Counteracting the loss of release for indomethacin-copovidone ASDs.

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The bioavailability of an active pharmaceutical ingredient (API) with low water solubility can be enhanced by dissolving the API in a polymer matrix generating an amorphous solid dispersion (ASD), which used as tablets. Upon ASD dissolution, the polymer and the API are supposed to simultaneously release from the ASD. However, ASDs often show simultaneous and fast release at low API to polymer ratios (low drug loads (DL)), while ASDs with high DL show a loss of API release. This study explained this phenomenon via investigating the release kinetics and phase behavior of an ASD consisting of the API indomethacin (IND) and the polymer copovidone both experimentally and theoretically. Modeling the experimental release kinetics, we were able to predict the formation of an ASD layer at the ASD-water interface, which almost exclusively contains amorphous indomethacin (IND). Our phase-diagram predictions and experimental data verify that water-induced phase separation during ASD dissolution. Whereas the evolving copovidone-rich phase dissolves, the IND-rich phase remains undissolved and forms a super-hydrophobic layer that covers the remaining inner core of the ASD, thus finally completely preventing its dissolution.

Figure 1 shows the measured and modeled release kinetics of IND-copovidone ASDs with DLs of 0.1, 0.3, and 0.5 in water. The release of IND was found to be highest for the ASD with the lowest DL 0.1. After 70 minutes, both IND and copovidone fully released from the ASD (Figure 1a).

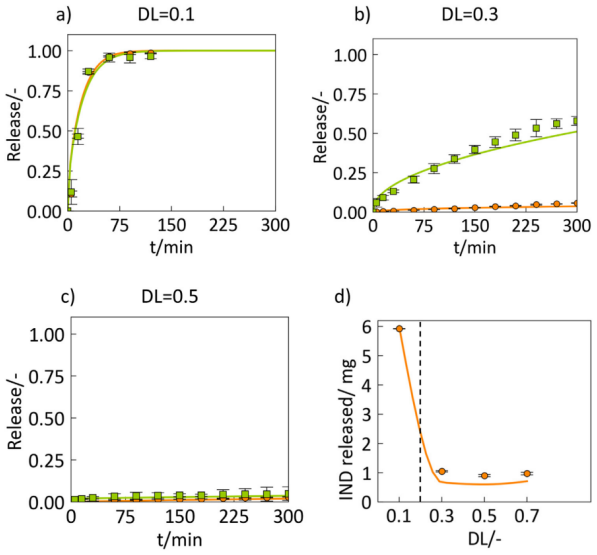

Figure 1. Releases of IND and copovidone from IND-copovidone ASDs and with DLs of 0.1 (a), 0.3 (b), and 0.5 (c) at 25 °C. Experimental data points are displayed as green squares for copovidone and as orange circles for IND. Model results are displayed as solid lines. (d) released mass of IND after 300 min as a function of the ASD DL.

For the ASD with a DL 0.3 (Figure 1b), the IND release was only 5 % after 300 min while the copovidone release was still 58 %. Counterintuitively, the higher the drug load of the ASD, the lower the absolute mass of IND released (Figure 1d). Thus, increasing the DL beyond 0.2 does not increase the mass of released IND, but only increases the mass of IND remaining undissolved in the ASD.

The phase diagram of the IND-copovidone-water ternary system predicted by PC-SAFT shows a large miscibility gap between IND and water (Figure 2).

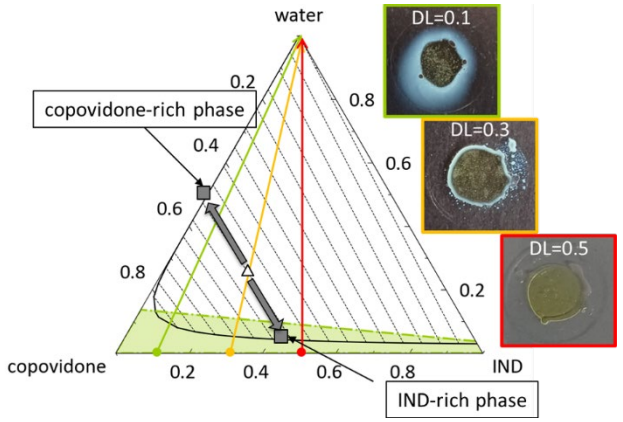

Figure 2. Phase diagram of the IND-copovidone-water system at 25 °C. The solid black line frames the miscibility gap. Green, yellow, and red arrows show the pathways for ASDs of different DLs (0.1, 0.3, and 0.5) during the release experiment. The white triangle exemplifies the demixing of a wet ASD along a tie line (dashed black lines).

During the release of an ASD, the ASD-water system moves along a line that connects the lower side of the triangle with its upper edge indicating pure water. The ASD with DL 0.3 demixes upon water sorption into a continuous IND-rich phase and copovidone-rich droplets. IND accumulates near the ASD-water interface and covers the inner of the ASD with a poorly-water-soluble IND layer which becomes thicker the higher DL is (about 80 μm**).** Since the solubility of IND is poor, at DL 0.5 even the polymer release (Figure 1c) breaks down. Thus, increasing the DL of the ASD beyond 0.2 will not lead to a further increase the amount of IND released. If higher DLs are required, full release of IND from the ASDs is only guaranteed if the size of the ASD is reduced below the size of the layer. Otherwise, significant amounts of polymer and IND remain in the ASD and thus will not be released at all.

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