Research paper

Numerical simulation of hot-melt extrusion processes for amorphous solid dispersions using model-based melt viscosity

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ABSTRACT

Simulation of HME processes is a valuable tool for increased process understanding and ease of scale-up. However, the experimental determination of all required input parameters is tedious, namely the melt rheology of the amorphous solid dispersion (ASD) in question. Hence, a procedure to simplify the application of hot-melt extrusion (HME) simulation for forming amorphous solid dispersions (ASD) is presented. The commercial 1D simulation software Ludovic® was used to conduct (i) simulations using a full experimental data set of all input variables including melt rheology and (ii) simulations using model-based melt viscosity data based on the ASDs glass transition and the physical properties of polymeric matrix only. Both types of HME computation were further compared to experimental HME results. Variation in physical properties (e.g. heat capacity, density) and several process characteristics of HME (residence time distribution, energy consumption) among the simulations and experiments were evaluated. The model-based melt viscosity was calculated by using the glass transition temperature (T_g) of the investigated blend and the melt viscosity of the polymeric matrix by means of a T_g-viscosity correlation. The results of measured melt viscosity and model-based melt viscosity were similar with only few exceptions, leading to similar HME simulation outcomes. At the end, the experimental effort prior to HME simulation could be minimized and the procedure enables a good starting point for rational development of ASDs by means of HME. As model excipients, Vinylpyrrolidone-vinyl acetate copolymer (COP) in combination with various APIs (carbamazepine, dipyridamole, indomethacin, and ibuprofen) or polyethylene glycol (PEG 1500) as plasticizer were used to form the ASDs.

1. Introduction

In formulation development, the so-called enabling technology hot-melt extrusion (HME) is often used to overcome the poor solubility of active pharmaceutical ingredients (APIs) by forming amorphous solid dispersions (ASDs). Unfortunately, the extrusion process based formulation development is often API-consuming and expensive in terms of time and personal [1–4]. To reduce the effort in early development, several methods and techniques to facilitate a rational procedure have been previously reported [5–8].

A very common example is the use of small-scale co-rotating twin-screw extruders prior the production scale [5,9–11]. It reduces the batch size down to as little as 5 g and they are accepted as screening tools for solid dispersion formulations. Unfortunately due to fundamental differences between lab-scale extruders (e.g. 9 mm screw diameter) and larger scale extruders, a rational scale-up is not feasible [8]. To perform process development and scale-up, extruders of 10–12 mm, respectively 24–27 mm screw diameter should be used instead but this

increases the batch size to approx. 50 g/h up to 20 kg/h. Furthermore, the scale-up to production scale can be conducted volumetrically or adiabatically [7,8,12,13]. The most crucial process characteristics in scale-up are the residence time distribution (RTD) and the specific mechanical energy (SME) [12]. Both parameters should be kept constant by adjusting the various other extrusion parameters (e.g. temperature, screw configuration, screw speed and feed rate) during scale-up.

Another way to perform a rational screening of solid dispersion formulations are micro-scale testing methods by using thermo-analytical techniques such as differential scanning calorimetry (DSC) [14–20], melt rheology [21–23], hot-stage microscopy (HSM) [8,9] and many more. For example, differential scanning calorimetry can be used to determine the glass transition temperature (T_g) for later process conditions [8,24] or for the API-solubility characterisation within the polymeric matrix. This solubility prediction can be conducted by using the melting point depression method [14–16], dissolution endpoint method [17–19] or by using the API/polymer ratio-dependent glass

transition temperature (T_g) [20,25]. Hot-stage microscopy is a very powerful analytical technique to determine the miscibility of compounds and to assess first hints for an applicable temperature range in extrusion [8,9]. Melt rheology is particularly useful in that it can be used to identify possible process conditions [23,26]. The main advantage of all these methods is the small amount of material required to obtain significant knowledge for subsequent hot-melt extrusion processing. In general, they enable the estimation of a feasible extrusion range and they can be very helpful to predict the shelf life of extruded formulations.

An even more theoretical approach is the simulation of HME processes [27–30] and the use of molecular modelling [14,31,32] or solubility parameters [5,8,24] to estimate a good and early starting point prior any experimental consideration. Prediction of glass transition temperature (T_g) [31], API solubility within the polymeric matrix [5,24,33] and detailed computation of extrusion runs represent only a few applications in HME process analytics. In the case of adiabatic scale-up from small-scale to production-scale extrusion, HME simulation can be most appropriate solution to identify adiabatic conditions in small-scale extruders [13]. The high impact of barrel set temperature here is disguising adiabatic conditions, especially for small scale extruders ($< = 12$ mm) where heat conduction governs energy uptake rather than viscous dissipation. However, adiabatic conditions can be identified by employing HME simulation. At the end, all mentioned approaches and methods, such as mini-scale twin screw extruders, micro-scale testing methods and HME simulation, enable a rational development of ASDs to overcome the poor solubility of modern APIs. This leads to a not only trial-and-error based formulation but a process development in the sense of quality by design.

Regarding the extrusion computation, a major drawback is the need for experimental input data (e.g. melt viscosity) in order to run the simulation properly. In early stage development, several formulations for an API have to be tested, which is time-consuming, especially in the case of rheological measurements. To enable certain "shortcuts" regarding the estimation of melt viscosity by using only the T_g of the formulation has already been reported in our previous work [34]. To continue this work, we applied our model-based estimates of T_g-viscosity correlation to simulate HME processes for forming ASDs.

The objective of our study reported here was the comparison of extrusion experiments with the computations of the commercial 1D simulation software Ludovic®. The software was fed either with measured melt viscosity data of the respective ASD (including API) or with model-based melt viscosity data by using the T_g of the investigated blends. To evaluate the application of our first estimates of the melt viscosity by using only T_g, several process characteristics of HME (e.g. residence time distribution, energy consumptions) and physical properties (e.g. heat capacity, density, melt rheology) of various mixtures has been investigated. The goal was not to replace extrusion experiments but more to enable a good and early starting point for HME trials by using only the T_g of a desired ASD and characteristics of the polymeric matrix in HME simulation. Therefore, a rational development is supported. This leads to a reduction of needed extrusion trials to define the best formulation and process conditions for forming ASDs. As model excipient, vinylpyrrolidone-vinyl acetate copolymer (COP) in combination with various API or PEG as plasticizer were used to form ASDs.

2. Material and methods

2.1. Material

Dipyridamole (DPD) was obtained from Swapnroop Drugs & Pharmaceuticals (Maharashtra, India) and Indomethacin (IMC) was purchased from Swati Spentose Pvt. Ltd (Mumbai, India). PEG 1500 (PEG) were obtained from Alfa Aesar (Karlsruhe, Germany). Vinylpyrrolidone-vinyl acetate copolymer (copovidone, Kollidon® VA 64, COP), Carbamazepine (CBZ) and Ibuprofen (IBU) were kindly

Table 1
Physicochemical properties of substances under investigation [34].

Substance	Molecular weight [g/mol]	Melting point [°C]	Glass transition temperature [°C]
Indomethacin (IMC)	358	160	44
Carbamazepine (CBZ)	236	175	53
Dipyridamole (DPD)	505	167	38
Ibuprofen (IBU)	206	75	− 44
PEG 1500 (PEG)	1500	47	− 42
Copovidone (COP)	45,000–70,000	–	107

donated by BASF SE (Ludwigshafen, Germany) (Table 1). The APIs were chosen due to their various physicochemical characteristics. The API or plasticizer weight fraction was experimentally adjusted to a specific glass transition temperature (T_g) of the blend, as was already reported in our previous work [34].

2.2. Methods

2.2.1. Preparation of physical mixtures

For DSC trials, a MM400 ball mill (Retsch GmbH, Haan, Germany) with 30 Hz and 3×5 min milling cycles was used. For extrusion trials, physical mixtures were prepared by using a Turbula mixer (Willy A. Bachofen AG – Maschinenfabrik, Muttenz, Swiss) for 10 min at 50 rpm.

2.2.2. Helium pycnometer

The true density of powder blends and extrudates were analysed by using the helium pycnometer AccuPyc 1330 (Micromeritics GmbH, Norcross, USA). During measurements, the chamber was purged with 20 purge cycles and a fill pressure of 136.86 kPa·g. Subsequently, samples were analysed with a fill pressure of 136.86 kPa·g and an equilibration rate of 0.0345 kPa·g/min. The sample was analysed in 25 runs or until a standard deviation of 0.01% was reached. For every material, the procedure was repeated two times.

2.2.3. Differential scanning calorimetry (DSC)

A DSC 2 (Mettler Toledo, Gießen, Germany) equipped with an auto sampler, nitrogen cooling and nitrogen as purge gas (30 ml/min) was used. The system was calibrated with n-octane, indium and zinc standards. At least three samples of approximately 10 mg of each mixture were analysed, using 40 μl aluminium pans with a pierced lid. Heat capacities were measured against a sapphire standard in TOPEM® mode (modulated DSC) with 1 K pulse height, 15–30 s pulse width and an underlying heating rate of 2 K/min. Prior to heat capacity analysis, the samples were annealed at elevated temperatures to promote a homogenous distribution of the API/plasticizer in the polymeric matrix.

2.2.4. Extrusion trials and residence time distribution (RTD)

For hot-melt extrusion, a co-rotating twin-screw extruder ZE 12 (Three-Tec GmbH, Seen, Switzerland) with a functional length of 25:1 L/D, 12 mm screws, 2 mm die and a maximum torque of 15 N·m was used. The screw configuration is shown in Fig. 1. The throughput was kept constant at 2.0 g/min and the screw speed was set to 100 rpm to enable a high filling ratio of the extruder. Mean residence times (MRTs) were measured with iron oxide (Sicovit® Red 30 E 172, BASF SE, Ludwigshafen, Germany) and calculated by using ExtruVis3 (ExtruVis, Riedstadt, Germany). To determine the feed rate during MRT measurements more precisely, the extruded material was collected and weighed over time. Afterwards, the feed rate was adjusted to a range of $2.0 \pm 5\%$ g/min. The extrusion barrel temperature was set to 150 °C. Furthermore, extrusion data of our previous work were also considered for extrusion simulation in this work [34]. The specific mechanical energy (SME) of extrusion experiments was calculated by using following equation (Eq. (1)),