W1091

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[1]) 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, the impact, 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 Guidelines[2].

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 (16800xg 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.

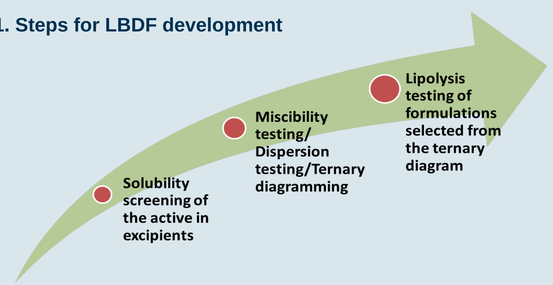
Solubility studies – Solid/Semi-solid excipients

Known compositions of Fenofibrate and excipients were stirred overnight at approximately 50°C after melting the excipients at 20°C above their melting points. Molten mixtures were transferred to microscope slides, cover slip applied and equilibrated to 25°C for at least 24 hours. Samples were analyzed with thermal, cross-polarized microscopy using a 30°C/minute heating ramp from RT to 60°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 each excipient were combined and vortexed to mix. If needed, blends were heated to melt the excipients. The mixtures were visually inspected for homogeneity after standing at room temperature over night. Dispersion testing of homogeneous excipient blends was performed in a USP dissolution apparatus II (paddles) at 37°C by mixing 2g of blend in 400mL of DI water for 30 minutes. Particle size testing of the resulting microemulsions was performed with a Nicomp DLS 3000 at 37˚C, 90˚ scatter angle and 0.692cP viscosity. Each sample was analyzed in duplicate for 5 minutes for each run.

Figure 1. Steps for LBDF development



Lipolysis Testing

Selected formulations were dispersed in digestion media at 37°C using a pH-Stat apparatus according to the Lipid Formulation Consortium Guidelines[3]. Porcine pancreatic enzymes (4mL), prepared by extraction of 1g ground porcine pancreas in 5mL of 2mM Tris buffer (pH 6.5), was added to 36mL of digestion media to initiate the digestion process which was studied up to 60 minutes after a 10 minute predigestion dispersion phase conducted without enzymes. Fatty acids liberated by digestion were continually titrated to pH 6.5 with 0.1 N NaOH. Aliquots (1mL) were periodically removed, mixed with 5µL of 4-bromophenylboronic acid (1.0M) as a lipase inhibitor, and then centrifuged at 21000xg for 30 minutes. The supernatant was diluted 100µL to 10mL with 50/50 (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. Lauroglycol™ 90 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

		Solubility (mg/mL)	
Trade Name	Description	25°C	37°C
Capryol™ 90	**Propylene glycol monocaprylate NF (Type II)**	**121**	**212**
Gelucire® 44/14	Lauroyl polyoxylglycerides NF	125	NA
Gelucire® 48/16	**Polyoxyl stearate (Type I) USP-NF**	**128**	**NA**
Labrafac® Lipophile WL 1349	Medium chain triglycerides NF /JPE	77	140
Labrafil® M 1944 CS	Oleoyl polyoxyl-6 glycerides NF	61	102
Labrasol® ALF	Caprylocaproyl polyoxyl-8 glycerides NF	97	156
Lauroglycol™ 90	**Propylene glycol monolaurate NF/EP (Type II)**	**84**	**162**
Lauroglycol™ FCC	Propylene glycol monolaurate NF/EP (Type I)	83	150
Maisine™ CC	Glyceryl monolinoleate NF	49	89
Plurol® Oleique CC 497	Polyglyceryl-3 dioleate NF	30	42
Transcutol® HP	Diethylene glycol monoethyl ether NF/EP	158	266

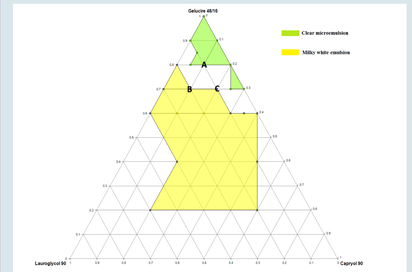
Miscibility, Dispersion testing and Ternary Diagram

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/g.

Lipolysis Testing

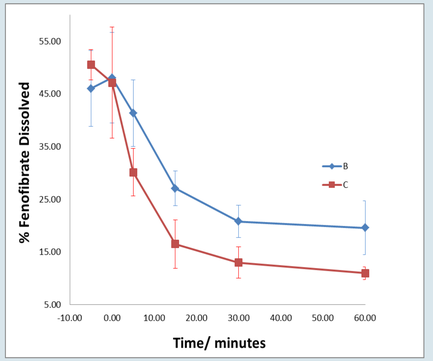
In a preliminary lipolysis screening, Formulation A solubilized 26% of the Fenofibrate load of 80mg/g, while Formulations B and C solubilized over 45% of the Fenofibrate (>1.0 mg/mL, an 11-fold increase in solubility). Subsequently, Formulations B and C underwent complete lipolysis testing (60 min, n=3). 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.

Figure 2. Ternary diagram of Fenofibrate placebo formulations



Gelucire® 48/16	Lauroglycol™ 90	Capryol™ 90	Fenofibrate 80mg/g	Formulation Designation
0.8	0.1	0.1		A
0.7	0.2	0.1		B
0.7	0.1	0.2		C

Figure 3. In-vitro digestive performance test of Fenofibrate formulations B and C from Figure 2



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 Lauroglycol™ 90 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.

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3. Williams H, Sassene P, Kleberg K et al. Toward the Establishment of Standardized In Vitro Tests for Lipid-Based Formulations, Part 1: Method Parameterization and Comparison of In Vitro Digestion Profiles Across a Range of Representative Formulations. *Journal of Pharmaceutical Sciences*. 2012;101(9):3360-3380.

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