Poster nr. R6269

Creating a Lipid Formulation Classification System

Martin L. Christiansen,[1] Philip Sassene,[1] Ditlev Birch,[1] Hywel D. Williams,[2] Marilyn Calderone,[3] Vincent Jannin,[4] Annabel Igonin,[5] Eduardo Jule,[5] Jan Vertommen,[5] Ross Blundell,[3] Hassan Benameur,[5] Christopher J.H. Porter,[2] Colin W. Pouton[2] and Anette Müllertz[1]

1. Department of Pharmaceutics, The University of Copenhagen, Universitetsparken 2, DK-2100, Copenhagen, Denmark . 2.Monash Institute of Pharmaceutical Sciences, Parkville, Melbourne, Australia, 3052. 3. Sanofi R&D, Montpellier, France. 4. Gattefossé SAS, 36 chemin de Genas, 69804 Saint-Priest, France. 5. Global Pharmaceutical Sciences, Capsugel, France.

The LFCS Consortium: 4 - Solubilisation of a weak base during in vitro digestion of 8 lipid-based formulations under 3 different conditions.

Purpose: The LFCS Consortium aims to establish standardized in vitro tests that can characterize a wide range of lipid-based formulations (LBF). Here, we study solubilisation of cinnarizine (weak base, logP 6) in 8 LBF, as a performance indicator, during in vitro digestion under 3 conditions.

Methods: Using a pH-stat titrator (Titrando®, Metrohm), LBF Type I, II, IIIA/B, LBF containing medium-chain (MC) or long-chain (LC) lipids and lipid-free Type IV LBF all with incorporated cinnarizine (80% saturated solubility in the LBF), were digested using porcine pancreatic extract in 40ml intestinal digestion medium at pH 6.5 (37°C) with continuous stirring and sampling at 15 and 30 min. Three digestion conditions were used:

Standard bile salt (BS) / High lipid: 3 mM BS / 1 g LBF
High BS / High lipid: 10 mM BS / 1 g LBF
Standard BS / Low lipid: 3 mM BS / 0.16 g LBF

Digestion samples were separated by centrifugation and the drug content in the oily phase (OP), colloidal aqueous phase (AP) and pellet was determined by HPLC.

Results: Reducing the dose of both MC and LC LBF under standard fasted conditions resulted in increased precipitation at 15 and 30 min digestion. For all LC LBF the precipitation of cinnarizine increased when BS level was increased. For the MC LBF, increasing BS level solubilised more drug in AP for I-MC and II-MC, but not for IIIA and IIIB-MC, emphasizing the role of BS for digestion of low-surfactant formulations. For Type IV no increased precipitation was seen upon reducing the LBF dose at standard BS levels, whereas increasing BS level at standard LBF dose decreased precipitation. This indicates the different behavior of LBF with low level of digestible components. None of the eight formulations resulted in a decrease of cinnarizine level in AP during digestion.

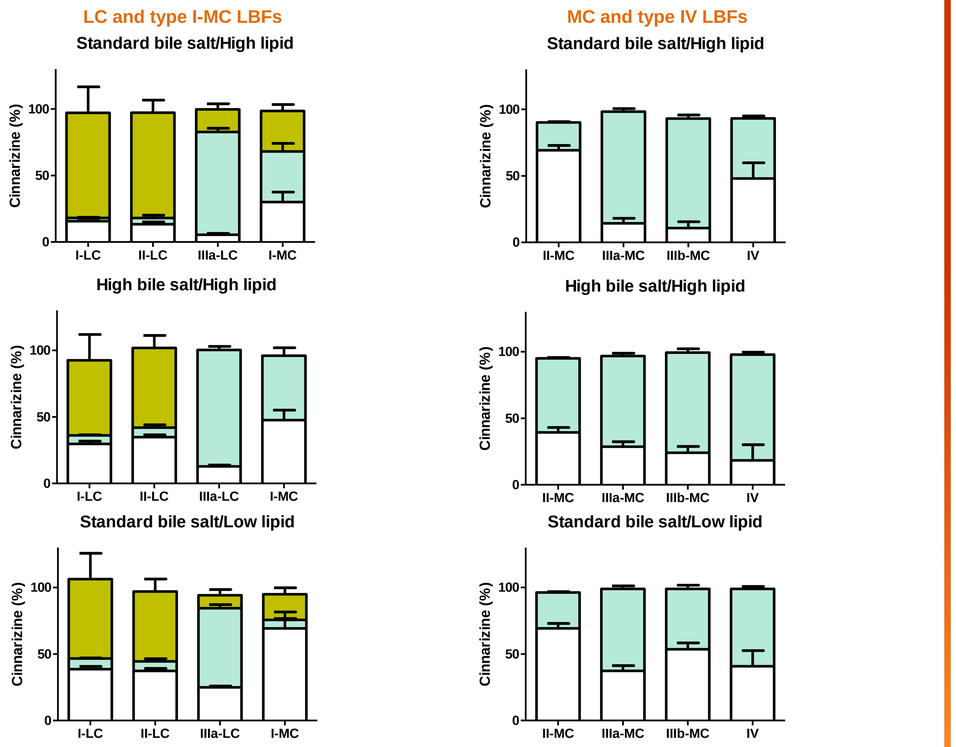

Figure 1. The drug distribution at the end point(30 min) of digestion of all 8 formulations evaluated in the LFCS. Left panel shows the poorly dispersed formulations forming an oil phase in standard test conditions(Standard bile salt/High lipid). Right panel shows the readily dispersed formulations which do not form an oil phase in standard test conditions. Oil Phase Aqueous Phase and Pellet phase

Table 1: The composition of the eight formulations investigated by the LFCS and the corresponding solubilities of cinnarizine in the formulations.

	Type I	Type II	Type IIIA	Type IIIB	Type IV
	100%	35% / 65%	35% / 65%	50% / 25% / 25%	50% / 50%
LC	36	32	30	-	-
MC	42	38	38	36	-
Lipid Free	-	-	-	-	40

Long-chain (LC) lipids: Corn oil and Maisine™ 35-1 (in a 1:1 ratio)
Medium-chain (MC) lipids: Captex 300 and Capmul MCM EP (in a 1:1 ratio)
Lipophilic surfactant: Tween 85
Hydrophilic surfactant: Cremophor EL
Cosolvent: Transcutol HP

Conclusions

For all 8 LBF, the amount of cinnarizine solubilised by the aqueous phase seemed unaffected by the extent of LBF digested. Decreasing the dose of MC and LC LBF resulted in increased cinnarizine precipitation for all LBF, inspite of a lower cinnarizine dose. The standardised *in vitro* lipolysis model is useful for the evaluation of LBF containing a weak basic drug and identification of the parameters that lead to precipitation.