Rational Development of Solid Dispersions via Hot-Melt Extrusion Using Screening, Material Characterization, and Numeric Simulation Tools

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ABSTRACT: Effective and predictive small-scale selection tools are inevitable during the development of a solubility enhanced drug product. For hot-melt extrusion, this selection process can start with a microscale performance evaluation on a hot-stage microscope (HSM). A batch size of 400 mg can provide sufficient materials to assess the drug product attributes such as solid-state properties, solubility enhancement, and physical stability as well as process related attributes such as processing temperature in a twin-screw extruder (TSE). Prototype formulations will then be fed into a 5 mm TSE (~1–2 g) to confirm performance from the HSM under additional shear stress. Small stress stability testing might be performed with these samples or a larger batch (20–40 g) made by 9 or 12 mm TSE. Simultaneously, numeric process simulations are performed using process data as well as rheological and thermal properties of the formulations. Further scale up work to 16 and 18 mm TSE confirmed and refined the simulation model. Thus, at the end of the laboratory-scale development, not only the clinical trial supply could be manufactured, but also one can form a sound risk assessment to support further scale up even without decades of process experience. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2297–2310, 2013

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INTRODUCTION

At the transition of a new chemical entity from research into development, the available amount of drug substance is usually the limiting factor in pharmaceutical development. Work packages such as excipient compatibility, development of an oral solution, and selection of a solid oral formulation approach compete over around 50 g of active pharmaceutical ingredient (API). In combination with an API exhibiting poor aqueous solubility and related to that insufficient bioavailability, material sparing selection tools for enabling technologies are, hence, mandatory. Amorphous solid dispersions prepared by hot-melt extrusion (HME), where the API is molecularly dispersed and physically stabilized in a polymeric matrix, are one effective enabling tool to overcome poor solubility and bioavailability.[1]

However, the HME process predominantly used in the plastic industry is designed for high-throughput products up to 50 t/h.[2] Even laboratory scale in the plastic research is related to extruder sizes around 30 mm in screw diameter, which translates into feed rates around 4–6 kg/h.[3–6] This would be still far too much material to facilitate early drug product development. It is hence inevitable to employ a strategy, which includes the elements of screening, miniaturized equipment, and numeric simulation at continuous performance control to successfully develop a melt-extruded solid dispersion product at the limited material resources in early drug product development.

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Independent of the manufacturing process, the first obstacle in designing a solid dispersion is the selection of an appropriate polymer. Ideally, the API should "dissolve" in the polymer and must not degrade in combination with the polymer or other excipients at the applied process conditions. At the same time, the polymer needs to minimize molecular mobility of the API within the matrix to preserve the dissolution performance connected to the amorphous solid state throughout the shelf life of the drug product.[7,8] A selection tool ideally provides information on all of the above-mentioned characteristics of solid dispersions. Although chemometric prediction tools such as the various solubility parameters[9–17] have the potential of selecting a matching polymer[18,19] without API consumption, their prediction accuracy is often inaccurate at limitation to binary mixtures.[20,21]

Slightly more API is necessary when miscibility is experimentally assessed using differential scanning calorimetry (DSC). Especially modulated DSC reveals glass transitions and/or melting points for solid-state characterization, which facilitates not only polymer selection but also gives some rough estimates on physical stability and processing temperature during HME.[22–26] Still, DSC samples can hardly be further characterized in relation of drug product performance; especially dissolution performance or concurrent solid-state characterization tools such as X-ray powder diffraction (XRPD) and Raman spectroscopy. Similar to casted films as a screening tool for spray-dried dispersions,[27] hot-stage microscopy in combination with polarized light has the potential to be a powerful predictor for HME. Although-–similar to the DSC method-–the hot-stage microscope (HSM) does not introduce any mechanical stress (e.g., shear stress), solid-state changes (i.e., melt and dissolution processes) can be monitored precisely. Visualizing melt and dissolution processes dependent on temperature is suspected to be more predictive for the processing temperature of a melt in the extruder compared with glass transition temperature (T_g) readings from DSC.

After selection of a suitable polymer matrix, first extrusion runs need to be conducted on small-scale equipment (~20 g batches) to transfer the evaluated screening results into the performance of an extrusion product without wasting too much material (i.e., API). As the performance and the quality attributes of an amorphous solid dispersion can be regarded as a function of its solid state,[28] some authors reported the use of process analytical technology (PAT) such as Raman or near infrared (NIR) probes to facilitate a successful scale up.[29–33] However, the application of those rather sophisticated PAT tools compared with conventional temperature, torque, and pressure measurements is also described as critical because of the process-dependent readings (e.g., temperature, pressure, flow turbulence, and compactness).[34–37] Hence, employing PAT alone is rather generating limited process understanding. In combination with simulation-supported process knowledge of, for example, hot spots along the screw, the use of PAT tools such as Raman or NIR could be placed more beneficial or even proofed to be redundant. The aim of the present work is hence to propose an efficient and reliable procedure to identify and manufacture solid dispersions via HME from micro- to pilot-scale. Different screening approaches are compared and ranked. Material characterization and numeric simulation are used as standard tools to generate increased process understanding.

EXPERIMENTAL

Materials

Copovidone-NF (Kollidon VA 64), Polyethylene Glycol-NF (PEG 6000), and Poloxamer-NF (Poloxamer 188) were purchased from BASF (Ludwigshafen, Germany). Amino methacrylate copolymer-NF (Eudragit E 100) was obtained from Evonik (Darmstadt, Germany), and Isomalt-NF (GalenIQ 960) was obtained from Beneo-Palatinit GmbH (Mannheim, Germany). All materials used were of pharmaceutical grade. Buffers were of analytical grade. Indometacin was obtained from TCI Europe N.V (Zwijndrecht, Belgium) in laboratory reagent grade (>98%).

Preparation of Physical Mixtures

The physical mixtures of Indometacin and excipient for HSM experiments were all prepared by weighing the components in a 2 mL glass vial and treating the mixture in a ball mill for 8 min. No loss of crystallinity was observed upon milling. For extrusion experiments and rheological measurements, the drug and the polymers were mixed in a Turbula mixer (Willy A. Bachofen AG, Muttenz, Switzerland) for 15 min after passing the materials through a 0.25 mm sieve.

Hot Stage Microscopy

A Zeiss Axioplan2 (Carl Zeiss AG, Jena, Germany) optical microscope equipped with a temperature-controlled Linkam LTS350 hot stage (Linkam Scientific Instruments Ltd., Tadworth, United Kingdom) was used to observe the crystal form change or the crystal dissolution processes under temperature control with snapshots taken by an AxioCam ICC1 (Carl Zeiss Microscopy GmbH, Jena, Germany) camera throughout the process. To guarantee intimate contact between the two materials, the binary mixtures were ball milled. A sample of 15 mg was placed onto a glass slide and a heat rate of 10°C/min was applied.