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Research paper

Preparation of carbamazepine–Soluplus® solid dispersions by hot-melt extrusion, and prediction of drug–polymer miscibility by thermodynamic model fitting

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ABSTRACT

Hot-melt extrusion (HME) is a dust- and solvent-free continuous process enabling the preparation of a variety of solid dosage forms containing solid dispersions of poorly soluble drugs into thermoplastic polymers. Miscibility of drug and polymer is a prerequisite for stable solid dispersion formation. The present study investigates the feasibility of forming solid dispersions of carbamazepine (CBZ) into polyethylene-glycol–polyvinyl caprolactam–polyvinyl acetate grafted copolymer (Soluplus®) by hot-melt extrusion. Physicochemical properties of the raw materials, extrudates, co-melted products, and corresponding physical mixtures were characterized by thermo-gravimetric analysis (TGA), differential scanning calorimetry (DSC), attenuated total reflectance infrared (ATR-FTIR) spectroscopy and hot stage microscopy (HSM), while miscibility of CBZ and Soluplus® was estimated on the basis of the Flory–Huggins theory, Hansen solubility parameters, and solid–liquid equilibrium equation. It was found that hot-melt extrusion of carbamazepine and Soluplus® is feasible on a single-screw hot-melt extruder without the addition of plasticizers. DSC analysis and FTIR spectroscopy revealed that a molecular dispersion is formed when the content of CBZ does not exceed ~5% w/w while higher CBZ content results in a microcrystalline dispersion of CBZ form III crystals, with the molecularly dispersed percentage increasing with extrusion temperature, at the risk of inducing transformation to the undesirable form I of CBZ. Thermodynamic modeling elucidated potential limitations and temperature dependence of solubility/dispersibility of carbamazepine in Soluplus® hot-melt extrudates. The results obtained by thermodynamic models are in agreement with the findings of the HME processing, encouraging therefore their further application in the HME process development.

1. Introduction

Hot-melt extrusion (HME) is a continuous process of converting a raw material into a product of uniform shape and density by forcing it through a die under high temperature and pressure, thereby making possible to extrude solids resistant to shear forces [1]. By selecting a suitable exit die, a variety of solid dosage forms including granules, pellets, tablets, suppositories, implants, stents, transdermal and transmucosal systems, and ophthalmic inserts can be produced [2,3]. HME does not require the use of solvents and for this reason it was first introduced in the pharmaceutical industry as an alternative to solvent-dependent processes [2,3]. It has certain advantages over traditional pharmaceutical manufacturing techniques. Being a solvent and dust-free process it is environmentally friendly, and since it is a continuous process, fewer steps are involved, which reduces the production cost and makes scaling-up easier [4].

The basic HME materials are thermoplastic matrix forming polymeric binders, the properties of which influence both the processing conditions and the characteristics of the extruded dosage form, such as dispersibility of active ingredient, its stability and release rate [3]. All components of the hot-melt extruded formulation must be thermally stable at the processing temperature, which is usually around 20–30 °C lower than the melting point of the drug [3]. Due to the intense mixing during the hot-melt processing, and depending on the miscibility of the drug with the polymer, different types of solid dispersions may be formed, including eutectic mixtures, microfine crystalline dispersions or solid solutions (substitutional, interstitial or amorphous) [5]. In

Abbreviations: ATR, attenuated total reflectance; CBZ, carbamazepine; DSC, differential scanning calorimetry; FTIR, Fourier-transform infrared; HME, hot-melt extrusion; HSM, hot stage microscopy; MW, molecular weight; PM, physical mixtures; PRU, polymer repeat units; SLE, solid–liquid equilibrium; TGA, thermogravimetric analysis; XRD, X-ray diffraction.

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this dispersed state, the dissolution of drug can be improved or modified and bad taste can be masked by appropriate selection of polymer [6–8].

The term "solid solution" most often refers to single-phase systems with molecularly dispersed active ingredient, whereas solid dispersions refer to binary or multi-phase systems. Miscibility of the drug with the polymer is a prerequisite for stable solid dispersion formation. If the drug can be dissolved in the polymer, then a single-component system is formed, comprising an amorphous phase. Therefore, it is important to attempt prediction of drug–polymer miscibility and drug solubilization prior to setting-up HME process, especially in the case of newly developed drugs of limited availability.

Different approaches have been used to study the drug–polymer miscibility. According to Flory–Huggins lattice theory [9], the free energy of mixing ΔG_M is related to the number of moles, n, and volume fraction, Φ, of the drug and polymer by the following equation:

$$\frac{\Delta G_M}{RT} = n_{drug} \ln \Phi_{drug} + n_{polymer} \ln \Phi_{polymer} + \chi n_{drug} \Phi_{polymer} \quad (1)$$

where R and T are the gas constant and the absolute temperature, respectively, and χ is an interaction parameter that accounts for the enthalpy of mixing and is an indication of drug–polymer miscibility. Due to the connectivity of the polymer repeat units (PRUs), for most drug and polymer combinations, the configurational entropy of any polymer is negligible and the first two terms on the right part of Eq. (1) are constant. Therefore, miscibility is determined by the enthalpic cohesive or adhesive interactions expressed by the last term [10]. Negative values of the interaction parameter χ indicate strong, adhesive interactions favoring miscibility, whereas positive values indicate strong cohesive interactions.

Miscibility of the drug with polymer can also be studied by monitoring the changes of the onset temperature T_g in the melt endothermic peak and heat of fusion ΔH_{fus} of the drug [11]. Melting endotherms may result from both fusion and solution of the drug in the polymer. A decrease in the T_g and ΔH_{fus} with increasing proportion of polymer indicates miscibility [12]. Also, a single melting endotherm and T_g between the T_g values of pure drug and excipient indicates a complete miscibility, whereas two separate melting endotherms indicate partial miscibility [4,12]. For miscible drug–polymer systems, lowering of the drug melting point due to the presence of polymer is well documented [10,13–15] and can be related to the interaction parameter, χ, by the following equation [10]:

$$\left(\frac{1}{T_M^{mix}} - \frac{1}{T_M^{pure}}\right) = \frac{-R}{\Delta H_{fus}} \left[\ln \Phi_{drug} + \left(1 - \frac{1}{m}\right) \Phi_{polymer} + \chi \Phi_{polymer}^2\right] \quad (2)$$

where T_M^{pure} and T_M^{mix} are the melting temperatures of the pure drug and of drug in the presence of the polymer, respectively; ΔH_{fus} is the heat of fusion of the pure drug, and m is the ratio of the polymer to drug volume (calculated as molar volumes from the true density).

Another approach to drug–polymer interaction is the concept of solubility parameter, δ, originally introduced by Hildebrand and Scott [16] and later modified by Hansen [17] who proposed that the total solubility parameter δ_t is determined from the contribution of interactions between dispersion forces (δ_d), polar interactions (δ_p) and hydrogen bonding (δ_h) of the functional groups:

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (3)$$

Hansen solubility parameter can be estimated using the group contribution method of Van Krevelen and Hoftyzer [18,19]. Compounds with similar values of Hansen solubility parameter are likely to be miscible, and Greenhalgh et al. [20] further classified drug–polymer miscibility on the basis of the difference $\Delta\delta_t$ between the solubility parameters. For $\Delta\delta < 7.0$ MPa$^{1/2}$ miscibility is likely to occur, but for $\Delta\delta > 10$ MPa$^{1/2}$ it is not.

A large number of drugs present bioavailability problems due to poor solubility and different formulation approaches have been used to tackle this problem. The use of solubilizers (surfactants, complexation agents, co-solvents, etc.) is a possibility and of particular interest to HME are solubilizers which in ambient conditions exist in solid state [21,22]. However, most of them have limited solubilization capacity and/or inability to form solid dispersions [23]. Polyethyleneglycol–polyvinyl caprolactam–polyvinyl acetate grafted copolymer (PEG6000/vinylcaprolactam/vinylacetate copolymer, Soluplus®, BASF, Germany) is a new thermoplastic polymer designed for use in HME. It is an internally plasticized amphiphilic molecule, capable of forming solid solutions with drugs, thus improving dissolution [24]. It acts both as a matrix former and solubilizer for the drug in water, and is considered of forming fourth generation solid dispersions [25,26]. In addition, it is amorphous and due to its low glass transition temperature is easily extrudable, thus eliminating the need of plasticizer addition in the formulation. It also has good thermal stability, good flowability and low toxicity [23,24,27,28].

Carbamazepine (CBZ) is an antiepileptic drug classified as BCS class II due to its low solubility and high permeability (0.12 mg/ml and 4.3×10^{-4} cm/s respectively, [29]). It is known to exist in four anhydrous crystalline forms: P-monoclinic (form III), triclinic (form I), trigonal (form II) and a C-monoclinic (form IV), of which form III is found in commercial pharmaceutical formulations [30–32]. Due to its narrow therapeutic index and relatively high plasma concentration variability [33], a uniform dispersion of CBZ in the dosage form and adequate dissolution rate are very important to achieve desired therapeutic effect. Hardung et al. [23] demonstrated that Soluplus® can increase CBZ solubility up to 5 times, independently of the pH due to the non-ionic nature of the polymer, which makes Soluplus® an excellent candidate for the development of carbamazepine HME solid dispersions. Preparation of carbamazepine–Soluplus® solid dispersions has been reported using various techniques such as co-melting [34], extrusion with a twin-screw extruder [35] and solvent casting or hot-melt extrusion [36]. It was reported that mixtures of up to 10% w/w of CBZ in Soluplus® can form a molecular dispersion when extruded on a twin-screw hot-melt extruder, whereas crystalline form III was observed in extrudates containing 30% w/w of CBZ [35]. In another study on carbamazepine and Soluplus® [36], it was demonstrated that higher amount of molecularly dispersed CBZ can be obtained via solvent casting method in comparison to the hot-melt extrusion method. These reports did not go in detail to elucidate the thermodynamic properties of pure materials and their dispersions, nor were there attempts to analyze the miscibility of materials. One of the promising methods to improve the chemical stability of amorphous solid dispersions is the cocrystalization technique. It was reported that a stable dispersion of CBZ-nicotinamide cocrystal in Soluplus®, using the hot-melt extrusion or melting method, is feasible [37].

In the present work miscibility of CBZ and Soluplus® and suitability for preparation of a solid dispersion by HME is investigated, applying thermodynamic modeling and physicochemical characterization of the materials, their physical mixtures and their HME dispersions prepared using a single screw extruder and also by fusion (co-melting). There are no previous reports of such an elaborate analysis of CBZ and Soluplus® properties relevant to the preparation of solid dispersions by the HME method.