Predicting Formulation Windows for Efficient Lipid-Based Drug Delivery Systems

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The preclinical development of lipid-based drug delivery systems (LBDDS) requires a very high experimental effort to ensure the efficient formulation and administration of active pharmaceutical ingredients (APIs). Hereby, it is of utmost importance that the API does not crystallize in the LBDDS while storage or after oral administration to the human body. For the first time, we proposed an in-silico tool to predict the degree and location of API crystallization in a LBDDS before and after administration. This allows formulation scientists to design LBDDS with minimum experimental effort.

Since many newly developed active pharmaceutical ingredients (APIs) possess very limited bioavailability, lipid-based drug delivery systems (LBDDS) are used to increase the efficient administration of these APIs into the human body. In these, the API is dissolved in a mixture of a lipid and excipients, which prevents the API from crystallizing during storage and during its pass through the gastrointestinal tract.
The solubility of the API in the water-free LBDDS is the maximum API amount that can be kept amorphous during storage. This solubility of ibuprofen (IBU) in a LBDDS containing the lipid tricaprylin ($TG8_08_08_0$) and the two excipients caprylic acid ($MC8_0$) and ethanol was predicted using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) (dashed lines in Figure 1). For example: given an IBU loading of 40 wt% in the LBDDS, IBU will crystallize during storage for all LBDDS compositions located on the left side of the dashed red line, whereas it will remain dissolved for all LBDDS compositions located right of the red dashed line.

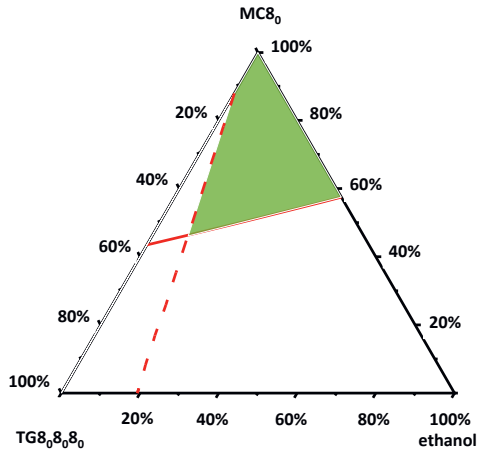

Figure 1: Overlay of the IBU solubility in the water free LBDDS (dashed lines) and in a partitioning test with water (solid lines) to define a formulation window, in which a LBDDS does not show IBU crystallization neither during storage nor during administration. The green area indicates the formulation window for an IBU load of 40 wt% in the LBDDS.

The maximum amount of IBU that can be kept in solution during a partitioning test with water (mixing ratio 1/200 LBDDS/water) was predicted to simulate the mixing conditions after oral administration into the human body (solid lines in Figure 1).

Again: for all LBDDS located below the solid red line, IBU was predicted to crystallize after mixing the LBDDS with water, if the IBU load in the LBDDS is 40 wt%.
The two informations were combined in Figure 1. The dashed and solid lines enclose the formulation window (green area for 40 wt%), in which IBU will not crystallize during storage or after administration. Outside this formulation window, IBU will crystallize either in the formulation or after oral administration.
The predicted results from Figure 1 were experimentally validated (Figure 2). An excipient mixture of 83.5 w% $TG8_08_08_0$ and 16.5 wt% ethanol was used. In this mixture an IBU load of 37 wt% was dissolved. According to the predictions, IBU crystallization was expected not to occur in the water-free LBDDS but was expected after mixing with water. As can be seen clearly in Fig. 2, IBU did crystallize after being in contact with water and it mostly crystallized in the lipid phase (bottom left side) of the LBDDS/water system. This could be explained by the loss of the hydrophilic excipient ethanol from the LBDDS into the aqueous phase, which decreased the IBU solubility in the LBDDS phase and induced IBU crystallization there.
The results of this work now enable formulation developers to in-silico design promising LBDDSs for target APIs without the need of expensive and time-consuming trial-and-error methods.

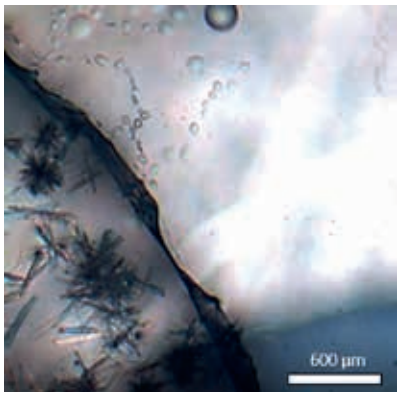

Figure 2: Microscope image of an LBDDS (IBU: 37.4 wt%. $TG8_08_08_0$: 52.3 wt%, ethanol 10.3 wt%) crystallization test with water at 37 °C.

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Publications:
J. Brinkmann, I. Becker, P. Kroll, C. Luebbert, G. Sadowski, Int. J. Pharm. 595, 120266 (2021).
M. Jaworek, N. Gajardo-Parra, G. Sadowski, R. Winter, C. Held, Colloids Surf. B. 208, 112127 (2021).