Triglycerides as Solvents for Pharmaceuticals

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Lipid-based drug delivery systems (LBDDSs) are a promising option to increase the bioavailability of active pharmaceutical ingredients (APIs). In the simplest case, APIs can be dissolved in a triglyceride (TG). However, choosing the best-suited TG, requires a mechanistic understanding of how its properties influence the API solubility and therewith the thermodynamic stability of those formulations. The influences of TG chain length and degree of saturation on API solubility were investigated in this work. Solubility experiments and thermodynamic modeling were combined to allow screening for best-suited LBDDS. This method enables straight-forward formulation development and complements the commonly-used trial and error methods in pharmaceutical industry.

Low water solubility and membrane permeability resulting in low bioavailability impact the majority of newly-developed active pharmaceutical ingredients (APIs) and are thus challenging limitations in pharmaceutical development. It has been shown that bioavailability can be enhanced via formulating the APIs in lipid-based drug delivery systems (LBDDS). LBDDS are usually multicomponent mixtures, which contain a variety of lipids and excipients. In its simplest form, the API is dissolved in only one pure lipid. The most-used lipids are natural oils (e.g. soybean oil), which mostly contain triglycerides (TGs). TGs comprise a glycerol backbone and three fatty-acid ester side groups. Those side groups may differ in chain length and degree of saturation.

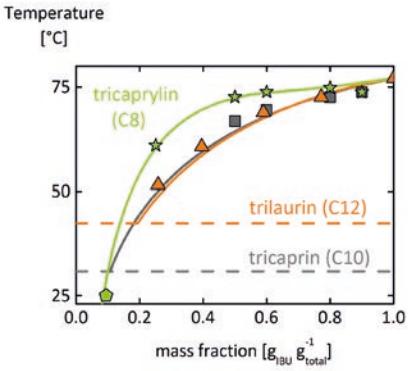

Figure 1: Phase diagrams of IBU in saturated, medium-chained TGs. Symbols are experimental values, solid lines mark the PC-SAFT modeling. Dashed lines are the calculated eutectic temperatures.

Solubility of the APIs in TGs was measured via differential scanning calorimetry at high temperatures. The Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) was then applied to extrapolate these solubilities to lower temperatures. Figure 1 shows the influence of fatty-acid chain length on the solubility of the API ibuprofen (IBU) in three fully-saturated TGs, namely tricaprylin ($TG8_08_08_0$), tricaprin ($TG10_010_010_0$) and trilaurin ($TG12_012_012_0$). As to be seen, IBU solubility as well as the eutectic temperature increase only slightly with increasing TG chain length. This means that at high temperatures the solubility of IBU in $TG10_010_010_0$ or $TG12_012_012_0$ is higher than in $TG8_08_08_0$, but IBU will crystallize at room temperature (25 °C).

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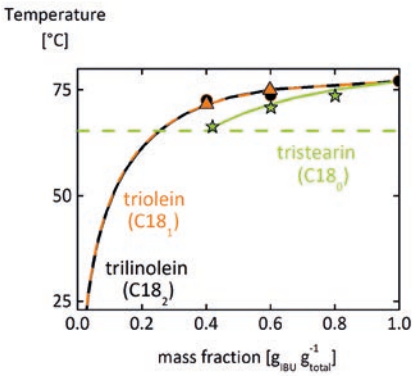

Figure 2: Phase diagrams of IBU in saturated and unsaturated TGs of fatty acids with the same chain length. Symbols are experimental data, lines are PC-SAFT modeling. The dashed green line is the calculated eutectic temperature of $TG18_018_018_0$.

The second structural impact investigated in this work is the influence of the TG degree of saturation on API solubility. Therefore, three TGs with the same side-chain lengths (18 carbon atoms) and different degrees of saturation were compared. Tristearin ($TG18_018_018_0$) is completely saturated, triolein ($TG18_118_118_1$) possesses one double bond in each fatty-acid side chain and trilinolein ($TG18_218_218_2$) two double bonds in each fatty-acid side chain. As depicted in Figure 2, the API solubility strongly decreases by introducing the first double bond in the side-chain, but is not further affected by a higher degree of unsaturation. Moreover, the number of double bonds dramatically decreases the TG melting points, which enables formulating liquid LBDDS at 25 °C. For IBU in $TG18_018_018_0$ the solubility line ends at the eutectic temperature of 65.5 °C, which does not allow formulating liquid LBDDS at ambient temperatures.

It can be summarized that changing fatty-acid chain length revealed to increase the solubility of IBU in TGs only slightly but results in unfavorable, crystalline formulations at 25 °C for $TG10_010_010_0$ or longer side chains. TG unsaturation leads to a distinct decrease of solubility, which makes saturated $TG8_08_08_0$ more favorable for LBDDS formulations with IBU than unsaturated TGs. Thus combining thermodynamic measurements and modeling with PC-SAFT is an appropriate method for screening optimal TG/API combinations for LBDDS and helps finding best-suited TGs for LBDDS.

Publications:
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