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Research paper

Preparation and recrystallization behavior of spray-dried co-amorphous naproxen–indomethacin

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ABSTRACT

To improve the dissolution properties and the physical stability of amorphous active pharmaceutical ingredients, small molecule stabilizing agents may be added to prepare co-amorphous systems. The objective of the study was to investigate if spray-drying allows the preparation of co-amorphous drug–drug systems such as naproxen–indomethacin and to examine the influence of the process conditions on the resulting initial sample crystallinity and the recrystallization behavior of the drug(s). For this purpose, the process parameters inlet temperature and pump feed rate were varied according to a 2^2 factorial design and the obtained samples were analyzed with X-ray powder diffractometry and Fourier-transformed infrared spectroscopy. Evaluation of the data revealed that the preparation of fully amorphous samples could be achieved depending on the process conditions. The resulting recrystallization behavior of the samples, such as the total recrystallization rate, the individual recrystallization rates of naproxen and indomethacin as well as the polymorphic form of indomethacin that was formed were influenced by these process conditions. For initially amorphous samples, it was found that naproxen and indomethacin recrystallized almost simultaneously, which supports the theory of formation of drug–drug heterodimers in the co-amorphous phase.

1. Introduction

The limited water solubility of new drug candidates presents a major problem during pharmaceutical development as these drugs are unlikely to result in sufficient absorption and thus bioavailability after application via the oral route [1,2]. For an active pharmaceutical ingredient (API) to become orally bioavailable, it has to dissolve in the digestive media before the drug molecules can pass the intestinal membrane and appear in the blood stream to reach the therapeutic level. Especially for drugs belonging to class II of the biopharmaceutics classification system [3,4] an increase in the water solubility can have a considerable impact on oral bioavailability as in this class the solubility and possibly the dissolution rate present the rate limiting step for drug absorption.

In order to increase the solubility of an API without modifying its chemical structure, the integrity of the respective crystal lattice may be reduced by either mechanical activation, melting or fast precipitation from a solution to form an amorphous phase [5]. However, the physical stability of single component amorphous phases is limited [6] and this may lead to recrystallization during pharmaceutical processing steps [7]. Therefore amorphous APIs are often processed together with a stabilizing agent [8]. Typically, the API is homogenously mixed with a hydrophilic, pharmaceutical polymer to form a glass solution, in which the respective compounds form a blend on the molecular level [9,10]. However, this approach has its drawbacks because of the hygroscopicity of the polymers [11], the often limited miscibility of both compounds [8] or due to manufacturing and processing problems [12–14].

As an alternative, co-amorphous systems may be prepared, which utilize a second small molecule instead of a polymer as the stabilizing agent [6]. Distinct molecular interactions at an equimolar ratio of the involved compounds have been shown to be important for the increased physical stability of co-amorphous systems [15]. Systems comprising two pharmacologically suitable APIs [16], two excipients [17] as well as API plus excipient [18,19] are already described in the literature. If two pharmacologically matching APIs such as naproxen and indomethacin or

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ranitidine and indomethacin are combined, no excipient is necessary to stabilize the amorphous phase [16,20–22]. But even if therapeutically inactive amino acids such as arginine or phenylalanine are used as excipients to stabilize for example amorphous indomethacin, the drug load in the amorphous phase can still reach up to 70% [18], because of the low molecular weight of the amino acids. Furthermore, an additional increase in not only the solubility but also the dissolution rate may be expected with APIs that form a co-amorphous formulation [21].

Despite the promising potential of co-amorphous systems, only few reports exist on the manufacturability of co-amorphous systems by common industrial pharmaceutical processes. Most of the co-amorphous systems already described in the literature were prepared by ball-milling [6], but the mechanical activation approach is assumed to be a process which may lead to an incomplete disruption of the molecular order of a crystalline compound, leaving crystalline or high energy sites behind. These may induce recrystallization during further processing [23,5]. Due to the usually rather high melting temperature of crystalline solids, degradation of compounds may occur during melt-quenching, and therefore this option to prepare amorphous solids appears unsuitable in many cases [22,18]. As a third option, fast precipitation from the solution for example by spray-drying can be used to transform two crystalline compounds into a co-amorphous form, in case a suitable solvent can be found [15]. Spray drying provides the opportunity to vary the thermal stress that is applied to the product during the process by regulation of the respective process parameters [24] and also offers the possibility for a scaled up preparation of co-amorphous systems [25] and the subsequent formulation into oral solid dosage forms [26]. Therefore, in the present study, equimolar co-amorphous naproxen–indomethacin [21] was chosen as a model system to investigate the manufacturability of a drug–drug co-amorphous system by spray-drying. Furthermore, the influence of the process parameters inlet temperature and pump feed rate on the initial sample crystallinity, the recrystallization behavior and the individual recrystallization rates of both drugs were investigated by evaluation of the corresponding XRPD and FTIR data.

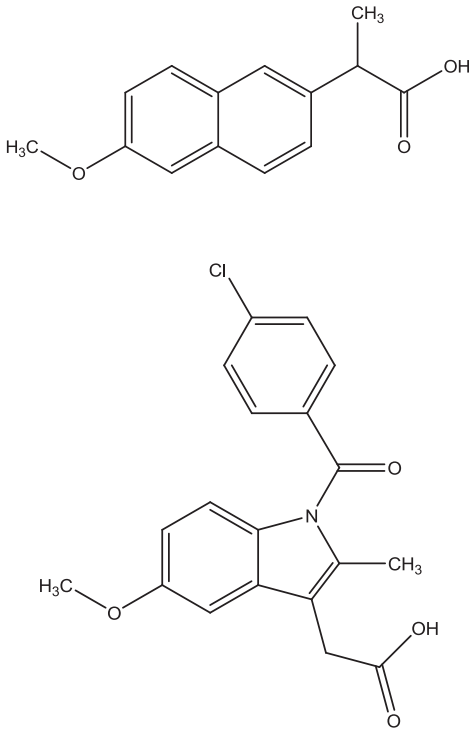

Fig. 1. Structural formula of naproxen (top) and indomethacin (bottom).

2. Materials and methods

2.1. Materials

Crystalline naproxen (cNAP, M = 230.26 g/mol) and crystalline γ-indomethacin (γ-IND, M = 357.79 g/mol) were purchased from Fagron (Barsbüttel, Germany) and used as received (Fig. 1). As reference sample (REF), equimolar co-amorphous naproxen–indomethacin was prepared by quench-cooling the melt of the equimolar physical mixture of crystalline naproxen and γ-indomethacin using liquid nitrogen [21]. Acetone (99.8%) was purchased from VWR (Radnor, USA).

2.2. Methods

2.2.1. Spray-drying

Spray-drying was performed with a Mini Spray Dryer B-290, equipped with the Inert Loop B-295, a high performance cyclone (all three from Büchi, Flawil, Switzerland) and an external Ismatec Reglo Analog peristaltic pump (IDEX Health and Science, Glattbrugg, Germany). Nitrogen was used as atomizing gas [24]. For each spray-drying run, 5 g powder consisting of cNAP and γ-IND at an equimolar ratio was dissolved in 50 ml of acetone. During all runs, the parameters atomizing gas feed and aspirator rate were kept constant at their maximum levels of 100%, respectively. The pump feed rate (PFR) and inlet temperature were varied both according to a 2^2 full factorial design including a center point, resulting in five combinations of process conditions. Three spray-drying runs were performed separately at each of these five process conditions (Table 1).

2.2.2. Storage of the powder samples

The obtained product was gently mixed with mortar and pestle and subsequently stored for up to 28 d in a desiccator in open sample tubes under dry conditions over phosphorous pentoxide and 21 °C in an air conditioned room. XRPD and FTIR analysis were performed after 0, 7, 14 and 28 d of storage to investigate the recrystallization behavior of the samples.

2.2.3. Thermogravimetric analysis (TGA)

To determine the residual acetone content in the samples, TGA was performed under isothermal conditions for 2 h at 100 °C with approximately 50 mg of each of the 15 freshly prepared samples using a Pyris 1 TGA (Perkin Elmer, Waltham, USA).

Table 1
Overview of the spray-drying process conditions.

Sample name	150/0.3	150/3.0	100/1.5	50/0.3	50/3.0
Inlet temperature (°C)	150	150	100	50	50
Pump feed rate (ml/min)	0.3	3.0	1.5	0.3	3.0
Mean outlet temperature (°C)	71.5 ± 1.5	68.0 ± 3.8	48.0 ± 7.8	33.5 ± 3.3	30.8 ± 0.3
Process duration (min)	150	15	30	150	15