Creating a Lipid Formulation Classification System

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The LFCS Consortium: 1 - Effect of saturation level of a neutral drug and a weakly acidic drug on the performance of lipid-based formulations during *in vitro* digestion

- **Purpose:** The LFCS Consortium aims to establish standardized *in vitro* tests that are able to discriminate between a range of lipid-based formulations (LBF).
- **Here, we investigate the impact of drug (fenofibrate or tolfenamic acid) saturation level in eight LBFs on performance during *in vitro* digestion.**
- **Methods:** Using a pH-stat titrator (Titrando®, Metrohm), 1 g of Type I, II and IIIA/B LBF containing medium-chain (MC) or long-chain (LC) lipids and lipid-free Type IV LBF incorporating fenofibrate (at 20-100% of saturated solubility in the formulation) or tolfenamic acid (at 60-100% of saturated solubility in the formulation) (Table 1), were digested using porcine pancreatic extract in 40 ml intestinal digestion medium (pH 6.5, 37°C, 3 mM:0.75 mM BS:PL) with continuous stirring (see [1] for further details). Digestion samples were separated by centrifugation and the drug content in the poorly-dispersed 'oily' phase, colloidal aqueous phase and pellet determined by HPLC. Drug solubility was determined in 'blank' aqueous phase digests (AP_{BLANK}) obtained via the digestion of drug-free LBFs to estimate the extent of supersaturation
- **Results:** Digestion of Type I-LC, II-LC and IIIA-LC, and I-MC LBF (see Table 1 for LBF compositions) did not lead to drug precipitation, even at fenofibrate or tolfenamic acid drug loads ≥ 80% saturation. Type II-MC and IIIA-MC LBF also maintained tolfenamic acid in solution at high saturation levels whereas fenofibrate precipitated. Precipitation during the digestion of Type IIIB-MC and IV LBF was more evident irrespective of drug, however, fenofibrate precipitated at a lower (>20-40%) saturation levels than tolfenamic acid (>60-80%). The tendency for fenofibrate and tolfenamic acid to precipitate correlated with the degree of drug supersaturation obtained on digestion.
- **Conclusion:** A trend toward increasing drug precipitation with increasing saturation level (dose) was evident during *in vitro* digestion of MC LBF and Type IV LBF containing either neutral (fenofibrate) or acidic (tolfenamic acid) drugs. Drug precipitation occurred at lower saturation levels for fenofibrate, however, the very high lipid solubility of fenofibrate dictated that this occurred at high absolute drug loads in the formulation. A threshold supersaturation level was also identified that predetermined the fate of fenofibrate or tolfenamic acid irrespective of LBF-type.

Table 1: Saturated solubility of fenofibrate and tolfenamic acid at 37°C in the eight LBFs investigated by the LFCS Consortium. LC; long-chain, MC; medium-chain lipids.

Composition (% w/w)	LBF-type	Fenofibrate solubility in LBF (mg/g)	Tolfenamic acid solubility in LBF (mg/g)
50% corn oil, 50% Maisine™ 35-1	I-LC	98.1	8.8
32.5% corn oil, 32.5% Maisine™ 35-1, 35% Tween® 85	II-LC	99.9	20.6
32.5% corn oil, 32.5% Maisine™ 35-1, 35% Cremophor® EL	IIIA-LC	106.8	26.0
50% Captex® 300, 50% Capmul® MCM EP	I-MC	149.6	17.3
32.5% Captex® 300, 32.5% Capmul® MCM EP, 35% Tween® 85	II-MC	135.6	25.9
32.5% Captex® 300, 32.5% Capmul® MCM EP, 35% Cremophor® EL	IIIA-MC	143.1	32.6
25% Capmul® MCM EP, 50% Cremophor® EL, 25% Transcutol HP	IIIB-MC	152.1	54.8
50% Cremophor® EL, 50% Transcutol HP	IV	189.1	77.0

Results: 'Partially' digested formulations

- Type I, II, IIIA LC and I-MC LBFs are partially and slowly digested in our *in vitro* digestion models.[1,2] **Fig. 1** shows that undigested/poorly dispersed oil phase (yellow bars) provides a solubilizing reservoir for the incorporated drug, particularly for fenofibrate, which is more lipophilic than tolfenamic acid.
- The remainder of the dose for both drugs was predominantly solubilized in the aqueous phase (light blue bars). The low drug concentration/high drug solubility in this phase however meant that supersaturation ratios (SR) were generally low explaining the lack of precipitation. Digestion of the Type IIIA-LC containing fenofibrate led to higher supersaturation (SR = 2.8 and 3.0), though this did not trigger precipitation.

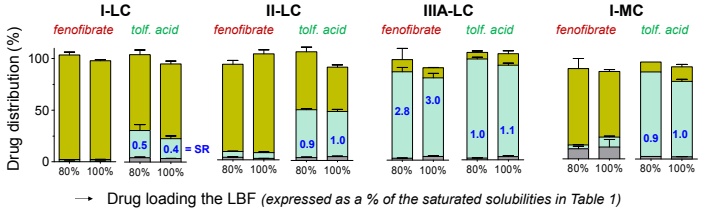

Fig. 1: Effect of 30 min *in vitro* digestion of Type I-LC, II-LC, IIIA-LC and I-MC LBFs on the distribution of fenofibrate and tolfenamic acid across partially digested OIL PHASE, AQUEOUS PHASE (AP) and PELLET (n = 3, ± 1 SD).
Supersaturation ratio (SR) = drug in AP / solubility in AP_{BLANK}

Conclusions

Increasing saturation level (dose) of either neutral or acidic drugs in LBFs led to an increased risk of precipitation during *in vitro* digestion. While this precipitation risk varied with LBF-type and the drug used, precipitation was only evident in instances where the supersaturation ratio exceeded a 'threshold' value of 2.5.

1. Williams HD et al., 2012. J Pharm Sci. **101** (9) pp 3360-3380. 2. Williams HD et al., 2012. Mol Pharm *In press*

Results: 'Completely' digested formulations

- Increasing fenofibrate saturation level (i.e., dose) in Type II-MC, IIIA-MC, IIIB-MC and IV LBF increased supersaturation post-digestion, in turn promoting drug precipitation and decreased concentrations of solubilized drug over time (**Fig. 2**, left panels).
- Because of lower supersaturation ratios, tolfenamic acid only precipitated from the Type IIIB-MC at 100% saturation and Type IV >40% saturation (**Fig. 2,** right panels).
- **Fig. 3** below relates the precipitation risk and onset to the maximum supersaturation ratio (SR^M) attained on digestion,[2] which is simply the dose in the LBF divided by solubility in the digested LBF (AP_{BLANK}). Consistent with danazol,[2] precipitation of fenofibrate and tolfenamic acid was evident above a threshold SR^M of 2.5-3:

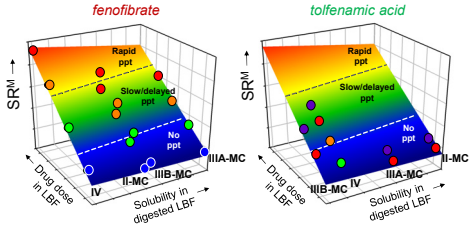

Fig. 3: 3D plots mapping drug precipitation on digestion of LBFs according to the maximum supersaturation ratio (SR^M).
ppt= precipitation (evident in Fig. 2). SR^M = dose / solubility in AP_{BLANK}

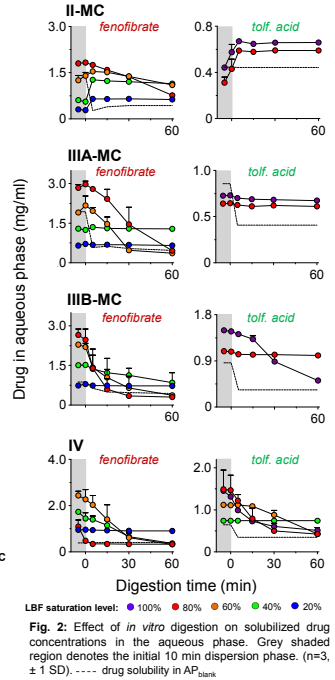

Fig. 2: Effect of *in vitro* digestion on solubilized drug concentrations in the aqueous phase. Grey shaded region denotes the initial 10 min dispersion phase. (n=3, ± 1 SD). ---- drug solubility in AP_{blank}