Evaluation of Drug–Polymer Solubility Curves Through Formal Statistical Analysis: Comparison of Preparation Techniques

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ABSTRACT: In this study, the influence of the preparation technique (ball milling, spray drying, and film casting) of a supersaturated amorphous dispersion on the quality of solubility determinations of indomethacin in polyvinylpyrrolidone was investigated by means of statistical analysis. After annealing of the amorphous dispersions above the crystallization temperature for 2 h, the solubility curve was derived from the glass transition temperature of the demixed material using the Gordon–Taylor relationship and fitting with the Flory–Huggins model. The study showed that the predicted solubility from the ball-milled mixtures was not consistent with those from spray drying and film casting, indicating fundamental differences between the preparation techniques. Through formal statistical analysis, the best combination of fit to the Flory–Huggins model and reproducibility of the measurements was analyzed. Ball milling provided the best reproducibility of the three preparation techniques; however, an analysis of residuals revealed a systematic error. In contrast, film casting demonstrated a good fit to the model but poor reproducibility of the measurements. Therefore, this study recommends that techniques such as spray drying or potentially film casting (if experimental reproducibility can be improved) should be used to prepare the amorphous dispersions when performing solubility measurements of this kind. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

An increasing number of new drug candidates have a low oral bioavailability because of poor aqueous solubility and obtaining a formulation that ensures high and consistent absorption of these compounds constitutes a great challenge to pharmaceutical scientists.[1] In order to address this challenge, several formulation strategies have been described, including the utilization of the amorphous form.[2] As the free energy of the amorphous form of a drug is higher than that of the corresponding crystalline state, the apparent solubility and dissolution rate is increased.[3] However, the amorphous form is thermodynamically unstable causing the drug to nucleate and recrystallize over time.[4,5] Hence, the stabilization of the amorphous form is critical for this formulation approach to succeed. One way of stabilizing an amorphous drug against crystallization is to molecularly disperse it in amorphous polymers[6] and therefore, the successful development of such dispersions is dependent on the drug–polymer miscibility and solubility. If the drug is miscible and molecularly dispersed in the polymer below solubility equilibrium, it will most likely remain stable.[7,8] Thus, determination of the drug–polymer solubility at typical storage temperatures is of great interest.

Different experimental approaches have been proposed to determine the solubility of crystalline drugs in polymers. However, as most pharmaceutically relevant drugs and polymers are solid at ambient temperature, the solubility equilibrium is difficult to reach.[9] Until recently, the solubility of crystalline drugs in polymers has mainly been determined by variations of the "melting point depression" method.[7,9–11] Common for these methods is that differential scanning calorimetry (DSC) is used to detect the completion of a dissolution endotherm for a physical mixture of crystalline drug and polymer. Sun et al.[11] suggested a protocol where a drug–polymer mixture, at a given concentration of the drug, is milled and annealed at different temperatures until equilibrium is reached and subsequently scanned for a residual dissolution endotherm. The absence of a dissolution endotherm indicates that the dissolution is completed and that the dissolution temperature is located below the annealing temperature. This procedure is then repeated at different temperatures in order to determine the equilibrium solubility temperature corresponding to the initial concentration.[11] Even though this method provides accurate solubility curves, the long annealing stages and numerous DSC scans make it very time-consuming.

As a consequence thereof, Mahieu et al.[12] suggested an optimization of the scanning protocol developed by Sun et al.,[11] taking advantage of the fact that recrystallization is generally faster than dissolution. In this method, a supersaturated

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amorphous dispersion is annealed at different temperatures above the recrystallization temperature until equilibrium is reached. The equilibrium solubility concentration is then derived directly from the glass transition temperature (T_g) of the demixed material using the Gordon–Taylor relationship.[13] By repeating this at different temperatures, a part of the solubility curve is obtained, and by fitting to the Flory–Huggins model,[14] the solubility at ambient temperature can be obtained by extrapolation.[12] Results from both of the aforementioned methods are in general agreement, demonstrating that although the new method does not give access to an extended part of the solubility curve, it can be used to determine drug solubility in polymers up to ten times faster than the previously proposed methods.[12]

Mahieu et al.[12] prepared the supersaturated amorphous dispersion by co-milling a physical mixture of polymer and crystalline drug. However, previous work has shown that milling may yield a higher T_g of amorphous dispersions compared with spray drying.[15] As the equilibrium solubility concentration is derived directly from the T_g of the demixed material, even a small deviation in T_g will have great influence on the solubility curve, according to the Gordon–Taylor relationship.[13] Thus, if refined, this method is of great practical relevance for the screening of drug–polymer systems as the solubility curve can be obtained in less than 24 h.

Spray drying is an important process for preparing amorphous dispersions, but it requires a comparatively large quantity of drug, making it difficult to implement early in the development process where most drug candidates are made in small quantities. In order to overcome this limitation, preparation techniques such as film casting and ball milling have been suggested for screening of amorphous dispersion formulations at smaller scales.[16–18] Film casting and spray drying are "bottom-up" techniques that rely on the same fundamental process principles (rapid solvent evaporation), and therefore it is expected that film casting can provide early information on drug–polymer solubility in spray-dried solid dispersions. However, to our knowledge, no methodical comparison of preparation techniques has been reported defining the most suitable for drug–polymer solubility measurements of this kind. Therefore, the the current study aim to investigate whether the preparation technique (ball milling, spray drying, or film casting) of a supersaturated amorphous dispersion has an influence on the solubility curve using the indomethacin–polyvinylpyrrolidone (IMC-PVP) binary system previously investigated by several authors including Sun et al.[11] and Mahieu et al.[12]

As the predictive power of such solubility curves has not previously been studied, the preparation techniques and the confidence of the solubility curves in this study will be compared and evaluated through formal statistical analysis by considering both the intra- and intervariability of the measurements. The ultimate aim is to provide an extension of the work of Mahieu et al.[12] by refining the experimental protocol and propose a mathematical tool to evaluate the confidence of the data in relation to the Flory–Huggins model.[14]

EXPERIMENTAL

Materials

Indomethacin was purchased from Hawkins, Inc. Pharmaceutical Group (Minneapolis, Minnesota). Amorphous Kollidon® 12 PF (PVP K12, M_w = 2000–3000 g/mol) was kindly supplied by BASF (Ludwigshafen, Germany).

Ball Milling

Indomethacin and PVP K12 (85:15, w/w, 1000 mg) were ball milled in a Mixer Mill MM400 (Retsch GmbH, Haan, Germany). Samples were placed into a 25 mL milling jar containing two 12 mm stainless steel ball bearings and milled at 20 Hz for a total of 8 h at 5°C. Alternating milling periods (75 min) with pauses (5 min) were used to prevent overheating of the sample. Amorphous IMC was prepared using the same protocol.

Spray Drying

Indomethacin and PVP K12 (85:15, w/w, 1000 mg) were dissolved in 10 mL of acetone-ethanol (80:20, v/v) and spray dried using a 4M8-TriX spray drier (ProCepT, Zelzate, Belgium). Solutions were fed at a rate of 3 g min^{-1} (addition rate <10% of lower explosion limit = 3.7 g min^{-1}) and atomized with a 0.5-mm two-fluid nozzle at a pressure of 1.3 bar (20 NL min^{-1}). Heated air was drawn through the open loop drying system at 500 NL min^{-1} with a temperature of 100°C.

Film Casting

Indomethacin and PVP K12 (85:15, w/w, 100 mg) were dissolved in 1 mL of acetone-ethanol (80:20, v/v) and casted on a Teflon-coated 76 × 26 mm^2 Menzel-glass placed on a Jenway 1100 Hotplate (Bibby Scientific Ltd., Staffordshire, UK). Samples were prepared using a plate temperature of 200°C and a total solution volume of 500 μL was pipetted onto the hot glass yielding 50 mg of film. After solvent evaporation, the film was scraped of the glass plate and gently grounded using a mortar and pestle.

Differential Scanning Calorimetry

The DSC thermograms were acquired using a DSC Q2000 (TA Instruments Inc., New Castle, Delaware). Sample powders (2–4 mg) were analyzed in Tzero Aluminium Hermetic pans with a perforated lid and scanned from −10-200°C at a heating rate of 5°C min^{-1} with a modulation of ±0.21°C amplitude and 40 s period of modulation and purged with 50 mL min^{-1} pure nitrogen gas. Temperature and enthalpy of the DSC instrument was calibrated using indium as a standard. The melting temperatures (T_m; peak) and T_gs (midpoint) were determined using the Universal Analysis 2000 (version 4.5A) software.

X-ray Powder Diffraction

X-ray powder diffraction (XRPD) measurements were performed on an X'Pert PRO MRD diffractometer (PANalytical, Almelo, The Netherlands) equipped with a TCU 100 temperature control unit and an X'Celerator detector using nickel-filtered CuKα radiation (λ = 1.5406 Å) at 45 kV and 40 mA. Samples were placed on zero background (0-BG) Si-plates and measured over the angular range 3-40° 2θ at a scanning rate of 1.20° 2θ min^{-1}. Results were analyzed using X'Pert Data Viewer (version 1.2) software.

Density

The true densities of the powders were determined using an AccuPyc 1330 helium pycnometer (Micromeritics Instruments Corporation, Norcross, Georgia). Prior to the measurements, samples were stored for 24 h at 60°C to remove any sorbed

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