European Journal of Pharmaceutics and Biopharmaceutics 88 (2014) 795–806

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Prediction of oral absorption of cinnarizine – A highly supersaturating poorly soluble weak base with borderline permeability

Mark Berlin [a], Karl-Heinz Przyklenk [b], Annette Richtberg [b], Wolfgang Baumann [b], Jennifer B. Dressman [a,*]

[a] Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany
[b] Hennig Arzneimittel GmbH & Co KG, Flörsheim am Main, Germany

ARTICLE INFO

Article history:
Received 6 June 2014
Accepted in revised form 20 August 2014
Available online 6 September 2014

Keywords:
Dissolution
Supersaturation
Precipitation
Cinnarizine
Permeability
Absorption
Physiologically based pharmacokinetic model

ABSTRACT

Two important driving forces for oral absorption of active pharmaceutical ingredients are drug dissolution and permeability in the gastrointestinal tract. Poorly soluble weak bases typically exhibit high solubility under fasted gastric conditions. However, the solubility of such drugs usually decreases drastically in the fasted small intestine, constraining drug absorption. Since there is a discrepancy in solubility between the fasted state stomach and intestine, it is crucial to examine the influence of dissolution, supersaturation and precipitation on the oral absorption of poorly soluble weak bases during and after fasted state gastric emptying.

Cinnarizine is a poorly soluble weak base with borderline permeability, exhibiting supersaturation and precipitation under simulated fasted state gastric emptying conditions. Interestingly, supersaturation and precipitation of cinnarizine under fed state conditions is not expected to occur, since the drug shows good solubility in fed state biorelevant media and exhibits a positive food effect in pharmacokinetic studies. The present work is aimed at investigating the dissolution, supersaturation and precipitation behavior of marketed cinnarizine tablets under fasted and fed state conditions using biorelevant dissolution and transfer methods. In order to predict the *in vivo* performance of these cinnarizine formulations, the *in vitro* results were then coupled with different physiologically based pharmacokinetic (PBPK) models, which considered either only dissolution or a combination of dissolution, supersaturation and precipitation kinetics. The results of the *in silico* predictions were then compared with *in vivo* observations.

The study revealed that under fasting conditions, plasma profiles could be accurately predicted only when supersaturation and precipitation as well as dissolution were taken into account. It was concluded that for poorly soluble weak bases with moderate permeability, supersaturation and precipitation during fasted state gastric emptying may have an essential influence on oral drug absorption and thus on *in vivo* drug performance.

1. Introduction

The prediction of oral drug absorption of active pharmaceutical ingredients (APIs) is a topic which is gaining importance in pharmaceutical research and development. Early investigations have shown that oral absorption of APIs is generally limited by two key factors, gastrointestinal (GI) solubility and intestinal permeability [1]. The introduction of biorelevant media, which mimic the fluids of the GI tract, has facilitated the assessment of the *in vivo* behavior of poorly soluble drugs [2–4]. Biorelevant dissolution testing has become a significant tool for qualitative *in vitro–in vivo* correlation of drugs, especially of BCS class II compounds [5–7]. Further, coupling of biorelevant dissolution with physiologically based pharmacokinetic (PBPK) models opens the

Abbreviations: API, active pharmaceutical ingredient; AUC, area under the curve; BCS, biopharmaceutics classification system; C_{max}, maximal concentration; FaSSGF, Fasted State Simulated Gastric Fluid; FaSSIF, Fasted State Simulated Intestinal Fluid; FaSSIF-V2, Fasted State Simulated Intestinal Fluid – version 2; FaSSIF-V2(PO_4), Fasted State Simulated Intestinal Fluid – version 2 with phosphate buffer; f_d, fraction of drug dissolved; FeSSGF, Fed State Simulated Gastric Fluid; FeSSIF-V2, Fed State Simulated Intestinal Fluid – version 2; GER, gastric emptying rate; GI, gastrointestinal; HPLC, high pressure liquid chromatography; k_p, precipitation constant; P_{app}, apparent permeability; P_{eff}, effective permeability; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; PSA, polar surface area; PTFE, polytetrafluoroethylene; rpm, rotations per minute; SAP, surface activity profiling; t_{max}, time of maximal concentration; Vd, volume of distribution; Vd/F, apparent volume of distribution.

* Corresponding author. Institute of Pharmaceutical Technology, Goethe University Frankfurt, Max-von-Laue-Strasse 9, 60438 Frankfurt am Main, Germany. Tel.: +49 (0) 69 798 29680.
E-mail address: dressman@em.uni-frankfurt.de (J.B. Dressman).

http://dx.doi.org/10.1016/j.ejpb.2014.08.011
0939-6411/

possibility of quantitatively assessing the *in vivo* performance of such APIs [7–13].

Dissolution testing under simulated intestinal conditions is generally a very useful tool to assess the *in vivo* behavior of poorly soluble drugs, but it may have limited predictive power in the case of weak bases. While weakly basic drugs tend to dissolve well in the stomach, their solubility in the upper small intestine is significantly lower due to the considerably higher pH values in this environment. In order to evaluate the behavior of weak bases during gastric emptying, Kostewicz et al. introduced the transfer method [14]. The study revealed that certain weakly basic drugs tend to supersaturate and then precipitate when moving from the stomach into the intestine. On the other hand, creation of a supersaturated solution of the drug may lead to an enhanced driving force for uptake from the small intestine [15,16]. Thus, it is important to understand both the degree of supersaturation that can be achieved and the tendency to precipitate in the small intestine during and after gastric emptying in order to quantitatively describe the *in vivo* performance of weak bases with PBPK models.

Several commercial PBPK simulation software, such as SimCyp®, PKSim® and GastroPlus®, permit the incorporation of supersaturation and precipitation kinetics into their models [17]. Shono and co-workers developed a STELLA® model which considered possible supersaturation and precipitation of the weak base, nelfinavir [18]. Yet the model used only a statistical estimation of precipitation of the drug; no *in vitro* supersaturation and precipitation investigations were carried out. The STELLA® software has also successfully been used to quantitatively predict the *in vivo* performance of a BCS class IV base which showed minor supersaturation in the fasted state transfer model [19]. Likewise in a recent study on dantrolene precipitation from a salt formulation in the fasted GI tract, Kambayashi et al. were able to predict the plasma profile of this compound by using dissolution and precipitation data obtained from fasted state biorelevant dissolution testing [20]. However, since dantrolene is a poorly soluble weak acid, its gastrointestinal behavior is expected to be quite different than that of weak bases such as cinnarizine.

Cinnarizine is a lipophilic weak base ($pK_{a1} = 1.95$ and $pK_{a2} = 7.47$ (both basic)) with a molecular weight of 368.514 g/mol and an octanol–water distribution coefficient ($\log P$) of 5.6 [21,22]. It exhibits a polar surface area (PSA) of 2.4–11.8 Å and low solubility at pH values greater than 4.5 [21,23,24]. A study on weak bases has shown cinnarizine to supersaturate and precipitate when being transferred from a highly acidic compartment (0.1 M HCl) into Fasted State Simulated Intestinal Fluid (FaSSIF) adjusted to a pH value of 5.5 [25]. Interestingly, no supersaturation was observed when the drug was moved from a compartment containing the McIlvaine buffer (pH 5.0) into FaSSIF (pH 6.5). This observation could partially explain the gastric acidity dependent bioavailability of cinnarizine, which has been observed in humans and dogs [26,27]. A permeability investigation of cinnarizine in the Caco-2 cell culture model has shown a moderate P_{app} value of 4.2×10^{-6} cm/s in comparison with mannitol (1.1×10^{-6} cm/s), a poorly permeable reference compound [28]. Pharmacokinetic investigation of cinnarizine in beagle dogs revealed an oral bioavailability of 55–60%. The authors concluded that reduced oral bioavailability values are attributed to presystemic metabolism rather than to permeability constraints [21]. Cinnarizine demonstrated a positive food effect in pharmacokinetic studies on Arlevert® (20 mg cinnarizine tablets) in healthy human volunteers. The administration of Arlevert® after a high fat meal resulted in a moderate increase of C_{max} and AUC values by 8% and 44%, respectively. One possible explanation for the food effect is that there is precipitation of cinnarizine in the small intestine in the fasted state, but not in the fed state. Another factor for the food effect could be cinnarizine instability, which was recently reported in *ex vivo* studies by Koumandrakis et al. [29]. However, it is not known to what extent degradation of the compound takes place *in vivo*.

The aim of this study was to analyze the pre-absorptive behavior of three different marketed formulations of cinnarizine in order to predict their *in vivo* performance. The roles of drug dissolution, supersaturation and precipitation were examined using biorelevant dissolution and transfer methods. An advanced STELLA® model, enabling the introduction of supersaturation and precipitation kinetics obtained from *in vitro* investigations, was developed for cinnarizine. The model included permeability restrictions, permitting incorporation of Caco-2 permeability data for the prediction of the drug flux through the human intestine. The *in vitro* results were then entered into the model, which included disposition parameters obtained from available *in vivo* data. Finally, the simulation results were compared with observed *in vivo* plasma profiles.

2. Materials and methods

2.1. Chemicals and reagents

Stugeron® 25 mg tablets (lot ACL1800) were purchased commercially from Janssen-Cilag AG, Baar, Switzerland. Arlevert® 20 mg/40 mg Cinnarizine/Dimenhydrinate tablets (lot 324011), 30 mg/60 mg Cinnarizine/Dimenhydrinate tablets (Cinnarizine 30 mg) (lot 11/228) and cinnarizine drug substance (lot ZR001575PUE521-MIC) were kindly donated by Hennig Arzneimittel GmbH, Flörsheim, Germany. Long-life heat-treated and homogenized milk, containing 3.5% fat (UTH) was purchased from AF Deutschland GmbH, Düsseldorf, Germany. Glyceryl monooleate (GMO, Rylo M19 Pharma, 99.5% monoglyceride, lot 173403-401989490) 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. Sodium taurocholate (lot 2011040152) was obtained from Prodotti Chimici E Alimentari S.P.A., Basaluzzo, Italy. Sodium oleate powder (82.7% pure, lot 51110) was purchased from Riedel-de Haën, Seelze, Germany. Pepsin (0.51 U/mg, lot 1241256) was purchased from Fluka Chemie AG, Buchs, Switzerland. Maleic acid (lot BCBC3155) was obtained from Sigma–Aldrich, Steinheim, Germany. Ammonium acetate (lot A0028716849), sodium acetate trihydrate (lot A792767747) and monobasic sodium phosphate monohydrate (lot A02140949112) were of analytical grade and purchased from Merck KGaA, Darmstadt, Germany. Acetic acid (lot 12B220509), acetonitrile (lot I691330327), hydrochloric acid (lot 10L060526), methanol (lot I630607212), sodium chloride (lot 10J110040) and sodium hydroxide (lot 09G300017) were of analytical grade and acquired from VWR International, Leuven, Belgium.

2.2. Biorelevant media composition

Biorelevant media were used for solubility studies as well as for dissolution tests and transfer experiments. Media characterizing the pre- and postprandial conditions of the stomach were Fasted State Simulated Gastric Fluid, FaSSGF, and Fed State Simulated Gastric Fluid, FeSSGF [3,4].

Conditions in the pre- and postprandial intestine were simulated by Fasted State Simulated Intestinal Fluid, FaSSIF-V2, and Fed State Simulated Intestinal Fluid, FeSSIF-V2 [4]. In the fed state the bile salt secretion is known to be higher, resulting in higher bile salt and lecithin concentrations in FeSSIF-V2 than in FaSSIF-V2. Moreover FeSSIF-V2 contains glycerol monooleate and sodium oleate which represent products of lipolysis of dietary fats.