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.

RESULTS

Pharmacokinetic study
• Absolute bioavailability of the 5 formulations: 24–35%.
• The AUC₀₋₆₉ values of SBO-MAPC, SNEDDS* and SNEDDS*-MAPC were significantly larger than SUSP.
• Only SBO-MAPC and SNEDDS*-MAPC exhibited higher AUC₀₋₂₄ 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.

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 ¹²³I and ¹²⁵I, 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

<table>
<thead>
<tr>
<th>Percentage (w/w)</th>
<th>Soybean oil</th>
<th>Maisine 35-1</th>
<th>Kolliphor EL</th>
<th>Lipoid S LPC 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBO</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SBO-MAPC</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SNEDDS*</td>
<td>20</td>
<td>20</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>SNEDDS*-MAPC</td>
<td>20</td>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

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
• The AUC₀₋₆₉ values of SBO-MAPC, SNEDDS* and SNEDDS*-MAPC were significantly larger than SUSP.
• Only SBO-MAPC and SNEDDS*-MAPC exhibited higher AUC₀₋₂₄ 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.
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