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Combined effects of the drug distribution and mucus diffusion properties of self-microemulsifying drug delivery systems on the oral absorption of fenofibrate

Yushi Sunazuka[a,1], Keisuke Ueda[a,1,*], Kenjirou Higashi[a], Yusuke Tanaka[b], Kunikazu Moribe[a]

[a] Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan
[b] Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hiro-koshingai, Kure, Hiroshima 737-0112, Japan

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ABSTRACT

We present the absorption improvement mechanism of fenofibrate (FFB), a Biopharmaceutics Classification System (BCS) class II drug, from self-microemulsifying drug delivery systems (SMEDDS), centered on improving the diffusion of FFB through the unstirred water layer (UWL). Four SMEDDS formulations containing Labrafac™ lipophile WL 1349 (WL1349) or Labrafil® M 1944CS (M1944) oils and NIKKOL HCO-40 (HCO40) or NIKKOL HCO-60 (HCO60) surfactants were prepared. Every SMEDDS formulation formed microemulsion droplets of approximately 30 nm. *In vitro* tests showed that the microemulsion droplets containing M1944 had relatively small FFB solubilization capacities, causing larger amounts of FFB to be dissolved in the bulk water phase, compared to the droplets containing WL1349. The diffusivity of the microemulsion droplets through the mucin solution layer was enhanced when using HCO40 compared to HCO60. The oral absorption in rats was the highest when using the SMEDDS formulation containing M1944 and HCO40. High FFB distribution in the bulk water phase and fast diffusion of microemulsion droplets through the mucus layer contributed to the efficient delivery of FFB molecules through the UWL to the epithelial cells, leading to enhanced FFB absorption.

1. Introduction

Poorly water-soluble drugs with high permeability through the intestinal membrane are categorized as class II drugs in the Biopharmaceutics Classification System (BCS) (Amidon et al., 1995). Sixty to seventy percent of new drug candidates in recent years have been categorized as class II drugs (Fong et al., 2015). BCS class II drugs have low oral bioavailability owing to their poor dissolution in water. The use of lipid-based formulations is one of the most effective technologies to enhance oral absorption of BCS class II drugs (Yang, 2010). Pre-dissolving the drugs in the lipid components of these formulations allows BCS class II drugs to circumvent the dissolution process and overcome the issue of low solubility in the gastrointestinal tract (Porter et al., 2007; Singh et al., 2009). Pancreatic lipases in the small intestine metabolize the lipid components, releasing the drug contained in the lipid formulation (Fatouros et al., 2007; Williams et al., 2013). In recent years, self-microemulsifying drug delivery systems (SMEDDS) have attracted attention as a promising and practical lipid-based formulation strategy (Feeney et al., 2016; Kawabata et al., 2011). SMEDDS formulations are mixtures of oils, surfactants, and co-surfactants (Dokania and Joshi, 2015; Kawabata et al., 2011). The formulations emulsify spontaneously in the gastrointestinal tract through contact with water and through gentle agitation provided by gastrointestinal motility, producing nano-sized microemulsions (Hong et al., 2016). High diffusivity of the resultant microemulsion droplets efficiently carries the drug to the absorptive surface of intestinal epithelial cells (Feeney et al., 2016). In addition, the large surface area of the droplets allows efficient drug release by rapid lipid digestion (Salvia-Trujillo et al., 2013). Thus, SMEDDS formulations have advantages in terms of oral drug absorption compared with simple lipid formulations. Improvements in the oral absorption of BCS class II drugs by SMEDDS formulations have been confirmed in previous studies (Shen and Zhong, 2006; Singh et al., 2009; Subramanian et al., 2004; Wei et al., 2005; Wu et al., 2006).

Conventionally, the components of the SMEDDS formulations are

Abbreviations: AUC, area under the plasma concentration-time curve; BCS, biopharmaceutics classification system; FFA, fenofibric acid; FFB, fenofibrate; HCO40, NIKKOL HCO-40; HCO60, NIKKOL HCO-60; HPLC, high performance liquid chromatography; M1944, Labrafil® M 1944CS; PEG, polyethylene glycol 400; SMEDDS, self-microemulsifying drug delivery systems; SR, supersaturation ratio; UWL, unstirred water layer; WL1349, Labrafac™ lipophile WL 1349

* Corresponding author.
E-mail address: keisuke@chiba-u.jp (K. Ueda).
[1] These authors contributed equally to this study.

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Table 1
Components and ratio of each SMEDDS formulation (wt%). Each formulation contains 120 mg/g of FFB.

Components	SMEDDS-W40	SMEDDS-W60	SMEDDS-M40	SMEDDS-M60	PEG
WL1349	25	25			
M1944			25	25	
HCO40	50		50		
HCO60		50		50	
PEG	25	25	25	25	100

selected based on simple screenings, such as evaluation of the emulsification efficacy of the formulation or the drug capacity of each component (Kang et al., 2004; Patel and Vavia, 2007; Sprunk et al., 2012). However, the efficient development of SMEDDS formulations with enhanced oral absorption rates requires formulation optimization based on a mechanistic understanding of drug absorption from SMEDDS formulations. The oral absorption rate of a drug is determined by the rate-limiting step in the intestinal absorption process (Takano et al., 2008), which varies depending on the physiochemical properties of the drug. Rate-limiting steps are classified into several categories including dissolution, diffusion through the unstirred water layer (UWL), and permeation through the epithelial cell membrane (Sugano et al., 2010). For BCS class II drugs, the dissolution and/or diffusion through the UWL, including the mucus layer, are the main impediment to absorption due to their poor dissolution properties and high permeation rates through the intestinal membrane (Dahan and Hoffman, 2008). SMEDDS formulations overcome the issue of drug dissolution as the drugs are predissolved in the formulations. Thus, drug diffusion through the UWL becomes the main barrier to oral absorption of BCS class II drugs (Dahan and Hoffman, 2008; Kataoka et al., 2012). A promising strategy for the development of SMEDDS formulations with enhanced oral absorption rates would be to optimize the components of the formulations to improve the efficiency of drug diffusion through the UWL.

The aims of this study were to elucidate the effects of each component of SMEDDS formulations on drug absorption and to propose a mechanism-based optimization strategy for SMEDDS formulations using *in vitro* testing. Fenofibrate (FFB) was used as a model BCS class II drug (Yang, 2010) and SMEDDS formulations composed of different oils and surfactants were prepared. The effect of the different components on FFB diffusion through the UWL was then evaluated *in vitro*. More specifically, FFB distribution between the microemulsion droplets and the bulk water phase and the diffusion of the microemulsion droplets through the mucin layer were evaluated. Furthermore, the oral absorption of FFB from the different formulations was investigated *in vivo*. Finally, we explained how the physiochemical properties of each microemulsion affected the improved oral absorption of FFB.

2. Materials and methods

2.1. Materials

NIKKOL HCO-40 (HCO40) and NIKKOL HCO-60 (HCO60) were kindly provided by Nikko Chemicals Co., Ltd. (Tokyo, Japan). Labrafac™ lipophile WL 1349 (WL1349) and Labrafil® M 1944CS (M1944) (Gattefossé, St Priest, France) were kindly gifted by CBC Co. Ltd. (Tokyo, Japan). FFB was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Mucin from porcine stomach (type II) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Polyethylene glycol 400 (PEG) was purchased from Nakarai Tesque (Kyoto, Japan). All other materials and solvents were of reagent grade.

2.2. Preparation of the SMEDDS formulations

WL1349 and M1944 were used as the oils. The surfactants were HCO40 and HCO60, and PEG was used as a co-surfactant. The SMEDDS formulations were prepared by mixing one oil, surfactant, and co-surfactant at a weight ratio of 1:2:1 at 60 °C. FFB was completely dissolved in the SMEDDS formulations (120 mg/g) by heating and mixing. Prior to use, all formulations were equilibrated at 37 °C in order to avoid any effect caused by temperature changes during the sample dilution. Four different SMEDDS formulations were prepared. The SMEDDS formulation containing WL1349 and HCO40 was named SMEDDS-W40. Similarly, the other three formulations were named SMEDDS-W60, SMEDDS-M40, and SMEDDS-M60. A PEG-only formulation was also prepared by dissolving FFB in PEG (120 mg/g). The PEG formulation was maintained at 60 °C until use to keep the FFB dissolved. The composition of each SMEDDS and the PEG formulation is described in Table 1.

2.3. Droplet size distribution

The SMEDDS formulations were diluted 37 times (w/w) with saline and shaken at 100 rpm in a water bath at 37 °C for 20 min to obtain microemulsions. The droplet size distributions of the prepared microemulsions were evaluated by dynamic light scattering using Microtrac UPA (Nikkiso Co., Ltd., Tokyo, Japan).

2.4. FFB concentration within the microemulsions

Each SMEDDS and the PEG formulation containing FFB was diluted 37 times (w/w) with saline and shaken at 100 rpm at 37 °C. Aliquots were taken from each microemulsion at 1, 2, and 4 h. Samples were centrifuged at 20,000 × *g* for 10 min to separate the precipitated FFB. The FFB concentration in the supernatant was quantified by HPLC.

2.5. FFB solubility of the microemulsions

FFB-free SMEDDS and PEG formulations were diluted 37 times (w/w) with saline and shaken at 100 rpm in a water bath at 37 °C for 20 min to obtain microemulsions and a PEG solution. An excess amount of FFB powder was added to each sample. The solutions were shaken in a water bath at 37 °C for 48 h and centrifuged at 20,000 × *g* for 10 min. The FFB concentration in the supernatant was then quantified by HPLC to determine the FFB solubility in each microemulsion and in the PEG solution.

2.6. Mucin permeation study

A mucin solution was prepared using the modified method described in a previous report (Zhang et al., 2015). Briefly, 3% (w/w) porcine gastric mucin was added to 20 mM phosphate buffer (pH 6.8). The mixture was gently stirred for 2 h on ice to obtain a mucin solution. Then, the mucin solution was placed in an incubator at 37 °C with continued stirring until use. Twenty minutes before the permeation study, the SMEDDS formulations were diluted 37 times (w/w) with phosphate buffer and shaken at 100 rpm in a water bath at 37 °C to form microemulsions.

A Transwell® permeable support (Corning Inc., NY, USA) was used for the permeation study. To form the mucin solution layer, 25 µL of prepared mucin solution was added to the Transwell® insert with a porous polyester membrane (pore size: 3.0 mm). Then, 100 µL of each microemulsion was gently added on top of the mucin solution layer.

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