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Creating a Lipid Formulation Classification System

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The LFCS Consortium: 3 - Effect of saturation level of a highly lipophilic drug on the performance of lipid-based formulations during in vitro digestion

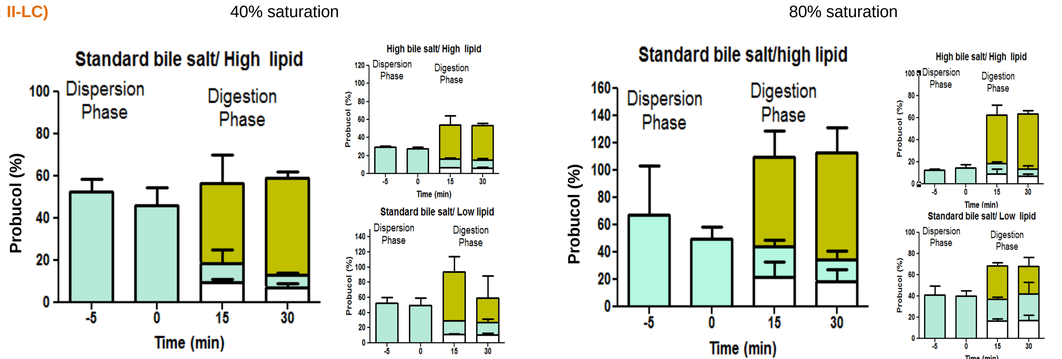
- **Purpose:** The LFCS Consortium aims to establish standardized in vitro tests that can characterize a wide range of lipid-based formulations (LBF). Here, we investigate the **impact of probucol saturation levels in eight LBF on performance during in vitro digestion under three different digestion conditions.**

- **Methods:** Using a pH-stat titrator (Titrando®, Metrohm), LBF Type I, II, IIIA/B, LBF containing medium-chain (MC) or long-chain (LC) lipids and lipid-free Type IV LBF all with incorporated probucol (40-80% of its saturated solubility in the LBF), were digested using porcine pancreatic extract in 40ml intestinal digestion medium at pH 6.5 (37°C) with continuous stirring. Three digestion conditions were used:
  - Standard bile salt / High lipid: (3 mM BS / 1 g LBF)
  - High bile salt / High lipid: (10 mM bile salt / 1 g LBF)
  - Standard bile salt / Low lipid (3 mM BS / 0.16 g LBF)
- Digestion samples were separated by centrifugation and the drug content in the oily phase, colloidal aqueous phase (AP) and pellet was determined by HPLC. Solubility of probucol was determined at 24hrs in the AP for 8 LBF under the 3 conditions.

- **Results:** The AP from the digestion of all 8 LBF was highly supersaturated with probucol compared to the crystalline solubility. At 40% saturation level, the amount of probucol in the AP remained unchanged throughout the digestion of all 8 LBF in all three conditions. Probucol was more prone to precipitate when a low dose of LBF was applied, eventhough less drug was added. Similarly at 80% saturation level; reducing the dose leads to a larger precipitation of probucol. In general a low precipitation level is seen for probucol, however there is a trend towards decreased precipitation at high BS levels, especially for IIIa-LC, IIIa-MC, IIIb-MC and IV.

Results:

A: II-LC)



B: IIIa-LC)

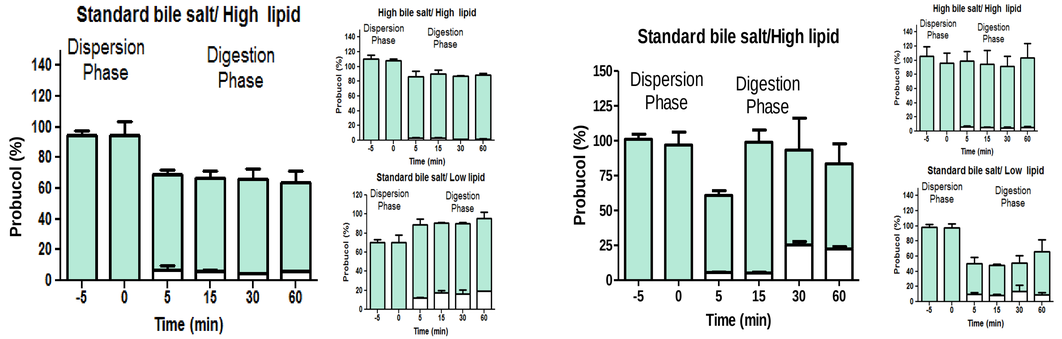
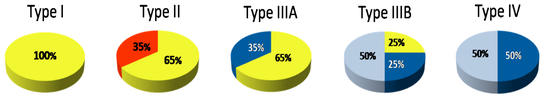


Figure 1. The digestion of LFCS formulations of type II-LC and type IIIa-LC under all three digestion conditions at two saturation levels. The concentration of probucol in the AP (panel A) was unaffected by the progressive digestion of a type II-LC formulation. In contrast, the amount of probucol in the AP during the digestion of a type IIIa-LC formulation (panel B) was affected by the saturation level. Oil Phase= ▭ AP=▭ and pellet= ▭.

Figure 2: The composition of the eight formulations investigated by the LFCS and the corresponding solubilities of probucol in the formulations.



	Type I	Type II	Type IIIA	Type IIIB	Type IV
LC	64	70	81	-	-
MC	84	81	87	84	-
Lipid Free	-	-	-	-	94

Long-chain (LC) lipids: Corn oil and Maisine™ 35-1 (in a 1:1 ratio)
Medium-chain (MC) lipids: Captex 300 and Capmul MCM EP (in a 1:1 ratio)
Lipophilic surfactant: Tween 85
Hydrophilic surfactant: Cremophor EL
Cosolvent: Transcutol HP

Conclusions

The amount of probucol solubilised by the aqueous phase seemed unaffected by the extent of LBF digested, both at 40% & 80% saturation level for I-LC, II-LC, I-MC & II-MC, mainly due to retention in the oil phase. The decrease in amount solubilised in the AP observed for IIIa-LC, IIIa-MC, IIIb-MC and IV when decreasing the LBF load, indicates that the amount of solubilised probucol was affected by the extent of digestion products in these formulations.