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A Mechanistic Model to Facilitate Process Development of Hot-Melt Extrusion to Produce Solid Dispersions for Increased Bioavailability of Low Water-Soluble Drugs

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Introduction: Oral drug delivery in form of amorphous solid dispersion can increase bioavailability of low-soluble active pharmaceutical ingredients (API). Hot-melt extrusion has become a recognized, solvent-free, and continuous method to produce amorphous solid dispersions of API in polymers. The large number of material properties and process parameters and thereof resulting combinations make a fully experimental process optimization impossible. To tackle this problem, we propose a mechanistic model that predicts product properties and therefore has the potential to significantly decrease the number experiments. This may reduce time, costs and risks associated with process development and therefore promotes hot-melt extrusion as an attractive method to increase API bioavailability.
Aims: The present study aims to create and validate a mechanistic model that enables for rational material selection and process design by linking those variables to the product properties of hot-melt extrudates for pharmaceutical use.
Methods: The theory of the scalable model is based on the mean residence time (MRT) of the material in the extruder and the time to dissolution (TTD) of the API in the molten polymer during the extrusion process. The MRT was calculated based on an extended model of Gao et al. [1] in combination with the model of Potente et. al. [2]. The TTD was modeled by combining the Flory-Huggins theory for polymer-solvent miscibility and the approximated solution of the dissolution time of a solid sphere in an unbound, stagnant liquid by Rice et. al. [3], which we extended by a variable solute concentration. The diffusion coefficient of the API in the molten polymer was obtained by calculating the mean square displacement of API molecules in molten polymer simulated by molecular dynamics. The overall MRT and MRT of compartments was measured by tracer pulse experiments. The exit die pressure and the pressure decay along the screw axis was measured with a pressure sensor at the die and a known point of zero pressure. We measured the TTD by a series of extrusions at defined MRTs and quantitative x-ray powder diffraction of the resulting extrudates as well as hot stage microscopy. Molecular dynamics were performed using Desmond in Maestro using the OPLS_2005 force field. The model computation was done in Wolfram Mathematica.
Results: Comparison of measured and modelled data support the mechanistic concepts on which the MRT and the TTD models are based. When looking at absolute predicted values, all compartments of the MRT model were predicted with good accuracy (correlation factor of 0.996 to 0.892 with slopes 1.04 to 1.39). The modelled overall MRT deviates from the measurement (correlation factor 0.828 and with slope 0.44). Further work will be necessary to improve this part of the model. The experimental results for TTD of a system Terbinafine in Soluplus showed good agreement with modelled values. Further findings include that the MRT at a certain temperature seems to be the responsible determinate that affects TTD and not screw speed when working with constant geometries.
Conclusions: It was possible to develop a sophisticated model for hot-melt extrusion in the pharmaceu-tical context as well as to establish experimental methods to prove the model.

Keywords: hot-melt extrusion, amorphous solid dispersion, process modeling, bioavailability.

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