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Review

PBPK models for the prediction of *in vivo* performance of oral dosage forms

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ABSTRACT

Drug absorption from the gastrointestinal (GI) tract is a highly complex process dependent upon numerous factors including the physicochemical properties of the drug, characteristics of the formulation and interplay with the underlying physiological properties of the GI tract. The ability to accurately predict oral drug absorption during drug product development is becoming more relevant given the current challenges facing the pharmaceutical industry.

Physiologically-based pharmacokinetic (PBPK) modeling provides an approach that enables the plasma concentration–time profiles to be predicted from preclinical *in vitro* and *in vivo* data and can thus provide a valuable resource to support decisions at various stages of the drug development process. Whilst there have been quite a few successes with PBPK models identifying key issues in the development of new drugs *in vivo*, there are still many aspects that need to be addressed in order to maximize the utility of the PBPK models to predict drug absorption, including improving our understanding of conditions in the lower small intestine and colon, taking the influence of disease on GI physiology into account and further exploring the reasons behind population variability. Importantly, there is also a need to create more appropriate *in vitro* models for testing dosage form performance and to streamline data input from these into the PBPK models.

As part of the Oral Biopharmaceutical Tools (OrBiTo) project, this review provides a summary of the current status of PBPK models available. The current challenges in PBPK set-ups for oral drug absorption including the composition of GI luminal contents, transit and hydrodynamics, permeability and intestinal wall metabolism are discussed in detail. Further, the challenges regarding the appropriate integration of results from *in vitro* models, such as consideration of appropriate integration/estimation of solubility and the complexity of the *in vitro* release and precipitation data, are also highlighted as important steps to advancing the application of PBPK models in drug development.

Abbreviations: ABL, Aqueous Boundary Layer; BCS, Biopharmaceutics Classification System; BDDCS, Biopharmaceutical Drug Disposition Classification System; BE, Bioequivalence; CYP, Cytochrome P450; P_{eff}, effective permeability; EP, European Pharmacopoeia; ER, Extended Release; FE, Fold Error; GI, Gastrointestinal; IR, Immediate Release; IVIVC, *in vitro–in vivo* Correlation; MMC, Myoelectric Motor Complex; MR, Modified Release; OrBiTo, Oral Biopharmaceutical Tools; BA, Oral Bioavailability; PBPK, Physiologically Based Pharmacokinetic Modeling; QbD, Quality by Design; QC, Quality Control; UGT, UDP Glucuronosyltransferase; FDA, US Food and Drug Administration; USP, United States Pharmacopeia.

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It is expected that the "innovative" integration of *in vitro* data from more appropriate *in vitro* models and the enhancement of the GI physiology component of PBPK models, arising from the OrBiTo project, will lead to a significant enhancement in the ability of PBPK models to successfully predict oral drug absorption and advance their role in preclinical and clinical development, as well as for regulatory applications.

Contents

1. Introduction

Physiologically-based pharmacokinetic (PBPK) models traditionally employ what is commonly known as a "bottom-up" approach. The concept is to describe the concentration profile of a drug in various tissues as well as in the blood over time, based on the drug characteristics, site and means of administration and the physiological processes to which the drug is subjected. Thereby, PBPK modeling takes into account the factors influencing the absorption, distribution and elimination processes (Rowland et al., 2011). In PBPK modeling, parameters are determined *a priori* from *in vitro* experiments and the physiology, utilizing *in silico* predictions to predict *in vivo* data. In one of the earliest invocations of the PBPK approach, a Swedish physiologist and biophysicist, Teorell, developed a five compartment scheme to reflect the circulatory system, a drug depot, fluid volume, kidney elimination and tissue inactivation (Teorell, 1937a,b). The next advances came over 20 years later, when Edelman and Liebmann recognized that the total body water was not equally accessible, but rather should be divided into plasma, interstitial-lymph, dense connective tissue and cartilage, inaccessible bone water, transcellular and intracellular components (Edelmann and Liebmann, 1959). A few years later, physiological models were introduced to describe the handling of drugs by the artificial kidney as well as to describe the pharmacokinetics of thiopental and methotrexate (Bischoff and Dedrick, 1968; Bischoff et al., 1971; Dedrick and Bischoff, 1968). In the early years however, *in silico* predictions were hampered by lack of capacity in computing as well as large gaps in physiological knowledge. Further, the design of *in vitro* experiments, particularly in the area of predicting drug release, transport and metabolism, was still at a rather rudimentary stage. As knowledge in these areas grew, and more powerful computers became commonplace, it was possible to create better PBPK models and they became more widely used, such that for example, in 1979, a review of PBPK models for anticancer drugs was published (Chen and Gross, 1979). As early as 1981, the brilliant pharmacokineticist, John Wagner, foresaw applications of pharmacokinetics to patient care such as individualization of patient dose and dosage regimen, determination of the mechanism of drug–drug interactions, prediction of pharmacokinetics of drugs in man from results obtained in animals using physiologically based models, development of sophisticated computer programs to obtain population estimates of pharmacokinetic parameters and their variabilities, therapeutic monitoring and prediction of the time course of the intensity of pharmacological effects. In the meantime, many of these ideas have been turned into reality, or are being turned into reality, through the application of PBPK models (Wagner, 1981).

The first commercial software to attempt a comprehensive description of the gastrointestinal (GI) tract in the context of a PBPK model was GastroPlus™. The first version, introduced in 1998, used a mixing-tanks-in-series approach to describe the movement of drug from one region in the GI tract to the next, with simple estimations of dissolution based on aqueous solubility and absorption rate constants based on existing pharmacokinetic data. Even at this stage, it was possible to obtain a reading on whether absorption (uptake across the GI mucosa) or solubility/dissolution