A Fast and Reliable Empirical Approach for Estimating Solubility of Crystalline Drugs in Polymers for Hot Melt Extrusion Formulations

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ABSTRACT: A novel empirical analytical approach for estimating solubility of crystalline drugs in polymers has been developed. The approach utilizes a combination of differential scanning calorimetry measurements and a reliable mathematical algorithm to construct complete solubility curve of a drug in polymer. Compared with existing methods, this novel approach reduces the required experimentation time and amount of material by approximately 80%. The predictive power and relevance of such solubility curves in development of amorphous solid dispersion (ASD) formulations are shown by applications to a number of hot-melt extrudate formulations of ibuprofen and naproxen in Soluplus®. On the basis of the temperature–drug load diagrams using the solubility curves and the glass transition temperatures, physical stability of the extrudate formulations was predicted and checked by placing the formulations on real-time stability studies. An analysis of the stability samples with microscopy, thermal, and imaging techniques confirmed the predicted physical stability of the formulations. In conclusion, this study presents a fast and reliable approach for estimating solubility of crystalline drugs in polymer matrixes. This powerful approach can be applied by formulation scientists as an early and convenient tool in designing ASD formulations for maximum drug load and physical stability. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2847–2858, 2014

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INTRODUCTION

Solid dosage forms of poorly water-soluble drugs are increasingly being formulated as amorphous solid dispersions (ASDs) to improve the drug's aqueous dissolution and bioavailability.[1–6] Typical ASD formulation strategy involves dispersing and stabilizing the amorphous form of the drug in a polymer matrix. Several methods such as melt quenching,[7,8] hot-melt extrusion,[9–12] spray drying,[13] ball milling,[13,14] and freeze-drying[15] have been successfully employed for manufacturing ASD formulations.

The main reason for improved aqueous dissolution and bioavailability of these formulations is that a drug in its amorphous form tends to have a higher solubility than its crystalline form because no energy is required to break crystal lattice during dissolution of the former.[16] Therefore, it is necessary that the drug is well stabilized against crystallization to ensure constant bioavailability during the shelf-life of the ASD formulation.

The physical stability or drug recrystallization tendency of an ASD formulation primarily depends on the solubility of the crystalline drug in the polymer at the storage temperature.

If the drug load in the formulation is less or equal to the saturation solubility of the drug in the polymer at the storage temperature, the ASD formulation will be thermodynamically stable and the drug will not crystallize during storage. Thus, solubility of a crystalline drug in the polymer is directly related to stabilization of the amorphous drug against crystallization. ASD formulations with a drug load that exceeds the drug solubility in the polymer matrix can be considered physically stable for a certain time frame if the glass transition temperature (T_g) of the ASD formulation is (much) above the storage temperature. Such formulations are the so-called kinetically stabilized systems because the excess drug will slowly phase separate and subsequently crystallize over time. However, if the molecular mobility is slow enough (i.e., the T_g is sufficiently higher than the storage temperature), these systems can be physically stable for pharmaceutically relevant time periods. Drug loading and long-term physical stability are therefore intrinsically antagonist properties that need to be critically taken into consideration when designing an ASD formulation.[17]

Determining the solubility of a crystalline drug in polymer can be very challenging because of the high viscosity of polymers, which makes equilibrium solubility difficult to reach and construction of solubility curves very time-consuming.[17]

Several methods based on differential scanning calorimetry (DSC) have been reported for determining drug solubility in polymer. They include determining the drug solubility in monomer or dimer liquid model mimicking the polymer,[18,19] determining drug melting point depression/dissolution in physical mixtures,[20,21] and determining temperatures at which phase separation vanishes as a function of drug loading in an ASD.[22]

Of these methods, drug solubility determination in the monomer or dimer liquid model of the polymer seems to be the easiest and fastest approach because of the faster drug dissolution kinetics compared with polymer. However, solubility data generated by this method do not likely reflect the true solubility of the drug in the polymer. Because polymers consist of long chains of covalently bonded monomers, the entropic contribution to mixing in polymers is very low compared with the monomer–dimer liquid model of the polymer. This can lead to

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incorrect estimation of the drug solubility in polymer when the monomer or dimer liquid model of the polymer is applied.

Likewise, determining the temperature at which phase separation vanishes and correlating this temperature to drug solubility in polymer also can be misleading. The reason for this is that the determined temperature actually corresponds to miscibility temperature of two amorphous phases rather than the drug's solubility temperature (T_s).

Perhaps the most accurate method so far is determining the drug melting point depression or dissolution temperature in drug–polymer physical mixtures. Yu and coworkers[20,21] have proposed briefly the cryomilling of drug–polymer mixtures to obtain a homogeneous dispersion of small-size crystals in the polymer matrix prior to DSC experiments. The homogenization and the size reduction are both expected to increase the dissolution kinetics by reducing the diffusive mixing necessary for dissolution.[20] However, the DSC methods described by the authors are fairly time-consuming and may take several days of experimentation to construct a complete solubility curve by this method.

Recently, Mahieu et al.[17] reported a new DSC-based protocol for faster determination of drug solubility in polymer matrix. This protocol makes use of the fact that a supersaturated drug–polymer solution annealed above T_g of the solution but below the T_s will approach equilibrium concentration through demixing and subsequent recrystallization of the drug. The T_g of the equilibrium solution is then used to estimate the equilibrium concentration of the drug by extrapolation from a T_g–drug load plot. This approach seems quicker compared with that reported by Yu and coworkers.[20,21] However, it cannot be applied to systems where T_g of the amorphous drug is higher than the T_g of the polymer.[17] Furthermore, it may not be suitable for drugs that have low crystallization tendency from the undercooled melt, such as ritonavir, lopinavir, and itraconazole.[23]

In this paper, we describe a simple, fast, and reliable approach for estimating solubility of crystalline drugs in some polymers used in the pharmaceutical industry for hot-melt extrusion, namely, Soluplus®, copovidone, polyvinylpyrrolidone (PVP), and polyvinylacetate (PVAc). The simplicity of this method is due to the fact that we have been able to establish an empirical mathematical algorithm that accurately describes the solubility curve of a drug in any of these polymers. This empirical algorithm was applied to data from our laboratory as well as published data, and good agreement was found in all cases. With such an algorithm-based approach, accurate determination of drug solubility for a single drug–polymer mixture is sufficient to construct the complete solubility curve, thereby saving approximately 80% experimentation time. Through extrapolation of the solubility curves, drug solubility in the polymer at 25°C (room temperature) and 5°C was estimated for some selected drug–polymer systems. To confirm the estimated solubility values under these conditions and evaluate the predictive power of the approach, ASD extrudates of these drug–polymer systems were manufactured by hot-melt extrusion and placed on storage.

EXPERIMENTAL

Materials

Naproxen, ibuprofen, itraconazole, acetaminophen, and ibuprofen sodium were purchased from Sigma–Aldrich (Steinheim, Germany). Soluplus® and copovidone were obtained from BASF SE (Ludwigshafen, Germany). Nifedipine was purchased from Acros Organics (Geel, Belgium).

Differential Scanning Calorimetry

Differential scanning calorimetry experiments were performed on a Mettler Toledo DSC1 (Mettler-Toledo GmbH, Giessen, Germany) coupled with a Huber TC100MT cooling system (Huber Kältemaschinenbau GmbH, Offenburg, Grmany). Nitrogen was used as the purging gas. Indium standards were used for temperature and heat of fusion calibration. Hermetically sealed 40 μL aluminum pans with or without pierced lids and sample weights between 5 and 10 mg were used throughout the study.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) investigations were performed on a Thermo Scientific Nicolet IS10 FTIR spectrometer (Thermo Fisher Scientific GmbH, Dreieich, Germany) using an attenuated total reflection (ATR) accessory with a ZnSe crystal. Samples were placed on the ZnSe crystal and 128 scans were collected for each sample at a resolution of 4 cm^{-1}.

FTIR Spectroscopic Imaging

Fourier transform infrared imaging was conducted on a continuous scan spectrometer coupled with a macro sample chamber (Bruker Optics GmbH, Ettligen, Germany) and a Focal Plane Array detector (Santa Barbara Focalplane, Goleta, California). The macro chamber was equipped with a Golden Gate™ diamond ATR crystal accessory (Specac Ltd., Orpington, United Kingdom). Thin samples were placed on the diamond crystal and images were acquired with a spectral resolution of 8 cm^{-1} and 16 coadded scans. The size of the images is 0.58×0.64 mm^2 with a spatial resolution of approximately 10–15 μm.

Polarized Light Microscopy

Polarized light microscopy (PLM) experiments were conducted under ambient conditions using a Leica DMLM optical microscope (Leica Microsystems, Wetzlar, Germany) equipped with a Leica DF320 digital camera (Leica Microsystems, Wetzlar, Germany).

Methods

Preparation of Drug–Polymer Physical Mixtures

Drug–polymer mixtures with drug loads ranging from 20 to 90 wt % were prepared by cryomilling. Each mixture was prepared by accurately weighing the drug and the polymer into the milling vial and then milled at 10 Hz for 16 min in eight cycles on a SPEX freezer/mill model 6750 (SPEX SamplePrep, Metuchen, New Jersey).

Determination of Drug Solubility in Polymer by DSC

The methods reported by Yu and coworkers[20,21] were applied for the determination of the solubility of the drugs in the polymers. For drug–Soluplus® mixtures, sample-containing DSC pans were annealed at 25°C under high vacuum (20 mbar) for 12 h and kept in desiccators prior to the DSC measurement. In the case of drug/copovidone mixtures, the sample-containing DSC pans were annealed at 100°C for 2 min on the DSC equipment before measurement. These pre-measurement sample treatments were performed to reduce plasticizing effect of water on the measurements. A slow heating rate of 1.5°C/min was