Predicting the Supersaturation Behavior of Indomethacin in Aqueous Solution

Interplay of kinetics of dissolution, recrystallization, and solid-state transformation

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Amorphous formulations of active pharmaceutical ingredients (APIs) represent a valuable tool towards addressing the ever-existing challenge of bioavailability limitation during administration of poorly water-soluble APIs. Yet, it has often been observed that formulations with proven long-term stability - even at high relative humidity - only performed superior to their crystalline counterparts for a much shorter period than expected when subjected to dissolution tests. The mechanisms at play – dissolution, solution crystallization, and solid-state transformation-, while generally not unknown to the scientific community, were assessed and combined quantitatively for the first time in this work.

Goal of this work was to develop individual kinetic models for dissolution, solution crystallization, and solid-state transformation of indomethacin (IND) in aqueous solution. Each model was parameterized by fitting independent kinetic data. The models were integrated with one another to make predictions for supersaturation profiles when these mechanisms occur simultaneously. Figure 1 visualizes this concept.

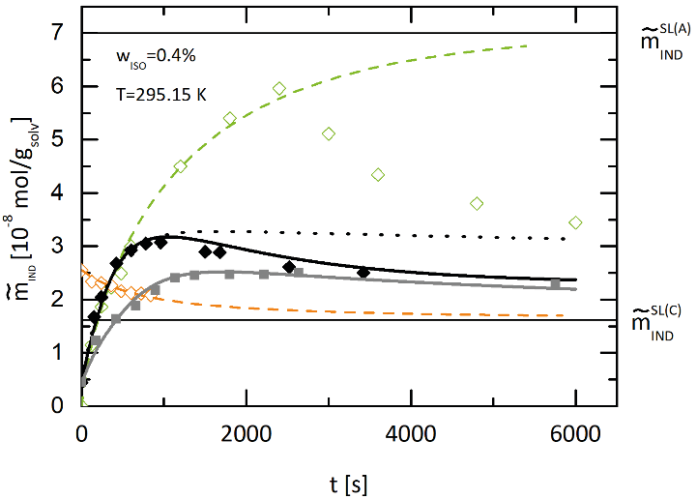

Figure 1: Dissolution (green), desupersaturation (orange) and supersaturation (black) profile of 30 mg amorphous IND in the presence of 9 mg crystalline IND seeds at 295.15 K and 460 rpm in aqueous solution containing 0.4 wt% isopropanol (ISO). Squares and diamonds represent experimental data. Dashed lines represent fits to separate kinetic models for dissolution and desupersaturation. Dotted lines represent predictions of supersaturation profiles without accounting for solid-state transformation, while the solid lines include these kinetics. The supersaturation profile of 20 mg amorphous IND is shown in grey.

Dissolution and desupersaturation profiles were measured in this work and fitted to a chemical-potential-gradient model. Solid-state transformation kinetics represented by amorphicity functions *φ(t)* were derived from literature data and compared with own measurements. For the first time, such kinetics were quantitatively evaluated. Interestingly, as can be seen in Figure 2, data from independent sources (infrared spectral analysis, intrinsic dissolution rate measurement) yielded very similar kinetics. Moreover, in contrast to the results obtained from long-term stability test performed at high relative humidity (up to 98%), such transformations seem to occur on the time scale of minutes rather than days. It was found that when accounting for such transformations in the kinetic modelling, surprisingly accurate predictions are obtained. Conversely, when disregarding the solid-state transformation, the supersaturation profile is substantially overestimated. This shows that solid-state transformation causes the therapeutic window of application to be considerably shorter than one would expect. Inhibiting this transformation represents a key element when tuning the enhancement of bioavailability. The proposed model was successfully validated for robustness under different conditions, such as different amounts of amorphous and crystalline solid as well as solvent compositions.

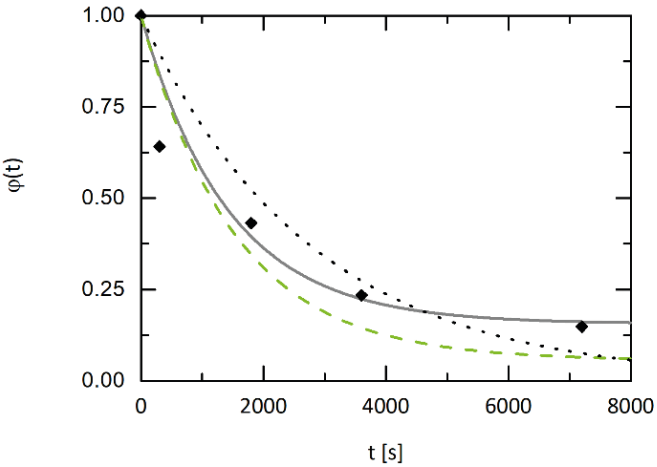

Figure 2: Amorphicity function *φ(t)* of amorphous IND in aqueous solution at 295.15 K. The black squares represent evaluation of infrared spectral data taken from the literature. The grey, solid line and green, dashed line represent evaluations of intrinsic dissolution rate measurement at different flow rates taken from the literature. The black, dotted line represents an evaluation of intrinsic dissolution rate measurement performed within this work.

Publications:
R. Schneider, Y. Ji, G. Sadowski, Dissolution and Crystallization of Amorphous Active Pharmaceutical Ingredients (APIs), Presentation at 10th Crystal Forms 2019, 9 June 2019, Bologna.

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