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Research Paper

Lipidic dispersion to reduce food dependent oral bioavailability of fenofibrate: *In vitro*, *in vivo* and *in silico* assessments

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ABSTRACT

Novel formulations that overcome the solubility limitations of poorly water soluble drugs (PWSD) are becoming ever more critical to a drug development process inundated with these compounds. There is a clear need for developing bio-enabling formulation approaches to improve oral bioavailability for PWSD, but also to establish a range of predictive *in vitro* and *in silico* biopharmaceutics based tools for guiding formulation design and forecasting *in vivo* effects. The dual aim of this study was to examine the potential for a novel lipid based formulation, termed a lipidic dispersion, to enhance fasted state oral bioavailability of fenofibrate while assessing the predictive ability of biorelevant *in vitro* and *in silico* testing. Formulation as a lipidic dispersion improved both dissolution and solubilisation of fenofibrate through a combination of altered solid state characteristics and incorporation of solubilising lipidic excipients. These changes resulted in an increased rate of absorption and increased maximal plasma concentrations compared to a commercial, micronised product (Lipantil® Micro) in a pig model. Combination of biorelevant *in vitro* measurements with *in silico* physiologically based pharmacokinetic (PBPK) modelling resulted in an accurate prediction of formulation performance and forecasts a reduction in food effects on fenofibrate bioavailability through maximising fasted state dissolution of fenofibrate.

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1. Introduction

Designing novel formulations to enhance the oral bioavailability of poorly water soluble drugs has long been a key driver of the pharmaceutical industry. The poor intrinsic solubility of Biopharmaceutical Classification Scheme (BCS) class II compounds has stifled development of many emerging therapeutic compounds. With up to 75% of drug development candidates displaying poor aqueous solubility, the bioavailability limitations posed still form an unmet challenge for pharmaceutical drug development [1].

The absorption of these poorly water soluble drugs (PWSD) is limited by their poor solubility and resultant slow dissolution rate within gastrointestinal fluid [2]. In addition these drugs can commonly display variable food effect bioavailability, with poor solubility being a strong predictor of positive food effects [3,4]. Ingested lipids interact with bile salts and phospholipids in the post-prandial intestinal milieu to solubilise PWSD [5]. While this can enhance absorption of PWSD, it can also lead to variable bioavailability during clinical use depending on the prandial state at the time of dose administration, potentially resulting in loss of efficacy [6]. Formulations that enhance bioavailability of these compounds, maximising it in the fasted state, will therefore result in reduced food effects [7,8].

Formulation techniques that enhance bioavailability of PWSD in a predictable and reproducible manner are becoming increasingly critical. The design of these bio-enabling formulation approaches can be described using the concept of the "spring and parachute" approach [9]. Facilitation of dissolution is thought of as providing an initial "spring", while inclusion of solubilising excipients or precipitation inhibitors can act as a "parachute", retarding the transition back to a lower energy, crystalline form. Critically, the selection of formulation methods and/or excipients to maximise oral bioavailability is best guided by reliable and predictable *in vitro* biopharmaceutical screening.

The advent of Developability Classification System (DCS), based on a revised BCS, has placed greater focus on understanding of the

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factors affecting drug and formulation performance *in vivo*. By sub-dividing BCS class II compounds into class IIa and IIb, based on more biorelevant screening, the DCS enables earlier prediction of drug limitations in development, guides formulation strategy and can be used to estimate formulation performance [2]. Complete oral absorption for dissolution rate limited (class IIa) drugs can generally be achieved by simply controlling particle size, surface area and wettability, while solubility limited candidates (class IIb) require more complex solubilisation techniques, such as nanonisation, solid dispersion, salt or co-crystal formation or inclusion of solubilising excipients, such as lipids and surfactants [2,10].

It is also imperative when designing bio-enabling formulation strategies to establish reliable *in vitro–in vivo* correlations. While solubility, dissolution and permeability tests are often a merit for conventional formulations, more advanced biorelevant screening tools and computational modelling approaches are needed for reliably predicting *in vivo* performance [3]. *In silico* physiologically based pharmacokinetic (PBPK) modelling builds on the available of *in vitro* data and is being increasingly used to forecast formulation and food effects. Several programs are now commercially available for model generation and application to assess *in vivo* performance, including Gastroplus®, Simcyp® and PK-Sim® [11]. Combination of *in vitro* solubility, dissolution and precipitation testing with *in silico* data modelling has shown to be particularly effective at predicting *in vivo* performance of oral dosage forms [12–14].

Fenofibrate is an orally active, lipid regulating, BCS class II compound, and is a good model for the assessment of formulation strategies to enhance bioavailability and eliminate food effect [12,13]. The Lipantil Micro® formulation, a micronised product, displays food dependent bioavailability, and therefore requires administration with food. A re-formulated product, Lipantil® Supra was developed using NanoCrystal® technology, to overcome this limitation and allows food independent administration and dose reduction [7,8,15].

The aim of this study was to explore an alternative bio-enabling formulation approach to overcome food dependent bioavailability using lipid based formulations. Lipid based formulations (LBFs) have been widely investigated for their ability in enhancing solubilisation within the GI tract, generating supersaturation and increasing drug absorption and have been shown to eliminate food effect *in vivo* [16–18]. Solubilisation of PWSD within a lipid-based, liquid carrier allows delivery within a capsule which self emulsifies on dispersion in GI fluids, maintaining drug solubilisation. Co-administration of lipids as formulation excipients may promote formation of mixed micelles enhancing solubilisation and induce secretion of bile salts and phospholipids *in vivo*, mimicking the fed state environment [19,20].

This study has the dual objective of investigating the potential for a novel LBF, termed a lipidic dispersion, to enhance bioavailability of fenofibrate in fasted pigs, while assessing of the ability of *in vitro* and *in silico* biopharmaceutical tools to predict *in vivo* formulation performance. The novel formulation is based on a modification of previous work and combines solid dispersion and lipid formulation techniques, addressing challenges associated with the delivery of dissolution rate and solubility limited drugs [21].

2. Materials and methods

2.1. Chemicals and materials

Olive Oil 'highly refined, low acidity' (C18 triglycerides), Tween 85 (polyoxyethylene-(20)–polysorbitan trioleate), sodium taurocholate (>95%) and sodium oleate (⩾82% fatty acids, as oleic acid) were purchased from Sigma–Aldrich (Ireland). Cremophor RH 40 (polyoxyl-40-hydrogenated castor oil) and Kollidon® 30 (polyvinylpyrrolidone (PVP) K30) were received from BASF (Germany). Lipantil® Micro 67 mg hard capsules were obtained from Abbott Healthcare Products Ltd. (UK). Glycerol monooleate (GMO, Rylo MG19 Pharma®, 99.5% monoglyceride) was received from Danisco Specialities (Denmark). Fenofibrate and fenofibric acid were purchased from Kemprotec Ltd. (UK). Hard Gelatine Capsules (Size 0) were obtained from Capsugel (Coni-Snap®). Lecithin (Lipoid E PC S, >98% pure) was kindly donated by Lipoid GmbH (Ludwigshafen, Germany). All other chemicals and solvents were of analytical grade or HPLC grade respectively and were purchased from Sigma–Aldrich (Ireland).

2.2. Preparation of fenofibrate loaded solid dispersion

A solid dispersion of fenofibrate and PVP K30, in a 1:4 ratio, was prepared using a Büchi mini spray dryer B-290 (BÜCHI labortechnik AG, Switzerland). Fenofibrate and PVP-K30 were dissolved in dichloromethane (40 mg PVP/ml), and dried in an inert nitrogen atmosphere. The operating parameters were as follows: inlet temperature: 55 °C, outlet temperature: 40 °C, pump rate: 14% and aspiration rate: 100%. The solid dispersion was collected from cyclone separator and stored in a desiccated environment at room temperature. Physical mixtures of the same ratios were also prepared by mixing fenofibrate and PVP K30 thoroughly in a mortar until a homogenous mixture was obtained.

2.3. Preparation of lipidic dispersion

An LBF composed of 40% long chain triglyceride (LCT) (Olive oil), 20% surfactant (Cremophor RH 40) and 40% co-surfactant (Tween 85) was prepared as previously described [21]. Fenofibrate and PVP (1:4) were dissolved in dichloromethane (40 mg PVP/mL). Subsequently, the LBF was added to the solution and mixed using a magnetic stirrer. The total weight ratio of constituents (fenofibrate:PVP:LBF) was 1:4:5. The solution was spray dried using parameters defined in the previous section. A blank formulation was prepared under similar conditions, but without the addition of drug, with a 4:5 ratio of PVP to LBF. Both drug loaded and blank lipidic dispersions resulted in the formation of a free-flowing white powder. These formulations were stored in a desiccated environment and fenofibrate content was assayed and found to be stable over a storage period of six months.

2.4. Physiochemical characterisation

2.4.1. Thermal analysis

Differential scanning calorimetry (DSC) analyses were carried out using a DSC Q1000 (TA Instruments, Hertfordshire, UK). Sealed samples and reference pans were loaded into the sample chamber at ambient temperature, equilibrated to 25 °C and held at this temperature for 5 min. Samples were heated at 3 °C/min with an applied modulation of ±1 °C every 60 s from −40 to 200 °C. The nitrogen gas flow rate was 50 ml/min. Analysis of the DSC thermograms was conducted with Universal Analysis 2000 software (TA Instruments, Hertfordshire, UK).

2.4.2. Powder X-ray diffraction

Powder X-ray diffraction (PXRD) was carried out using on a Stadi MP Diffractometer (Stoe GmbH, Germany). Samples were radiated using a copper anode (Cu Kα radiation, $\lambda = 1.5406$ Å, 40 kV, 40 mA). The scanning angle ranged from 3.55° to 60° of 2ϑ, with a scanning speed of 0.07°/s. The diffraction patterns were analysed using Philips X'Pert High Score software (version 1.0a).

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