Application of Film-Casting Technique to Investigate Drug–Polymer Miscibility in Solid Dispersion and Hot-Melt Extrudate

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ABSTRACT: Determination of drug–polymer miscibility is critical for successful development of solid dispersions. This report details a practical method to predict miscibility and physical stability of drug with various polymers in solid dispersion and, especially, in melt extrudates by applying a film-casting technique. Mixtures of itraconazole (ITZ) with hydroxypropylmethylcellulose phthalate (HPMCP), Kollidon® VA 64, Eudragit® E PO, and Soluplus® were film-casted, exposed to 40°C/75% RH for 1 month and then analyzed using differential scanning calorimetry (DSC), powder X-ray diffractometry, and polarized light microscopy (PLM). ITZ had the highest miscibility with HPMCP, being miscible at drug to polymer ratio of 6:4 (w/w). There was a downward trend of lower miscibility with Soluplus® (miscible at 3:7, w/w, and a few microcrystals present at 4:6, w/w), Kollidon® VA 64 (2:8, w/w) and Eudragit® E PO (<1:9, w/w). PLM was found more sensitive to detect drug crystallization than DSC and powder X-ray diffractometry. There was general correlation between results of film casting and hot-melt extrusion (HME) using a twin screw extruder. For ITZ–Soluplus® mixtures, HME at 4:6 (w/w) resulted in a single phase, whereas drug crystallization was observed at higher drug load. HME of ITZ–Kollidon® VA 64 mixtures also correlated well with the miscibility predicted by film casting. J Pharm Sci 104:2142–2152, 2015

Keywords: solid dispersion; hot-melt extrusion; polymer; itraconazole; drug–polymer miscibility; film casting; amorphous; crystallization; polarized light microscopy; thermal analysis

INTRODUCTION

Amorphous drugs are high-energy materials having higher kinetic solubility and dissolution rates than their crystalline counterparts and, therefore, preferred in the dosage form development of poorly water-soluble drugs. However, the high-energy solids may relax with time resulting in the elimination of microstructure and the growth of local crystalline domains, which ultimately result in crystallization of materials.[1–4] Thus, amorphous drugs are often physically unstable in solid dosage forms. One contributing factor to the physical instability is moisture sorption as the amorphous form is also highly susceptible to moisture uptake.[5] Andronis et al.[3] observed that moisture sorption was higher in amorphous indomethacin relative to its crystalline form, which led to faster nucleation and crystal growth of drug by affecting molecular mobility.

One way of enhancing physical stability of amorphous drugs in solid dosage forms is by solid dispersion. In solid dispersions, drugs are usually dispersed in solid polymeric matrices either molecularly or in their amorphous forms.[6–8] In general, the homogenous dispersions of drugs in suitable polymers increases glass transition temperature (T_g) of the systems as compared with amorphous drugs alone and the resulting increase in viscosity and possible drug–polymer interaction restrict molecular mobility of drugs, thus preventing nucleation of crystalline form and retarding crystal growth.

Although solid dispersions may be kinetically stable for a certain period of time, amorphous drugs may eventually phase separate from solid dispersions depending on their miscibility with polymers and other materials used as carriers and convert to more stable crystalline forms. This leads to reduced product performance, decreased shelf-lives, and lower bioavailability.[9] Many different factors, including chemical nature, molecular weight, viscosity, and T_g of polymers as well as possible molecular interactions between drug and polymer can influence the drug–polymer miscibility. Thus, the selection of appropriate polymeric carriers is critically important for the successful development of solid dispersions. Earlier, we characterized thermal and rheological properties of PVP[10], cellulose[11], and methacrylate-based polymers[12] to help in the selection of appropriate polymers for the preparation of solid dispersion by melt extrusion. Apart from understanding the physicochemical properties of polymers used, it is also important for the successful development of solid dispersions to understand the miscibility between drugs and polymers used. It is, therefore, essential that appropriate polymeric carriers are selected by conducting drug–polymer miscibility screening. The present investigation focuses on the development of a practical method for studying drug–polymer miscibility by using a model drug, itraconazole (ITZ), and representative polymers from the three above-mentioned classes.

The drug–polymer miscibility may be defined as the ability of drug to disperse in a polymer matrix and form a single phase

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without phase separation and drug crystallization. The final concentration of the solubilized drug is dictated by its miscibility with polymer.[13] A review of literature indicates that the drug–polymer miscibility is often determined using theoretical models based on thermodynamic principles.[14] Among the theoretical models, the Hildebrand–Scott model utilizes thermodynamic principles that were originally developed to predict the miscibility of nonpolar solvents.[15] In this model, the cohesive energy density using molar volume and heat of vaporization are used to obtain a constant known as the solubility parameter (δ). It is likely that materials with similar δ values will be miscible with each other. This theory was modified by other researchers in their attempts to predict the miscibility of drugs with polar solvents and with carriers in dry solids.[16–20] However, the predictive value of the theory in selecting polymers for solid dispersion is rather limited.[21]

Another method based on thermodynamic principles, known as the Flory–Huggins method, has also been used to predict drug–polymer miscibility. It is based on a model that considers the system as a hypothetical "lattice" in space.[17] The major limitation of this lattice-based model was the uncertainty in relative contributions of enthalpy and entropy to the process and, as a result, deviations were found between experimental results and theoretical predictions.[21]

One major limitation of studying drug–polymer miscibility in solid dispersion is that drug molecules exhibit low-molecular mobility at temperatures below T_g, which makes it difficult to ascertain whether the drug–polymer miscibility predicted by theoretical calculations are actually valid or not and whether the solid dispersion would be physically stable upon prolonged storage. It is important that reliable drug–polymer miscibility results are obtained within a relatively short time available during preformulation testing of drug candidates. Several researchers stored samples at high temperatures (i.e., near their T_g) to increase molecular mobility and facilitate any drug crystallization.[22,23] Other researchers have used differential scanning calorimetry (DSC) technique to determine drug–polymer miscibility at glass transition temperatures. For example, Forster et al.[24] used this approach to predict the formation of glassy solutions upon melt extrusion of two model drugs with different excipients. However, there are numerous reports[25–27] indicating that when the data obtained at high temperature or near T_g are extrapolated to lower room temperature, the results often deviate from the experimentally observed values. Johari and Shanker[28] also showed the inaccuracy of such methods. They observed that the heat capacity measured using analytical methods, such as DSC, includes specific heat data originating from configurational entropy as well as from the nonconfigurational source. According to them, the nonconfigurational entropy does not contribute to structural relaxation necessary for phase separation, and hence the results deviate from actual miscibility when extrapolated from a high temperature to a low temperature. Thus, the drug–polymer miscibility results are affected by temperature as well as by the analytical technique used.

Because of the complexity of the theoretical methods and their limitations in predicting drug–polymer miscibility, there is a need for a practical method that may be used during the preformulation testing of drugs to screen different polymers for their miscibility with polymers and to ascertain the extent of miscibility in the selected polymer. In one such method, the drug solubility was determined in dilute solutions of monomers and dimers related to the polymer used and the results were then used to predict drug–polymer miscibility.[29] However, such a method overlooks the structural aspects of solids, such as limitation on molecular motion and orientation in a solid matrix structure. Other experimental approaches, such as preparing solid dispersions in small scale by hot-melt extrusion (HME),[30] have also been explored to prescreen polymers. As mentioned earlier, any recrystallization of drug in such a method becomes very slow because of high viscosity of polymers in solid state, and, in most cases, the solid dispersions do not reach thermodynamic equilibrium state in a relatively short period of time available for preformulation screening.[31] The lack of adequate amounts of drugs to prepare melt extrudates with many different polymers for preformulation screening may also be an issue.

In an attempt to develop a predictive tool that may be used in the preformulation setting, Kolter et al.[32] developed a film-casting method in which drug–polymer films prepared by using polyvinyl-based polymers were cast on glass plates, stored at 23°C/54% RH for 7 days and analyzed microscopically. The authors concluded that the film casting was a useful technique to rank-order polymers for their solubilization capacity of various drugs. Although not used specifically for the purpose of prescreening different polymers, Janssens et al.[33] compared physical stability of ITZ by casting films of ITZ–Eudragit® E 100 mixture and compared the results with those obtained after spray drying of mixtures. The results suggested that a thermodynamic equilibrium between drug and polymer may be ascertained more rapidly in films than observing the physical stability of spray-dried products. Similarly, Weuts et al.[34] applied the method to investigate the miscibility of etravirine with hydroxypropylmethylcellulose. Thus, the film-casting technique could prove to be a useful tool to systematically assess the miscibility of drugs with various polymers during preformulation testing. However, all of the studies mentioned above were rather limited in their scopes, and more in-depth studies to explore the value of film casting for drug–polymer miscibility screening are needed. In the absence of such studies, the film-casting technique has not yet been widely adopted by the pharmaceutical industry during preformulation studies for the development of solid dispersion formulations.

In recent years, the interest in solid dispersion of poorly water-soluble drugs has increased greatly in the pharmaceutical field after introduction of the HME technology to prepare such formulations.[35–37] The primary objective of the present study was to investigate the capability of film-casting technique to predict drug-polymer miscibility and to rank-order different polymers such as cellulose ether, polyvinylpyrrolidone, polymethacrylate, and polyvinyl acetate-polyvinyl capralactone graft copolymers for miscibility with a poorly water-soluble drug, ITZ. The results obtained from film casting were then correlated with the physical stability of solid dispersions prepared by the HME process.

MATERIALS AND METHODS

Materials

Names, structures, and selected physicochemical properties of the polymers and drug used are given in Table 1. Kollidon® VA 64 (polyvinylpyrrolidone vinyl acetate copolymer) and Soluplus® (polyvinyl caprolactam–polyvinyl