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Research Paper

Solid-state properties and dissolution behaviour of tablets containing co-amorphous indomethacin–arginine

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ABSTRACT

Co-amorphous drug formulations provide the possibility to stabilize a drug in its amorphous form by interactions with low molecular weight compounds, e.g. amino acids. Recent studies have shown the feasibility of spray drying as a technique to manufacture co-amorphous indomethacin–arginine in a larger production scale. In this work, a tablet formulation was developed for a co-amorphous salt, namely spray dried indomethacin–arginine (SD IND–ARG). The effects of compaction pressure on tablet properties, physical stability and dissolution profiles under non-sink conditions were examined. Dissolution profiles of tablets with SD IND–ARG (TAB SD IND–ARG) were compared to those of tablets containing a physical mixture of crystalline IND and ARG (TAB PM IND–ARG) and to the dissolution of pure spray dried powder.

Concerning tableting, the developed formulation allowed for the preparation of tablets with a broad range of compaction pressures resulting in different porosities and tensile strengths. XRPD results showed that, overall, no crystallization occurred neither during tableting nor during long-term storage. Dissolution profiles of TAB SD IND–ARG showed an immediate release of IND by erosion. The solubility of crystalline IND was exceeded by a factor of about 4, which was accompanied by a slow crystallization. For TAB PM IND–ARG, an in situ amorphization of IND in the presence of ARG was observed. As a result, a supersaturation was obtained, too, followed by a faster crystallization compared to TAB SD IND–ARG. In conclusion, the AUC_{24h} of TAB SD IND–ARG was twofold higher than the AUC_{24h} of TAB PM IND–ARG. Interestingly, different plateaus were obtained for TAB SD IND–ARG, TAB PM IND–ARG and pure SD IND–ARG after 24 h dissolution, which could be explained by the formation of different polymorphic forms of indomethacin.

1. Introduction

Formulation development of poorly water-soluble drugs is a major challenge in pharmaceutical industry. One common approach to improve the solubility and dissolution rate of these drugs is the generation and stabilization of their amorphous form. Several polymers are known to act as stabilizers by diminishing the molecular mobility of the amorphous drug and therefore inhibiting the nucleation and crystal growth. Nevertheless, only a few authorized products are available demonstrating the problems of physical instability during shelf life.

As a promising alternative to polymers, low molecular weight compounds were introduced as stabilizers for amorphous drugs. Allesø et al. [1] prepared co-amorphous formulations consisting of two low molecular weight drugs by ball milling. These formulations exhibited a high physical stability and an improved intrinsic dissolution over the single amorphous drugs. Another possibility is the use of amino acids as described by Löbmann et al. [2,3]. They investigated two poorly water-soluble drugs, carbamazepine and indomethacin, which were combined with various amino acids by ball milling, leading to the amorphization of both components, drug and amino acid. Amongst others, a high stability was obtained for co-amorphous indomethacin–arginine because of strong ionic interactions [3]. The intrinsic dissolution could also be enhanced over the amorphous drug.

Since co-amorphous formulations were, so far, mainly prepared by ball milling in a small scale, Jensen et al. [4] have investigated the feasibility of spray drying to prepare drug-amino acid formulations in a larger scale. Despite the differences in solubility of drug

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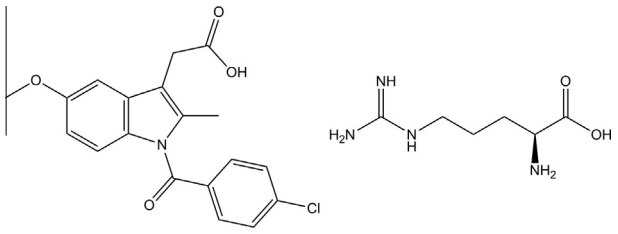

Indomethacin L-arginine

Fig. 1. Chemical structures of indomethacin and L-arginine.

and amino acid, they were successful in preparing the amorphous salt indomethacin–arginine, which exhibits comparable properties to the ball milled formulation. As spray drying makes co-amorphous indomethacin–arginine available in a larger amount, the further processing to a final drug product is of interest.

Generally, the processing of an amorphous intermediate into a final dosage form poses a crystallization risk, as external influences, such as humidity, temperature or mechanical stress, might occur. Since amorphous drugs are intended to be administered orally, formulating them into tablets is a common approach. However, during tablet manufacturing, mechanical stress is applied to the compounds resulting in a compression of the material. This might result in a crystallization of the drug and can therefore have implications on the stability and the dissolution behaviour of the amorphous drug product.

The aim of this study was to develop an appropriate tablet formulation for spray dried indomethacin–arginine (SD IND–ARG) in terms of tablet properties, physical stability and dissolution behaviour. Tablets were prepared at various compaction pressures and characterized with respect to their porosity, tensile strength and disintegration time. The uniformity of dosage units was examined. Properties of tablets containing SD IND–ARG (TAB SD IND–ARG) were compared to those of tablets containing a physical mixture of crystalline IND and ARG (TAB PM IND–ARG). The effect of compression on the physical stability of the co-amorphous form was evaluated directly after tableting and after storage for 10 months. Non-sink dissolution was performed for TAB SD IND–ARG and compared to the dissolution of TAB PM IND–ARG and pure SD IND–ARG. In order to examine an effect of ARG on the solubility, dissolution was also compared to tablets containing crystalline IND without ARG (TAB IND).

2. Materials and methods

2.1. Materials

Micronized indomethacin (IND, γ form) was purchased from Teva (Caronno Pertusella, Italy) and L-arginine (ARG) from Fagron (Barsbüttel, Germany). The chemical structures are given in Fig. 1. For tableting, β-mannitol (Parteck® M200, Merck, Darmstadt, Germany), croscarmellose sodium (Ac-Di-Sol® SD-711, FMC BioPolymer, Brussels, Belgium), colloidal silicon dioxide (Aerosil® 200, Evonik, Hanau, Germany) and magnesium stearate (Parteck® LUB MST, Merck, Darmstadt, Germany) were used. Acetone (HPLC grade, Sigma–Aldrich, Poole, UK) and Milli-Q® water (Merck Millipore, Darmstadt, Germany) were used for spray drying and ethanol (reagent grade) for the preparation of αIND. Acetonitrile (HPLC grade, VWR, Fontenay-sous-Bois, France), distilled water and phosphoric acid 85% (Carl Roth, Karlsruhe, Germany) were used for HPLC analysis. Dissolution medium was prepared with KH_2PO_4 (AppliChem, Darmstadt, Germany) and 0.1 N potassium hydroxide solution (reagent grade).

2.2. Methods

2.2.1. Preparation methods

2.2.1.1. Spray drying of indomethacin–arginine. SD IND–ARG was prepared in a 1:1 molar ratio (1:0.49 weight ratio) by spray drying from a 4% w/v solution in acetone/water (70:30 v/v) using a mini spray dryer B-290 (Büchi, Flawil, Switzerland). The outlet temperature was 50 °C at a flow rate of 6 mL/min. The detailed approach is described by Jensen et al. [4]. The product was stored at 23 °C in Duma® Twist-Off containers with an integrated desiccant (PE-HD, IB35015, Gerresheimer, Düsseldorf, Germany).

2.2.1.2. Tablet preparation. The composition of tablet formulations is listed in Table 1. For TAB SD IND–ARG, a premixture was prepared with SD IND–ARG and 2.6% colloidal silicon dioxide (1% of the final tablet weight) by passing the material through a number 1000 sieve. The corresponding amount of this premixture was blended with mannitol and croscarmellose sodium utilizing a Turbula® T2A mixer (W.A. Bachofen, Basel, Switzerland) at 50 rpm for 20 min. Magnesium stearate was added and the final tableting mixture was blended for 2 min under the same conditions. Tableting mixtures with crystalline IND were prepared accordingly, but with the premixture containing pure indomethacin and colloidal silicon dioxide. For tablets containing PM IND–ARG, ARG was milled using mortar and pestle before use. The batch size was 25 g in each case.

Flat faced tablets with a diameter of 8 mm were prepared using a rotary die press (Pressima MX Eu-B/D, IMA Kilian, Cologne, Germany) with 10 rpm at 21 °C and 45% RH. The die was filled manually resulting in tablet weights of 200 ± 2 mg and a drug load of 50 mg IND per tablet. The compaction pressures were monitored by strain gauges at the upper and the lower punch. Data of the upper punch were analysed with MS3200 software (version 2.02, IMA Kilian, Cologne, Germany). Tablets were stored at 23 °C or 40 °C in a desiccator over silica gel.

2.2.2. Tablet characterization

Tablet porosity was calculated based on the helium pycnometric density (AccuPyc 1330 V2.04N, Micromeritics, Norcross, USA), the tablet volume and the tablet mass. The correct tablet volume was verified by measuring tablet height and diameter with a caliper. The tensile strength was calculated according to Fell and Newton [5] after determining the mechanical strength of tablets with a diametral strength tester (2.3 mm/s, TBH 210, Erweka, Heusenstamm, Germany). Porosity and tensile strength were determined for ten tablets. The disintegration time was determined with an automated apparatus (DT2, Sotax, Allschwil, Switzerland) according to the European Pharmacopoeia 8.2 [6] using discs ($n = 6$). For the investigation of the uniformity of dosage units [7], 100 mg of tableting mixture was dissolved in 500 mL demineralized water and the drug content was determined by HPLC analysis ($n = 10$). The tableting mixture was investigated instead of tablets because no demixing was expected during the tableting process by filling the material for each tablet manually into the die.

Table 1
Composition of tablet formulations (%).

	TAB SD IND–ARG	TAB PM IND–ARG	TAB IND
SD IND–ARG	37.2	–	–
IND (crystalline)	–	25.0	25.0
ARG (crystalline)	–	12.2	–
Mannitol	55.8	55.8	68.0
Croscarmellose sodium	5.0	5.0	5.0
Colloidal silicon dioxide	1.0	1.0	1.0
Magnesium stearate	1.0	1.0	1.0