Creating a Lipid Formulation Classification System

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The LFCS Consortium: 4 - Effect of formulation surfactants on the extent of *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: In the present poster, we present how the extent of lipolysis is affected by the type of surfactants.

- LBFs are exposed to enzymatic digestion through the GI-tract, thus the impact of different formulation surfactants on the extent of digestion is of interest in LBF development.

Methods

- Table 1 below lists the composition of eight long-chain (LC) and medium-chain (MC) LBFs investigated within the LFCS. Formulations were incorporated with danazol at 80% of its solubility (37ºC) in the pure formulation.
- **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, 37 C) before digestion was commenced on addition of 4mL porcine pancreatin suspension (150, 300, 600 or 900 USP units/mL).
- **Effect of calcium** The initial calcium levels were varied (0, 1.4, 5, or 10mM) in a digestion medium (pH 6.5, 2mM tris-maleate, 150mM NaCl, 3mM sodium taurodeoxycholate, 0.75mM phosphatidyl choline, 37 C), and digestion was commenced on addition of 4mL porcine pancreatin suspension (600 USP units/mL)
- Digestion was continuously monitored using a pH-stat titrator (Titrando®, Metrohm). Particle size was measured with a Malvern Zetasizer ZS.

Table 1: Composition of the eight LBFs investigated by the LFCS Consortium

LBF type	Composition (% w/w)							
	Corn oil	Maisine^{TM} 35-1	Tween 85	Cremophor EL	Captex	Capmul	Transcutol	Danazol
I-LC	50	50	-	-	-	-	-	6.7 mg/g
II-LC	32.5	32.5	35	-	-	-	-	13.5
III-LC	32.5	32.5	-	35	-	-	-	15.2
I-MC	-	-	-	-	50	50		19.8
II-MC	-	-	35	-	32.5	32.5	-	21.8
IIIA-MC	-	-	-	35	32.5	32.5	-	22.7
IIIB-MC	-	-	-	50	-	25	25	39.0
IV	-	-	-	50	-	-	50	52.4

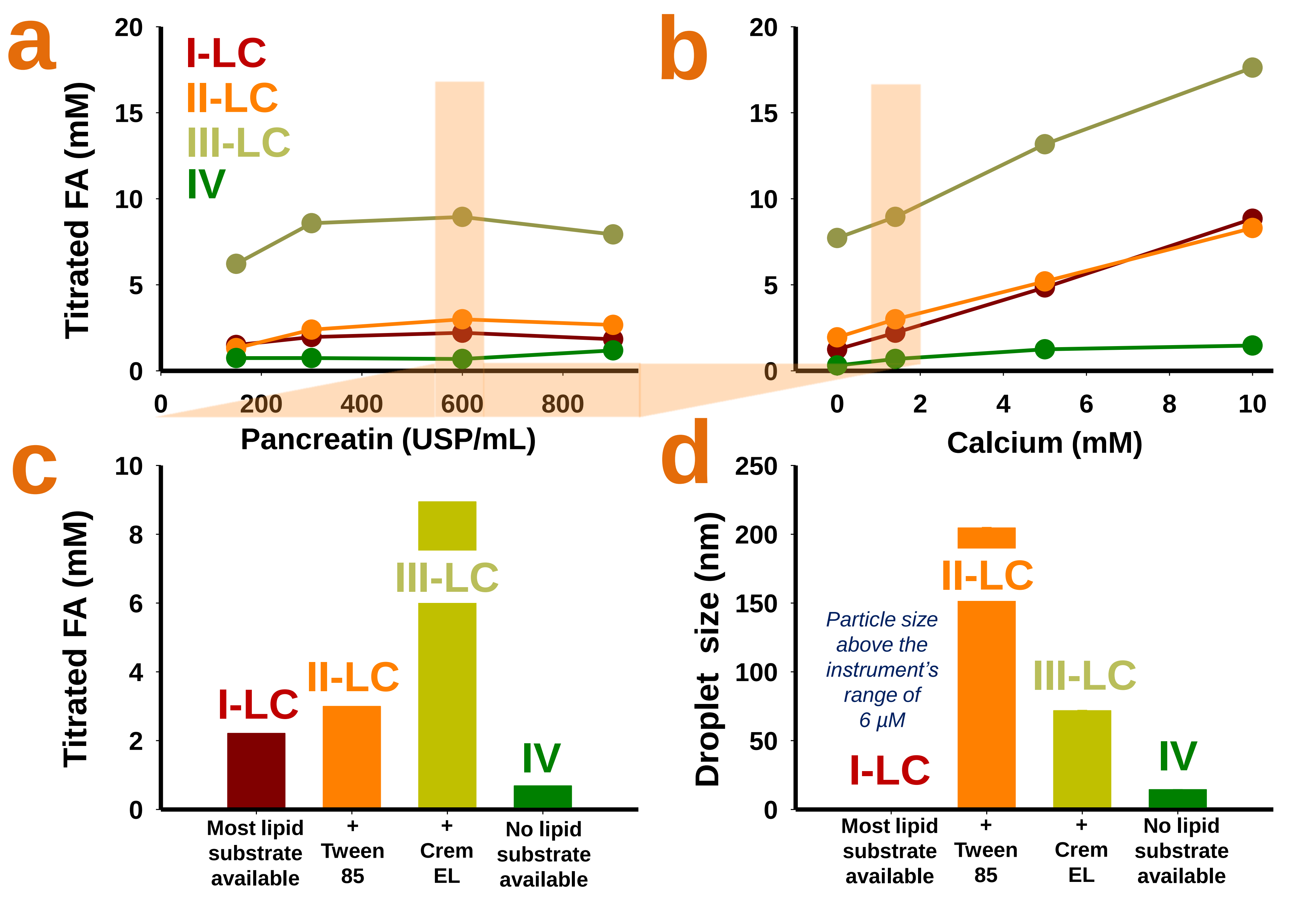

Fig. 1: Effect of increasing **(a) pancreatin** and **(b) calcium** on the *in vitro* digestion of various LBFs. Data points show titrated fatty acids after 30 min digestion at pH 6.5. **(c)** FFA release during lipolysis at 1.4 mM; calcium and 600 USP units/mL, as a function of formulation type. **(d)** Particle size of emulsion particles after 10 minutes dispersion, before initiation of digestion.

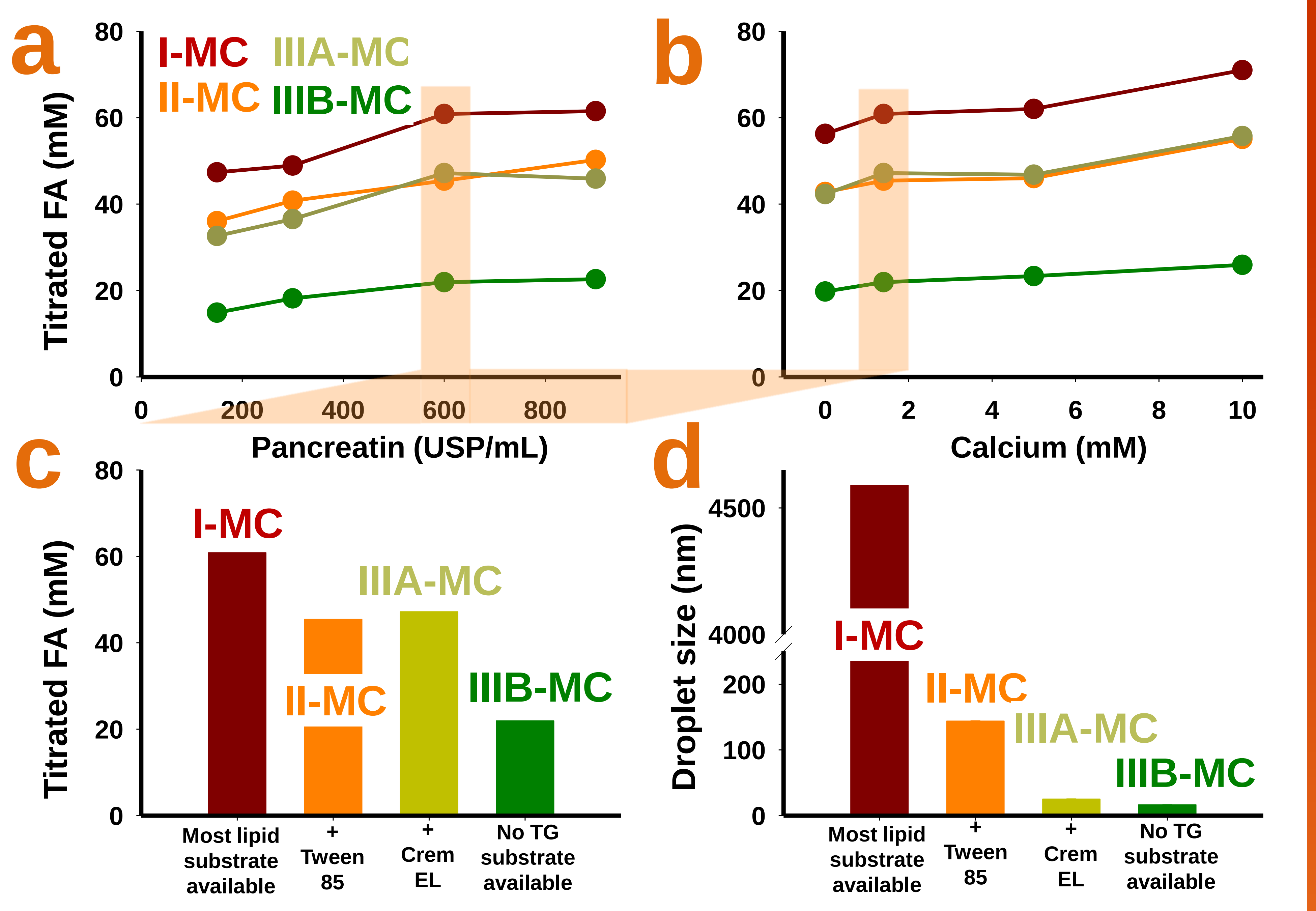

Fig. 2: Effect of increasing **(a) pancreatin** and **(b) calcium** the *in vitro* digestion of various LBFs. Data points show titrated fatty acids after 30 min digestion at pH 6.5. **(c)** FFA release during lipolysis at 1.4 mM; calcium and 600 USP units/mL, as a function of formulation type. **(d)** Particle size of emulsion particles after 10 minutes dispersion, before initiation of digestion.

Discussion

- For LC-LBFs, the extent of lipolysis is poor when no surfactant is present, while lipolysis extent is greatly enhanced by Cremophor-EL but NOT by Tween 85.
- For MC-LBFs, more lipolysis is obtained in the absence of surfactant - corresponding to the highest substrate content. The loss in lipid content is partially compensated by addition of both Cremophor-EL and Tween 85
- Cremophor EL decreased particle size more than Tween 85 for both LC and MC-LBFs. For the LC-LBFs, high digestibility is correlated to small particle size (<100nm), while particle size does not dramatically influence the digestibility of MC-LBFs

Conclusion: Important effects of different lipids and surfactants on digestibility of LBF is identified and need to be further elucidated to facilitate optimal development of LBF.