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Original Research Paper

In silico product design of pharmaceuticals

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ARTICLE INFO

Article history:
Received 8 October 2015
Accepted 14 February 2016
Available online 18 March 2016

Keywords:
Personalized medicine
Simulation
Rheology
Imaging
Continuous manufacturing
Extrusion

ABSTRACT

The increasing demand for personalized medicine necessitates the production of easily customizable dosage forms. As the number of possible dosage forms may scale toward infinity, their uniqueness requires a versatile production platform and numerical simulation in order to be manufactured efficiently. A mathematical description of these systems is the only feasible approach to manage such diverse properties of different products. However, experimental verification is still essential for evaluation of processability and related concomitant phenomena, such as possible solid state changes that may occur during production and storage.

1. Introduction

Future manufacturing lines for pharmaceutical production will increasingly be based on continuously operating lines that enable flexible dosing of pharmaceuticals for personalized needs [1]. These tailor-made medicinal products may rely on recent innovations within genomics and diagnostics, which can be used as an input in defining patients' individual dosing regimes. Conceivably also the patient's dose may be adjusted according to input from e.g. telemedicine devices that have online data monitoring and can gather important biological and clinical parameters such as blood plasma concentrations of the drug compound measured [2,3]. Based on these possibilities, there is a need for more fundamental research enabling a manufacturing-on-demand based health-care system [4] and drug product development based on therapy-driven target drug delivery profiles [5].

One approach for flexible dosing is hot melt extrusion (HME) based production that enables manufacturing of innovative product shapes that can be easily divided into the required dose [6,7]. The manufacturing of such dosage forms in a personalized medicine scenario requires continuous monitoring of the product in order to assure that it complies with the desired drug loading and product consistency [1]. HME provides the possibility to process medicines into the desired size and shape using various die geometries. Circular dies can be used for the production of rods that can subsequently be pelletized or

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Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2016.02.010

spheronized, or flat dies may be used for the production of films. Furthermore, downstream injection molding provides an even broader array of possible sizes and shapes of the final product [8]. Finally, the emerging capabilities of 3D printing production platforms provide infinite possibilities for manipulation of the final product size and shape (limited by resolution) and could become the leading production platform for personalized medicine [9]. The recent FDA approval of SPRITAM, a 3D printed orally dissolving tablet, further emphasizes that 3D printing is a viable method for production of innovative drug formulations [10].

Many pharmaceutical processes, including HME, require a powder feed. Powder feeding into an extruder may necessitate a flow in a restricted geometry similar to powder flow in a hopper. Numerous investigations on powder flow in hoppers and silos have been performed during the last century and many of these investigations have been based on Janssen's work dating back to 1895 [11]. More recent efforts to solve the pressures persisting within these loaded silo and hopper structures by finite element modeling have also been pursued [12–16]. In addition, HME processing typically involves production of a molten polymer–active compound mixture, and once extruded, the solid state composition of the mixture can have an impact on the product properties, such as mechanical strength and dissolution rate. One of the most critical quality attributes of these products is achieving a stable solid form composition, and possible changes to the solid form during processing can have a significant impact on the product quality. As for the example shown by Young et al., hot-melt extruded products can recrystallize from the amorphous state [17]. It is therefore important to design the processing conditions such that an optimal product can be produced.

In any process involving polymer melts, including HME, understanding the rheology of the polymeric excipients is of crucial importance. Moreover, the addition of active pharmaceutical ingredients (APIs) can significantly affect the flow properties of polymer melts: many small molecule APIs that are soluble in the polymeric excipients used in HME can act as plasticizers and thereby decrease the viscosity of the melt compared to the pure polymer [18–21]. At concentrations beyond the solubility limit, the API is suspended as solid material, which may increase the viscosity of the melt [21]. Melt flow processes of polymers and their mixtures involve complex rheology due to their non-Newtonian and viscoelastic behavior. Additionally, flow behavior of highly filled dispersions increases the difficulty in prediction of the extrusion process outcome and necessitates the understanding of the fundamental rheological properties. Simulation of the hot melt extrusion process can reduce costs and development time compared to trial-and-error approaches, making it an efficient tool in the product and process design phase and when scaling up the process for mass production. For an accurate and reliable HME simulation, material parameters such as melt density, heat transfer properties, and viscosity as a function of temperature and shear rate must be characterized [22].

It is often beneficial to obtain an insight into these factors by a computational approach. Therefore, in addition to the experimental part, we report a computational approach (*in silico* product design). The primary aim of the computations was to evaluate the mechanical properties and dissolution rate of the extrudates, and the secondary aim was to evaluate the stresses within a hopper representing the powder feeding system for an extruder.

2. Materials and methods

The finite element method (FEM) was utilized for the computational approach by numerical analysis. COMSOL Multiphysics v. 4.4. (Stockholm, Sweden) was used to build the geometry of the extrudate and powder hopper as well as to construct the mesh and to solve the partial differential equation systems.

For the experimental approach, a model formulation consisting of nitrofurantoin monohydrate and PEO was used. The extrusion was performed on a 5 ml lab scale extruder (Xplore micro compounder, Geleen, The Netherlands) equipped with two co-rotating screws, three individually controlled heating zones, and a recycling channel that enables recirculation of the melt within the barrel. The API–polymer mixture was fed into the hopper manually. After the desired recirculation time, the melt was extruded through a circular die (Ø = 15 mm), and the extrudates were cooled at room temperature.

XRPD measurements on the extrudates were performed using an X'Pert PRO θ/θ X-ray diffractometer (PANalytical, Almelo, The Netherlands). The diffractograms were obtained in Bragg–Brentano reflection mode utilizing a PIXel detector (PANalytical). The operating voltage and current were 45 kV and 40 mA, respectively. A continuous scan over 2θ was performed in the range from 4 to 40°C with a step time of 96.4 s/point and a point resolution of 0.026 °C.

NIR chemical (NIR-CI) images of the extrudates were obtained with a spectrometer (Headwall Photonics model 1002A-00371, Fitchburg, MA, USA). This NIR chemical imaging camera is a prototype kindly provided by FOSS (FOSS A/S, Hilleroed, Denmark). NIR chemical images of extrudates were recorded in the wavelength range of 1100–1700 nm. The spectrometer was adapted to a line mapping configuration with a line consisting of 320 pixels. Spectra were recorded in diffuse reflectance mode with a resolution of 50 × 312 μm/pixel.

NIR-CI data processing was performed using MATLAB 7.1 (The MathWorks, Natick, MA) software and in-house routines under the name of HYPER-Tools (freely available on demand) together with PLS Toolbox (Eigenvector Research Inc., Wenatchee, USA). Since the raw data from NIR-CI measurement consist of information both from the sample and from the instrument, background correction is necessary. The high reflectance standard Spectralon™ (Labsphere, Inc., North Sutton, NH, USA) was used as a background reference. Areas containing non-sample information were eliminated by masking. Standard Normal Variate transformation, Savitzky–Golay smoothing with window size of 13 and polynomial order of 2, together with mean-centering were applied as pre-processing methods.

Measurement of flow properties of polyethylene oxide (PEO) was used as an example of a widely used polymeric excipient in pharmaceutical applications. PEO melt (viscosity average molecular weight M_v = 100.000 g/mol) was characterized in steady state rotational shear (SS) and small angle oscillatory shear (SAOS) at three different temperatures using an AR-G2