Creating a Lipid Formulation Classification System

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The LFCS Consortium: 3 - Effect of calcium and pancreatin concentration on *in vitro* digestion of a range of lipid-based formulations

Introducing the LFCS Consortium

- The LFCS Consortium is a non-profit organization consisting of both academic and industrial partners with the overall objective of developing standardized *in vitro* tests for lipid-based formulations (LBFs). Work presented here details some of the experiments undertaken in the first year of the LFCS Consortium**.**

STUDY AIM: Here, we study the impact of calcium and pancreatin levels on: (i) the digestion (rate and extent) of LBFs, and (ii) the fate of an incorporated model poorly soluble drug (danazol).

- Pancreatic lipase exhibits product inhibition due to steric hindrance by generated free fatty acids (FFA). FFA are precipitated by calcium, allowing progressive digestion of LBFs**.**

Methods

- The composition of concept long-chain (LC) and medium-chain (MC) LBFs are presented in poster 4 (3744). **Effect of pancreatin:** One gram LBF (containing danazol) was initially dispersed in 36mL digestion medium (pH 6.5, 2mM tris-maleate, 1.4mM calcium,150mM NaCl, 3mM sodium taurodeoxycholate, 0.75mM phosphatidyl choline 37C) before digestion was commenced on addition of 4mL porcine pancreatin suspension (150, 300, 600 or 900 USP units/mL). **Effect of calcium:** Calcium levels were varied (0, 1.4, 5, or 10mM) and added either initially or continuously during digestion. Digestion was commenced on addition of 4mL porcine pancreatin suspension (final concentration in the vessel: 600 USP units/mL).
- Digestion was continuously monitored using a pH-stat titrator (Titrando®, Metrohm). Digestion samples were separated by centrifugation and danazol concentration in the poorly dispersed oil phase, aqueous phase and pellet was determined by HPLC.

Discussion

- Increasing the pancreatin level in the digestion vessel does not importantly affect the extent of digestion for either LC- or MC-LBFs, though a small increase is more pronounced for MC-LBFs (24% and 40% for III-LC and IIIA-MC, respectively, when pancreatin was increased from 150-600 mM) (**Fig. 1a** and **3a**).
- The calcium addition scheme does not affect the total extent of digestion, but a more constant digestion rate is obtained when calcium is added continuously. This effect is more distinct for LC-LBFs (**Fig. 2a&b** and **4a&b**). Increasing the amount of calcium affects the extent of digestion of LC-LBFs more than MC-LBFs (128% vs. 24% for III-LC and IIIA-MC, respectively when calcium was increased from 0-10 mM).
- The drug distribution data reveal a tendency for the LC-LBFs (III-LC in particular) to improve solubilization capacity of the digestion medium on increased digestion (more drug is in the aqueous phase). Conversely, increased digestion of MC-formulations caused a loss of solubilization capacity of the digestion medium and increased precipitation of danazol.

Conclusion: Definitive and optimal parameters for *in vitro* digestion cannot be set without further evaluations of more drug compounds and LBFs.

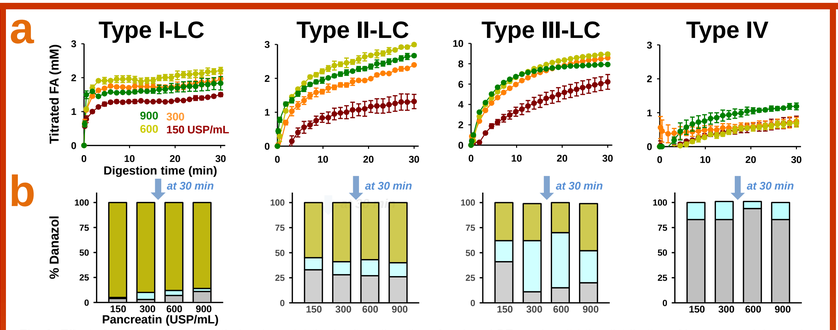

Fig. 1: Effect of increasing **pancreatin** levels on **(a)** the *in vitro* digestion of various LBFs and on **(b)** the distribution of incorporated danazol (80% saturation in the pure formulation) between partially digested OIL PHASE, AQUEOUS PHASE and PELLET after 30 minutes digestion (n = 3).

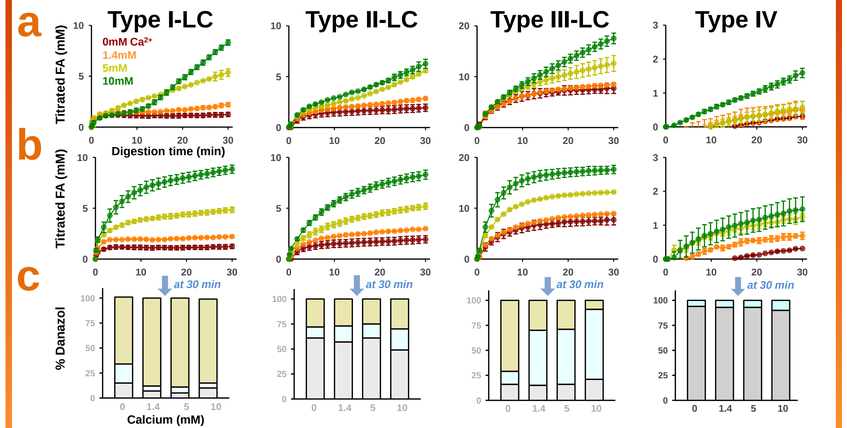

Fig. 2: Effect of increasing **(a)** continuous and **(b)** initial **calcium addition** in the *in vitro* digestion of various LBFs and **(c)** on the distribution of incorporated danazol (80% saturation in the pure formulation) between partially digested OIL PHASE, AQUEOUS PHASE and PELLET after 30 minutes digestion (n = 3).

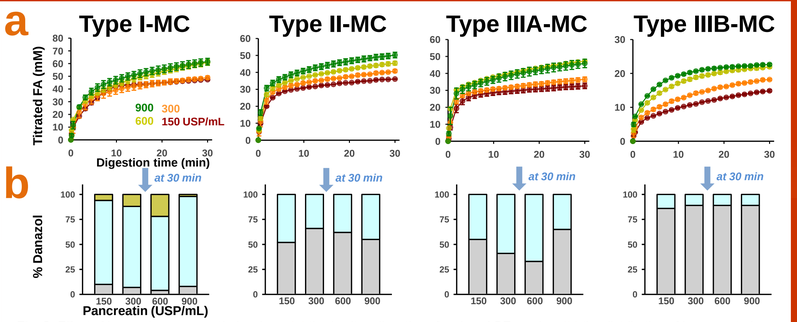

Fig. 3: Effect of increasing **pancreatin** levels on **(a)** the *in vitro* digestion of various LBFs and on **(b)** the distribution of incorporated danazol (80% saturation in the pure formulation) between partially digested OIL PHASE, AQUEOUS PHASE and PELLET after 30 minutes digestion (n = 3).

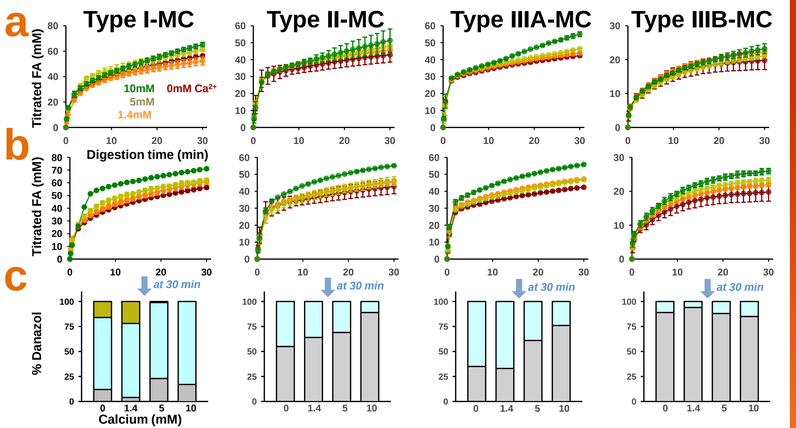

Fig. 4: Effect of increasing **(a)** continuous and **(b)** initial **calcium addition** in the *in vitro* digestion of various LBFs and **(c)** on the distribution of incorporated danazol (80% saturation in the pure formulation) between partially digested OIL PHASE, AQUEOUS PHASE and PELLET after 30 minutes digestion (n = 3).

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