Hywel D. Williams[1], Philip Sassene[2], Karen Kleberg[2], Jean-Claude Bakala-N'Goma[3], Frédéric Carrière[3], Marilyn Calderone[4], Vincent Jannin[5], Annabel Igonin[6], Anette Partheil[7], Delphine Marchaud[5], Jan Vertommen[6], Mario Maio[7], Ross Blundell[4], Hassan Benameur[6], Anette Müllertz[2], Colin W. Pouton[1] and Christopher J.H. Porter[1]

1. Monash Institute of Pharmaceutical Sciences, Parkville, Melbourne, Australia, 3052. 2 Department of Pharmaceutics, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100, Copenhagen, Denmark. 3. Laboratoire d'Enzymologie Interfaciale et de Physiologie de la Lipolyse, CNRS UPR 9025, Marseille, France. 4. Sanofi R&D, France. 5. Gattefossé SAS, 36 chemin de Genas, 69804 Saint-Priest, France. 6. Global Pharmaceutical Sciences, Capsugel, Division of Pfizer, France. 7. Merck KGaA, Darmstadt, Germany.

The LFCS Consortium: 2 - Effect of drug saturation level on lipid-based formulation performance during *in vitro* digestion

Introducing the LFCS Consortium

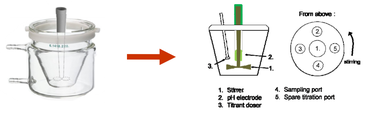
- The LFCS Consortium is a non-profit organization consisting of both academic and industrial partners with the overall objective of developing standardized *in vitro* tests for lipid-based formulations (LBFs). Work presented here details some of the experiments undertaken in the first year of the LFCS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

STUDY AIM: In the present poster, we investigate how increasing the drug saturation level in a range of lipid-based formulations affects performance during *in vitro* digestion.

- Formulations are grouped together according to their digestibility – formulations in the first results panel were only partially digested during the experiments while formulations in the second panel appeared to be completely digested (evidenced by no oil phase).

Methods

- One gram LBF was initially dispersed in 36mL digestion medium (pH 6.5, 2mM tris-maleate, 150mM NaCl, 1.4mM calcium, 3mM NaTDC, 0.75mM phosphatidyl choline, 37 C) before digestion was commenced on addition of 4mL porcine pancreatin suspension (600 USP units/mL).
- Digestion was continuously monitored over 30 minutes using a pH-stat titrator (Titrando®, Metrohm) shown in **Fig. 1.** Digestion samples were separated by centrifugation and danazol concentration in the floating oil phase, aqueous phase and pellet was determined by HPLC.
- Danazol equilibrium solubility was determined in "blank" aqueous phase digests ($AP_{DIGESTS}$) obtained following the digestion of drug-free LBF.



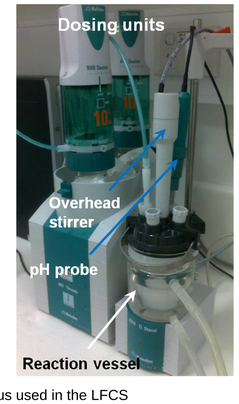


Fig.1: Photographs and schematic diagram of the digestion apparatus used in the LFCS

Results: "Partially" digested LBFs

- The effect of increasing danazol saturation level in Type I-III long-chain (LC) and Type I medium-chain (MC) formulations on the distribution of the drug is shown in **Fig. 2a.**
- For the LC formulations, the fraction of drug in each digestion phase was consistent on increasing danazol saturation level. As a result, the concentration of danazol solubilized in the aqueous phase generally increased with increasing drug loading, and above a 60% saturation level in Type II and III formulations, there was evidence of supersaturation (**Fig. 2b**). Danazol concentration in the aqueous phase varied amongst the LC formulations which reflected (i) the degree of digestion and (ii) the maximum solubility in anhydrous formulation which followed the rank order IIIA-LC > II-LC > I-LC.
- Contrastingly, the Type I-MC formulation showed evidence of drug precipitation above 60% saturation, (**Fig. 2a**) and thus, the highest solubilized drug concentrations were not achieved at the highest drug loading in this formulation type (**Fig. 2b**).

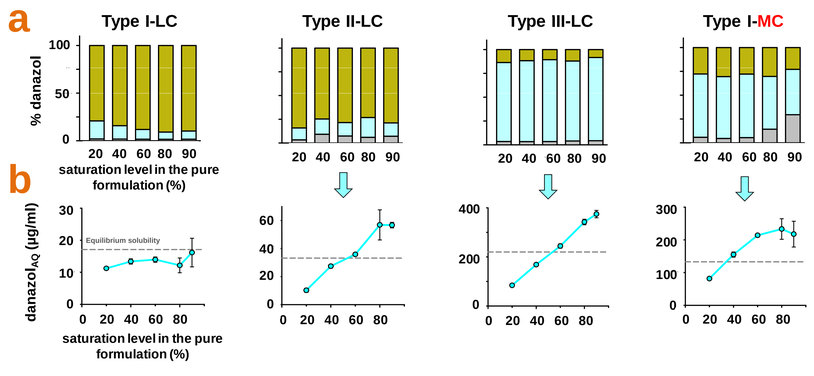


Fig. 2: Effect of increasing danazol saturation level in partially digested lipid formulations on (a) the distribution of drug between the partially digested OIL PHASE, AQUEOUS PHASE and PELLET after 30 minutes digestion and (b) the concentration of danazol in the aqueous phase. The dashed grey line denotes the equilibrium solubility of danazol in the drug-free digests of each formulation (n = 3).

Results: "Completely" digested LBFs

- Type II-MC, IIIA/B-MC and Type IV formulations all of these four formulations showed a trend of poorer performance (increasing drug precipitation) with increasing saturation level (**Fig. 3a**). The trend reflected the lipophilicity of the formulation with the most lipophilic, the Type II-MC formulation, showing good performance up to 60% saturation, while the least lipophilic, the Type IV formulation, showed significant precipitation at all saturation levels.
- Danazol concentrations in the aqueous phase revealed that these formulations could not maintain drug in a supersaturated state when loaded above a critical saturation level (**Fig. 3b**).

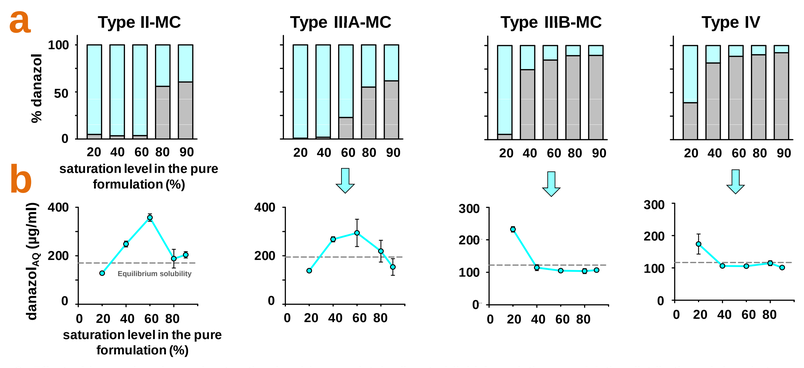


Fig. 3: Effect of increasing danazol saturation level in completely digested lipid formulations on (a) the distribution of drug between the AQUEOUS PHASE and PELLET after 30 minutes digestion and (b) the concentration of danazol in the aqueous phase. The dashed grey line denotes the equilibrium solubility of danazol in the drug-free digests of each formulation. (n = 3)

Conclusions

The *in vitro* digestion test proved effective in discriminating between good and bad performance of a range of LBFs: Long-chain LBFs maintained drug solubilization during digestion of formulations containing increasing drug saturation while medium-chain and lipid-free formulations did not.