Prediction of Polymorphic Transformations of Paracetamol in Solid Dispersions

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Received 14 January 2014; revised 25 March 2014; accepted 4 April 2014

Published online 30 April 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23992

ABSTRACT: A novel approach employing variable-temperature X-ray powder diffraction (VTXRPD) was used to exploit its suitability as an off-line predictive tool to study the polymorphic transformations of paracetamol (PMOL) in melt-extruded hydrophilic polymer matrices. Physical mixtures (PMs) and extruded formulations of PMOL with either polyvinyl caprolactam graft copolymer (Soluplus®) or vinylpyrrolidone–vinyl acetate copolymer (Kollidon®) in the solid state were characterized by using differential scanning calorimetry, hot-stage microscopy, and scanning electron microscopy. The experimental findings from VTXRPD showed that the stable Form I (monoclinic) of PMOL transformed to the metastable polymorph Form II (orthorhombic) at temperatures varying from 112°C to 120°C, in both the PMs and extrudates suggesting an effect of both temperature and identity of the polymers. The findings obtained from VTXRD analysis for both the PMs and the extruded formulations were confirmed by in-line near-infrared (NIR) monitoring during the extrusion processing. In the NIR study, PMOL underwent the same pattern of polymorphic transformations as those detected using VTXPRD. The results of this study suggest that VTXRPD can be used to predict the polymorphic transformation of drugs in polymer matrices during extrusion processing and provides a better understanding of extrusion processing parameters. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1819–1828, 2014

Keywords: polymorphs; transformation; variable-temperature XRPD; caprolactam; extrudates; near-infrared spectroscopy; Polynorphism; drug delivery; crystals

INTRODUCTION

Solid dispersions are commonly used for the development of pharmaceutical dosage forms where one or more active pharmaceutical ingredients (APIs) are dispersed in a matrix in the solid state.[1] Various techniques have been seen reported for the preparation of solid dispersions including hot spin mixing,[2] spray drying,[3,4] coevaporation or coprecipitation,[5] freeze-drying,[6] supercritical fluid processing,[7] and hot-melt extrusion (HME).[8,9] Over the last decades, HME processing has attracted significant interest for the development of pharmaceutical solid dispersions resulting in increased drug solubility of water-insoluble drugs, taste masking of bitter APIs, and sustained release or controlled release formulations.

Hot-melt extrusion is an emerging processing technology used for the manufacture of pharmaceutical solid dispersions as it combines the advantages of a solvent-free process with that of fewer production steps, is relatively easy to scale-up, and has the potential to operate in a continuous mode. However, it is important to obtain not only a detailed understanding of the physicochemical properties and polymorphic state of the drug in the extruded formulations but also during HME processing, where possible drug transformations or interactions may take place. Such knowledge is important as the solid-state properties of the drug can affect both the stability and the dissolution behavior of the developed pharmaceutical formulations. It is well known that an API may exist in a number of physical states in polymer matrices of solid dispersions.[10,11] These include crystalline dispersions (substitutional and interstitial), molecular dispersions (continuous or discontinuous), and amorphous dispersions (the drug is present as a separate amorphous phase). Previous studies[11] have demonstrated that melt extruded dispersions can undergo phase separation, which can lead to crystallization or polymorphic transformations of the API. Several analytical approaches have been developed to characterize the distribution of the drug(s) in the polymer matrices, phase separation phenomena, and amorphous/crystalline ratio of the drug.[10,11] In addition, in-line process analytical tools have been used in an attempt to provide a more detailed understanding of possible drug transformations and solid-state characterization of drug/copolymer blends during extrusion.[12] However, identification, prediction, and characterization of solid dispersions involving polymorphic transformations are difficult to undertake during the extrusion process and, to date, this topic has received little attention.

Studies of drug/polymer physical mixtures (PMs) may provide significant insights into the physical properties of the drug and possible transformations that can take place during HME. Variable-temperature X-ray powder diffraction (VTXRPD) analysis has previously been used to characterize solid-state pharmaceutical reactions including crystal transformations.[13,14] This technique is a powerful tool that can be used to explore such changes as it can be used to facilitate the simultaneous quantification of multiple solid phases.[15,16] In the current study, we exploited the ability to use VTXRPD to identify polymorphic transformations of paracetamol (PMOL)

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Journal of Pharmaceutical Sciences, Vol. 103, 1819–1828 (2014)

in drug/copolymer PMs and compared the results to those obtained by in-line near-infrared (NIR) monitoring[16–18] during HME processing of the same drug/polymer composition. PMOL was selected as a model API as it exists in three polymorphic forms,[9] namely Form I (monoclinic), Form II (orthorhombic), and Form III (unstable), in decreasing order of stability and melting point. This approach could potentially be employed as an effective tool to predict and characterize polymorphic transformations of drug substances for the development of solid dispersions via HME.

MATERIALS AND METHOD

Materials

Paracetamol was kindly donated by Mallinckrodt Chemical Ltd. (Covidien) (UK). Soluplus® (SOL) and Kollidon® (VA64) were also donated by BASF (Germany). All materials were used as received.

Hansen Solubility Parameters (δ) and Flory–Huggins Interaction Parameter (*x*): Drug–Copolymer Miscibility

Hansen solubility parameters were used to predict the miscibility of PMOL with the polymers in solid dispersions. The Hansen[19] solubility parameters (δ) of both the drug as well as the polymers were calculated by considering their chemical structure. In order to determine the theoretical drug/polymer miscibility, the solubility parameters were calculated by using the Hoftyzer and van Krevelen method[19,20] using the following equation:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \tag{1}$$

where

$$\delta_d = \frac{\Sigma F_{di}}{V_i}, \delta_p = \frac{\sqrt{\Sigma F_{pi}^2}}{V_i}, \delta_h = \frac{\Sigma E_{hi}}{V_i}$$

i, structural groups within the molecule; δ, the total solubility parameter; F_{di}, molar attraction constant due to molar dispersion forces; F^2_{pi}, molar attraction constant due to molar polarization forces; E_{hi}, hydrogen bonding energy, and V_i, the group contribution to molar volume.

The Flory–Huggins (F–H) interaction parameter, χ, of the model system was determined under two different conditions using the Nishi–Wang (Eq. (2))[21] equation based on melting point depression data and Hildebrand and Scott (Eq. (3))[22] correlations with the solubility parameters. The F–H interaction parameter (χ) for all of the drug/polymer binary mixtures was calculated by using the following equations. The value determined by Nishi–Wang represents the interactions between the two substances, specifically at the melting temperature, which may not be extrapolated to other temperatures.

$$\frac{1}{T_m} - \frac{1}{T_m^0} = -\frac{R\upsilon_{drug}}{\Delta H_{drug}\upsilon_{poly}}\left[\ln\phi_{drug} + \left(1 - \frac{1}{m_{poly}}\right) \times (1 - \phi_{drug}) + \chi_{drug-poly}(1 - \phi_{drug})^2\right] \tag{2}$$

where υ is the molar volume of the repeating unit, m is the degree of copolymerization, ϕ is the volume fraction, and χ is the crystalline–amorphous copolymer interaction parameter. T_m and T_m^0 are the temperatures of the crystalline melting peak of the pure drug and the melting peak of the drug in the presence of the polymer in the system, respectively.

The F–H interaction parameter (χ) can be also estimated by the method developed by Hildebrand and Scott using the following equation[22]:

$$\chi = \frac{\upsilon(\delta_{drug} - \delta_{poly})^2}{RT} \tag{3}$$

where R is the gas constant, T is the absolute temperature, and υ the volume per lattice site and δ_{drug} and δ_{poly} are the solubility parameters of drug and copolymers, respectively.

HME Process

Paracetamol formulations, using either SOL or VA64, were carefully mixed in 100 g batches for 10 min each prior to extrusion. A Turbula TF2 Mixer (Basel, Switzerland) was used to thoroughly blend the powder formulations. The drug/polymer ratios (w/w, %) used were 40:60, 50:50, and 60:40 for both polymers. Extrusion of all PMOL-based formulations was performed using a Eurolab 16 twin screw extruder (Thermo Fisher, Germany) equipped with a 2 mm rod die with a screw speed of 50–100 rpm (feed rate 0.5–1 kg/h). The temperature profile used for all formulations was 50°C/100°C/115°C/120°C/120°C/120°C/120°C/120°C/120°C/120°C (from feeding zone → die). The extrudates produced (strands) were milled for 5 min at 400 rpm by using a Pulverisette ball milling system using eight balls (1.5 cm diameter) (Retsch, Germany) to obtain granules (<500 μm).

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used to study the surface morphology of the hot-melt extrudates. The samples were mounted on an aluminum stub using double-sided adhesive carbon tape and placed in a low humidity desiccator prior to analysis. Samples were sputter coated with gold, and microscopy was performed using a Cambridge Instruments Stereo-Scan S360 (UK), SEM operating at an accelerating voltage of 20 kV.

Thermal Analysis (DSC and MTDSC)

A Mettler-Toledo 823e (Greifensee, Switzerland) differential scanning calorimeter (DSC) was used to carry out DSC scans of the pure API, PMs of API/polymers and API/polymer extrudates. Samples (3–5 mg) were placed in sealed aluminum pans with pierced lids. The samples were heated at 1–10°C/min from 0°C to 220°C under an atmosphere of dry nitrogen. In addition modulated temperature differential scanning calorimetry (MTDSC) studies were performed from 20°C to 150°C with an underlying heating rate of 1°C/min. The pulse height was adjusted to 1°C–2°C with a temperature pulse width of 15–30 s.

Hot-Stage Microscopy

Characterization of PMOL in the molten polymeric carrier was assessed using hot-stage microscopy (HSM). During testing, an Olympus BX60 microscope (Olympus Corporation, Center Valley, Pennsylvania) with Insight QE camera (Diagnostic