European Journal of Pharmaceutics and Biopharmaceutics 73 (2009) 107–114

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling

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ARTICLE INFO

Article history:
Received 19 March 2009
Accepted in revised form 17 May 2009
Available online 22 May 2009

Keywords:
Food effects
Dissolution
Prediction
PBPK modeling
Celecoxib

ABSTRACT

Since the rate-determining step to the intestinal absorption of poorly soluble drugs is the dissolution in the gastrointestinal (GI) tract, postprandial changes in GI physiology, in addition to any specific interactions between drug and food, are expected to affect the pharmacokinetics and bioavailability of such drugs. In this study, *in vitro* dissolution testing using biorelevant media coupled with *in silico* physiologically based pharmacokinetic (PBPK) modeling was applied to the prediction of food effects on the absorption of a poorly soluble drug, celecoxib, from 200 mg capsules. A PBPK model was developed based on STELLA® software using dissolution kinetics, solubility, standard GI parameters and post-absorptive disposition parameters. Solubility, dissolution profiles and initial dissolution rate from celecoxib 200 mg capsules were measured in biorelevant and compendial media. Standard GI parameters (gastric emptying rate and fluid volume) were varied according to the dosing conditions. Disposition parameters were estimated by fitting compartmental models to the oral PK data, since intravenous data are not available for celecoxib. Predictions of food effects and average plasma profiles were evaluated using the AUC and C_{max} and the difference factor (f_1). An approximately 7-fold difference in the maximum percentage dissolved was observed in *in vitro* dissolution tests designed to represent the fed and fasted states. By contrast, the food effect estimated by simulating the plasma profiles with the PBPK model predicted only a slight delay in the peak plasma level (~1 h), and modest increases in the C_{max} and AUC of ~1.9-fold and 1.3-fold in the fed state, respectively. The PBPK approach, combining *in silico* simulation coupled with biorelevant dissolution test results, thus corresponds much better to the food effect observed for celecoxib *in vivo*. Additionally, point estimates of AUC and C_{max} as well as f_1 calculations demonstrated clear advantages of using results in biorelevant rather than compendial media in the PBPK model.

1. Introduction

The first step in the intestinal absorption process from an orally administered dosage form is drug dissolution in the gastrointestinal (GI) tract. For poorly soluble drugs, especially those with high intestinal permeability, dissolution can be considered as the rate-determining step to drug absorption.

In vivo dissolution of the drug depends not only on the physicochemical characteristics of the drug (particle size, molecular size, solubility, etc.), but also on the physiological conditions (motility, available fluid volume, fluid viscosity, food components, etc.).

One approach to improve the oral bioavailability of lipophilic drugs is to administer them with a meal [1,2]. However, the food effect on drug absorption is rather complex, as it can involve specific interactions between the drug and food as well as the physiological changes in the GI tract between the prandial states [3,4]. Various strategies for predicting food effects on intestinal absorption have been reported in the literature [5]. Using the Biopharmaceutics Classification System (BCS), about 70% of compounds could be correctly categorized into three groups according to the food effect observed (no effect, negative effect and positive effect) [6]. On the other hand, Custodio et al. suggested utilizing the Biopharmaceutical Drug Disposition Classification System (BDDCS) to predict food effects on the extent of drug availability, since these can be influenced by the inhibition of transporters and metabolism with

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doi:10.1016/j.ejpb.2009.05.009

high-fat meals [7]. Gu et al. established a more predictive statistical model based on physicochemical parameters of the drug and dosing conditions [8]. Since all these predictions are based solely on drug substance properties, they may well be useful in the early drug screening stage, but formulation effects on dissolution kinetics and physiological factors in the GI tract which can also affect intestinal absorption of the drug are not addressed.

In vitro dissolution tests using biorelevant media has proven to be a useful tool to predict *in vivo* performance of drug products [9]. Dissolution media simulating pre- and post-prandial states in the small intestine, Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF) have been applied to establish *in vitro–in vivo* correlations (IVIVC) of oral dosage forms [10–12]. Recently, the media compositions have been updated, based on human aspirate data, to reflect the physiology in the GI tract more closely than the previous versions [13]. Combined with rational selection of apparatus, the hydrodynamics and physiologically reasonable media volumes, it should be possible to mimic the conditions in the GI tract more closely and investigate the *in vivo* performance of drug products in the fasted and fed states. Recently, successful predictions of orally administered drugs using *in silico* PBPK modeling softwares, e.g., GastroPlus®, PK-Sim®, etc., have also been reported [14–16]. These *in silico* techniques use physiological parameters based on the prandial states and available *in vitro* data of drug (solubility, dissolution, permeability, metabolism and disposition of the drug) to simulate the plasma profiles. They are becoming a powerful tool in drug research and development for the quantitative prediction of PK profiles.

In this study, the *in vitro* biorelevant dissolution tests were coupled with *in silico* PBPK modeling using the STELLA® software to simulate plasma profiles and hence predict food effects on the absorption of a lipophilic model compound in humans. Celecoxib, a cyclooxygenase-2 (COX-2)-specific inhibitor with poor aqueous solubility, was chosen as the model compound in this study. Although it is categorized as BCS Class II (low solubility–high permeability) [17], there is only a modest increase in bioavailability when the capsules are ingested in the fed state to healthy adult volunteers [18]. This behavior deviates from the positive food effect generally observed for the BCS Class II compounds and thus provided a useful case example for combining *in vitro* with *in silico* techniques.

2. Materials and methods

2.1. Chemicals and reagents

Celebrex® 200 mg capsules (Pfizer Inc., lot C080351) were purchased commercially. Celecoxib drug substance (lot 070901) was purchased from Kemprotec Ltd., Middlesbrough, UK. Long-life, heat-treated and homogenized milk (UHT milk) containing 3.5% fat (Milfina Hochwald, Kaiserslautern, Germany) was purchased commercially. Glyceryl monooleate (GMO, Rylo M19 Pharma®, 99.5% monoglyceride, lot 173403-2202/107) was kindly donated by Danisco Specialities, Brabrand, Denmark. Egg phosphatidylcholine (Lipoid E PC®, 99.1% pure, lot 108015-1/42) was kindly donated by Lipoid GmbH, Ludwigshafen, Germany. 37% hydrochloric acid (conc. HCl) and pepsin (Ph. Eur., 0.51 U/mg, lot 1241256) were obtained from Fluka Chemie AG, Buchs, Switzerland. Maleic acid (99% pure, lot 4039128) was purchased from Sigma–Aldrich Chemie GmbH (Steinheim, Germany). Sodium oleate (82.7% pure, lot 51110) was obtained from Riedel-de Haën, Seelze, Germany. Sodium taurocholate (NaTC, 97% pure, lot 2007100274) was used as received from Prodotti Chimici Alimentari SpA, Basaluzzo, Italy. Sodium hydroxide solution (0.1 N NaOH) and hydrochloric acid solution (0.1 N HCl) were purchased from VWR International GmbH (Darmstadt, Germany). Dichloromethane, acetonitrile, glacial acetic acid, sodium acetate trihydrate, sodium chloride (NaCl), potassium dihydrogen phosphate and NaOH pellets were all of analytical grade and purchased from Merck KGaA (Darmstadt, Germany).

2.2. Media preparation

The compositions and the preparation procedures of the media used for dissolution tests and solubility have been described previously [13,19,20]. Fasted State Simulated Gastric Fluid (FaSSGF), as described by Vertzoni et al. [20], was used to represent the fasted gastric conditions. A recently developed medium, Fed State Simulated Gastric Fluid (FeSSGF), which is a mixture of buffer solution and UHT milk (50:50), was used to simulate the gastric conditions postprandially [13]. Simulated Gastric Fluid without pepsin (SGF_{sp}) (USP 31) was used as a control. For the upper small intestine, updated versions of Fasted State Simulated Intestinal Fluid (FaSSIF-V2) and Fed State Simulated Intestinal Fluid (FeSSIF-V2) in addition to their predecessors (FaSSIF and FeSSIF) were used. The compositions of these media were recently revised to be more biorelevant, based on analysis of human aspirate samples [13]. Simulated Intestinal Fluid without pancreatin (SIF_{sp}) (USP 31) was also used as a compendial control. Tables 1 and 2 summarize the compositions of the simulated gastric and intestinal media used in this study.

2.3. Analytical methods

2.3.1. The high-performance liquid chromatography (HPLC) system

The samples obtained from solubility and dissolution tests were quantitatively analyzed for celecoxib concentration using an isocratic HPLC system. The HPLC system consisted of a pump (Merck Hitachi L7100), an autosampler (Merck Hitachi L-7200) and a UV detector (Merck Hitachi L-7400). The chromatograms were evaluated with EZChrom Elite™ Version 2.8 Software (Biochrom Ltd., Cambridge, UK). Analytical column used was YMC-Pack Pro C18 100 mm × 4.6 mm I.D., S-3 μm (YMC Co., Ltd., Kyoto, Japan). The mobile phase comprised 55% acetonitrile and 45% water with the flow rate 1.0 mL/min. The injection volume was 10 μL. The detection wavelength was set at 254 nm. The analysis was performed under ambient conditions.

2.4. Solubility measurements

The shake-flask method was employed for celecoxib solubility determination in all media. Measurement was performed by adding an excess amount of the drug substance to a medium in a glass vial. The vial was incubated in a water bath at 37 °C and shaken vigorously at appropriate intervals. Samples were taken after at

Table 1
Composition of the gastric media.

	SGF_{sp}	FaSSGF	FeSSGF
Composition			
Sodium taurocholate (mM)	–	0.08	–
Lecithin (mM)	–	0.02	–
Pepsin (mg/mL)	–	0.1	–
Sodium chloride (mM)	34.2	34.2	237.0
Hydrochloric acid (mM)	71.0	25.1	–
Glacial acetic acid (mM)	–	–	17.1
Sodium acetate (mM)	–	–	29.8
Milk/buffer	–	–	1/1
Characteristic parameter			
pH	1.2	1.6	5.0
Osmolality (mOsm kg^{-1})	–	120.7 ± 10	400 ± 10
Buffer capacity (mmol L^{-1} ΔpH^{-1})	–	–	25 ± 2