Evolution of a Detailed Physiological Model to Simulate the Gastrointestinal Transit and Absorption Process in Humans, Part II: Extension to Describe Performance of Solid Dosage Forms

KIRSTIN THELEN,[1,2] KATRIN COBOEKEN,[2] STEFAN WILLMANN,[2] JENNIFER B. DRESSMAN,[1] JÖRG LIPPERT[2]

[1]Johann Wolfgang Goethe University, Institute of Pharmaceutical Technology, 60438 Frankfurt am Main, Germany

[2]Bayer Technology Services GmbH, Competence Center Systems Biology and Computational Solutions, 51368 Leverkusen, Germany

Received 8 December 2010; revised 23 August 2011; accepted 28 October 2011

Published online 28 November 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22825

ABSTRACT: The physiological absorption model presented in part I of this work is now extended to account for dosage-form-dependent gastrointestinal (GI) transit as well as disintegration and dissolution processes of various immediate-release and modified-release dosage forms. Empirical functions of the Weibull type were fitted to experimental *in vitro* dissolution profiles of solid dosage forms for eight test compounds (aciclovir, caffeine, cimetidine, diclofenac, furosemide, paracetamol, phenobarbital, and theophylline). The Weibull functions were then implemented into the model to predict mean plasma concentration–time profiles of the various dosage forms. On the basis of these dissolution functions, pharmacokinetics (PK) of six model drugs was predicted well. In the case of diclofenac, deviations between predicted and observed plasma concentrations were attributable to the large variability in gastric emptying time of the enteric-coated tablets. Likewise, oral PK of furosemide was found to be predominantly governed by the gastric emptying patterns. It is concluded that the revised model for GI transit and absorption was successfully integrated with dissolution functions of the Weibull type, enabling prediction of *in vivo* PK profiles from *in vitro* dissolution data. It facilitates a comparative analysis of the parameters contributing to oral drug absorption and is thus a powerful tool for formulation design. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:1267–1280, 2012

Keywords: modeling; simulation; prediction; gastrointestinal tract; absorption; dosage forms; pharmacokinetics; PBPK; dissolution; Computational ADME

INTRODUCTION

A revised physiologically based model for the prediction of passive intestinal absorption of dissolved drugs administered to humans in the fasted state was presented in part I of this work.[1] The model combines detailed knowledge of the human gastrointestinal (GI) anatomy and physiology such as effective surface areas, GI fluid secretion and absorption rates, with a precise representation of the mucosa, which is crucial to oral drug absorption and intestinal first-pass metabolism. A data set of 111 passively absorbed, readily soluble drug substances with reported fractions of dose absorbed (f_{abs}) was used in the first part of our study to fit the optimal set of coefficients of a modified semiempirical equation used for intestinal permeability calculation. After combining the revised oral absorption model with an established physiologically based whole-body model,[2–5] the integrated model was used to predict the plasma concentration–time profiles following administration of oral solutions or suspensions of eight model drugs not contained in the training data set. It was shown that with the help of the revised model, plasma concentration–time profiles of drugs with diverse physicochemical properties can be predicted well. In part II, we apply the model to solid oral dosage forms.

Capsules, tablets, and pellets are convenient, easy to ingest, and low-cost option for oral drug administration. Therefore, the development of solid oral dosage forms for new chemical entities is the favored option in drug development. To support the formulation design and development, accurate mechanistic models that can predict the *in vivo* performance can

Correspondence to: Kirstin Thelen (Telephone: +49-214-30-34287; Fax: +49-214-30-50698; E-mail: kirstin.thelen@bayer.com)

Journal of Pharmaceutical Sciences, Vol. 101, 1267–1280 (2012)

have significant impact on the efficiency of drug development.

In vitro dissolution tests are used at several stages of the drug development process, for example, for the development of new drug products, for quality control of oral formulations, and to assist the test of bioequivalence. Standardized *in vitro* dissolution test methods have been established, and in combination with biorelevant dissolution media [e.g., fasted state simulated intestinal fluid (FaSSIF) or fed state simulated intestinal fluid (FeSSIF)], these tests can provide useful prediction of the *in vivo* disintegration and dissolution behavior of orally administered dosage forms.[6–9] A key goal is to relate the *in vitro* drug release information to the *in vivo* drug profiles. The quantitative correlation between *in vitro* and *in vivo* data is often referred to as "*in vitro–in vivo* correlation" (IVIVC). IVIVC enables effective dosage form optimization with a minimal number of trials in man, allows specification of dissolution acceptance criteria, and can be used as a surrogate for further bioequivalence studies.[10]

We now extend the model revised in part I to include parameters and functions that describe the disintegration and dissolution processes in the GI tract. A Weibull function[11] was fitted to the *in vitro* dissolution profiles of various dosage forms for the same eight model drugs used as test set in part I (aciclovir, caffeine, cimetidine, diclofenac, furosemide, paracetamol, phenobarbital, and theophylline) and then implemented in the oral absorption model. The plasma concentration–time profiles of the test compounds were predicted directly from the established models for administration of drug in solution (DIS) combined with the predefined dissolution profiles. In addition, sensitivity analyses were performed to assess the influence of variability in gastric emptying on the oral drug pharmacokinetics (PK) of diclofenac and furosemide.

METHODS

Model Extension

The structure of the revised oral absorption model has already been described in part I of the study.[1] The extended structure of this absorption model is illustrated in Figure 1.

To enable modeling of GI transit and disintegration of the dosage form, an independent species, solid dosage form (e.g., " Tablet"), was added to the revised model. By doing so, the solid dosage form and DIS can be emptied from the stomach and transported along the intestine at different rates. Once released from the solid dosage form and dissolved within the luminal fluids according to the dissolution function, the drug is transferred from the solid dosage form species to the DIS species and is then transported along the GI tract according to the transport rate of DIS.

The GI transit patterns of DIS and particles less than 2 mm in diameter, both of which empty relatively quickly from the stomach in the fasted state, have already been described.[1] Drugs administered in the form of an immediate-release solid dosage form such as a conventional immediate-release tablet or a gelatine capsule will disintegrate/dissolve quickly in the fluids of the stomach and the coadministered liquids and can thus be assumed to exhibit gastric emptying patterns similar to orally administered suspensions or solutions. However, GI transit patterns of larger, nondisintegrating particles can differ considerably from that of the DIS, especially with regard to gastric emptying time (GET). Solid oral dosage forms can have many shapes, but, in general, they can be divided into two categories, namely, single-unit and multiple-unit systems. Whereas single-unit preparations with modified-release characteristics typically remain intact as a nondisintegrating unit throughout some or most of the GI tract, multiple-unit preparations are composed of many individual subunits such as pellets or small tablets and, as such, disperse in the GI fluids.[12–13]

In the fasted state, gastric emptying is under control of the migrating myoelectric complex or MMC.[14–15] Three consecutive phases of activity can be identified: Phase I is a resting period with low-amplitude waves, phase II activity is characterized by intermittent spikes and contractions, and phase III represents a short phase of intense distal and proximal gastric contractions; these phase III contractions, also known as the "housekeeper" waves, completely empty the stomach. The MMC patterns are of particular importance, because for the majority of nondisintegrating single-unit dosage forms such as matrices or enteric-coated tablets, the particle size is too great to allow transit together with emptying of the fluid. These dosage forms will be typically retained until the next phase III activity passes through the stomach. Thus, for units larger than 2 mm in diameter, the greatest factor in gastric residence time is the phase of the motility cycle at the time of drug administration. The median time to empty is estimated to be half the duration of the MMC cycle or about 1 h.[15] However, both high intersubject and intrasubject variability can be expected due to the dependency on the cycle phase at administration and because the length of each cycle varies considerably ranging from few minutes to over 3 h.[14,16–21] After feeding, the MMC cycle is immediately broken; a normal meal disrupts the activity for about 3–4 h.[15]

Like the stomach, the intestine exhibits distinct fasted and fed motor patterns. In the model, the transit of dissolved drug through the small intestine is described with the help of a sigmoidal function.[122–23]