Dissolution Behavior of Regorafenib Amorphous Solid Dispersion Under Biorelevant Conditions

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Introduction

Today, about 70 % of new active pharmaceutical ingredients (APIs) show 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[1,2]. In this study, the BCS II drug regorafenib monohydrate (RGF) has been prepared as an ASD by solvent evaporation. Biorelevant dissolution properties of different formulations and the resulting precipitates will be investigated.

Materials and Methods

Materials and preparation of ASD

Via rotary evaporation, ASDs of 20 % m/m API regorafenib monohydrate (RGF, Bayer) with povidone K25 (PVP, BASF) or hydroxypropyl methylcellulose acetate succinate 716G (HPMCAS, Dow Chemical) were prepared, named RGF_PVP and RGF_HPMCAS, respectively.

Differential scanning calorimetry (DSC)

Using a DSC 1, after a first heating step at 60 °C for 60 min, the samples were heated up, in duplicate, to 220 °C with a rate of 5 K/min.

Biorelevant dissolution studies

All studies were performed in USP dissolution vessels at 37 ± 0.5 °C under stirring at 75 rpm. Biorelevant fasted state simulated gastric fluid (FaSSGF) and fasted state simulated intestinal fluid (FaSSIF) were used. For one-compartment dissolution studies, 200 mg ASD were dissolved in 750 mL FaSSIF. For two-compartment dissolution experiments, 200 mg ASD were dissolved in 250 mL FaSSGF for 30 min. Subsequently, 500 mL concentrated FaSSIF media were added to level bile salt concentration and pH to FaSSIF conditions (see Figure 1). All samples were filtered through a 0.2 µm polypropylene syringe filter and diluted for HPLC analysis.

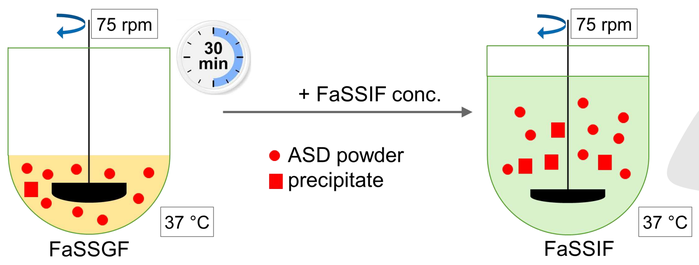

Figure 1. Scheme of two-compartment dissolution studies.

Results and Discussion

Both formulations, RGF_PVP and RGF_HPMCAS, formed an ASD. The produced ASDs did not show the characteristic RGF melting events in DSC, indicating the amorphous nature of both formulations (see Figure 2).

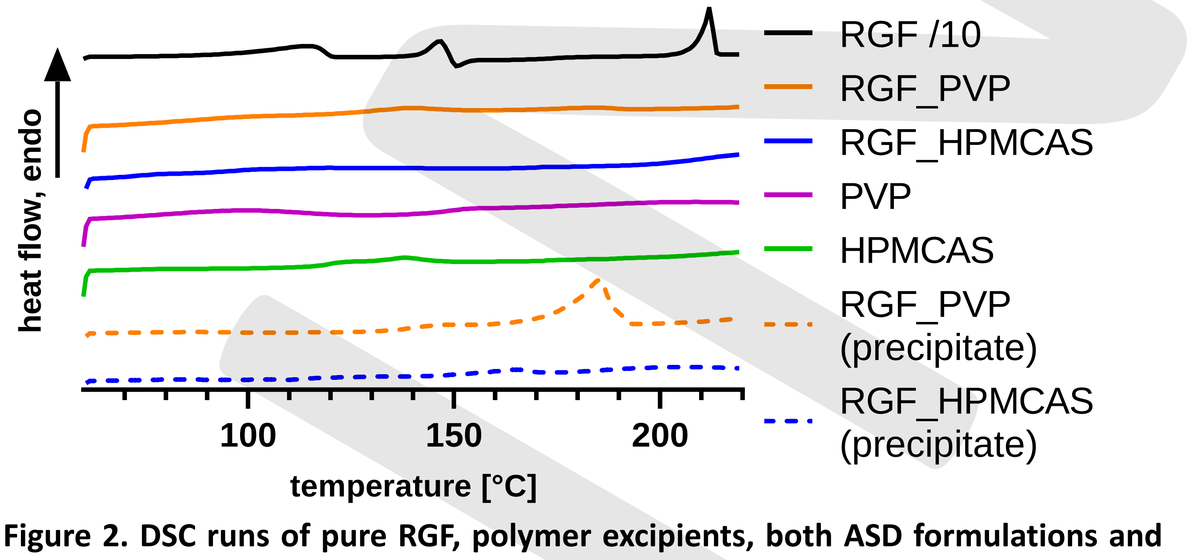

Figure 2. DSC runs of pure RGF, polymer excipients, both ASD formulations and the occurring precipitates. RGF signal was divided by 10 for illustration reasons.

While RGF from RGF_PVP showed a faster dissolution (see Figure 3), the supersaturation was less stable, compared to RGF HPMCAS.

one-compartment dissolution in FaSSIF

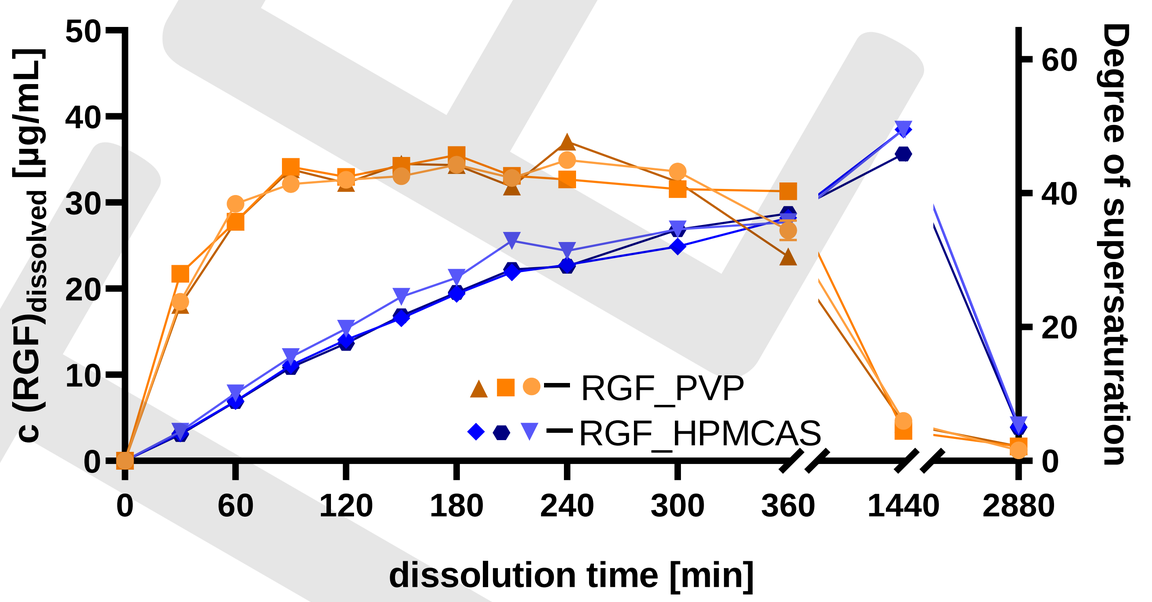

Figure 3. One-compartment dissolution in FaSSIF of the ASDs. Single curves are shown.

The results from two-compartment dissolution studies are shown in Figure 4. In the first 30 min, no RGF was detectable in FaSSGF for both formulations. After addition of FaSSIF media, RGF_PVP rapidly dissolved to the same concentration like in the one-compartment dissolution study, followed by continuous decrease in API concentration.

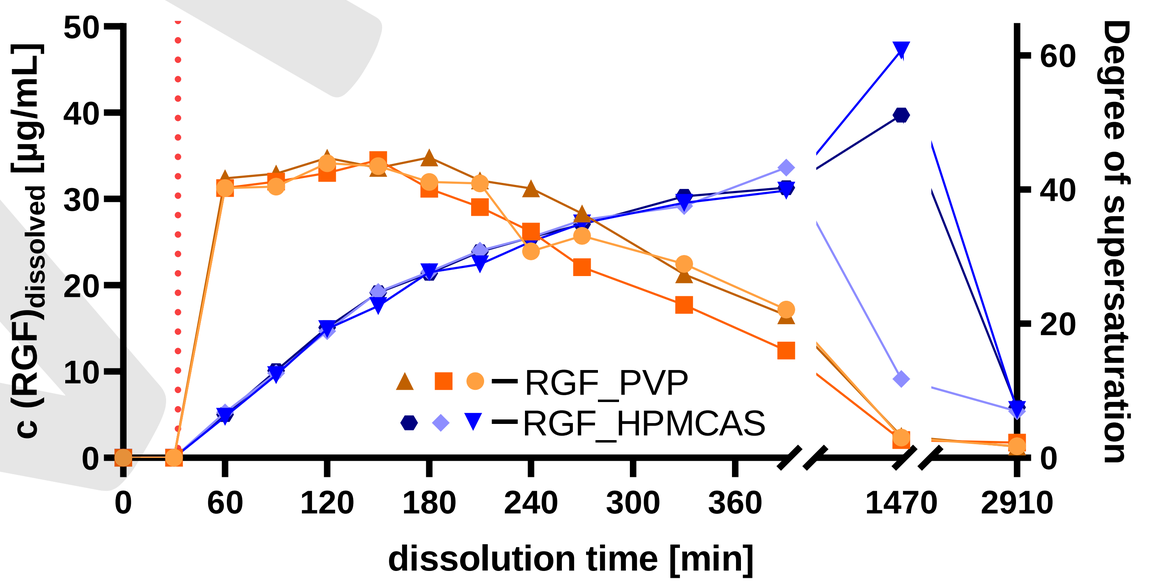

Figure 4. Two-compartment dissolution. The red line indicates the media change from FaSSGF to FaSSIF media. Single dissolution curves are shown.

In contrast, the RGF dissolution from RGF_HPMCAS formulation did not seem to be affected by media change, except for the 24 h sample. Here, precipitation induction could explain the strong deviations between the runs. These findings indicate a high robustness of RGF_HPMCAS towards the media shift from gastric to intestinal conditions.
Besides the dissolution profiles, also the character of the occurring precipitates differs completely, as can be demonstrated in Figure 2. For RGF_PVP, the resulting precipitates are found to be in crystalline state. However, the precipitates from RGF_HPMCAS do not show a specific melting event of a known RGF modification, assuming an amorphous co-precipitate consisting of RGF and HPMCAS.

In further experiments we aim to explore the different precipitation behaviors and its manipulation strategies. Additionally, dissolution-permeation studies are planned to estimate their impact *in-vivo*.

CONCLUSION

Production of two different regorafenib ASDs was successfully performed. Biorelevant dissolution studies revealed high robustness of the RGF_HPMCAS formulation towards biorelevant media change. The solid state properties of the occurring precipitates range from crystalline to amorphous, depending on the chosen polymer. In further studies, impacts on dissolution robustness and permeation experiments will be conducted.

References: [1] Brough, C., Williams, R.O. III; Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug delivery. Int. J. Pharm. 453, 157-166 (2013).
[2] Kostewicz, E. et al.; Forecasting the oral absorption behavior of poorly soluble weak bases using solubility and dissolution studies in biorelevant media. Pharm. Res. 19, 345-349 (2002).

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