In vitro solubilization, *in vivo* absorption and biodistribution of fenofibrate from lipid-based drug delivery systems containing monoacyl phosphatidylcholine

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PURPOSE

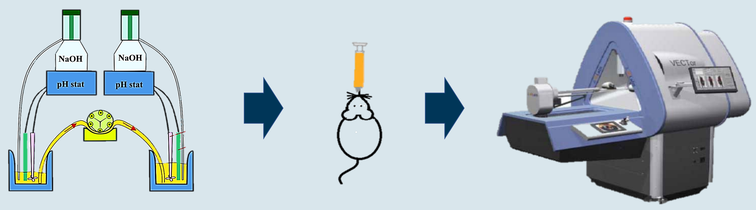
To investigate the effect of incorporating monoacyl phosphatidylcholine (MAPC) into lipid-based drug delivery systems (LbDDS) on the *in vitro* solubilization, *in vivo* oral absorption and biodistribution.

METHODS

Four LbDDS (Table 1) and one aqueous suspension (SUSP) (35 mg/mL fenofibrate in 0.5% HPMC) were formulated. *In vitro* lipolysis experiments simulating gastric and intestinal lipid digestion in rats were conducted. The *in vivo* bioavailability of the five formulations was determined in a pharmacokinetic study in rats (n = 5). Biodistribution in rats was investigated in a parallel study (n = 3); fenofibrate and triolein were labeled with ^{123}I and ^{125}I, respectively, and the biodistribution was determined using dual-isotope single photon emission computed tomography (SPECT) / computed tomography (CT).

Table 1: Composition of LbDDS before adding fenofibrate to obtain a fenofibrate concentration of 35 mg/g LbDDS

	Percentage (w/w)			
	Soybean oil	Maisine 35-1	Kolliphor EL	Lipoid S LPC 80
SBO	100	-	-	-
SBO-MAPC	70			
SNEDDS*	20	20	60	-
SNEDDS*-MAPC	20	20	30	30



In vitro lipolysis model

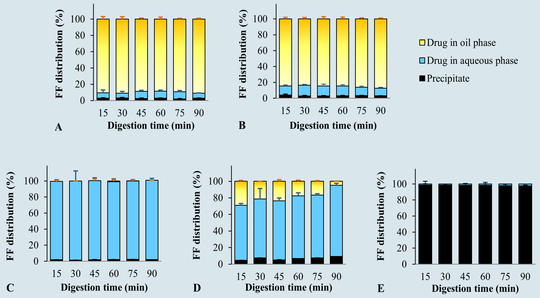
Pharmacokinetic study

In vivo imaging study

RESULTS

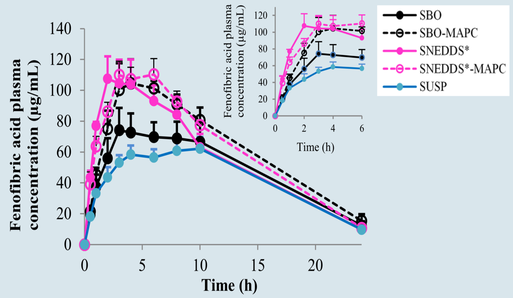
In vitro lipolysis

- At the beginning of the *in vitro* intestinal lipolysis, SBO-MAPC emulsified better and there was a slightly higher fenofibrate level in the aqueous phase than SBO (i.e., 6% in SBO vs. 14% in SBO-MAPC at 30 min).
- Adding MAPC to SNEDDS* increased fenofibrate distribution into the oil phase (i.e., 0% for SNEDDS* vs. 71% for SNEDDS*-MAPC at 30 min).
- No substantial effect of MAPC on drug precipitation was observed during the *in vitro* lipolysis.



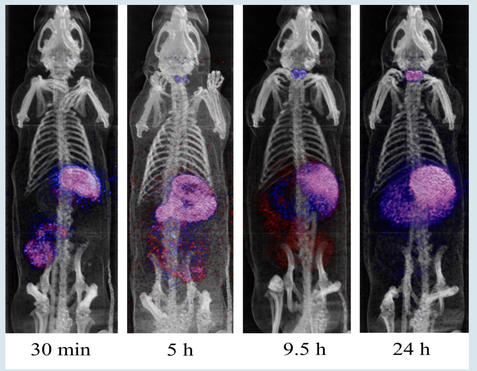
Pharmacokinetic study

- Absolute bioavailability of the 5 formulations: 24–35%.
- The $AUC_{0-6\ h}$ values of SBO-MAPC, SNEDDS* and SNEDDS*-MAPC were significantly larger than SUSP.
- Only SBO-MAPC and SNEDDS*-MAPC exhibited higher AUC_{0-24h} than SUSP.
- The pharmacokinetic data can be explained by enhanced emulsification of SBO-MAPC compared to SBO and a higher drug distribution into the oil phase from SNEDDS*-MAPC and SBO-MAPC compared to SNEDDS* as observed in the *in vitro* lipolysis data.



In vivo imaging study

- A significant amount of radioactivity (i.e., 28–59% and 24–60% of radiolabelled drug and lipid, respectively) remained in the stomach after 24 h.
- Rat stomach was constantly full despite fasting overnight, possible due to intake of faeces and bedding materials. Incomplete gastric emptying may thus be the reason for the low absolute bioavailability.
- Slow gastric emptying was likely a rate-limiting process for the drug absorption.



CONCLUSIONS

- Incorporating MAPC into SBO and SNEDDS* enhanced fenofibrate absorption in rats compared to SUSP.
- This absorption enhancing effect may be explained by the combination of adequate capacity to emulsify and the lipophilicity of the formulation.
- A high concentration of drug stayed in the stomach which explains the low absolute bioavailability.

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