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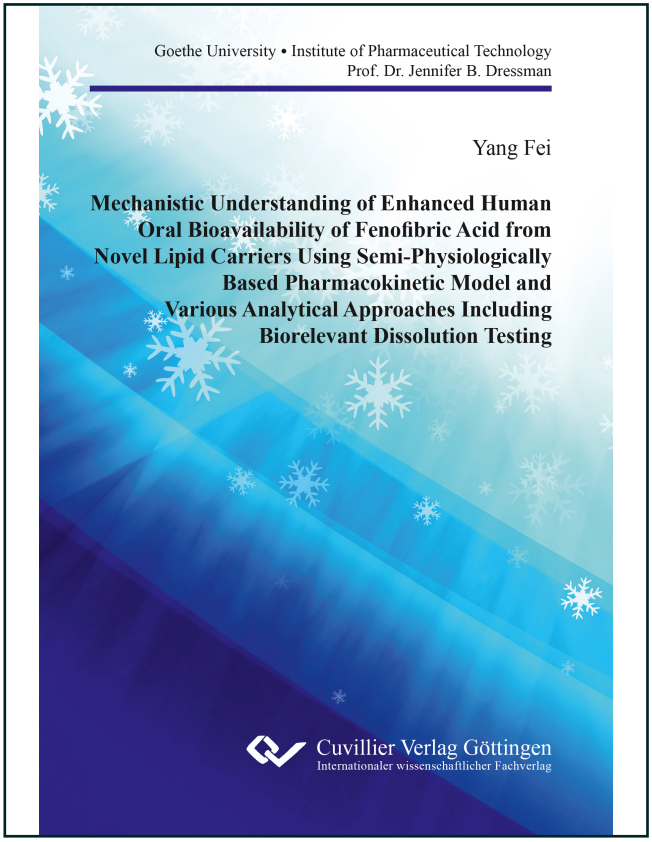
Mechanistic Understanding of Enhanced Human Oral Bioavailability of Fenofibric Acid from Novel Lipid Carriers Using Semi- Physiologically Based Pharmacokinetic Model and Various Analytical Approaches Including Biorelevant Dissolution Testing



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Chapter 1. Introduction

1.1 Lipid-based formulation – an overview

Lipid-based formulations (LBFs) are not a recent invention (Hauss, 2007), their history dates back to more than 50 years ago (Feeney et al., 2016). However, LBFs do not occupy a large segment of the market for the oral delivery of poorly soluble drugs (Hauss, 2007). The majority of formulation endeavors remains solid state, e.g. blending, complex formation, and/or solid dispersion of active pharmaceutical ingredient (API) with solid excipients. API modifications such as salt formation, modification of particle size and/or morphology etc. are also applied often. Sometimes, a solid formulation can prove to be very difficult, especially for drugs with extremely high lipophilicity or a pronounced food effect. In such cases, lipid-based formulations may be an appropriate alternative (e.g. Lin et al., 2011; Wei et al., 2010). In addition, lipid formulations have some advantages over traditional, solid formulations in product development. Nowadays, several types of lipid-based drug delivery systems, such as emulsions, suspensions, oil solutions, and self-microemulsifying drug delivery systems (SMEDDSs) are available (Han et al., 2009). The mechanisms by which lipid formulations can improve bioavailability of poorly soluble drugs include: by direct presentation of the drug in solubilized form in the gastrointestinal (GI) tract, thus avoiding slow dissolution from solid state (Mohsin et al., 2009) and, utilization of alternative uptake pathways through the lymph circulation. If physical stability issues can be solved, the perspective of LBFs will be even more promising in the future.

1.2 Oral Lipid-based formulation with examples

There are numerous examples showing significantly enhanced absorption of poorly soluble drugs using LBFs under fasted condition (e.g. Humberstone and Charman, 1997; Porter et al., 2008). Among them, the application of oral solutions and lipid suspensions include: acetyl sulfisoxazole, dicumarol, griseofulvin, antimalarial amine, cinnarizine, cyclosporin, DDT, halofantrine, probucol, seocalcitol, vitamin D_3, progesterone and dexamethasone. Examples of studies investigating drugs from

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oil-in-water emulsions include: danazol, griseofulvin, penclomedine, phenytoin, vitamin E, ibuprofen and acyclovir. In addition, examples of studies of SEDDSs and SMEDDSs include: cyclosporin, halofantrine, ontazolast, vitamin E, coenzyme Q_{10}, simvastatin, biphenyl dimethyl dicarboxylate, indomethacin, progesterone, tocotrienols, danazol, carvedilol, solvent green 3, silymarin, atorvastatin, itroconazole, atovaquone, seocalcitol, disopyramide, ibuprofen, ketoprofen and tolbutamide (e.g. as summarized by Porter et al., 2008).

An extensive review of commercially available oral LBFs was published by Hauss (Hauss, 2007). According to his analysis, oral lipid-based products began entering the marketplace around 1981. As of 2005, at least 31 drugs in 41 lipid-based formulations intended for oral delivery were commercially available in the United States, the United Kingdom, and Japan. By 2007, they accounted for approximately 3% of commercially available oral formulations. Most of these LBFs were housed in soft gelatin capsules with the unit dose ranging from 0.25μg to 500mg. Most of them comprised both lipid excipients/surfactants and nonlipid excipients. Table 1-1 contains a summary of selected LBF products (Hauss, 2007).

Table 1-1

List of selected commercially available LBFs for oral administration in the United States in 2005 (table taken from Hauss, 2007).

Molecule	Trade name	Company	Date of initial marketing
Amprenavir	Agenerase®	GlaxoSmithKline	2000 in the U.K.
Bexarotene	Targretin®	Ligand	2001 in the U.K.
Calcitriol	Rocaltrol®	Roche	1996 in the U.K. (capsules only)
Ciprofloxacin	Cipro®	Bayer	
Cyclosporin A	I. Neoral®	Novartis	1995 in the U.K.
CyclosporinA	II. Sandimmune®	Novartis	

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Table 1-1 (*Continued*)

CyclosporinA	III Gengraf®	Abbott	
Cyclosporin A	IV Cyclosporin capsules	Sidmak	
Doxercalciferol	Hectorol®	Bone care	
Dronabinol	Marinol®	Roxane and Unimed	
Dutasteride	Avodart™	GlaxoSmith Kline	2003 in the U.K. (capsules only)
Isotretinoin	Accutane®	Roche	1983 in the U.K.
Lopinavir and ritonavir	Kaletra®	Abbott	2001 in the U.K.
Progesterone	Prometrium®	Solvay	
Ritonavir	Norvir®	Abbott	1999 in the U.K.
Saquinavir	Fortovase™	Roche	1998 in the U.K. Discontinued in 2006
Sirolimus	Rapamune®	Wyeth-Ayerst	2001 in the U.K.
Tipranavir	Aptivus®	Boehringer Ingelheim	
Tolterodine tartrate	Detrol® LA	Pharmacia & UpJohn	2001 in the U.K.
Tretinoin	Vesanoid®	Roche	2001 in the U.K.
Valproic acid	Depakene®	Abbott	

1.3 The Lipid Formulation Classification System and its application

The Lipid Formulation Classification System (LFCS) was first described by Pouton (Pouton, 2000). LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation (Porter et al., 2008). As summarized in Table 1-2, type I LBFs consists of excipients that comprise of API in triglycerides or an oil-in-water emulsion which can be stabilized by a small amount of emulsifier(s). This category exhibits poor initial aqueous dispersion. Thus it requires digestion to generate more amphiphilic products in order to promote drug transfer into the colloidal aqueous phase. Type II LBFs are isotropic mixtures of lipids and lipophilic surfactants,

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Table 1-2

The Lipid Formulation Classification System (LFCS) showing typical compositions and properties of lipid-based formulations (table taken from Porter et al., 2008; Pouton, 2006).

Increasing hydrophilic content →					
	Type I	Type II	Type IIIA	Type IIIB	Type IV
	Typical composition (%)				
Triglycerides or mixed glycerides	100	40-80	40-80	<20	-
Water-insoluble surfactants (HLB<12)	-	20-60	-	-	0-20
Water-soluble surfactants (HLB>12)	-	-	20-40	20-50	30-80
Hydrophilic co-solvents	-	-	0-40	20-50	0-50
Characte-ristics	Non-dispersing; requires digestion	SEDDS without water-soluble components	SEDDS/SMEDDS with water-soluble components	SMEDDS with water-soluble components and low oil content	Oil-free formulation based on surfactants and cosolvents
Particle size of dispersion (nm)	Coarse	100-250	100-250	50-100	<50
Significance of aqueous dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

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Table 1-2 (*Continued*)

Solvent capacity advantage	GRAS status; simple; excellent capsule compatibility	Unlikely to lose solvent capacity on dispersion	Clear or almost clear dispersion; drug absorption without digestion	Clear dispersion; drug absorption without digestion	Good solvent capacity for many drugs; disperses to micellar solution
Solvent capacity disadvantage	Formulation has poor solvent capacity unless drug is highly lipophilic	Turbid o/w dispersion (particle size 0.25–2μm)	Possible loss of solvent capacity on dispersion; less easily digested	Likely loss of solvent capacity on dispersion	Loss of solvent capacity on dispersion; may not be digestible

which can self-emulsify to form fine oil-in-water emulsions when introduced in an aqueous solution. They can generate a large interfacial area, which in turn allows efficient partitioning of the API between the oil droplets and the aqueous phase, and facilitate effective absorption. Type III LBFs, usually referred to as Self-MicroEmulsifying Drug Delivery Systems (SMEDDS), are formed by inclusion of co-solvents with hydrophilic surfactants. Type IIIA formulations typically achieve a somewhat slower dispersion rate than the Type IIIB counterpart, although the risk of API precipitation on dilution is lower, given the higher lipid content. Type IV LBFs contain predominantly hydrophilic surfactants and cosolvents without natural lipids, thus represent the most hydrophilic category. They usually offer enhanced API loading and can produce extremely fine dispersions when introduced to aqueous media (see Table 1-2).

Many studies regarding development of LBFs within the LFCS framework, including some with fenofibrate (e.g. Hu et al., 2011; Mohsin et al., 2009; Ratanabanangkoon et al., 2008), have been published. Their major focus has been composition optimization by varying type and amount of lipid-based excipients with the help of phase diagram and dispersion experiments (Anby et al., 2012; Hu et al., 2011; Mohsin et al., 2009; Ratanabanangkoon et al., 2008; Williams et al., 2012). Prior

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to the present work (Fei et al., 2013c), however, few if any attempts have been made to simulate plasma concentration profiles following treatment with LBFs. In chapter 5, a novel *in vitro-in silico-in vivo* (*IVISIV*C) approach using *in vitro* biorelevant dissolution data and mechanistic *in silico* pharmacokinetic (PK) modeling will be discussed in detail.

1.4 Potential advantages / disadvantages of lipid formulations

LBFs share the feature that they are able to present the API as a stabilized solution over a period of time (ideally the GI transit time). In fact, the term "lipid-based formulation" means a variety of formulations that share many similarities (Table 1-3).

Table 1-3

Options for lipid formulation of poorly water-soluble drugs (table taken from Pouton, 2006).

Technology	Potential advantage	Potential disadvantage
Lipid solutions (LFCS Type I lipid systems)	Freedom to operate, safe and effective for lipophilic actives, drug is presented in solution avoiding the dissolution step	Limited to highly lipophilic or very potent drugs, requires encapsulation
Self-emulsifying drug delivery systems (SEDDS) and SMEDDS (LCFS Type II or Type III lipid systems)	Prior art available, dispersion leads to rapid absorption and reduced variability, absorption not dependent on digestion	Surfactant may be poorly tolerated in chronic use, soft gel or hard gel capsule can be used in principle but seal must be effective
Solid or semi-solid SEDDS	Could be prepared as a free flowing powder or compressed into tablet form	Surfactant may be poorly tolerated in chronic use, reduced problem of capsule leakage, physical stability of product questionable—drug or polymer may crystallize
Surfactant-cosolvent systems (LFCS Type IV 'lipid' systems)	Relatively high solvent capacity for typical APIs	Surfactant may be poorly tolerated in chronic use, significant threat of drug precipitation on dilution

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The disadvantages of LBFs are listed in the right column of Table 1-3. In short, the potential formulation difficulty, tolerance and stability issues should be noted.

1.5 Evaluation of oral lipid-based formulations

The design of LBFs can be challenging, particularly for appropriate selection of lipid excipients to ensure reliable *in vivo* performance (Griffin et al., 2014). Considerations should be taken not only for achieving maximum drug load in LBF, but also for maintaining the API in a solubilized state throughout the gastrointestinal exposure. For the past decade, although a variety of *in vitro* approaches was available, the influence of dilution, dispersion, precipitation and digestion on *in vivo* performance of LBFs is still unclear. In addition to the present *IVISIV*C approach (Fei et al., 2013c), updated and predictive *in vitro* tools for LBF characterization are still needed.

1.5.1 Dispersion

The dispersion test is a typical and useful approach to characterize dispersion property of LBFs. In earlier times, Mohsin et al. (2009) studied the dispersion behaviour of fenofibrate LBFs in 100mL water at 30°C. The amount and rate of API precipitated during dispersion were measured. However, the testing did not reflect *in vivo* conditions in the human GI tract well. Since the volume of fasted stomach is around 50mL and patients are taking a dose with 240mL of water, the average available volume for dispersion could be as high as 290mL. Considering the continuous emptying pattern of water from the stomach, the actual volume for dispersion could also be considerably less. In the small intestine, poorly soluble drugs will follow the colloid phases during dispersion/digestion and will finally end up in mixed micelles. When they dissociate in the unstirred water layer (UWL), the released drug will be absorbed as a free molecule. However, many of the mechanisms involved in the absorption processes are not completely understood (Müllertz et al., 2010). In order to address the *in vivo* conditions better, modified dispersion and dynamic dispersion testing methods (using USP dissolution apparatus) were evolved, as described by Griffin et al. (2014). Among these, microscopic and macroscopic

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evaluation of diluted fenofibrate LBF in biorelevant media was part of the work in Frankfurt, and will be described in detail in Chapter 4.

1.5.2 Digestion

One important aspect to consider when developing LBFs is the environment that the delivery system will meet upon ingestion. This includes both the gastrointestinal juices and the digestion processes. In the fasted intestine, the dispersed lipid formulation encounters a relatively small concentration of bile salt and presumably a low level of enzymes. Food intake induces secretion of gastric lipase in the stomach, where a minor proportion of lipid digestion (about 20-30%) takes place. The major part of digestion occurs in the small intestine and is catalyzed by pancreatic lipases.

The *in vitro* lipid digestion (lipolysis) model is recognized as an effective tool to facilitate improved evaluation of LBFs (e.g. Sek et al., 2002; Griffin et al., 2014). While the experimental detail of the model differs slightly between laboratories (Devraj et al., 2013a,b; Lee et al., 2013; Mu et al., 2013; Williams et al., 2013a,b), the basic principles are the same (see Fig. 1-1).

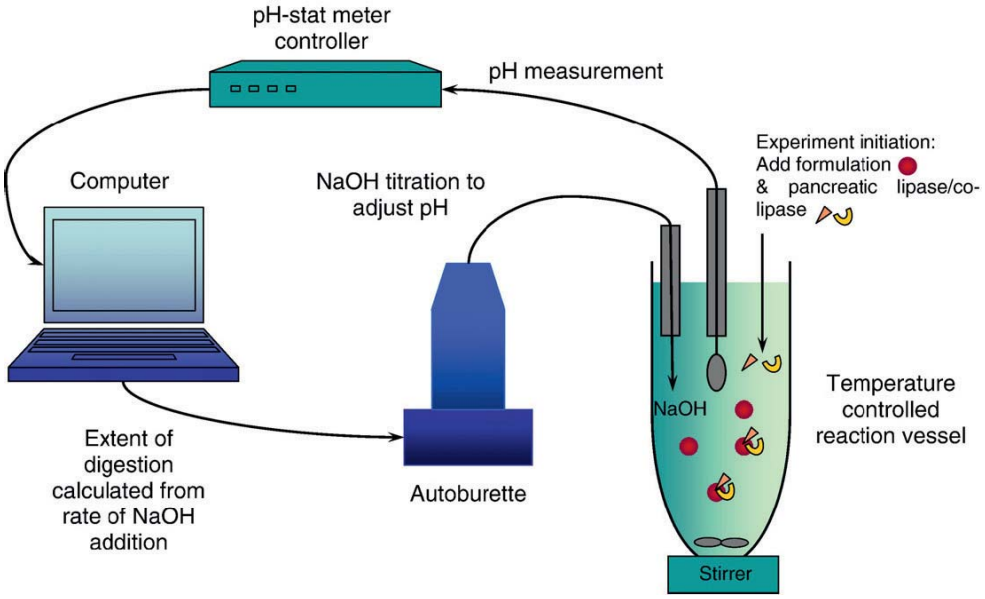

Fig. 1-1. Lipid digestion model for *in vitro* assessment of lipid formulations (figure taken from Porter et al., 2008).

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The model is built around a temperature controlled (37°C) vessel containing digestion buffer, bile salts (BS) and phospholipids (PL), into which the LBF is introduced. Digestion is initiated by addition of pancreatic lipase/co-lipase. The onset of lipid digestion results in liberation of fatty acids (FA), which in turn causes a transient drop in pH. This is quantified by a pH electrode, which is coupled with a pH-stat controller and autoburette. The liberated FA is automatically titrated via addition of an equimolar quantity of NaOH. Thus, the pH is maintained, and quantification of the digested lipid content is possible. Throughout the process, samples are taken and separated into a poorly dispersed oil phase, a highly dispersed aqueous phase and a precipitated pellet phase (see Fig. 1-2). Quantification of drug in solubilized form provides an indication of relative likelihood of the LBF regarding *in vivo* precipitation, and therefore provides a mechanism to rank-order potential *in vivo* performance for a series of lipid formulations (Porter et al., 2008).

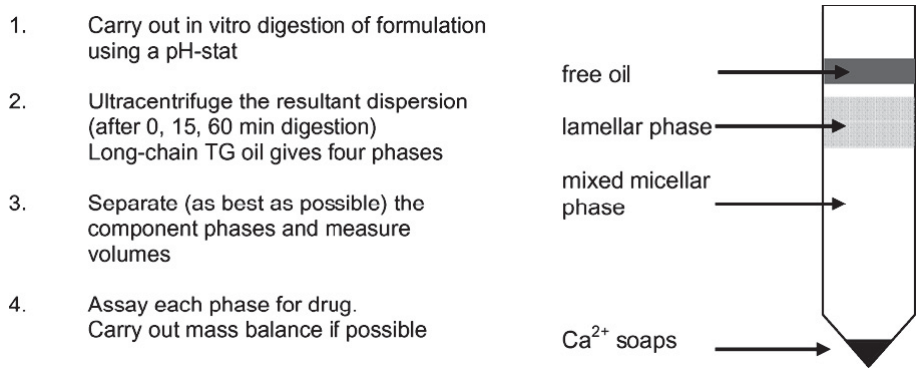

Fig. 1-2. *In vitro* simulation of the fate of LBF in the intestinal lumen (figure taken from Pouton, 2006).

It should be noted that however, this *in vitro* lipolysis method is not always *in vivo* predictive. For instance, Griffin et al. (2014) investigated the digestion behavior of three fenofibrate lipid formulations using above-mentioned *in vitro* model. While extensive precipitation was observed with the Type IIIB/IV formulation relative to the Type IIIA during *in vitro* digestion, no significant difference in *in vivo* bioavailability could be found in Landrace pigs following oral administration of these formulations.

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1.5.3 Dissolution

In vitro dissolution testing is widely used for quality control (QC) of drug release from formulations, including LBFs. However, *in vivo* relevance is not always ensured.

As an example of comparing performance of different lipid dosage forms, Shah et al. (1994) investigated *in vitro* release of Ro 15-0778 from an oral solution, a SEDDS, a spray-dried powder, and a micronized formulation. Samples were determined in USP2 and 900mL dissolution medium with 5% of surfactant (Alkamuls EL-719). Superior *in vitro* drug release was observed for the PEG400 solution and SEDDS (Fig. 1-3), indicating its usefulness in comparing LBF-enhanced release of poorly soluble drug against their solid dosage forms. However, this trend was not reflected well in *in vivo* results (data not shown). A potential reason for the lack of concurrence is that the presence of the solubilizing surfactant in the dissolution medium led to an underprediction of drug precipitation *in vivo* (Hauss, 2007).

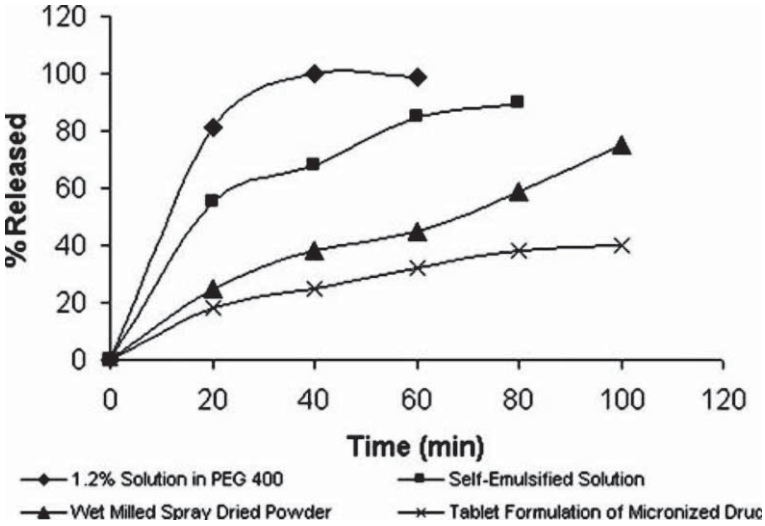

Fig. 1-3. *In vitro* release profiles of Ro 15-0778 from different formulations (Shah et al., 1994).

As another example, the effect of chain length, HLB and saturation of fatty acid present in the glyceride on Ro 15-0778 release from lipid-based solutions was evaluated using the paddle apparatus at 50rpm in 900mL of 5% Cremophor EL solution (Hauss, 2007; Shah et al., 1994). Drug release was optimal from a SEDDS

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