Journal of Pharmaceutical Sciences 105 (2016) 687–696

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Gastrointestinal Behavior of Weakly Acidic BCS Class II Drugs in Man—Case Study of Diclofenac Potassium

Jens Van Den Abeele [1], Joachim Brouwers [1], Ruben Mattheus [1], Jan Tack [2], Patrick Augustijns [1,*]

[1] Drug Delivery and Disposition, KU Leuven, Gasthuisberg O&N II 3000, Leuven, Belgium
[2] Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven 3000, Leuven, Belgium

ARTICLE INFO

Article history:
Received 22 July 2015
Revised 21 August 2015
Accepted 26 August 2015
Available online 16 September 2015

Keywords:
oral drug delivery
biopharmaceutics
clinical pharmacokinetics
gastrointestinal
supersaturation
precipitation
disposition
food effects
drug interaction
Biopharmaceutics Classification System (BCS)

ABSTRACT

This study aimed to investigate the gastrointestinal supersaturation and precipitation behavior of a weakly acidic Biopharmaceutics Classification System (BCS) Class II drug in healthy volunteers. For this purpose, a tablet containing 50 mg diclofenac potassium (Cataflam®) was predissolved in 240 mL of water and this solution was subsequently orally administered to five healthy volunteers under fasted and fed state conditions with or without concomitant use of a proton-pump inhibitor (PPI) (40 mg esomeprazole, Nexiam®). Subsequently, total diclofenac content and dissolved intraluminal drug concentrations as well as drug thermodynamic solubility were determined in gastrointestinal aspirates. In all volunteers, gastric supersaturation resulted in precipitation of diclofenac in the stomach. The extent of precipitation correlated well with gastric pH ($r = -0.78$). pH dependency of precipitation was corroborated by the absence of precipitate in the stomach after coadministration of a meal and/or a PPI. Diclofenac was found to be fully dissolved in the duodenum in all test conditions. It can be concluded that substantial pH-dependent gastric precipitation of a weakly acidic BCS Class II drug administered as a solution occurs in humans. With regard to its implications for intestinal absorption, results suggest the instantaneous redissolution of gastric drug precipitate upon transfer to the duodenum.

Introduction

One of the major drawbacks in the contemporary development of drugs for oral administration is the high rate of late-stage attrition among potential drug candidates. Although this is mainly related to efficacy and/or safety issues, unfavorable pharmacokinetic properties of drug formulations also contribute to this high attrition rate.[1,2] As drug development is an expensive and time-consuming process, early stage screening of drug candidate formulations is warranted to make this process more efficient.[3-6] For this purpose, biorelevant *in vitro* and *in silico* tools that adequately predict *in vivo* drug performance are needed. However, current tools used both in industry and academia often lack the necessary predictive power as they insufficiently mimic the complexity of the gastrointestinal tract (e.g. gastrointestinal motility, permeation, supersaturation/precipitation).[7] Optimization and validation of such predictive tools is therefore required based on an in-depth understanding of *in vivo* gastrointestinal drug behavior. To facilitate this need, an intraluminal sampling method, enabling the assessment of intraluminal drug concentrations after oral drug administration as a function of time, has previously been developed.[8] As gastrointestinal drug concentrations directly reflect intraluminal events, these unique *in vivo* data significantly contribute to resolving poorly understood intraluminal processes.

In the past, the main focus of drug absorption studies has been on elucidating gastrointestinal drug behavior at the site of absorption, i.e. the intestine. The stomach was often disregarded or considered to be a mere waiting room for drug transfer to the small intestine. Increasingly, the importance of the stomach with regard to drug disposition and absorption is being recognized as more studies focus on the *in vitro* evaluation of drug formulations in the stomach to explain systemic exposure to a drug of interest.[9-13] Furthermore, the *in vitro* representation of the stomach is

* *Correspondence to:* Patrick Augustijns (Telephone: +32-16-33-03-01; Fax: +32-16-33-03-05).
E-mail address: Patrick.augustijns@pharm.kuleuven.be (P. Augustijns).

http://dx.doi.org/10.1002/jps.24647
0022-3549/

continuously being optimized, once again indicating an increased awareness that gastric processes may have a significant influence on drug absorption further down the gastrointestinal tract.[14-16] Indeed, several gastric variables (e.g., pH, motility, gastric emptying) and processes taking place in the stomach (disintegration/dissolution, enzymatic degradation, lipid digestion, supersaturation, and/or precipitation) may influence subsequent drug absorption and systemic exposure to a drug of interest.

For drugs with a limited solubility in gastric fluids, supersaturation (i.e., concentrations exceeding the thermodynamic solubility) may occur in the stomach upon administration of a supersaturation-inducing dosage form (e.g. salt form, solid dispersion).[17] Because of the fact that supersaturation is a metastable state, subsequent drug precipitation may already take place in the stomach, thereby potentially jeopardizing the beneficial effect of the supersaturation-inducing form regarding intestinal absorption. Indeed, given that drug precipitated in the stomach must redissolve upon transfer to the duodenum to become available for absorption, these processes may substantially influence intestinal absorption and ultimately systemic exposure to a drug of interest. In contrast to several *in vivo* studies investigating supersaturation and precipitation in the duodenum,[18,19] *in vivo* data investigating these processes in the stomach are lacking. In particular, gastric supersaturation and/or precipitation of salts of poorly soluble weak acids has only been hypothesized and/or studied to some extent using *in vitro* methods.[9,10,20,21]

Furthermore, *in vivo* data on gastrointestinal drug behavior are needed to further facilitate the discussion regarding biowaiver extensions for *in vivo* bioequivalence (BE) testing.[22-24] Currently, *in vivo* BE studies may be replaced by *in vitro* dissolution testing for rapidly dissolving ($\geq$85% of drug dissolved within 30 min) Class I drugs (high permeability, high solubility) and very rapidly dissolving ($\geq$85% of drug dissolved within 15 min) Class III drugs (low permeability, high solubility) of the Biopharmaceutics Classification System (BCS).[25-27] It has been suggested to extend these biowaivers to BCS Class II weakly acidic drugs (high permeability, low solubility) with an acid dissociation constant (p*K*a) $\leq$4.5.[22,23,25,28-30] These compounds are termed as "poorly soluble" because of their low solubility in gastric media. However, as these compounds may be completely dissolved in the small intestine, i.e. the site of absorption, no solubility-related issues regarding absorption may arise in practice thus justifying the use of biowaivers for BCS Class II weak acids. This assumption needs to be confirmed *in vivo* as intestinal redissolution kinetics after gastric precipitation has not yet been studied.

This study aimed to investigate the *in vivo* gastrointestinal behavior of an orally administered, weakly acidic BCS Class II drug. Emphasis was put on investigating potential supersaturation and precipitation events in the stomach after oral administration of a solution of the salt of a weak acid and subsequent intestinal redissolution. Because of the fact that medicinal products are often taken together with a meal and that proton-pump inhibitors (PPIs) are widely used among the population, the influence of food and/or concomitant PPI use on the above-mentioned processes was investigated. Diclofenac potassium was selected as a model compound to study these processes because of (i) its BCS Class II properties and (ii) its potential for gastric supersaturation and precipitation (salt form).

Materials and Methods

Chemicals

Sodium acetate trihydrate ($NaOAc.3H_2O$) was purchased from Chem-Lab (Zedelgem, Belgium). Disodium monohydrogenphosphate dihydrate ($Na_2HPO_4.2H_2O$) and sodium dihydrogenphosphate monohydrate ($NaH_2PO_4.H_2O$) were acquired from Sigma-Aldrich (St. Louis, MO). Diclofenac free acid was purchased from Geigy (Basel, Switzerland) for *in vitro* testing and analytical purposes. Water was purified using a Maxima system (Elga Ltd., High Wycombe Bucks, UK). Acetonitrile was supplied by Fisher Scientific (HPLC grade; Leicestershire, UK). Methanol was purchased from Acros Organics (HPLC grade; Geel, Belgium). Acetic acid was acquired from VWR International (99%–100% p.a.; Dublin, Ireland).

Clinical Trial Medication

All medication used during the clinical trial, i.e. Cataflam® (50 mg diclofenac potassium, Novartis, Basel, Switzerland) and Nexiam® (40 mg esomeprazole; AstraZeneca, London, UK), was ordered via the hospital pharmacy of the University Hospitals Leuven (Belgium).

In Vivo *Characterization of the Gastrointestinal Behavior of Diclofenac*

Five healthy volunteers ($n = 5$; three women and two men) aged between 24 and 25 years were enrolled in a four-armed crossover study. Conditions tested encompass the administration of a diclofenac potassium solution in fasted and fed state conditions with or without concomitant PPI use. This solution was made by dissolving one tablet of Cataflam® (50 mg diclofenac potassium) in 240 mL of tap water (final concentration = 623 μM diclofenac potassium). To ensure diclofenac potassium was entirely dissolved, a sample of the obtained solution in tap water was centrifuged (20,817*g* for 5 min; Microcentrifuge 5424; VWR International), 10-fold diluted in methanol:water (50:50, v/v) and subsequently analyzed (compare section *Sample Analysis*) to determine the dissolved drug concentration. In all cases, diclofenac potassium was found to be fully dissolved. Exclusion criteria for participation were a history of gastrointestinal disease(s), (potential) pregnancy, frequent exposure to ionizing radiation during the previous year, and/or illness at the time of the study. These criteria were checked during a medical investigation performed by a doctor affiliated to the department of Gastroenterology of the University Hospitals Leuven. Furthermore, candidate volunteers suffering from hepatitis B, hepatitis C, and/or human immunodeficiency virus infection were excluded from participation to protect the integrity of the researchers performing the study. The study followed the tenets of the Declaration of Helsinki and was approved by the Federal Agency for Medicines and Health Products (FAHMP; EudraCT reference number 2013-004636-29) and the Medical Ethics Committee of the University Hospitals Leuven (ML10131). All volunteers provided written informed consent prior to the start of the trial. To ensure fasted state test conditions, participants were asked to refrain from the consumption of food and only drink water for 12 h prior to the study.

Double-lumen catheters [Salem Sump™ PVC Gastroduodenal Tube, 14 Ch (4.7 mm) × 108 cm; Covidien, Dublin, Ireland] were positioned in the antrum (lower region of the stomach, close to the pylorus) and the duodenum (D2/D3 segment) via nasal and/or oral intubation. The position of the aspiration catheters was checked using fluoroscopy (X-rays). Volunteers were sitting in an upright position in a hospital bed for the entire duration of the trial. Subsequently, the diclofenac potassium solution was orally administered after which gastroduodenal samples were aspirated (sample volume <3 mL) at predetermined time-points for 3 h, i.e. 0, 2, 7, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, and 180 min after intake of the diclofenac potassium solution. To avoid clogging