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The balance of physical stability and drug release in ternary fenofibrate/HPC/Eudragit L100-55 amorphous solid dispersions

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Introduction

Amorphous solid dispersions are state-of the art enabling technique for poorly water soluble active pharmaceutical ingredients (APIs). In an ASD, the API is molecularly dissolved in a suitable polymer matrix that stabilizes the amorphous state during storage against recrystallization and ensures a fast release during dissolution. They are a promising formulation approach for the bioavailability enhancement of poorly soluble APIs. Physical stability during storage (i.e. resistance against crystallization of the API) and a desirable dissolution profile (i.e. high aqueous API concentration, maintained for long time in the dissolution medium) are the key attributes that need to be optimized by a formulator.

Method: Formulation development

In-silico stage: Stability and dissolution
- Stability evaluation via PC-SAFT
- Miscibility of the polymers and API
- Solubility/ Crystallization driving force
- Tg of the blends

Manufacturing stage: Validation ASDs
- Spray drying of Eudragit L100-55/HPC-SSL ASDs
- Secondary drying and DSC/XRD assessment of stability/miscibility
- 15 wt.% Fenofibrate load, 50/50 polymer and 85/15 polymer (wt%-ratio)

Model validation: stability and dissolution
- Dissolution of Eudragit L100-55/HPC-SSL ASDs
- ‚regular' dissolution medium and dissolution medium with predissolved HPC (crystallization inhibitor)

Fig.1: Schematic overview over the combined in-silico and experimental strategy to develop the ternary ASDs

The intermolecular interactions among the formulated substances (active pharmaceutical ingredients (APIs) and polymers) were assessed using the in-silico model PC-SAFT.
The API parameters describing the size and API interactions are estimated based on a fit solubilities in organic solvents in an earlier work. Fenofibrate is an API with challenging formulatability (fast crystallization, poor solubility in ASD-relevant polymers, poor polymer miscibility, low water solubility) and thus selected as model API for this study.

In-silico stage: Physical stability

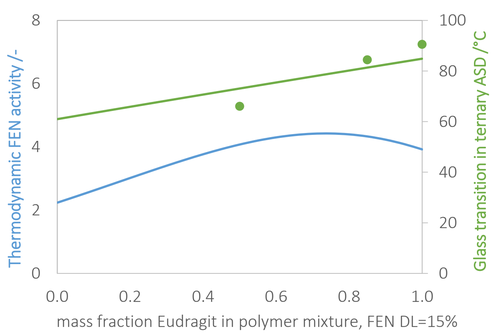


Fig. 2: PC-SAFT predicted activity of fenofibrate in polymer mixtures at 25°C (blue) and predicted Glass-transition of the ternary ASD blend.

- FEN reveals an activity maximum in the Eudragit L100-55/HPC-SSL mixture: weak physical stability in the blend
- The Tg is highest in pure Eudragit L100-55 and drops by addition of HPC-SSL
- The glass-transition of the blend is described accurately by the model
- The API is predicted to undergo amorphous phase separation prior to crystallization, the polymer blend itself is predicted to be miscible.
- The ternary ASDs are less stable from thermodynamic point of view (weak interactions API/polymer) but still kinetically stabilized: The ASDs are metastable and will crystallize, but crystallization is kinetically hindered.

Results: Storage stability

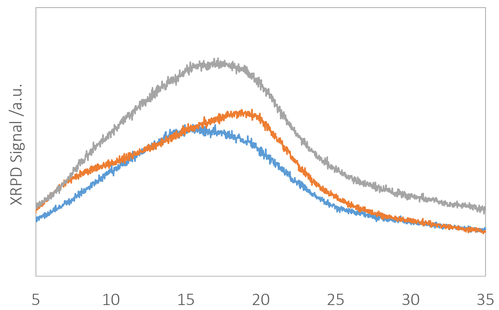


Fig. 3: XRD diffractograms of the ternary ASDs confirming the amorphicity of the ASDs after manufacturing (blue: ASD1 (pure Eud); orange: ASD2 (Eud/HPC 50/50); gray: ASD3 (Eud/HPC 85/15)

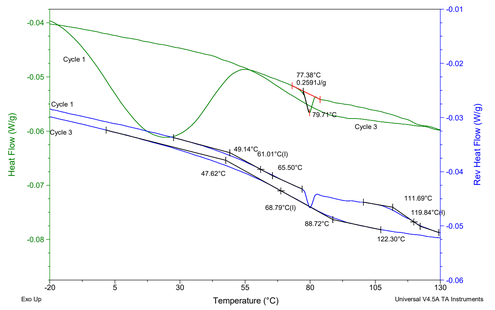


Fig. 4: DSC thermogram of the ASD containing 15% FEN, 42.5% Eudragit L100-55, 42.5% HPC-SSL (reversing heat flow: blue, non-reversing heat flow: green)

The spray-dried samples were found to be X-ray amorphous.
The 50/50 polymer blend ASD indicated amorphous phase separation in the DSC thermograms (2 Tgs) and XRD analysis (shift of peaks) as well as beginning of crystallization.

Results: Dissolution performance

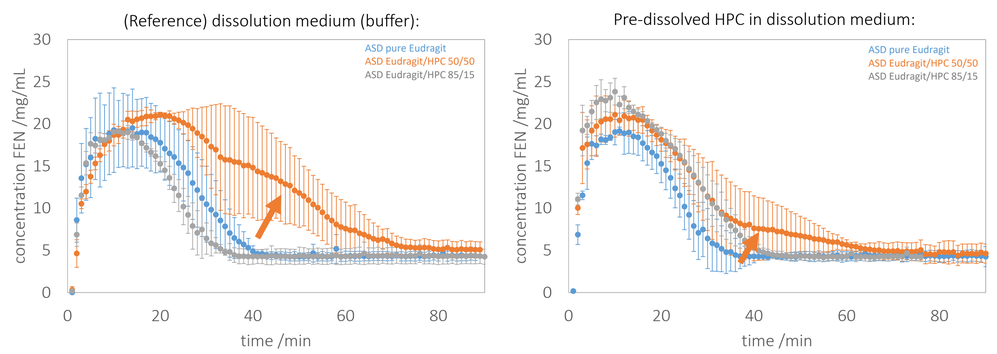


Fig. 5: Dissolution of ternary FEN/Eudragit L100-55/HPC-SSL ASDs at 37°C in phosphate buffer (pH=6.8). The left diagram shows the release profile in phosphate buffer alone, the right diagram shows the release profile with pre-dissolved HPC.

All ASDs revealed the classical spring/ parachute behavior (fast initial release and fast recrystallization from the supersaturated medium). The maximum concentration and final equilibrium FEN concentration was always the same.

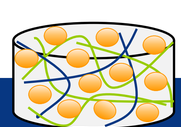
Mechanistic observations: HPC-SSL showed the best stabilization potential (recrystallization prevention) in the least physically stable ASD (ASD2: polymer ratio 50:50 w/w).
Pre-dissolved HPC does not show an improvement: **FEN recrystallization occurs first in the un-dissolved ASD particles and not in the aqueous phase.** The crystallization inhibitor (HPC-SSL) must be present molecular dispersed at the origin of API nucleation.

Conclusion

By addition of HPC-SSL to an ASD FEN/Eudragit L100-55, a physical stability decrease could be achieved, while improving the recrystallization behavior during dissolution studies. HPC was identified as suitable co-excipient that allows performing this stability finetuning.

Learnings

1. ASD physical stability and dissolution behavior often show an opposing behavior
2. HPC acts as storage stability/dissolution behavior finetuning agent
3. ASDs should be designed only as stable as necessary to achieve desirably good dissolution



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