Modeling the impact of tablet surface layers on the dissolution rate in water

Stefanie Dohrn, Gabriele Sadowski

This study utilized thermodynamic modeling to understand the behavior of amorphous solid dispersion (ASD) tablets during dissolution when exposed to water. It emphasizes the importance of the interfacial surface layers formed during dissolution and predicts drug load (DL)-dependent loss of release (LoR) that often prevents the complete dissolution of the tablet in water. The reasons for this are crystallization and/or liquid-liquid phase separation (LLPS) at the tablet surface. To this end, the phase behavior and glass transition of tablets composed of the drugs naproxen or venetoclax and of poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA64) in contact with water were predicted using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) and the Gordon-Taylor equation. The modeling results were found to be in perfect agreement with (non)dissolution experiments.

According to the concept depicted in Figure 1, the behavior of tablets in contact with water is influenced by water sorption, LLPS, crystallization, and the viscosity of the gel layer formed, impacting the dissolution performance. Phase changes can lead to surface passivation. The LoR mechanisms were categorized into two types, depending on whether the passivation is primarily driven by drug crystallization (LoR Type I) or LLPS (LoR Type II).

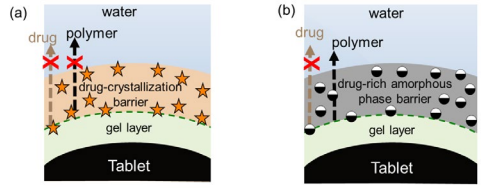

Figure 1: Schematic tablet/water surface of (a) LoR Type I and (b) Type II.

The DL-dependent release mechanisms for PVPVA64-based naproxen (LoR Type I) and venetoclax (LoR Type II) ASDs were predicted and experimentally investigated (Figures 2 and 3).

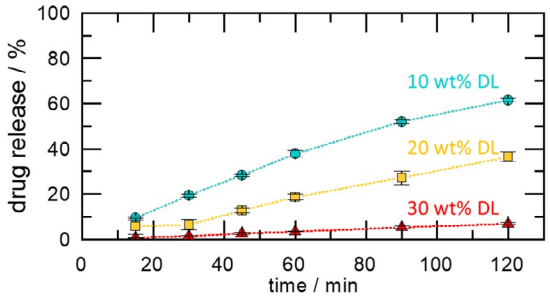

Figure 2: Release profile of naproxen at 37 °C from a naproxen/PVPVA64 ASD, with DLs of 10 wt % (blue circles), 20 wt % (yellow squares), and 30 wt % (red triangles).

The predictions were in excellent agreement with experimentally observed layer formation and its impact on the dissolution. It turned out that the drug-release levels strongly decreased with increasing DL. While the 10 wt % DL tablets released 60% of the naproxen, the 30 wt% DL tablets released only 10% of the naproxen at the same time (Figure 2). The predicted tablet/water phase behavior (Figures 3a and 3b) and DL-dependent phase transition at the tablet/water surface could experimentally be validated via microscopy images (Figures 3c-h).

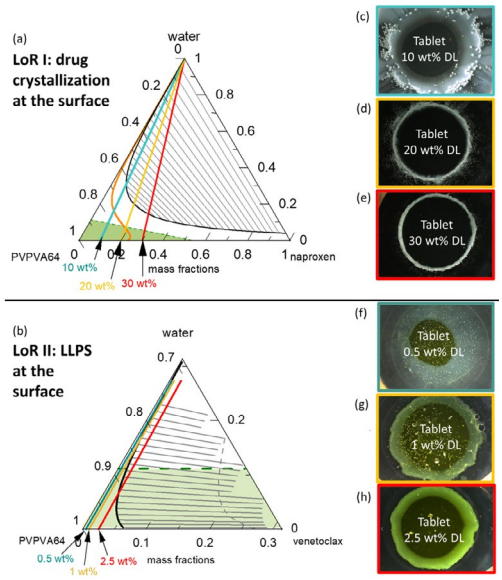

Figure 3: Ternary phase diagrams at 37 °C of (a) LoR Type I system: naproxen/PVPVA64/water and (b) LoR type II system: venetoclax/ PVPVA64/water. The green dashed lines represent the glass transition; the orange lines represent the solubility lines; the black lines represent the LLPS boundaries with gray tie lines; and the blue, yellow, and red straight lines represent the hydration pathways for different DLs. Tablet images after 40 min dissolution for DLs (c) 10 wt%, (d) 20 wt%, and (e) 30 wt% naproxen and (f) 0.5 wt%, (g) 1 wt%, and (h) 2.5 wt% venetoclax.

The presented modeling approach supports the understanding of a tablet release mechanism during dissolution and helps to identify the maximum DL of a tablet, which allows high drug release without undergoing phase changes during dissolution.

Contacts:
stefanie.walter@abbvie.com
gabriele.sadowski@tu-dortmund.de

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