International Journal of Pharmaceutics 532 (2017) 289–298

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Spray drying of poorly soluble drugs from aqueous arginine solution

Rami Ojarinta[a,*], Louise Lerminiaux[a,b], Riikka Laitinen[a]

[a] School of Pharmacy, University of Eastern Finland, P.O. Box 1627, 70211 Kuopio, Finland
[b] Laboratory for Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

ARTICLE INFO

Keywords:
Co-amorphous
Amino acid
Spray drying
Stability
Dissolution

ABSTRACT

Co-amorphous drug-amino acid mixtures have shown potential for improving the solid-state stability and dissolution behavior of amorphous drugs. In previous studies, however these mixtures have been produced mainly with small-scale preparation methods, or with methods that have required the use of organic solvents or other dissolution enhancers. In the present study, co-amorphous ibuprofen-arginine and indomethacin-arginine mixtures were spray dried from water. The mixtures were prepared at two drug-arginine molar ratios (1:1 and 1:2). The properties of the prepared mixtures were investigated with differential scanning calorimetry, X-ray powder diffractometry, Fourier-transform infrared spectroscopy and a 24 h, non-sink, dissolution study. All mixtures exhibited a single glass transition temperature (T_g), evidence of the formation of homogenous single-phase systems. Fourier transform infrared spectroscopy revealed strong interactions (mainly salt formation) that account for the positive deviation between measured and estimated T_g values. No crystallization was observed during a 1-year stability study in either 1:1 or 1:2 mixtures, but in the presence of moisture, handling difficulties were encountered. The formation of co-amorphous salts led to improved dissolution characteristics when compared to the corresponding physical mixtures or to pure crystalline drugs.

1. Introduction

If orally administered drugs are to be bioavailable, they have to possess sufficient water solubility. For some drugs (Biopharmaceutical classification system; Class II), the dissolution may even be the rate limiting step in drug absorption (Baghel et al., 2016). However, since the advent of combinatorial chemistry and high throughput screening techniques, the water solubility of new drug candidates has decreased drastically (Lipinski et al., 2001).

Utilizing the amorphous form of a drug is one of the numerous formulation methods intended to improve its dissolution properties (Laitinen et al., 2013). The increase in apparent solubility and hence bioavailability, is due to the higher internal energy in the amorphous form compared to the crystalline counterpart. On the other hand, this property may cause the amorphous drug to recrystallize during processing, storage, or dissolution. Nevertheless, it is now well established that with a proper selection of a polymer, the polymeric amorphous solid dispersion approach may improve the solid-state stability of the amorphous form as well as increase the stability of the supersaturated state in a solution (Baghel et al., 2016; He and Ho 2015). Despite intensive research, however, only a few amorphous solid dispersion based formulations have reached the global market (He and Ho, 2015). There are several challenges associated with these polymers e.g. the poor miscibility of some drugs with polymers, the hygroscopicity of polymers, incompatibility issues, and other poor formulation characteristics, such as poor flowability or compressibility (Lakio et al., 2015; Löbmann et al., 2011).

In an attempt to avoid the use of polymers, another subclass of solid dispersions, namely co-amorphous formulations, has been introduced (Dengale et al., 2016; Laitinen et al., 2013). In co-amorphous formulations, low molecular weight compounds are used instead of polymers to form an amorphous homogenous single-phase mixture (Dengale et al., 2016). In order to prepare co-amorphous systems, both pharmaceutically active substances and inactive excipients have been used, and both approaches have successfully stabilized the amorphous form and enhanced the dissolution properties of the studied drugs (Allesø et al., 2009; Jensen et al., 2014; Löbmann et al., 2011, 2013a).

It is known that the preparation method may affect certain properties of the amorphous drugs, such as their glass transition temperature (T_g), dissolution, and stability (Agrawal et al., 2013; Sakurai et al.,

Abbreviations: ARG, arginine; ACN, acetonitrile; DSC, differential scanning calorimetry; FTIR, Fourier-transform infrared spectroscopy; HPLC, high performance liquid chromatography; IBU, ibuprofen; IND, indomethacin; RH, relative humidity; SD, spray dried; TFA, trifluoro acetic acid; Tg, glass transition temperature; Tm, melting temperature; Trc, recrystallization temperature; XRPD, X-ray powder diffractometry

* Corresponding author.
E-mail address: rami.ojarinta@uef.fi (R. Ojarinta).

http://dx.doi.org/10.1016/j.ijpharm.2017.09.015
Received 19 July 2017; Received in revised form 5 September 2017; Accepted 7 September 2017
Available online 08 September 2017
0378-5173/

2012; Zhang et al., 2009). Preparation techniques of amorphous formulations can be roughly divided into fusion or melting techniques (e.g. melt quenching, hot melt extrusion), solvent techniques (e.g. solvent casting, freeze drying, spray drying), and techniques that involve mechanical activation (e.g. cryogenic grinding) (Baghel et al., 2016; Meng et al., 2015; Vasconcelos et al., 2016). A wide range of these techniques has been applied to manufacture the polymeric amorphous solid dispersions, but due to the several advantages, such as scalability from laboratory to industrial scale and option for continuous manufacturing, the hot melt extrusion and spray drying techniques have become the most popular techniques both in laboratory and especially on the industrial scale (Van Den Mooter 2012; Vasconcelos et al., 2016; Vo et al., 2013). Nonetheless, the majority of co-amorphous formulations have been prepared by less scalable and less efficient methods, such as melt quenching and ball milling (Chavan et al., 2016; Meng et al., 2015; Vasconcelos et al., 2016). During recent years, however, also the use of spray drying from organic solvents has been shown to be applicable for co-amorphous formulations (Beyer et al., 2016b; Craye et al., 2015; Jensen et al., 2016a).

In spray drying, a solution containing the solvent and the components of the co-amorphous mixture is sprayed into a hot air stream, with the rapid evaporation of the solvent, and the formation of homogenous amorphous solid particles (Vasconcelos et al., 2016). Additional advantages of spray drying against melting methods include the relatively low processing temperatures and beneficial particle morphology (Baghel et al., 2016). The challenge in the preparation of co-amorphous formulations via spray drying is to find a common solvent suitable for all the components, especially when combining a poorly water-soluble drug with a readily-soluble co-former. Since it is important to avoid the use of toxic and environmentally hazardous organic solvents, excipients, such as surfactants may be needed to enhance the dissolution of the drug, and subsequently to enable the spray drying (Craye et al., 2015). However, some tolerability issues may also be associated with the surfactants (Baghel et al., 2016). Thus, it would be preferable to find co-formers that alone would enhance the dissolution of the drug adequately to enable the spray drying from aqueous solutions containing only the co-former and the drug.

In the present study, co-amorphous mixtures of arginine (ARG) with ibuprofen (IBU) and indomethacin (IND) were prepared by spray drying. Unlike in the previous studies investigating spray drying co-amorphous formulations, only pure water was used as a solvent in order to avoid the challenges associated with additional excipients (Baghel et al., 2016; Beyer et al., 2016b; Craye et al., 2015; Jensen et al., 2016a). We also prepared the co-amorphous mixtures in a molar ratio of 1:2 in addition to the commonly utilized molar ratio of 1:1, since Jensen et al. (2016b) observed that with co-amorphous IND-ARG mixtures, the molar ratio of 1:1 may not possess the highest T_g values. The properties of these mixtures were then investigated with X-ray powder diffraction (XRPD), Fourier-transform infra-red spectroscopy (FTIR), and differential scanning calorimetry (DSC) to verify the changes in their solid-state, and to examine their physical stability. Additionally, the dissolution properties of the mixtures were studied in 24 h dissolution tests.

2. Materials and methods

2.1. Materials

IND was purchased from Hangzhou Dayanchem (Hangzhou, China), ARG from Sigma-Aldrich (Riedel-de Haan, Germany), and IBU was kindly donated by Orion Pharma (Espoo, Finland) (see Fig. 1 for chemical structures). Sodium chloride (NaCl; J.T. Baker, Deventer, Holland), hydrochloric acid (HCl, 37%; Riedel-de-Haën, Seelze, Germany), potassium dihydrogen phosphate (KH_2PO_4; Merck, Darmstadt, Germany), sodium hydroxide (NaOH; VWR Chemicals, Leuven, Belgium), and glacial acetic acid (Riedel de Haën, Germany) were used to prepare the buffer solutions (pH 1.2, 5.0 and 7.2). Phosphorus pentoxide (P_2O_5) was used to maintain 0% and sodium bromide (NaBr) to ensure 60% relative humidity (RH) conditions during storage.

Purified (class II; Elix 5, Millipore S.A.S., Molsheim, France) and ultrapurified (class I; Elga Purelab Ultra, Elga LabWater, UK) water were used throughout the study. If not specified, class II water was used. Acetonitrile (ACN; HiPerSolv for HPLC, VWR Chemicals, Leuven, Belgium) and trifluoro acetic acid (TFA, 55.5%; HPLC grade, Alfa Aesar, Karlsruhe, Germany) were used as components of the high performance liquid chromatography (HPLC) mobile phase.

2.2. Methods

2.2.1. Phase solubility test

To explore the effect of the ARG concentration on the solubilities of the model drugs, we added an excess of both drugs to 20 ml of 1%, 5% and 10% (m/V) ARG-water solution. The study was performed in triplicate in 50 ml Erlenmeyer flasks containing a magnetic stirrer bar (ambient conditions). After 3 days of stirring, a 5 ml sample from each flask was filtered through 0.22 µm membrane filter (Syringe Filter 30 mm Dia, PES 0.22 µm Membrane, Sterile, Porvair Sciences), and the filtrate was diluted with an adequate amount of 70/30 (V/V) ACN/class I water-mixture to reach concentrations between 1 and 100 µg/ml.

2.2.2. High performance liquid chromatography (HPLC)

The drug concentrations were measured in an HPLC that consisted of Gilson 321 pump, Gilson UV–vis 151 detector (both from Gilson Inc., Middleton, WI, USA), Gilson 234 auto injector (Gilson, Roissy-en-France, France), and a reversed phase column (Phenomenex Gemini NX 5 u C18 110A, 250 × 4, 60 mm, sr. nr. 590531-19, USA) with a pre-column. The mobile phase flow rate was set at 1.2 ml/min and the detection wavelengths were 221 nm for IBU and 225 nm for IND. The mobile phase consisted of 70% of ACN and 30% of class I water, which were acidified by addition of 0.1% of TFA.

We prepared a 100 µg/ml standard solution from both drugs by weighing 10 mg of drug and dissolving it into 100 ml of 70/30 ACN/class I water-mixture. Other standard solutions (1, 5, 12.5, 25, 50 µg/ml) were prepared by diluting the 100 µg/ml solution. Each standard solution was analyzed by HPLC to obtain standard lines that were found to be linear ($R^2 > 0.997$) in the examined concentration range.

2.2.3. Spray drying

Spray drying was conducted with a Büchi Mini Spray Dryer B-191 (Büchi Labortechnik AG, Flawil, Switzerland). The correct amount of crystalline drug was dissolved into 5% (m/V) ARG-class 1 water-solution to achieve drug-ARG-molar ratios of 1:1 or 1:2. When the drugs were completely dissolved (no solid material left) the solutions were spray dried under following conditions: inlet temperature 160 °C, outlet temperature 83 ± 6 °C, air flow rate 600 l/h, and pump rate 5.3 ± 0.2 ml/min. The correct molar ratios of the prepared powders were confirmed by completely dissolving an amount of mixtures corresponding to 20 mg of the drugs and measuring the total amount of dissolved drug by HPLC (see Supplementary material; Table S1).

2.2.4. Cryomilling

Crystalline IND was converted into an amorphous form in an oscillatory ball mill (Mixer Mill MM400, Retsch GmbH & Co., Haan, Germany). A total of 500 mg of crystalline drug was placed in a 25 ml milling chamber with two 12 mm stainless steel balls. The chambers were immersed in liquid nitrogen for two minutes prior to milling and every 10 min during the milling. The milling time was 60 min at 30 Hz milling frequency.

2.2.5. Preparation of IBU-ARG salt by slowly evaporating water

To investigate whether a crystalline IBU-ARG salt could be produced by slowly evaporating the solvent, 300 mg of IBU and a corresponding