Creating a Lipid Formulation Classification System

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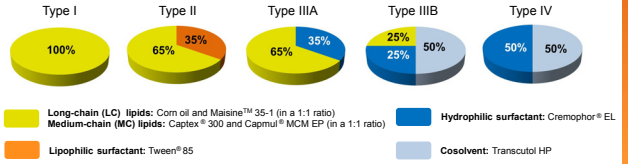
The LFCS Consortium: 2 - Toward the development of a new performance-based lipid formulation classification system (LF-P-CS)

- **Purpose:** The LFCS Consortium aims to establish standardized *in vitro* tests that are able to discriminate between a range of lipid-based formulations (LBFs).
- **Here, we explore the value of varying drug load and digestion conditions to better discriminate between LBF-type and suggest a novel performance-based classification system.**
- **Methods:** Type I, II and IIIA/B LBF containing medium-chain (MC) or long-chain (LC) lipids and Type IV lipid-free LBF (**Fig. 1**), with fenofibrate incorporated at 20-100% of saturated solubility in the formulation were investigated. LBF digestions were conducted using a pH-stat titrator (Titrando®, Metrohm) in 40 ml intestinal digestion medium (37°C) and were initiated via addition of porcine pancreatic extract. Three differing digestion conditions were used: standard fasted conditions (1 g of LBF, pH 6.5, 3 mM BS); dilute conditions (0.16 g LBF) and higher BS conditions (10 mM BS). Digestion samples were separated by centrifugation and the drug content in the poorly-dispersed 'oily' phase, colloidal aqueous phase (AP) and pellet determined by HPLC.
- **Results:** LBFs were assigned to three performance grades based on the degree of precipitation during digestion. Under standard conditions, Type I-LC, II-LC, IIIA-LC, I-MC LBF containing FFB at 80% saturation showed limited (<20%) drug precipitation and were classified as **Grade-A**, Type II-MC, IIIA-MC resulted in some precipitation (>20%) during digestion and were classified as **Grade-B.** Type IIIB-MC and IV resulted in precipitation on dispersion and digestion, and were classified as **Grade-C**. Lowering the drug load in Grade B/C LBF allowed greater differentiation of performance, resulting in the following rank order: II-MC>IIIA-MC>IIIB-MC>IV. Within Grade A, Type I-MC LBF showed increased drug precipitation on increasing bile salt (3-10 mM) and decreasing LBF concentration (1.0-0.16 g) whereas LC formulations did not.
- **Conclusion:** Application of performance criteria may offer a means of simple LBF classification based on behaviour during *in vitro* testing. LBF testing protocols that provide for increasing degrees of 'stress' increase the likelihood of precipitation on dispersion or digestion and may allow more effective rank ordering of formulation performance.

Fig 1: The eight LBFs investigated by the LFCS consortium[1,2] classified according to composition.



How can we discriminate?

- **Fig. 2** explores the possibility that dispersion, digestion in standard fasted conditions and digestion in diluted (i.e., 'stressed') conditions allows for discrimination between the performance of LBFs representative of Type I, II, III and IV.
- On dispersion, all LBFs except the Type IV LBF maintained all drug in a solubilized form (upper panel, **Fig. 2**). Type II-MC and IIIA-MC LBFs showed evidence of drug precipitation after digestion in standard fasted conditions, whereas equivalent LC LBFs and Type I-MC did not. In stressed digestion conditions (more diluted), the Type I-MC LBF precipitated. Type II-LC and IIIA-LC were therefore the 'best' (A-grade) formulations.
- Increasing drug loading and experiment duration as alternative 'stresses' to the performance of Type III A/B and IV LBFs is explored in **Fig. 3**. The use of higher drug loads allows for better discrimination between LBFs, particularly during the digestion phase (e.g., compare red/green/blue circles at ~110 mg). LBFs showing consistently good performance (i.e., A-grade) at both low and high drug loadings should be sought for reproducible and robust performance *in vivo*.

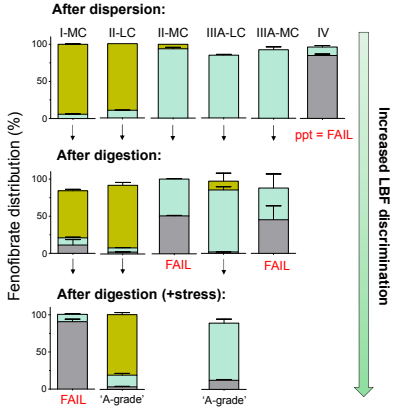


Fig. 2: Fenofibrate distribution across an OIL PHASE, AQUEOUS PHASE and PELLET following dispersion (top panel), 30 min digestion in standard fasted (middle panel) or 'stressed' (lower panel) conditions. n = 3, ± 1 SD. ppt; precipitation.

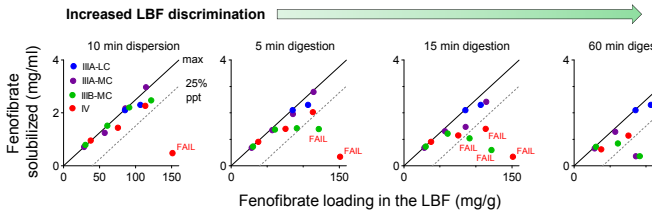
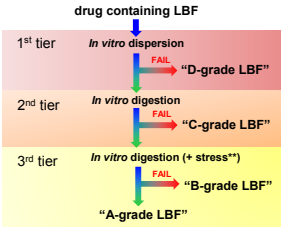


Fig. 3: Concentrations of solubilized fenofibrate as Type IIIA/B and IV LBFs are dispersed and digested. Performance of the LBFs at different drug loadings are shown. The solid black line represents the maximum fenofibrate concentration in the absence of precipitation.

A performance classification system



Classification will allow:

- Standardized performance criteria
- Discrimination between LBFs
- Improved LBF selection and design
- Increased understanding of LBF performance and testing

*** examples of 'stress' include:*
- increased drug loading,
- increased dilution,
- increased test duration (over 30 min).

- A **Lipid Formulation Performance Classification System** (LF-**P**-CS) may be constructed based on formulation performance across three experimental tiers intended to gradually increase formulation challenge, with A-grade formulations the most robust to precipitation.
- The LF-P-CS may provide an effective means of rank ordering formulation performance, however supporting *in vivo* studies are needed to endorse pass/fail performance criteria.

Conclusions

LBF testing protocols designed to gradually increase the degree of 'stress' will increase the likelihood of precipitation on dispersion or digestion, and may provide a means for more effective rank ordering of formulation performance. These protocols, coupled with *in vivo* performance data, are central to the establishment of a novel Lipid Formulation Performance Classification System (LF-P-CS).

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

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