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Research paper

Solid state properties and drug release behavior of co-amorphous indomethacin-arginine tablets coated with Kollicoat® Protect

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ABSTRACT

A promising approach to improve the solubility of poorly water-soluble drugs and to overcome the stability issues related to the plain amorphous form of the drugs, is the formulation of drugs as co-amorphous systems. Although polymer coatings have been proven very useful with regard to tablet stability and modifying drug release, there is little known on coating co-amorphous formulations. Hence, the aim of the present study was to investigate whether polymer coating of co-amorphous formulations is possible without inducing recrystallization. Tablets containing either a physical mixture of crystalline indomethacin and arginine or co-amorphous indomethacin-arginine were coated with a water soluble polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat® Protect) and stored at 23 °C/0% RH and 23 °C/75% RH. The solid state properties of the coated tablets were analyzed by XRPD and FTIR and the drug release behavior was tested for up to 4 h in phosphate buffer pH 4.5. The results showed that the co-amorphous formulation did not recrystallize during the coating process or during storage at both storage conditions for up to three months, which confirmed the high physical stability of this co-amorphous system. Furthermore, the applied coating could partially inhibit recrystallization of indomethacin during drug release testing, as coated tablets reached a higher level of supersaturation compared to the respective uncoated formulations and showed a lower decrease of the dissolved indomethacin concentration upon precipitation. Thus, the applied coating enhanced the AUC of the dissolution curve of the co-amorphous tablets by about 30%. In conclusion, coatings might improve the bioavailability of co-amorphous formulations.

1. Introduction

Many new drug candidates are poorly water soluble and therefore can show a low bioavailability. These problems may lead to delay or even the discontinuation of the further development of these drugs. Therefore, solubility enhancement is of particular interest in pharmaceutical research [1,2]. One approach to improve the solubility of poorly water soluble drugs is the use of the amorphous form of the drug, which has a higher free energy and therefore also shows a higher solubility than its crystalline counterparts [3,4]. However, this advantage comes at the cost of stability issues, as amorphous systems in general are thermodynamically unstable and can eventually recrystallize during down-stream manufacturing of the final dosage form, storage and administration (e.g. during dissolution) [3]. One approach to overcome these problems is the use of polymer-based glass solutions, where the amorphous drug is stabilized by incorporation into a hydrophilic (amorphous) polymeric carrier. However, because of some remaining drawbacks regarding formulation, scale up and physical stability of these glass solutions, there is still a need for further alternative techniques to stabilize amorphous drugs [5]. A recent and promising approach to overcome stability issues related to amorphous drugs is the use of co-amorphous systems, in which an active pharmaceutical ingredient (API) is combined with at least one other API [6–9] or a low molecular weight excipient, for example an amino acid [10–12]. Together, they form a homogenous single-phase system, in which both components are present in the amorphous state and interact on the molecular level, enhancing their physical stability. Besides this, the use of co-amorphous systems can have a further advantage by exhibiting a better dissolution behavior than the single amorphous form [7,10,13]. However, this relatively new approach needs further research, especially with regard to the behavior of the systems during down-streaming into the final dosage form.

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Additionally, there is only little experience regarding the effect of moisture on the stability of these systems, as many of the investigated co-amorphous systems have so far only been stored at dry conditions [14]. It is a well-known problem that moisture can act as plasticizer and thereby enable the recrystallization of the amorphous system, which in turn leads to a loss of the initial solubility enhancement [15,16]. Hence, it is also necessary to investigate the stability of co-amorphous systems during storage at humid conditions and perhaps to protect these formulations against moisture. One obvious possibility to protect co-amorphous systems might be the application of pharmaceutical coatings, which are well known for their improvement of the long-term stability of formulations by protection against water, gases, such as oxygen, as well as mechanical stress [4,17,18]. Hence, in the present study it was assumed that polymer coatings might be useful for the stabilization of co-amorphous formulations.

As stated above, amorphous and also co-amorphous systems can recrystallize during dissolution, leading to a decrease of the drug dissolution profile and thereby – dependent on rate and extent of recrystallization – to a partial or complete loss of the initial solubility enhancement [19]. Previous studies have shown that polymers in solid dispersions can prevent this recrystallization process, whereby different polymers can affect this process in different ways and to a different extent [20–22]. In this context, the crystallization inhibiting effect of the polymers does not necessarily depend on their presence in the formulation [22,23] in form of a glass solution with the drug, and therefore, in the present study it was investigated whether small amounts of a polymer, applied as a coating, could improve the drug release behavior of a co-amorphous formulation in the same way. If so, this beneficial effect of polymers in combination with the advantages of the co-amorphous approach, may lead to a significant improvement of drug dissolution. However, to benefit from a potential stabilizing effect during storage and dissolution, the co-amorphous formulation first has to withstand the coating process. This process involves the use of heat, mechanical stress and solvent exposure, which all can potentially induce a recrystallization of the co-amorphous system. To our knowledge there is no experience yet in the coating of co-amorphous formulations. Therefore, it was the aim of the present study to investigate whether coating of a co-amorphous formulation is generally possible without inducing recrystallization of the drug.

Recently, Lenz et al. developed the first co-amorphous tablet formulation, containing co-amorphous spray-dried indomethacin-arginine. The formulation was stable during the tableting process and upon storage for at least ten months at 0% RH/23 °C or 0% RH/40 °C [24]. Thus, in this study this co-amorphous system, with its corresponding crystalline formulation serving as reference, were prepared and coated with an aqueous solution of Kollicoat® Protect. The coated tablets were subsequently analyzed with regards to their solid state properties and drug release behavior. Additionally, drug release of the prepared formulations was examined after storage at 23 °C/75% RH, because so far there is no data available on the stability of co-amorphous indomethacin-arginine during storage at humid conditions.

2. Materials and methods

2.1. Materials

Crystalline γ-indomethacin (γ-IND) was purchased from Fagron (Barsbüttel, Germany) and L-arginine (ARG) from Merck (Darmstadt, Germany). For spray-drying, acetone from Biesterfeld (Hamburg, Germany) and Milli-Q® water (Merck Millipore, Darmstadt, Germany) were used. Tableting excipients were β-mannitol (Caelo, Hilden, Germany), croscarmellose sodium (Fagron, Barsbüttel, Germany), fumed silica (Aerosil® 200; Evonik, Hanau, Germany) and magnesium stearate (Fagron, Barsbüttel, Germany). Kollicoat® Protect was kindly supplied by BASF (Ludwigshafen, Germany) and dissolved in distilled water prior to coating. The chemical structures of its main components are shown in Fig. 1. The dissolution medium was prepared with KH_2PO_4 from Carl Roth (Karlsruhe, Germany). For HPLC analysis acetonitrile (HPLC grade; VWR, Radnor, USA), phosphoric acid 85% (Carl Roth, Karlsruhe, Germany) and Milli-Q® water (Merck Millipore, Darmstadt, Germany) were used.

2.2. Methods

2.2.1. Spray drying

For preparation of co-amorphous indomethacin-arginine (SD IND-ARG), the spray-drying approach developed by Jensen et al. was applied [25]. Briefly, γ-IND and ARG were mixed at a 1:1 M ratio and dissolved in acetone and water (70:30 v/v) to obtain a 4% (w/v) solution. Subsequently, 500 ml of this solution were spray dried with a Mini Spray Dryer B-290, equipped with an Inert Loop B-295 (both from Büchi, Flawil, Switzerland). Process parameters were as follows: 90 °C inlet temperature, 58 °C outlet temperature, flow rate 5 ml/min and drying air flow 30 m^3/h. The solid state properties of SD IND-ARG were confirmed by XRPD and FTIR.

2.2.2. Tablet preparation

The composition of the prepared tablet formulations is shown in Table 1. The preparation of the powder blends (PB) has previously been described by Lenz et al. [24]. In the current study, the batch size was 35 g for tablets containing the co-amorphous IND-ARG (SDT) and 25 g for those containing the crystalline physical mixture of IND and ARG (PMT). The premixtures (all ingredients except for magnesium stearate) as well as the final powder blend (Table 1) were blended with a Turbula® T 2 F mixer (W.A. Bachofen, Basel, Switzerland). Subsequently, the tablets were compacted in single press mode on a rotary die tablet press (Fette 102i, Fette Compacting, Germany). Biconvex tablets with a diameter of 8 mm suitable for coating were prepared resulting in tablet weights of 172 ± 7 mg for SDT and 204 ± 4 mg for PMT with a drug load of 25% each. SDT were prepared with a compaction pressure of

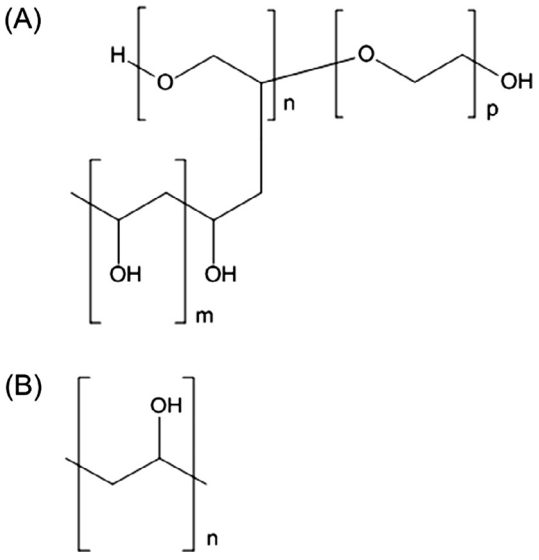

Fig. 1. Chemical structures of the main components of Kollicoat® Protect: (A) Polyvininyl alcohol-polyethylene glycol copolymer (55–65%), (B) polyvinyl alcohol (35–45%).