrystal were obtained in grinding experiments by neat and liquid assisted grinding as reported previously [1] while all POLAG led exclusively to form I formation. The addition of solid-state polymers in a milling procedure accelerated the cocrystallization rate, however, presence of the liquid polymers inhibited cocrystal formation due to both difficulties in mixing or dissolution of one of the components in liquid polymer. Changes in the polymer content and polarity of the matrix (controlled via chain length of polyethylene glycol), did not result in obtaining of TP:BZ (1:1) form II. Furthermore, time required for complete cocrystallization was significantly shorter (3-5 minutes) in the hot melt extrusion as compared to the grinding experiments (40 min). In contrast to TP:BZ cocrystal, the melting temperature of API and coformer of NCT:MA (2:1) cocrystal are significantly closer (m_{pNCT} = 129 °C, m_{pMA} = 135 °C) which simplifies extrusion process. In the examined range of polymer concentrations form I of NCT:MA (2:1) was obtained, similarly grinding of NCT and MA (neat, liquid assisted and polymer assisted grinding) resulted also in form I appearance of NCT:MA (2:1) cocrystal.

Polymers used in matrix assisted techniques can act as cocrystallization rate accelerating agents enabling to obtain higher cocrystal yield. In addition, polymers can act as the functional components of the formulation enabling to tailor important pharmaceutical parameters e.g. tabletability, dissolution rate or release profile. The addition of polymers in continuous cocrystallization via hot melt extrusion allows to reduce the time and temperature of the process enabling processing of thermolabile substances. Furthermore, control over polymorphic outcome enabled selective synthesis of a stable polymorph which prevents unwanted structural changes during formulation and storage of the final product. On these terms matrix assisted cocrystallization, as a modification of hot melt extrusion method, holds a promise in the development of polymorph selective cocrystallization processes.

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