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Research paper

Amino acids as co-amorphous stabilizers for poorly water soluble drugs – Part 1: Preparation, stability and dissolution enhancement

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ABSTRACT

Poor aqueous solubility of an active pharmaceutical ingredient (API) is one of the most pressing problems in pharmaceutical research and development because up to 90% of new API candidates under development are poorly water soluble. These drugs usually have a low and variable oral bioavailability, and therefore an unsatisfactory therapeutic effect. One of the most promising approaches to increase dissolution rate and solubility of these drugs is the conversion of a crystalline form of the drug into its respective amorphous form, usually by incorporation into hydrophilic polymers, forming glass solutions. However, this strategy only led to a small number of marketed products usually because of inadequate physical stability of the drug (crystallization). In this study, we investigated a fundamentally different approach to stabilize the amorphous form of drugs, namely the use of amino acids as small molecular weight excipients that form specific molecular interactions with the drug resulting in co-amorphous forms. The two poorly water soluble drugs carbamazepine and indomethacin were combined with amino acids from the binding sites of the biological receptors of these drugs. Mixtures of drug and the amino acids arginine, phenylalanine, tryptophan and tyrosine were prepared by vibrational ball milling. Solid-state characterization with X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) revealed that the various blends could be prepared as homogeneous, single phase co-amorphous formulations indicated by the appearance of an amorphous halo in the XRPD diffractograms and a single glass transition temperature (T_g) in the DSC measurements. In addition, the T_gs of the co-amorphous mixtures were significantly increased over those of the individual drugs. The drugs remained chemically stable during the milling process and the co-amorphous formulations were generally physically stable over at least 6 months at 40 °C under dry conditions. The dissolution rate of all co-amorphous drug–amino acid mixtures was significantly increased over that of the respective crystalline and amorphous pure drugs. Amino acids thus appear as promising excipients to solve challenges connected with the stability and dissolution of amorphous drugs.

1. Introduction

Today, approximately 90% of small molecular weight drug candidates under development have poor aqueous solubility [1]. This fact can be seen as one of the most pressing problems in drug research and development since most active pharmaceutical ingredients (API) are administered via the oral route, where dissolution in the gastric and intestinal fluids is one of the main prerequisites for the biological activity of any given API. Problems in finding an appropriate drug delivery system for poorly water soluble API can severely compromise the chance of the API to be further developed. Therefore, it is necessary to overcome problems associated with limited dissolution of an API in order to enable promising drug candidates to reach the patient.

One of the most promising approaches in the development of drug delivery systems to improve the efficacy of new drugs is the conversion of a crystalline drug to its respective amorphous counterpart [2]. However, the main drawback of the use of individual amorphous drugs is their physical instability during manufacturing, storage or administration with respect to their inherent tendency to recrystallize due to the fact that they are thermodynamically unstable [3]. One strategy to improve the stability of amorphous drugs is to incorporate them into amorphous polymers to create glass solutions [4], which can be described as molecular mixtures of a drug and a hydrophilic polymer. The

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increased physical stability of these amorphous systems can be explained (at least in part) by their increased glass transition temperature (T_g), compared to the T_g of the pure amorphous drug, resulting from the frequently high T_g of the polymers.

However, this approach has severe drawbacks, mainly due to the commonly high hygroscopicity of the polymers. Water, acting as a plasticizer, will strongly lower the T_g of the glass solution, soften the amorphous mixture, increase molecular mobility within the glass, and thus increase the likelihood for crystallization of the drug. Another drawback of the use of polymers in glass solutions can be limited miscibility of the drug into the polymer. Thus, often large amounts of polymer are required for sufficient drug loading and this in turn leads to large bulk volumes of the final dosage form [5].

Recently, interest towards binary amorphous drug formulations, comprising two compounds with small molecular weight, as an alternative to the use of antiplasticising polymers, has increased. In this approach, two pharmacologically suitable drug molecules were chosen and combined in order to prepare highly stable co-amorphous mixtures with improved dissolution properties [6–9]. The improved physico-chemical properties of these co-amorphous formulations could be explained by strong molecular interactions between the two compounds in the mixtures. A study with naproxen and cimetidine revealed an increased T_g of the co-amorphous binary mixture over those of the individual compounds [7]. The authors explained the finding by specific and strong interactions between the two components. Furthermore, it could be shown that the dissolution rate of a poorly water soluble drug in a co-amorphous mixture was faster than that of the individual drug (crystalline or amorphous). In addition, the dissolution rate was also dependent on the dissolution properties of the partner molecule in the mixture [7,8]. This very promising approach proved to be an alternative to glass solutions using polymers, especially when both drugs could be administered together in combination therapy. However, studies so far concentrated only on the use of two drugs–these had to be a pharmacologically relevant pair used in similar doses. Therefore, there is a need for a more generally applicable concept, such as using APIs and small molecular weight excipients that form strong interactions to stabilize the API in an amorphous form.

In this study, we have used amino acids as low molecular weight excipients and co-formers in co-amorphous drug formulations with the two poorly water soluble BCS class II drugs carbamazepine (CBZ) and indomethacin (IND). The amino acids were chosen based on the binding site of the biological receptors of the drugs, i.e. arginine (ARG) and tyrosine (TYR) from the IND binding cyclo-oxigenase 2 [10], and phenylalanine (PHE) and tryptophan (TRP) from CBZ binding neuronal Na^+ channels [11]. These amino acids naturally have strong interactions with the drug at the active site in the body. Therefore, we hypothesized that the functional groups of these amino acids might also interact with the drug in a solid-state co-amorphous mixture and are possible stabilizers for the amorphous drug in a co-amorphous blend, effectively preventing the drug from crystallization. Mixtures were prepared by vibrational ball milling of the drug with either one or two amino acids and their solid-state, stability and dissolution properties were investigated.

2. Materials and methods

2.1. Materials

Indomethacin (IND, M = 357.79 g/mol) and carbamazepine (CBZ, M = 236.27 g/mol) were purchased from Hawkins, Inc. Pharmaceutical Group (Minneapolis, USA). The amino acids L-arginine (ARG, M = 174.20 g/mol), L-phenylalanine (PHE, M = 165.19 g/mol), L-tryptophan (TRP, M = 204.23 g/mol) and L-tyrosine (TYR, M = 181.19 g/mol) were obtained from Sigma–Aldrich (St. Louis, USA). All compounds were used as received.

2.2. Methods

2.2.1. Preparation of the amorphous materials

Co-amorphous blends of drug and amino acids were prepared by vibrational ball milling (BM). The BM samples were produced by placing a total mass of 500 mg of the crystalline compounds, or the appropriate amount of drug and amino acid(s) at the molar ratios 1:1 or 1:1:1 with one or two amino acids, respectively, into 25 ml milling jars with two 12 mm stainless steel balls, and milling at 30 Hz for 90 min in an oscillatory ball mill (Mixer Mill MM400, Retch GmbH & Co., Haan, Germany), which was placed in a cold room (+6 °C).

2.2.2. X-ray powder diffraction (XRPD)

XRPD was performed using an X'Pert PANalytical X'Pert PRO X-ray Diffractometer (Almelo, The Netherlands) using Cu Kα radiation (λ = 1.54187 Å). An acceleration voltage and current of 45 kV and 40 mA were used. Samples were scanned in reflection mode between 5° and 35° 2θ with a scan speed of 0.067335° 2θ/s and a step size of 0.0262606°. Data were collected and analysed using the software X'Pert Data Collector (PANalytical B.V., Almelo, The Netherlands).

2.2.3. Differential scanning calorimetry (DSC)

DSC thermograms were obtained using a PerkinElmer Diamond DSC (PerkinElmer, Shelton, USA) under a nitrogen gas flow of 20 mL/min. Calibration of the DSC instrument was carried out using indium as a standard. Sample powders (approx. 10 mg) were analysed in 40 μl aluminium pans with pinholes. CBZ containing samples were analysed between −20 °C and 200 °C, and IND containing samples were analysed between −20 °C and 180 °C at a heating rate of 10 K/min. The glass transition temperatures (T_g, midpoint) were determined using PerkinElmer Pyris software (version 7.0.0.0110) and calculated as the mean of three independent measurements.

2.2.4. Theoretical T_g values (Gordon Taylor equation)

Since binary co-amorphous amino acid blends (ARG–PHE, ARG–TRP and PHE–TRP) could be prepared by vibrational ball milling as described under Section 2.2.1, the experimental glass transition temperatures of the ternary co-amorphous blends were compared for further interpretation with the theoretical T_g values predicted from the Gordon Taylor equation using the approach of Löbmann et al. [8]. In this approach, the ternary co-amorphous mixtures were regarded as non-interacting mixtures between the drug and the binary co-amorphous amino acid blends. Thus, the drug and the co-amorphous binary amino are inserted as individual components in the Gordon–Taylor equation which is given by the following equation:

$$T_{g12} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + K \cdot w_2} \quad (1)$$

where T_{g12} is the T_g of a ternary co-amorphous mixture, whereas T_{g1} and T_{g2} are the T_gs of the amorphous drug and the co-amorphous binary amino acid mixture, respectively. The weight fractions of each component in the mixture are represented by w_1 and w_2. K is a constant and can be further described by the following equation:

$$K = \frac{T_{g1} \cdot \rho_1}{T_{g2} \cdot \rho_2} \quad (2)$$

where ρ_1 and ρ_2 are the respective powder densities of the single amorphous components. The crystalline densities of the compounds