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Research paper

Influence of the cooling rate and the blend ratio on the physical stability of co-amorphous naproxen/indomethacin

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ABSTRACT

Co-amorphization represents a promising approach to increase the physical stability and dissolution rate of amorphous active pharmaceutical ingredients (APIs) as an alternative to polymer glass solutions. For amorphous and co-amorphous systems, it is reported that the preparation method and the blend ratio play major roles with regard to the resulting physical stability. Therefore, in the present study, co-amorphous naproxen-indomethacin (NAP/IND) was prepared by melt-quenching at three different cooling rates and at ten different NAP/IND blend ratios. The samples were analyzed using XRPD and FTIR, both directly after preparation and during storage to investigate their physical stabilities. All cooling methods led to fully amorphous samples, but with significantly different physical stabilities. Samples prepared by fast cooling had a higher degree of crystallinity after 300 d of storage than samples prepared by intermediate cooling and slow cooling. Intermediate cooling was subsequently used to prepare co-amorphous NAP/IND at different blend ratios. In a previous study, it was postulated that the equimolar (0.5:0.5) co-amorphous blend of NAP/IND is most stable. However, in the present study the physically most stable blend was found for a NAP/IND ratio of 0.6:0.4, which also represents the eutectic composition of the crystalline NAP/γ-IND system. This indicates that the eutectic point may be of major importance for the stability of binary co-amorphous systems. Slight deviations from the optimal naproxen molar fraction led to significant recrystallization during storage. Either naproxen or γ-indomethacin recrystallized until a naproxen molar fraction of about 0.6 in the residual co-amorphous phase was reached again. In conclusion, the physical stability of co-amorphous NAP/IND may be significantly improved, if suitable preparation conditions and the optimal phase composition are chosen.

1. Introduction

The majority of active pharmaceutical ingredients (APIs) is administered as solid dosage forms and reaches the blood stream by the oral route. This concept is convenient and cost effective, but has its limitations, as the API has to dissolve in the aqueous digestive media and to diffuse through the intestinal membrane [1]. Therefore, sufficient water solubility and membrane permeability are mandatory for APIs to become orally bioavailable. However, many of the new potential drug candidates are poorly water-soluble while they are acceptably permeable and therefore belong to class II of the Biopharmaceutics Classification System [2,3]. For these drugs, an increase of the solubility and thus the dissolution rate is required to improve their oral bioavailability [4,5].

Amorphous solids can be prepared by destruction of the integrity of the crystal lattice of a crystalline API by solution, melt or mechanical activation approaches [6]. As no long range order exists in amorphous solids, a lower energy barrier has to be overcome to dissolve the molecules. However, because of the higher internal energy of solids in the amorphous form compared to their respective crystalline counterparts, amorphous systems are physically unstable and tend to recrystallize during storage [7,8]. Furthermore, amorphous phases are sensitive to mechanical stress [9],

Abbreviations: cNAP, crystalline naproxen; DSC, differential scanning calorimetry; F_{am}, amorphous fraction; FC, fast cooling; FTIR, Fourier-transformed infrared spectroscopy; I_{Bragg}, intensity under the Bragg peaks; IC, intermediate cooling; I_{Halo}, intensity under the halo baseline; IND, indomethacin; NMF, naproxen molar fraction; NAP, naproxen; NAP/IND, naproxen-indomethacin; P_2O_5, phosphorous pentoxide; PC, principal component; PCA, principal component analysis; RIR, relative intensity ratio; SC, slow cooling; XRPD, X-ray powder diffractometry.

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thermal stress [10] as well as solvents [11], i.e. aspects which are important with regard to their manufacturability and processability. To improve the physical stability of amorphous phases, stabilizing agents such as pharmaceutical polymers are often used to prepare solid polymer solutions [1,12,13]. However, this approach is often accompanied by problems regarding the manufacturability [8,14,15], the hygroscopicity [16] of many polymers and the often limited miscibility of the APIs with polymers [1].

As an alternative to pharmaceutical polymers, low molecular weight molecules may be added as stabilizers to form co-amorphous systems, in which the involved molecules are mixed on a molecular level to form one single co-amorphous phase [17]. Co-amorphous systems comprising two excipients [18], two suitable APIs [19] or API plus excipient [20,21] have already been described in the literature. In these systems, molecular interactions [22,23] between the involved components play a major role. In co-amorphous naproxen/cimetidine and ranitidine-HCl/indomethacin, 1:1 interactions between the two compounds were observed [19,24]. Similarly, with co-amorphous naproxen/indomethacin (NAP/IND) the formation of heterodimers has been shown [25,22]. The "1:1 theory" is supported by previous studies reporting the highest physical stability for the respective equimolar co-amorphous systems [19,24,25]. The physical stability of the non-equimolar co-amorphous 1:2 and 2:1 blends was observed to be decreased and it was found that the respective excess components recrystallized first [19,24,25]. Therefore, specific interactions between the involved compounds in the co-amorphous phase have been suggested to be of major importance for the physical stability and recrystallization behavior of these systems [19,24,25,20]. In the present study, co-amorphous NAP/IND was chosen as a model system to examine its recrystallization behavior as a function of the molar ratio of NAP and IND in the co-amorphous phase in more detail to further evaluate the "1:1 theory" for co-amorphous binary systems.

For single-amorphous systems it was reported that the physical stability is dependent on the cooling rate during melt-quenching and that a faster cooling procedure results in more stable samples [10]. Therefore, the influence of the cooling rate during preparation of co-amorphous NAP/IND [25] by melt-quenching on the resulting physical stability of the system was also investigated. To quantify the molar fractions of naproxen and γ-indomethacin that recrystallized during storage, the respective X-ray powder diffractograms were evaluated with the relative intensity ratio method.

2. Materials and methods

2.1. Materials

Crystalline naproxen (cNAP, Mr = 230.26 g/mol, T_m = 158 °C) and γ-indomethacin (γ-IND, Mr = 357.79 g/mol; T_m = 162 °C) were purchased from Fagron (Barsbüttel, Germany) and used as received.

2.1.1. Preparation of equimolar co-amorphous naproxen-indomethacin with different cooling rates

An amount of 1 g of equimolar co-amorphous naproxen/indomethacin (NAP/IND) was prepared in triplicate by melting the equimolar physical mixture of cNAP and γ-IND at 170 °C for 10 min and applying three different cooling methods: **Fast cooling (FC)**: Liquid nitrogen (N_2) was poured onto the melts, which were subsequently transferred into a P_2O_5 desiccator. After the N_2 was fully evaporated while displacing the present air through a hole to avoid moisture sorption, the hole was closed until the samples reached room temperature again. **Intermediate cooling (IC)**: Within a P_2O_5 desiccator, the melts cooled down to room temperature. **Slow cooling (SC)**: The samples were covered with aluminum foil, transferred into a HAAKE C25P thermostat (Thermo Fisher, Waltham, USA) and cooled down to room temperature within 180 min.

2.1.2. Preparation of co-amorphous naproxen/indomethacin at different molar ratios

1 g of each of the respective physical mixtures was molten at 170 °C for 10 min and subsequently cooled down to room temperature inside a desiccator above P_2O_5 using the IC approach as described above. Ten different NAP/IND blends with the following naproxen molar fractions (NMFs) were prepared in triplicate: 0.1, 0.2, 0.3, 0.4, 0.5, 0.55, 0.6, 0.7, 0.8, 0.9.

2.1.3. Sample processing and storage

The differently prepared samples were homogenized, particle size-reduced and sieved (250 μm) in an air conditioned room at 6 °C by mortar and pestle before they were stored in open sample tubes within desiccators (21 °C, P_2O_5). The differently cooled samples were stored for up to 300 days while sampling was performed after 0, 56, 112 and 300 days. The samples at different naproxen molar fractions were stored for up to 112 days and analyzed after 0, 56 and 112 days.

2.2. Methods

2.2.1. X-ray powder diffractometry (XRPD)

An X'Pert PRO X-ray diffractometer (PANalytical, Almelo, The Netherlands; Cu Kα anode; λ = 1.5406 Å; 45 kV; 40 mA) was used to record X-ray powder diffractograms between 5 and 35° 2θ with a scan speed of 0.045° 2θ/min and a step size of 0.0131° 2θ. The obtained diffractograms were separately baseline offset-corrected and normalized to unit area [26] using The Unscrambler X software (ver. 10.3, CAMO Software, Oslo, Norway). Savitzky-Golay smoothing was performed using The Unscrambler X software (polynomial order: 1; 9 smoothing points) for better visualization.

2.2.2. Relative intensity ratio (RIR)

In order to quantify the total amorphous fraction (F_{am}) of the prepared samples directly after preparation and during storage, the relative intensity ratio (RIR) method was used to evaluate the XRPD data [27]. Briefly, the background determination function of the Highscore Plus software (ver. 2.2, PANalytical, Almelo, The Netherlands) was used to quantify the halo intensities (I_{Halo}), resulting from the amorphous portion of the samples and the Bragg peak intensities (I_{Bragg}), which emerge from the crystalline portion of the samples in each diffractogram. Subsequently, Eq. (1) was used to calculate the relative intensity ratio of the halo (RIR_{Halo}):

$$RIR_{Halo} = \frac{I_{Halo}}{(I_{Halo} + I_{Bragg})} \quad (1)$$

Based on the resulting values for RIR_{Halo} and the calibration function in Eq. (2), which was set up in a former study [28], the total amorphous fraction of each sample was calculated:

$$F_{am} = 150 \times RIR_{Halo} - 35.6 \quad (2)$$

2.2.3. Fourier transformed infrared (FTIR) spectroscopy

A Tensor 37 spectrometer (Bruker Optik GmbH, Ettlingen, Germany) equipped with a MIRacle attenuated total reflectance device with diamond crystal plate (Piketech, Madison, USA) and the Opus software ver. 7 was used to record infrared spectra over a range of 4000–400 cm^{-1} (128 scans, resolution 4 cm^{-1}). The spectral region between 1600 and 1800 cm^{-1} was selected [25] for further analysis, after baseline offset-correction as well