Multistage differential scanning calorimetry as a tool for the definition of process windows for the production of 3D-printing filaments for individualized medicines

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Text

Additive manufacturing techniques are promising tools for the production of individualized medicines as they offer a great degree of freedom towards the dose and drug release adjustment [1]. Fused filament fabrication, where a polymeric wire, the filament, is pressed through a hot nozzle and deposited layerwise to form a three-dimensional object, is one of the most advantageous techniques due to the simple apparatuses, the advantages of applicable thermoplastic pharma polymers as carriers and the small demand of pre- and post-processing in the dosage form production [1–3]. The filaments themselves consist of a polymeric matrix, which can dissolve or become permeable in gastric or intestinal fluids, and a drug. Such filaments may be produced by the pharmaceutical industry as an intermediate whilst the dosage forms may be produced decentralized close to application in the future supply chains [4]. Especially regarding broad dosage variations or combinative preparations with different drugs in a single dosage form, the drug load in the filaments needs to be maximized to minimize the dosage forms to a swallowable size [5]. This leads to a disperse fraction of the drugs inside of the matrices which are typically not completely miscible at the molecular range. As the interplay of the drug particles with the dissolved drug fraction and their influences on both the processes and the (intermediate-)product properties are not sufficiently understood yet, the aim of this work is a systematic investigation of the process window where drug particles are always present. This is intended to achieve high drug load on the one hand, but also to avoid supersaturated products that would undergo spontaneous, uncontrolled recrystallization on the other

hand. Therefore, a material and experimental effort-saving method for the definition of the demanded process window was developed.

To develop this method, different pharma polymers like hydroxypropylmethylcellulose (HPMC) were blended with different drugs like theophylline at different ratios and measured in a multistage differential scanning calorimetry (DSC). With this DSC method, a single sample was heated to different temperatures in cycles representing different stages of the process chain used in manufacturing of filaments and dosage forms. From the thermal events at the different heating and cooling stages, melting/glass transition of the matrices, drug dissolution in the melting/molten matrix, and the presence of crystalline drug in the final melt could be differentiated to enable the deduction of the process windows. The thermal data from DSC measurements were complemented with rheological data and imaging analysis via hot stage microscopy to implement their implications in process window definition.

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