A Systematic Approach to Lipid-Based Formulation Development for a Poorly Soluble API, Fenofibrate

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PURPOSE
Fenofibrate, a prodrug of Fenofibric acid, is a poorly water soluble drug (0.087 mg/mL) for treatment of hyperlipoproteinemias. With a low melting point of 80°C to 81°C and a log P value >5, it is an ideal candidate for a lipid-based formulation. The objectives of this work were to:
1) Develop self-emulsifying drug delivery systems (SEDDS) for Fenofibrate, according to an in-house set of formulation guidelines.
2) Apply a biorelevant test to evaluate the performance of the formulation in digestion media.
3) Evaluate, if any, of changes to formulation composition, on the in-vitro digestion performance of the formulation.

METHODS

General formulation development procedures
Formulations were developed by following the systematic approach shown in Figure 1 that is detailed in the Gattefossé Bioavailability Enhancement Formulation Guidelines2.

Solubility studies – liquid excipients
Excess drug was added to each excipient (Table 1) and stirred at 25°C or 37°C. At various intervals, aliquots were centrifuged (16800g for 30 min) at the study temperature. Fenofibrate in the supernatant was diluted to approximately 0.1mg/mL and quantitated by RP-UPLC. Equilibrium was deemed reached when consecutive solubility values were within 5% of each other, and the study was stopped.

Solubility studies – Solid/Semi-solid excipients
Known compositions of Fenofibrate and excipients were stirred overnight at approximately 50°C after the excipients at 25°C above their melting points. Molten mixtures were transferred to microscopy slides, cover slip applied and equilibrated to 37°C for at least 24 hours. Samples were analyzed with thermal, cross-polarized microscopy using a 30°C/minute heating ramp from RT to 80°C. The composition at which Fenofibrate crystals were observed above the melting point of the excipients marked the solubility of Fenofibrate in the excipient.

Excipient miscibility, dispersion testing and ternary diagramming
Excipients for further study were selected after consideration of their solubility values. Known ratios of Fenofibrate and excipients were stirred overnight at 50°C after the excipients at 25°C above their melting points. Molten mixtures were transferred to microscopy slides, cover slip applied and equilibrated to 37°C for at least 24 hours. Samples were analyzed with thermal, cross-polarized microscopy using a 30°C/minute heating ramp from RT to 80°C. The composition at which Fenofibrate crystals were observed above the melting point of the excipients marked the solubility of Fenofibrate in the excipient.

Lipolysis Testing
Selected formulations were dispersed in digestion media at 37°C using a pH-Stat apparatus according to the Lipid Formulation Consortium Guidelines. Porcine pancreatic enzymes (4ml), prepared by extraction of 1g ground porcine pancreas in 5ml of 20M Tris buffer (pH 8.5), was added to 35ml of digestion media to initiate the digestion process which was studied up to 80 minutes after a 10 minute predigestion dispersion phase conducted without enzymes. Fatty acids liberated by lipolysis were continually titrated to pH 6.5 with 0.1 N NaOH. Aliquots (1ml) were periodically removed, mixed with 56µl of 4-bromophenylboronic acid (1.0M) as a lipase inhibitor, and then centrifuged at 21000g for 30 minutes. The supernatant was diluted 100µl to 10ml, with 5050 (v/v) acetonitrile/water and analyzed by RP-UPLC.

RESULTS

Excipient selection for formulation development
Equilibrium solubility values of Fenofibrate in the study excipients are listed in Table 1 below. Among the excipients screened, three were selected (highlighted in bold, Table 1) for formulation development based on drug solubility and also the excipients’ known miscibility. Gelucire® 48/16 and Capryol® 90 provided solubilization and good miscibility with each other. Laurglycol® 80 was selected as a co-solvent because it is miscible with both excipients and also to see how subtle changes in excipient chemistry/formulation composition would impact its performance during digestion.

Table 1. Solubility values of Fenofibrate

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Solubility (mg/mL)</th>
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<tbody>
<tr>
<td>Capryol® 90</td>
<td>121</td>
</tr>
<tr>
<td>Gelucire® 48/16</td>
<td>77</td>
</tr>
<tr>
<td>Laurglycol® 80</td>
<td>61</td>
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</tbody>
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EXCIPENT COMPATIBILITY CHART

Combining excipients was evaluated using Ternary Diagramming. Twenty five placebo blends, at different ratios of the three excipients were subject to dispersion testing. Results are summarized in Figure 2. The average particle size of the microemulsions formed on dispersion ranged from 13nm to 350nm. Subsequently, three formulations representing points A, B, and C (composition in the table below Figure 2) were prepared by melting the combined excipients while heating and stirring, and then adding Fenofibrate at 80mg.

Lipolysis Testing

In a preliminary lipolysis screening, Formulation A solubilized 26% of the Fenofibrate load of 80mg, while Formulations B and C solubilized over 45% of the Fenofibrate (>1.0 mg/mL), an 11-fold increase in solubility. Subsequently, Formulations B and C underwent complete lipolysis testing 60 min, n=3. The results (Figure 3) demonstrate significant differences in the ability of Formulations B & C to maintain Fenofibrate solubility during digestion, relative to the predigestion dispersion phase.

CONCLUSIONS
1. It was possible to achieve an 11-fold increase in Fenofibrate solubility with lipid-based formulations, developed systematically, following the Gattefossé Formulation Guidelines.
2. In-vitro lipolysis testing demonstrated that even though Formulations B & C have similar solubilization capacity for Fenofibrate, their performance can significantly vary during digestion.
3. Formulation composition matters. A difference of 10% in Laurglycol® 80 vs. Capryol® 90 between formulations B and C, provided a significant difference in performance during the digestive test despite the similarity of the chemistries of these two excipients (C12 and C-10, respectively).
4. Solubility and dispersion testing are useful tools for characterizing and selecting formulations but are not necessarily predictive of formulation performance in biorelevant media during digestion.
5. LB formulations can be further optimized, for example, through use of a different combination of excipients, in order to maintain higher solubilities during digestion.

REFERENCES