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Hot Melt Extrusion and Spray Drying of Co-amorphous Indomethacin-Arginine With Polymers

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ABSTRACT

Co-amorphous drug-amino acid systems have gained growing interest as an alternative to common amorphous formulations which contain polymers as stabilizers. Several preparation methods have recently been investigated, including vibrational ball milling on a laboratory scale or spray drying in a larger scale. In this study, the feasibility of hot melt extrusion for continuous manufacturing of co-amorphous drug-amino acid formulations was examined, challenging the fact that amino acids melt with degradation at high temperatures. Furthermore, the need for an addition of a polymer in this process was evaluated. After a polymer screening via the solvent evaporation method, co-amorphous indomethacin-arginine was prepared by a melting-solvent extrusion process without and with copovidone. The obtained products were characterized with respect to their solid-state properties, non-sink dissolution behavior, and stability. Results were compared to those of spray-dried formulations with the same compositions and to spray-dried indomethacin-copovidone. Overall, stable co-amorphous systems could be prepared by extrusion without or with copovidone, which exhibited comparable molecular interaction properties to the respective spray-dried products, while phase separation was detected by differential scanning calorimetry in several cases. The formulations containing indomethacin in combination with arginine and copovidone showed enhanced dissolution behavior over the formulations with only copovidone or arginine.

Introduction

Amorphous drug formulations have extensively been studied over the latest few decades because their preparation is one approach to improve the dissolution rate and solubility of poorly water-soluble drugs. Common amorphous formulations comprise polymers, which act as stabilizer by reducing the molecular mobility of the amorphous drug and therefore the tendency for nucleation and crystal growth.[1] Several techniques for the preparation of amorphous formulations have been researched, which can be classified into solvent-based methods, like spray drying, fusion-based methods, for example, melt extrusion, or mechanical activation methods, for example, cryomilling.[2] Until now, only a few marketed amorphous products are available, for example, KALETRA® or ZELBORAF®, demonstrating the problems of physical instability during shelf-life.[3]

In the past years, co-amorphous formulations have attracted attention as an alternative to amorphous formulations. Here, the drug is stabilized in its amorphous form by utilizing at least one low molecular weight compound, namely a drug[4-8] or an excipient.[9-13] They are intended to overcome drawbacks related to amorphous formulations with polymers, like low drug loading due to limited solubility of drugs in polymers, or moisture sorption because of the hygroscopic nature of polymers.[14]

The use of amino acids for co-amorphous formulations has been evaluated by Löbmann et al.[15,16] Poorly water-soluble drugs were combined with amino acids by vibrational ball milling, resulting in the amorphization of drug and amino acid. For example, co-amorphous indomethacin-arginine (IND-ARG) exhibited a high physical stability and the intrinsic dissolution rate was improved in comparison to the amorphous drug alone. Further studies focused on providing a better understanding of co-amorphous drug-amino acid formulations. For this purpose, vibrational ball milling was mainly used as preparation technique in a laboratory scale.[17-19]

Subsequently, spray drying has been investigated as first scaleup preparation method by Jensen et al.[20] in comparison to vibrational ball milling. Despite the differences in solubility of the poorly water-soluble drug and the amino acids, which are only freely soluble in water, co-amorphous IND-amino acid formulations were

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successfully prepared by utilizing an acetone/water mixture as solvent. The amino acids used in this study were all basic (ARG, histidine, and lysine) resulting in ionic interactions with the acidic drug. Spray-dried (SD) IND-ARG exhibited comparable solid-state and dissolution properties to the ball milled formulation. In contrast, the co-amorphization of IND with histidine and lysine was not possible by ball milling. This demonstrates one major drawback of ball milling as preparation method, because the principle of amorphization is based on the disruption of the crystal lattice by kinetic activation, whereas the substances are molecularly dispersed in the spray drying solution facilitating the formation of an amorphous product when the solvent is rapidly removed.[20] Another solvent-based method described for the preparation of co-amorphous IND-ARG is inkjet printing, which was performed by Wickström et al.[21] in order to allow an individualized dosing. Furthermore, co-amorphization of IND with ARG has also been found to occur via freeze drying of an aqueous solution of both components with a low yield.[22]

Hot melt extrusion (HME), one leading technology for the preparation of amorphous drug-polymer formulations, provides the opportunity to prepare co-amorphous formulations in a larger scale in a solvent-free and continuous process. So far, no attempt was made to explore the feasibility of preparing co-amorphous drug-amino acid formulations via HME. This is probably due to the fact that amino acids melt with degradation at temperatures above 200°C, which usually prevents the use of this method.

The aim of this study was to prepare co-amorphous IND-ARG by HME and to investigate the need for an addition of a polymer. For this purpose, a suitable polymer was selected based on stability and non-sink dissolution data from a small-scale screening using solvent evaporation (SE). The effect of extrusion process parameters on the resulting product was evaluated by varying the temperature profile, screw speed, and feed rate. The obtained co-amorphous IND-ARG without or with copovidone (HME IND-ARG(-COP)) was characterized with respect to its solid-state properties, its vapor sorption, and its non-sink dissolution behavior. Furthermore, the physical stability was studied after storage at 23°C and 40°C. Results were compared to those of spray dried co-amorphous IND-ARG with copovidone (SD IND-ARG-COP), SD IND-COP, and SD IND-ARG, which has been studied before.[20,23]

Materials and Methods

Materials

Micronized IND (γ-form) was purchased from Teva (Caronno Pertusella, Italy) and L-ARG from AppliChem (Darmstadt, Germany). The polymers used in the study were COP (Kollidon® VA 64), povidone (P30, Kollidon® K30), and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (SOL, Soluplus®) from BASF (Ludwigshafen, Germany), hydroxypropylcellulose (HPC, Nisso HPC SSL; Nippon Soda, Tokyo, Japan), hydroxypropylmethylcellulose (HPMC, Pharmacoat® 603; Shin-Etsu, Tokyo, Japan), hydroxypropylmethylcellulose acetate succinate (HPMCAS, Aqoat AS-LF; Shin-Etsu), and basic butylated methacrylate copolymer (EPO, Eudragit® EPO; Evonik, Darmstadt, Germany). Acetone (HPLC grade; Sigma-Aldrich, Poole, UK) and distilled water were used for preparation of amorphous formulations. Acetonitrile (HPLC grade; VWR, Fontenay-sous-Bois, France), distilled water, and phosphoric acid 85% (Carl Roth, Karlsruhe, Germany) were used for HPLC analysis. Dissolution media were prepared with KH_2PO_4 (AppliChem, Darmstadt, Germany), potassium chloride (Grüssing, Filsum, Germany), 0.1 M potassium hydroxide, and 1 M hydrochloric acid (both reagent grade).

Methods

Preparation Methods

Spray Drying. Spray drying was performed using a mini spray dryer B-290 with an inert loop B-295 and a dehumidifier B-296 (BÜCHI, Flawil, Switzerland) according to Jensen et al.[20] The solutions of IND-ARG, IND-ARG-COP, and IND-COP I (Table 1) were prepared by dissolving IND and COP in acetone and, if used, ARG in distilled water. Solutions were mixed resulting in a solid content of 40 mg/mL (SD IND-ARG), 50 mg/mL (SD IND-ARG-COP), or 75 mg/mL (SD IND-COP I). The solvent finally consisted of 70:30 (vol/vol) acetone and distilled water. The batch size was 500 or 250 mL (SD IND-ARG). The solutions were SD with a feed rate of 6 mL/min, a nitrogen air flow of 40 m^3/h, and an atomizing air flow rate of 667 L/h. The inlet temperature was 90°C resulting in an outlet temperature of 50°C. The two-fluid nozzle had a diameter of 0.7 mm (SD IND-ARG) or 1.4 mm. The products were stored at 23°C and 40°C over silica gel and SD IND-ARG additionally at 23°C/60% relative humidity (RH).

Solvent Evaporation. Four hundred milliliter solution of IND-ARG was prepared as outlined below for spray drying solution. Two grams of polymer was dissolved in 50 mL solvent consisting of 70:30 (vol/vol) acetone and distilled water or, in the case of HPMC, of pure distilled water. Eight milliliter of IND-ARG solution was mixed with 2 mL polymer solution. Amino acid-free solutions were prepared by dissolving 26.8 mg/mL IND and 26.8 mg/mL polymer in acetone, and mixing 7.29 mL or 5.38 mL IND solution with 2.71 mL or 4.62 mL polymer solution. Samples were dried at 40°C for 4 h by reducing the pressure to 200 mbar after 2 h in order to remove residual water. Films were ground using mortar and pestle, were passed through a number 315 sieve, and analyzed by X-ray powder diffraction (see below). All formulations were prepared in triplicate.

Hot Melt Extrusion. A twin-screw extruder (Pharmalab 16 HME; Thermo Fisher Scientific, Karlsruhe, Germany) with a screw diameter *D* of 16 mm and a length of 40 D (640 mm) was used with a 3.0 mm die. Powder mixtures were blended with a Turbula® T2A mixer (W.A. Bachofen, Basel, Switzerland) at 50 rpm for 20 min and were fed to the extruder barrel using a loss-in-weight powder feeder (K-CL-24-KT 20; K-Tron, Niederlenz, Switzerland) (Fig. 1). The powder batch size was 300-500 g. ARG was dissolved in demineralized water at a temperature of 70°C (23% (wt/wt), batch size 200-500 g) and was added by a peristaltic pump (Ismatec® IPC; IDEX, Wertheim, Germany) through a nozzle with an inner diameter of 2.4 mm into the extruder barrel. In order to avoid crystallization of ARG, preheated stainless steel tubes were used. A detailed description of the manufacturing process is given in Manufacturing Feasibility Study.

Products were either cooled to room temperature or collected in aluminum pans and dried for 2 h at 40°C under a reduced pressure below 50 mbar (Heraeus vacutherm; Thermo Fisher Scientific). The material was ground using mortar and pestle, passed through a number 315 sieve and stored at 23°C or 40°C over silica gel.

Table 1
Composition (%) of the Investigated Formulations Prepared With Different Methods

Variable	IND-ARG	IND-ARG-polymer	IND-polymer I	IND-polymer II
IND	67.3	53.8	72.9	53.8
ARG	32.7	26.2	–	–
Polymer	–	20.0	27.1	46.2