Development and Characterization of a Regorafenib Amorphous Solid Dispersion

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Introduction

Today, about 70 % of new active pharmaceutical ingredients (APIs) show the properties of poor solubility and subsequently poor bioavailability[1]. One concept to overcome these issues is embedding the amorphous API into water-soluble polymers forming an amorphous solid dispersion (ASD), leading to a quick dissolution followed by a supersaturated state, the so-called spring and parachute approach[1].

In this study, the BCS II drug regorafenib monohydrate (RGF), which is indicated for the treatment of colon carcinoma, has been prepared as an ASD formulation by solvent evaporation. The ASD will be characterized concerning the morphological properties as well as with a dissolution experiment.

Materials and Methods

Materials and preparation of ASD and physical mixture (PM)

The matrix former povidone (PVP, Kollidon 30, BASF, Germany) and the API Regorafenib monohydrate (RGF, Bayer, Germany) were dissolved in a ratio of 80:20 w/w in acetone/ethanol, which were rapidly evaporated, followed by manual grinding and sieving. After drying the ASD was stored under light protection. The preparation of physical mixtures (PMs) was similar to ASD production, unless the missing dissolving and evaporation procedure.

Differential scanning calorimetry (DSC)

A DSC 821^e (Mettler-Toledo, Germany) was used with a heating and cooling rate of 10 K/min and a temperature range from 0 to 250 °C. Each analysis was performed in duplicate. For each sample two heating circles were performed.

X-ray powder diffraction (XRPD)

X-ray patterns of the ASD and PMs were recorded using an X'PertPRO system (PANalytical, Netherlands) with Cu Kα radiation (30 kV and 30 mA) in reflection mode from 10° to 50° using a step size of 0.017° with a scan speed of 60 s/step.

Polarized light microscopy (PLM)

PLM images were obtained using a Q500/550 microscope setup (Leica, Germany).

Dissolution studies

A therapeutic single dose of 200 mg of ASD were dissolved in distilled water under stirring (75 rpm) at 31 °C. Samples were taken manually through a 0.2 µm polypropylene syringe filter and diluted subsequently for HPLC analysis.

Results and Discussion

The solvent evaporation technique was successfully used to produce an ASD of RGF. The prepared ASD powder is completely amorphous in all characterization experiments by PLM, XRPD and DSC.

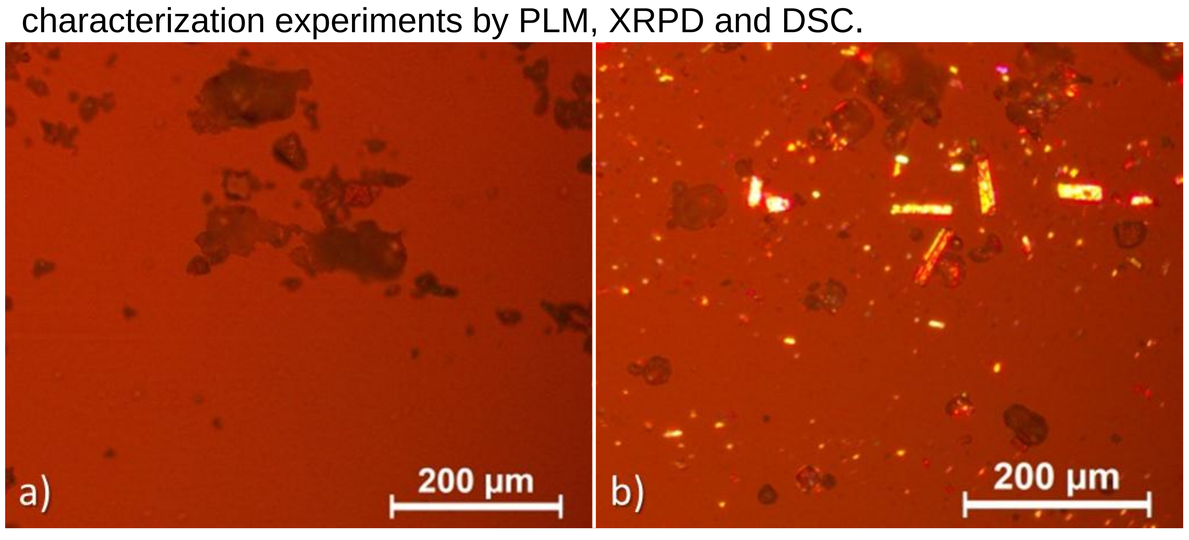

Figure 1. Polarized light microscopy images of the amorphous solid dispersion (a) and its corresponding physical mixture (b).

Figure 1 shows differences in the morphological structure between the ASD and its corresponding PM. Bright spots demonstrate birefringence that occurs at crystalline structures in the PM only.

These results can be confirmed by XRPD. The prepared ASD, its related PM and pure RGF are shown in Figure 2. Clear signals could be obtained for both, RGF and the PM, whereas the amorphous halo of the ASD sample suggests a crystallinity level of < 5%. Interestingly, the relative intensity of the RGF signals changes in the PM compared to pure RGF.

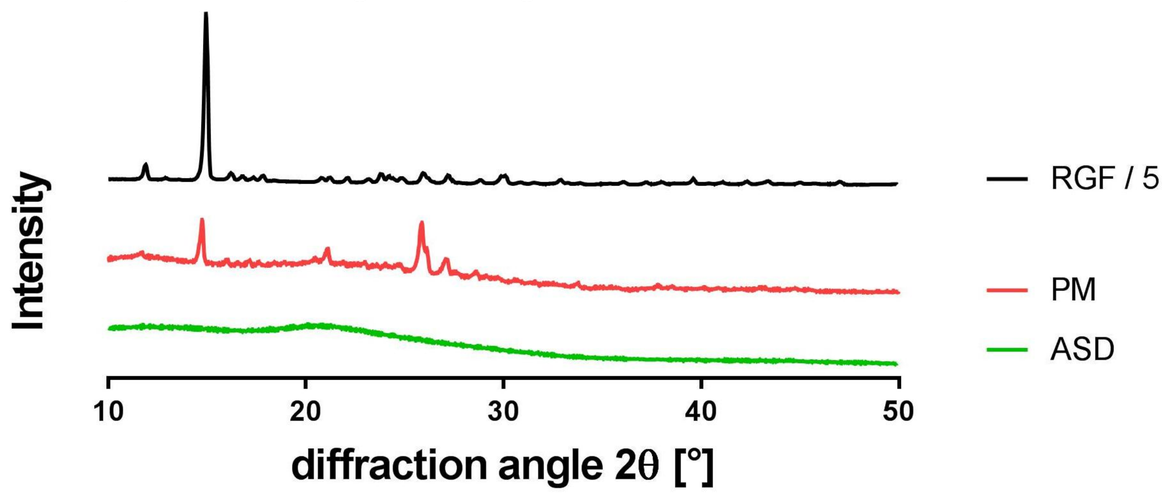

Figure 2. XRPD measurements show an amorphous signal for the amorphous solid dispersion in contrast to its physical mixture and pure regorafenib). The RGF signal was divided by 5 for illustration reasons.

Also the performed DSC experiments confirm the amorphous state of the ASD. Regorafenib exhibits sharp phase transitions, while the ASD shows a glass transition at 136 °C. Each second run of pure regorafenib shows amorphous behavior, indicating no recrystallization during the cooling step.

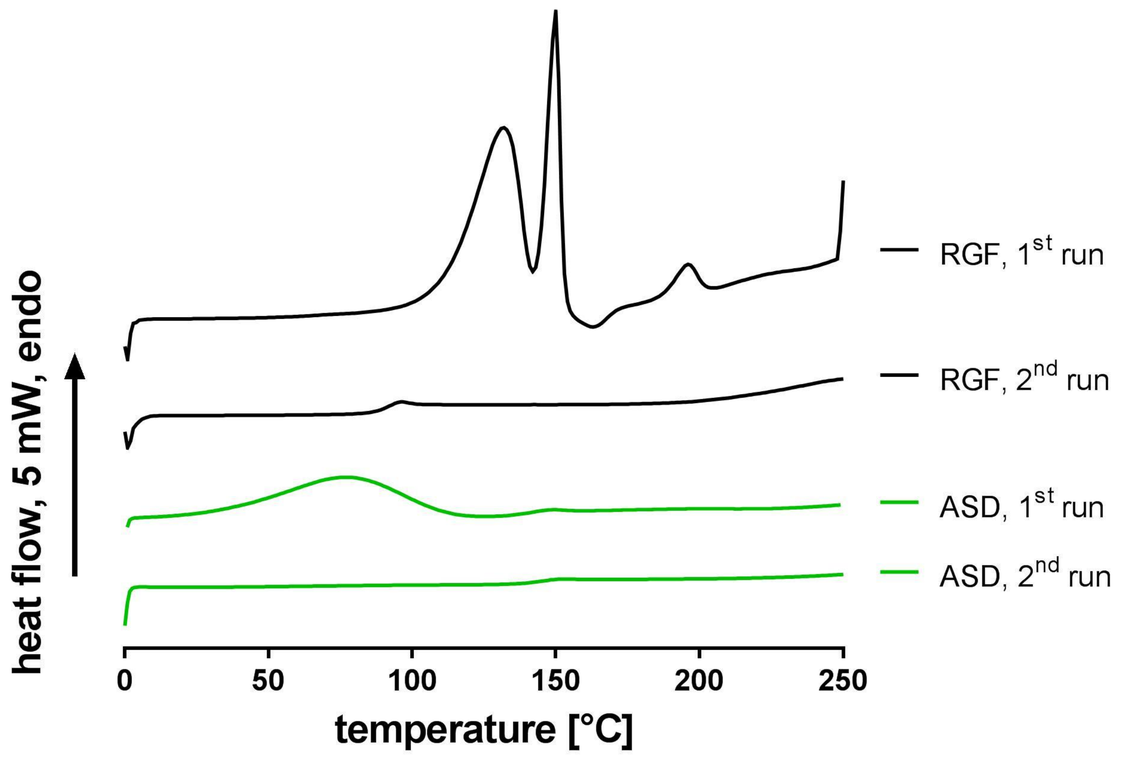

Figure 3. DSC analysis of the ASD (in green) and pure RGF (in black). For each sample two heating circles were performed.

Dissolution studies show high deviations, indicating an inconsistent dissolution behavior of the prepared RGF ASD in distilled water. Also, the experiment temperature seems to play an important role, since the expected spring and parachute profile could not be detected in a n=6 dissolution experiment as described above. Further, the use of different syringe filters with maximum pore sizes of 0.45 µm and 0.2 µm leads to distinguishable dissolution profiles, indicating an *in vitro* generation of nanostructures. In further dissolution studies biorelevant media will be used, as the presence of bile salts could lead to a significantly higher solubility of RGF[2] and subsequently more consistent results.

CONCLUSION

Production of regorafenib/povidone amorphous solid dispersion was successfully performed and the amorphous properties were confirmed by XRPD, PLM and DSC measurements. Dissolution studies in distilled water show inconsistent results at 31 °C. In further studies the dissolution and precipitation behavior of regorafenib using biorelevant media will be evaluated.

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