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Methods for the preparation of amorphous solid dispersions – A comparative study

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ABSTRACT

Solid dispersion is considered one of the most successful strategies for improving the dissolution and absorption of poorly water-soluble APIs. The primary focus of this study was to investigate the effects of methods of solid dispersion preparation on the pharmaceutically important physicochemical properties of a product based on Soluplus® as the polymer carrier and febuxostat as the model BCS II API. The methods of preparation evaluated were based on melt and solvent mechanisms. The samples prepared were evaluated by modulated differential scanning calorimetry, solid state NMR, Raman spectroscopy, XRPD, scanning electron microscopy, and BET analysis. Differences among the solid dispersions obtained by the specific methods and their mechanisms were clearly observed in *in-vitro* testing. The dissolution behaviour was shown to be influenced not only by particle characteristics such as the size and specific surface area, but also by the interactions between the API and the polymer matrix on the molecular level (e.g. non-covalent interactions). The set of measurements showed that similar methods of preparation do not lead to solid dispersion systems of similar characteristics. Surprisingly, similar dissolution profiles were found in samples prepared by very different methods although their physical-chemical characteristics differed significantly, and vice versa.

1. Introduction

Dispersions of poorly water-soluble APIs in solid inert hydrophilic polymer matrices, known as solid dispersions, have been established as an efficient approach enhancing the dissolution rate and hence the oral bioavailability of APIs being formulated this way [1–6]. The enhanced dissolution rate characteristic of solid dispersions can generally be attributed to one of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, solid solution formation and improved wettability due to intimate contact with a hydrophilic carrier, precipitation as a metastable crystalline form, or a decrease in substance crystallinity. Both the properties of the carrier-API composition and the method of production generally can influence the type of the solid dispersion formed, and thus the subsequent behaviour of the solid dispersion [7].

Further aspects of solid dispersions such as classification, methods of production including many details as well as choice of additives, mutual miscibility, mechanisms of API release, and methods of characterization have been studied extensively and presented in review articles [5,8,9].

Despite the intense study of solid dispersions, only a limited

Abbreviations: ASD, Amorphous Solid Dispersion; API, Active Pharmaceutical Ingredient; mDSC, modulated Differential Scanning Calorimetry; SSA, Specific Surface Area; ssNMR, solid state Nuclear Magnetic Resonance; T_m, Melting temperature; T_g, Glass transition temperature; HME, Hot-Melt Extrusion; SC, Slow Cooling; BC, Bench Cooling; FC, Fast Cooling; SD, Spray Drying; SE, Solvent Evaporation; RVE, Rotary Vacuum Evaporation; IR, Infrared; RS, Raman Spectroscopy; SEM, Scanning Electron Microscopy; BET, Brunauer Emmett and Teller; PSD, Particle Size Distribution; XRPD, X-Ray Powder Diffraction; PC, Principal Component; PCA, Principal Component Analysis; PLS, Partial Least Squares regression; (Soluplus®), polyvinyl-caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer.

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number of products are available on the market. The poor predictability of the physical stability of solid dispersions together with the difficult production at the industrial scale were identified as the main reasons [1,3].

Solid dispersions are commonly prepared by the solvent or hot-melt (fusion) methods [4,6]. In solvent-free methods, the crystal lattice structure is destroyed by high temperatures and by mechanical stress. However, imperfect amorphization, that is, the presence of remaining nuclei or small crystals, may lead to crystallization after preparation. On the other hand, in the solvent methods, the lattice structure is destroyed completely during the preparation process, but crystallization may be enhanced by the presence of residual solvents [10].

A very efficient solvent evaporation-based technology is spray drying (SD), since it allows for extremely rapid solvent evaporation, leading to a fast transformation of the API to the crystalized and/or amorphized form dispersed within solid carrier particles. An excellent review on all aspects of SD was published recently [11].

Frequently, the method of choice for manufacturing solid dispersions is hot-melt extrusion (HME), mainly because of the health, environmental, and subsequent financial issues associated with the lack of the use of solvents [12,13].

Further ways of preparation have been described, such as thermal adhesion granulation [12], ball milling [14], electrospinning [15], co-precipitation [16], supercritical fluid methods, spray freezing [2], etc. Solid dispersions prepared by different methods can exhibit differences in physicochemical properties, which might affect product performance, including manufacturability [17]. The dissolution behaviour of amorphous solid dispersions (ASDs) is known to be affected by many variables, such as the type of polymer, API-polymer ratio and interactions, aqueous solubility of components, wettability, and physical stability of the solid dispersion [1,18].The degree of molecular interactions was proven to be dependent on the actual-API-polymer miscibility [19].

Significantly lower aqueous solubility of solid dispersions prepared by SD compared to the bead milling method was reported despite the smaller particle size of the SD material. The differences were attributed to higher surface energy which results in the aggregation of particles of the SD solid dispersions, which in turn negatively effects aqueous solubility [20]. It has also been reported that the surface of a SD powder is dominated by less soluble material due to its adsorption into the air/liquid interface before they turn into dry particles [1].

Also, Joe and co-authors reported the solubility of solid dispersions to be dependent on the method used for their preparation, in the following order: solvent-evaporation method > solvent-wetting method > surface-attached method [6]. The authors have attributed the significant differences in the solubility of the samples to the size of particles, the contact area between the hydrophilic carrier and the API contained, and to the crystallinity of the API. Different particle morphologies, crystallinities, and dissolution rates were assigned to different mechanisms of particle formation by spray freezing and supercritical antisolvent precipitation methods in the comparison study [2,21]. The supercritical antisolvent precipitation method showed higher crystallinities of samples, which resulted in lower dissolution rates. A direct comparison of the solid state characteristics of solid dispersions prepared by the HME and solvent co-precipitation methods is presented in a study by Dong [16]. The authors reported the same spectroscopic, XRPD, true density and water sorption/desorption behaviour, but a larger specific surface area of co-precipitated ASD, which resulted in its faster dissolution. Other similar works presented characteristics of HM-extruded and SD solid dispersions varying in surface area, powder densities and flow characteristics, whereas in terms of the interactions between the drug and the carrier, the dispersions prepared by both methods are rather similar. The work concludes by suggesting that similar product performance can be obtained when the physical characteristics of materials are similar. However, differences in material properties may affect the physical stability of the solid dispersion, since the SD solid dispersion was shown to be physically less stable compared to the HME solid dispersion under accelerated stability conditions [22,23].

The aim to investigate the influence of the manufacturing process used in the preparation of glass solutions on the physicochemical characteristics of products has been described in another paper [14]. The study indicated that the preparation method is of importance in terms of chemical stability and processing, but that the choice of the manufacturing approach appears to have minimal influence on physical stability.

The primary focus of this study is to investigate the effects of the solid dispersion method on the physicochemical properties of the product. The same API-polymer primary mixture was used in the preparation of the solid dispersions in order, to eliminate any possible variation in the properties of the solids due to their chemical composition. Therefore, the differences in the properties of solid dispersions can be attributed to the molecular interactions and physicochemical properties induced by the preparation method used.

2. Materials and methods

2.1. Preparation of solid dispersions

Soluplus® (BASF, Ludwigshafen, Germany) was used as the hydrophilic carrier for the preparation of solid dispersions by the various methods described below. Febuxostat (Zentiva, k.s., Prague, Czech Republic) was used for the experiments as the model BCS II API and it was in pharmaceutical quality. The mixture (API-polymer ratio 1:2 w/w) was mixed for 15 min in a small container in a Turbula T50A blender and used for all the experiments. This mixture was also used as a physical mixture sample. For solvent methods, a mixture of febuxostat:Soluplus:ethanol (1:2:18, w/w) was prepared and then used in each case. The ethanol used in the study was 96% in Ph. Eur. quality. Water for injection (Ph.Eur.) was used in the sample preparation. All material gained using the procedures described below was ground in a grinding mortar, sieved manually using a 250 μm sieve, and kept in closed glass bottles.

2.1.1. Hot-melt extrusion (HME)

The Three-Tec ZE12 twin-screw mini extruder was used for the preparation of the sample. The material was conveyed into the extruder gravimetrically, using the Three-Tec ZD 9 FB-C-1M – 80 twin screw feeder. The following settings were used for production of the solid dispersion used for testing in this study: feeding rate 300 g/h, 100 rpm of the screws; 1.5 mm nozzle diameter; temperature set in five separate zones 100/135/135/135/135 °C.

2.1.2. Fusion method, subsequent cooling (fusion, SC)

Approximately 5 g of the drug-polymer mixture (1:2) was placed between two aluminium plates and put on the heater annealed to 180 °C. Aluminium plates were pressed together and shuffled rotationally in order to produce shear stress. This procedure took 10 min. Subsequent cooling was performed by putting the aluminium plates with the material between them in a tray dryer, which was set to cool down from 180 °C at the rate of 30 °C per hour until 30 °C was achieved.