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Research paper

Influence of variation in molar ratio on co-amorphous drug-amino acid systems

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ABSTRACT

Molecular interactions were investigated within four different co-amorphous drug-amino acid systems, namely indomethacin–tryptophan (Ind–Trp), furosemide–tryptophan (Fur–Trp), indomethacin-arginine (Ind-Arg) and furosemide-arginine (Fur-Arg). The co-amorphous systems were prepared by ball milling for 90 min at different molar ratios and analyzed by XRPD and DSC. Interactions within the co-amorphous samples were evaluated based on the deviation between the actual glass transition temperature (T_g) and the theoretical T_g calculated by the Gordon-Taylor equation. The strongest interactions were observed in the 50 mol% drug (1:1 M ratio) mixtures, with the exception of co-amorphous Ind-Arg where the interactions within the 40 mol% drug samples appear equally strong. A particularly large deviation between the theoretical and actual T_gs was observed within co-amorphous Ind-Arg and Fur-Arg systems. Further analysis of these co-amorphous systems by ^{13}C solid-state NMR (ssNMR) and FTIR confirmed that Ind and Fur formed a co-amorphous salt together with Arg. A modified approach of using the Gordon-Taylor equation was applied, using the equimolar co-amorphous mixture as one component, to describe the evolution of the T_gs with varying molar ratio between the drug and the amino acid. The actual T_gs for co-amorphous Ind-Trp, Fur-Trp and Fur-Arg were correctly described by this equation, confirming the assumption that the excess component was amorphous forming a homogeneous single component within the co-amorphous mixture without additional interactions. The modified equation described the T_gs of the co-amorphous Ind-Arg with excess Arg less well indicating possible further interactions; however, the FTIR and ssNMR data did not support the presence of additional intermolecular drug-amino acid interactions.

1. Introduction

The increase in solubility of amorphous materials compared to their respective crystalline forms provides significant potential in the development of poorly water soluble drugs. However, materials in a high energy state, such as amorphous drugs, have a tendency to convert back to the stable crystalline state as they are thermodynamically unstable. Several formulation strategies have thus been investigated in order to stabilize drugs in the amorphous form. A commonly used method for stabilizing amorphous drugs is their molecular incorporation into water soluble amorphous polymers, forming glass solutions. However, the physical stability of these systems may still be limited by several environmental factors such as humidity, heat and the limited solubility of drug molecules in commonly used pharmaceutical polymers [1]. The stability of amorphous systems is not only critical with regard to recrystallization during storage, but is often also a requirement in order to form a supersaturated solution by preventing recrystallization upon administration [2]. Currently, formulations on nanoscale have shown potential to improve the absorption of poorly-soluble drugs [3].

The molecular mobility of amorphous materials drastically increases at temperatures higher than the glass transition temperature (T_g), which represents a critical temperature for maintaining practically stable amorphous formulations. However, even below T_g, relaxation within the amorphous material occurs and crystallization is still possible. It has thus been suggested (as a rule of thumb) that storage at least 50 K below the T_g would be desirable to increase the likelihood of sufficient physical stability of the

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amorphous form to reach a shelf life of an oral dosage form of several years [4].

The antiplasticizing effect of most pharmaceutically used polymers increases the T_g of the glass solution compared to the amorphous drug alone. The T_g of binary mixtures is described by the Gordon-Taylor equation, which is based on the assumption that no interactions occur between the components of the glass solution. Negative deviation from the T_g calculated by the Gordon-Taylor equation is usually explained by residual water acting as a plasticizer and reducing the T_g [5]. In contrast, interactions between the two components such as hydrogen bonds are usually observed as positive deviations of the experimentally determined T_g from the predicted T_g [6].

In the field of solid dispersions, a recent development is the formation of co-amorphous systems (recently reviewed in [7]). The co-amorphous systems belong to the group of glass solutions, along with the more commonly known polymer-based glass solutions and both types are characterized by being single phase amorphous systems. In contrast to polymer-based glass solutions, co-amorphous formulations are based on the combination of at least two species of low molecular weight components that all are crystalline before being processed. The preparation of co-amorphous systems is mostly done by ball milling, and the fact that single Tgs are found by DSC indicates that the obtained systems were homogeneous mixtures [8–16]. One advantage of ball milling is that it is inflicting only very limited chemical degradation [17]; specifically, for some indomethacin systems degradation levels of less than 1.5% were found [13]. Recently, spray-drying has been demonstrated to be another suitable production method for the preparation of co-amorphous systems [18,19]. Co-amorphous formulations, in which a given drug is stabilized by another drug molecule, were introduced in order to reduce the amount of excipient needed and eventually to allow the simultaneous administration of several drugs in a single dosage form. Dissolution experiments revealed that the two drugs indomethacin (Ind) and naproxen (Nap) were likely to be released as pairs from the co-amorphous system, as identical dissolution profiles were observed (termed synchronized release) [8–10]. This was explained by the formation of Ind-Nap heterodimers in the co-amorphous mixtures prepared at various molar ratios [11]. For binary systems with a molar ratio different from 1:1, a modified approach of using the Gordon-Taylor equation was suggested. Here the 1:1 M ratio mixture is considered as a separate component and the excess drug as the other component, hereby including interactions in the calculations. The prediction of the experimentally determined T_gs was improved by this modified approach of using the Gordon-Taylor equation compared to the original equation [12].

Co-amorphous drug-amino acid mixtures have recently been introduced as an alternative to drug-polymer or drug-drug combinations. 1:1 M ratio mixtures (50 mol% drug) of varying co-amorphous drug-amino acid mixtures have been analyzed, resulting in practically stable amorphous systems with increased dissolution rate compared to the crystalline drugs [13]. Salt formation between the drug and the amino acid (Ind-arginine (Arg), Ind-histidine, Ind-lysine, Naproxen-Arg) resulted in a highly increased T_g of the co-amorphous system due to strong interactions. However, stable co-amorphous systems have also been reported without any detectable interactions [14,15].

The mechanism of formation of co-amorphous furosemide (Fur)-tryptophan (Trp) and co-amorphous Ind-Trp has been investigated, and in both cases the amino acid acts as an antiplasticizer, increasing the T_g of the co-amorphous system compared to the T_g of the pure amorphous drug. Furthermore, during formation of co-amorphous Fur-Trp by ball milling, the drug is dissolved in the amorphous amino acid while during formation of co-amorphous Ind-Trp the amino acid is dissolved in the amorphous drug [16].

In the current study, the properties of four co-amorphous systems (Ind-Trp, Fur-Trp, Ind-Arg, and Fur-Arg) were evaluated at different molar ratios. This was done through determination of the deviation between the experimentally determined T_g and the T_g calculated by the Gordon-Taylor equation. The co-amorphous mixtures were further compared to predictions based on the modified approach of using the Gordon-Taylor equation [12], in order to obtain a better understanding of the molecular composition within these mixtures. In addition, intermolecular interactions were analyzed by Fourier transformed infrared spectroscopy (FTIR) and ^{13}C solid-state nuclear magnetic resonance (ssNMR).

2. Materials and methods

The amino acids L-tryptophan (Trp) and L-arginine (Arg) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The drugs indomethacin (Ind) and furosemide (Fur) were acquired from Hawkins Pharmaceutical group (Minnesota, USA) and IPLA Laboratories Limited (Mumbai, India), respectively. All substances were of reagent grade and used as received.

2.1. Preparation of amorphous materials

Co-amorphous systems of Ind-Trp, Fur-Trp, Ind-Arg and Fur-Arg mixtures were prepared by ball milling a total of 500 mg powder of the crystalline starting materials for 90 min. The samples were milled in an oscillatory ball mill (Mixer mill MM400, Retch GmbH & Co., Hann, Germany) at a frequency of 30 Hz in 25 ml jars containing two stainless steel balls with a diameter of 12 mm, placed in a cold environment (6 °C). 11 different mixtures were prepared for each of the four co-amorphous combinations by varying the molar ratio between the drug and the amino acid (containing 9, 20, 25, 33, 40, 50, 60, 67, 75, 80, and 91 mol% drug). All samples were analyzed on the day of preparation.

2.2. Theoretical T_g values (Gordon-Taylor equation)

The theoretical T_g for a co-amorphous system consisting of two amorphous components can be calculated by applying the Gordon-Taylor equation [20]:

$$T_{g1,2} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2}$$

where $T_{g1,2}$ is the glass transition temperature of the co-amorphous mixture, w_1, w_2, T_{g1}, T_{g2} are the weight fractions and the glass transition temperatures for the two amorphous components and K is a constant expressed as follows:

$$K = \frac{T_{g1} \cdot \rho_{g1}}{T_{g2} \cdot \rho_{g2}}$$

where ρ_1 and ρ_2 are the densities of each of the two components. As pure arginine could not be transformed into an amorphous form via ball milling, the reported density of the crystalline substances was applied in all cases. The densities of Ind, Fur, Trp and Arg are 1.32, 1.61, 1.36 and 1.33 g cm^{-3} respectively [21–23].

2.3. X-ray powder diffraction (XRPD)

XRPD measurements were performed using an X'Pert PRO X-ray diffractometer (PANalytical, Almelo, The Netherlands) using Cu Kα radiation (λ = 1.54187 Å), an acceleration voltage of 45 kV and a current of 40 mA. Samples were scanned in reflection mode between 5° and 35° 2θ with a scan speed of 0.067° 2θ/s and a step size of 0.0262° 2θ. Data were collected and analyzed using the