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PBPK Modeling and Simulation: Application in Oral Absorption

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ABSTRACT

Nowadays, the pharmaceutical industry is facing increasing challenges of bringing new medicines to the market. Along with increasing rates of attrition during research and development, the financial burden is considered one of the key issues. Recent estimates have suggested the true cost of bringing a drug product to the market has risen to $2.56 billion. Because of that, one of the key emphases for the pharmaceutical industry is to improve the efficiency of the overall process and reduce the cost. Within the preclinical and formulation field, a sizeable effort has focused on building tools to predict the pharmacokinetic behavior of the drug candidate in drug discovery and development. Those tools allow researchers to identify potential limiting factors in oral absorption of a drug candidate as early as possible, optimize formulation-related factors to maximize absorption where possible, and design future studies more efficiently. The advantages of utilizing modeling and simulation approaches to understand, predict and optimize oral absorption are underlined in this article.

INTRODUCTION

It is well understood that the process of oral drug absorption is highly complex and often influenced by its ADME (absorption, distribution, metabolism and elimination) as well as physicochemical properties. When considering additional extrinsic (e.g. dose, fed, fasted, and concomitant medicines such as proton pump inhibitors) and intrinsic factors (e.g. variability in gastric pH, emptying time, and GI motility), the situation becomes even more convoluted because all of the above factors can interplay with each other making the interpretation of pharmacokinetic data even more challenging. The development of integrated modeling was introduced decades ago which made the de-convolution of the absorption process possible [1-3]. The work described a physical model for the fraction absorbed (FA) with plug flow (containing drug particles and dissolved drugs) theory. Unlike the tank model, this dynamic approach enables both dissolution and absorption to take place at the same time allowing researchers to model the drug absorption process. In this plug flow model, the effective intestinal permeability (Peff) of a drug in humans and animals was estimated based on in vitro data (i.e. Caco2 or MDCK) and was integrated into the calculation [4]. Since the removed or absorbed portion of solubilized drug effects in vivo solubility which further influences the dissolution of the drug as a function of time (transit time), two differential equations are used to express this type of relationship among dissolution, in situ concentration and absorption. By solving these two differential equations simultaneously using the numerical method (i.e. the Runge-Kutta method), FA can be obtained. This development allows the method to be able to be applied to a large number of compounds without excess in vivo work. This advantage quickly gained momentum among academic and industry researchers in this field, and more sophisticated advanced compartmental absorption and transit (ACAT) models have become the foundation for modern oral absorption modeling [3].

Following this work, Physiology, Pharmacokinetics (PK) and Pharmacodynamics (PD) were integrated into the picture. Nowadays, physiologically based (PB) Pharmacokinetic modeling (PBPK) becomes popular and several commercial software are available (e.g. Gastroplus (Simulations Plus, Lancaster, CA) and Simcyp (Certara, Sheffield, UK)). These PBPK platforms describe the absorption process using the multi-compartment approach **(Figure 1)** with both dissolution and absorption in each compartment to allow the best estimation of drug absorption in different segments of the GI tract. Meanwhile, the distribution, metabolism, and elimination are integrated accordingly. Furthermore,

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researchers continuously are working on new approaches to improve the prediction of oral absorption [5-8]. This software rapidly gain popularity within the industry as a critical tool in optimizing oral drug delivery in both discovery and development phases. The advantage of such a tool/model is to provide a clearer picture of each important process that affects oral exposure (dissolution, absorption, distribution, metabolism and elimination). This ability allows the researchers to troubleshoot and predict the formulation impact on the oral absorption with mechanistic understanding, for example, the impact of doses, change of solubility (e.g. amorphous versus crystalline), particle size and release rate (GI region) in the formulation on the exposure (PK) of the drug. Additionally, it helps to understand the rate-limiting step for the oral absorption of a drug. For a drug to reach systemic exposure, absorption is the first process. With the mechanistic understanding of how a formulation can influence the absorption and PK profile (i.e. Cmax, Tmax, AUC) of a drug upon oral dosing, as well as understanding the key rate-limiting step for absorption, formulators can better optimize a drug formulation earlier in the drug development cycle, reducing the need for formulation changes later in development.

The usage of this approach is not only limited to drugs in development but also for compounds at different stages of discovery. This is especially important since compounds in different stages of discovery may not be fully optimized and this application has been widely demonstrated to help compound selection and compound optimization. In this article, we will briefly discuss the approach in pre-clinical, clinical, and post drug launch stages.

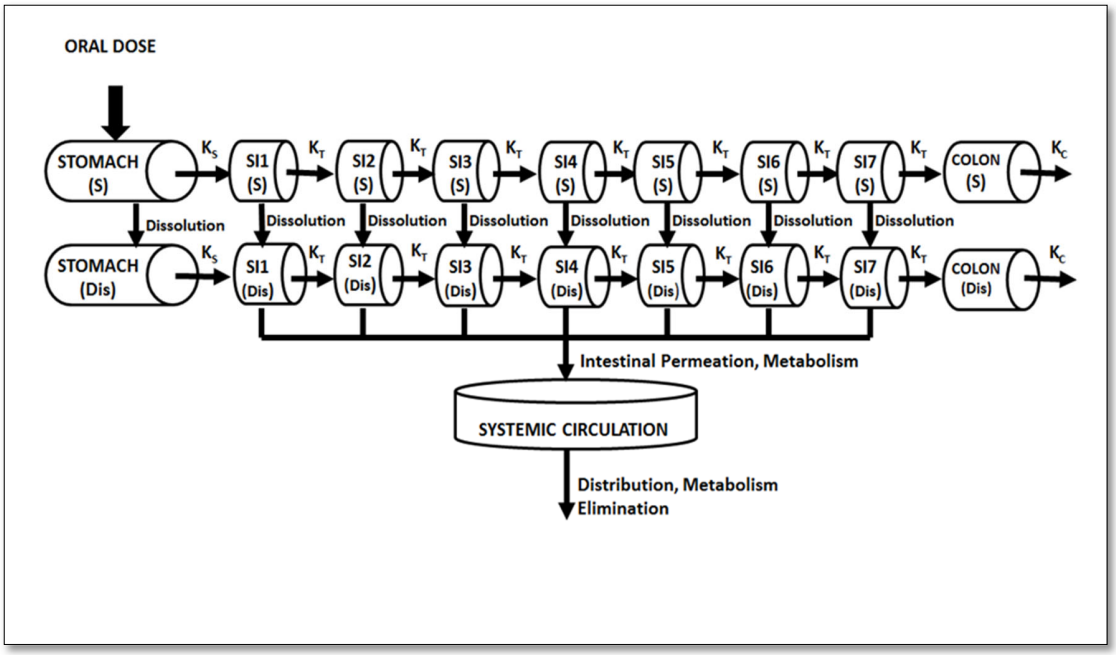

Figure 1. Multi-compartment physiologically based oral absorption model.

PRE-CLINICAL (DRUG DISCOVERY)

One of the key emphases of a drug discovery project is to advance discovery compounds through the development pipeline quickly. To achieve that goal, demonstrating the potential for acceptable PK/PD, efficacy, and safety becomes very critical. To satisfy the above, sufficient in vivo exposure must be achieved. However, oftentimes compounds passing the early screening may have good in vitro properties (PD) but with suboptimal ADME properties (PK). Therefore, achieving the desired target engagement via the preferred dosing routes (i.e. oral administration) may be challenging. At this stage, compound ADME data are still in the "revising" stage where key issues that are limiting in vivo exposure are not fully understood. Therefore, when an exposure issue is encountered, utilizing the modeling/simulation to understand the barriers for limiting exposure becomes very important. It is well known that during the structure optimization stage, compounds may often display multiple issues and some may not be easily understood, leading to some concerns being overlooked. For example, for compounds with low aqueous solubility and poor oral bioavailability, solubility is often treated as the primary suspect that limits oral bioavailability, leading to a strong emphasis being placed on improving solubility. This can lead to other potential mechanisms that may explain low oral bioavailability, such as non-sink permeation and gut metabolism, being overlooked, leading the optimization efforts heading in the wrong direction. In this scenario, modeling and simulation can play a critical role in helping to identify the "hidden" rate-limiting factor for oral absorption and guide us to the right direction [9-11]. Furthermore, the impact of other factors on oral exposure such as particle size, solubility, species, fasted/fed status and

dose can be simulated with greater confidence and the need for preclinical in vivo studies to assess exposure can be reduced. It is worth mentioning that although some software have the ability to predict ADME values, some actual in vitro measurements (i.e. Caco2, MDCK, solubility, Log D, pKa, plasma protein binding, hepatocyte intrinsic clearance) and a preliminary PK study (oral and IV) are highly encouraged to enable in vitro in vivo correlation (IVIVC) to be established. Meanwhile, validating the predicted ADME values is also important for improved accuracy. In some cases, based on the outcomes of the PBPK modeling, more in vitro/in vivo tests will be conducted to gain a full picture of the leading candidate compound. For example, Chiang et al., has reported a case that a compound has low oral exposure in dogs with reasonable MDCK permeability (usually tested at single donor concentration) and low solubility. In this case, modeling and simulation suggested that permeability might be the limiting factor and triggered the MDCK-MDR1 assay. Ultimately, intestinal efflux via Pgp was identified as a key contributor to poor oral exposure [12]. In a similar case, the metabolism was identified to be the limiting factor, not solubility [13]. Both cases revealed the impact and influence of modeling and simulation in the drug discovery stage. Since this influence is at the discovery stage which often decides the fate and the direction of the discovery program, the overall impact of modeling is very significant.

CLINICAL STAGE

The clinical stage is often considered as the most critical stage of the drug discovery and development since it is a key decision point for a new molecule and/or therapeutic target. In this stage, data such as exposure, tolerability, PK/PD and efficacy in humans are generated for evaluation. Due to the cost and ethical considerations, it is often more difficult to conduct multiple studies in human subjects to answer a specific question, hence, modeling plays a more important role in this stage. For example, the impact of the amount of an excipient on the human oral exposure in the formulation, the particle size of the API, and solid form are often considered during the development. Since testing all conditions and doses in humans are very difficult and expensive, modeling and simulation are used extensively in this area. Usually, the impact of each variable on oral absorption (hence the exposure) will be simulated providing the boundary condition. For example, **Figure 2** is a plot of the Bio Pharm model predicted % FA against reported % FA of Celebrex dosed in humans [9]. Although data some variability is observed, the model predicted the reduction of % FA following the increase in dose in humans. Such prediction is very useful to the clinical team regarding what to expect when doses are escalated, and the potential need for finding a new formulation if higher exposures are needed. Other capabilities of modeling and simulation such as prediction of the effect of food and the potential impact of co-administered proton pump inhibitors (leading to increased gastric pH) are extremely useful for compounds at the clinical stage to initiate or prioritize the assessment of these factors in clinical studies. On top of that, software which have the capability of modeling other relevant pharmacokinetic characteristics and situations such as drug-drug interaction (DDI), non-linear pharmacokinetics, and non-linear absorption (permeability) are also very popular at both preclinical and clinical stages. For example, the DDI evaluation of rifampin is well acknowledged for CYP450-mediated induction DDIs.

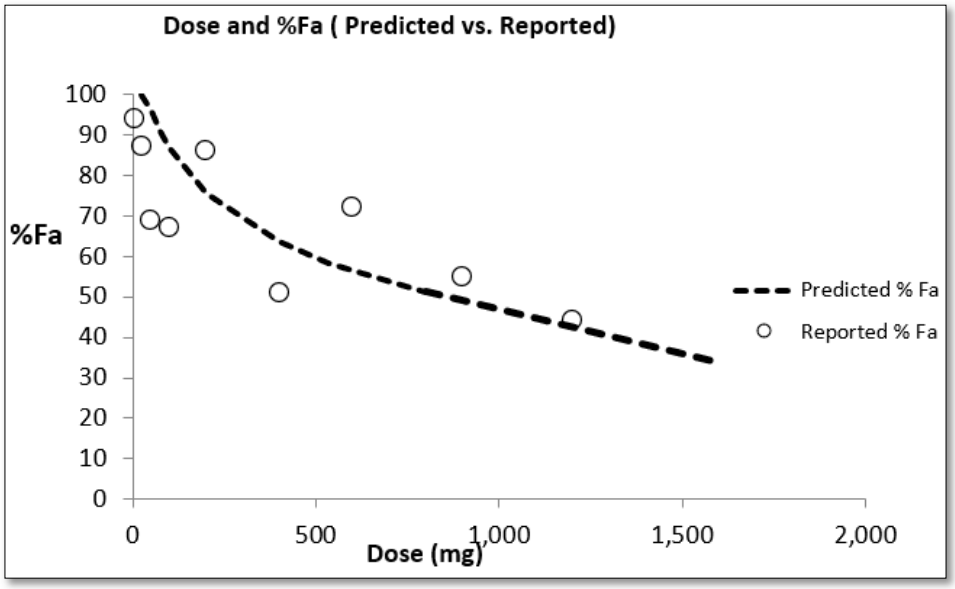

Figure 2. Bio Pharm Model Predicted % Fa against Reported % Fa of Celebrex Dosed in Human.

REGULATORY FILING

The usage of modeling and simulation can be expanded to support the requirements of the drug regulatory filing stage. The use of PBPK modeling to support filing has gained huge momentum in the past decade. Based on the PBPK review knowledge base of the U.S. Food and Drug Administration (FDA) Office of Clinical Pharmacology (OCP), there were 180 records between 2008 and 2015 addressing various clinical pharmacology issues. In 2016, both the European Medicines Agency (EMA) and the U.S. FDA issued draft guidance on the qualification and reporting of modeling and simulation to support filing. There are almost 100 label claims informed by PBPK modeling which includes evaluation such as DDI, absorption, ethnic bridging, and formulation. Some examples such as ibrutinib, panobinostat, alectinib and eiglustat used PBPK modeling to support claims on the approved prescribing information, instead of conducting a clinical study. For instance, simulation results were used extensively in the ibrutinib approved prescribing information, particularly with the assessment of drug interactions with CYP450 inducers and inhibitors. The overall trend towards acceptance of these innovative, efficient and cost-effective approaches from the regulatory agencies appears to be growing which encourages more investment in this area.

POST DRUG LAUNCH

The application of PBPK modeling and simulation plays an important role even after drugs are approved. For instance, PBPK modeling may support the modification of the original formulation specification of the drug product and potentially revise them for cost-saving. Another area is to support the prediction of the drug exposure of re-formulation for the extension of product lines. This kind of work is extremely valuable since it helps to identify the key attributes of the formulation and increases efficiency through streamlining of any necessary in vitro or in vivo studies. For example, **Figure 3** is the illustration of simulated ibuprofen human oral exposure of a fast onset formulation (i.e. soft gel) versus a regular tablet. In this exercise, the model predicted the increase of the absorption rate of ibuprofen due to the elimination of the dissolution step. Other similar approaches such as modeling and simulation to support the development of sustained or controlled release formulations are widely applied in the industry.

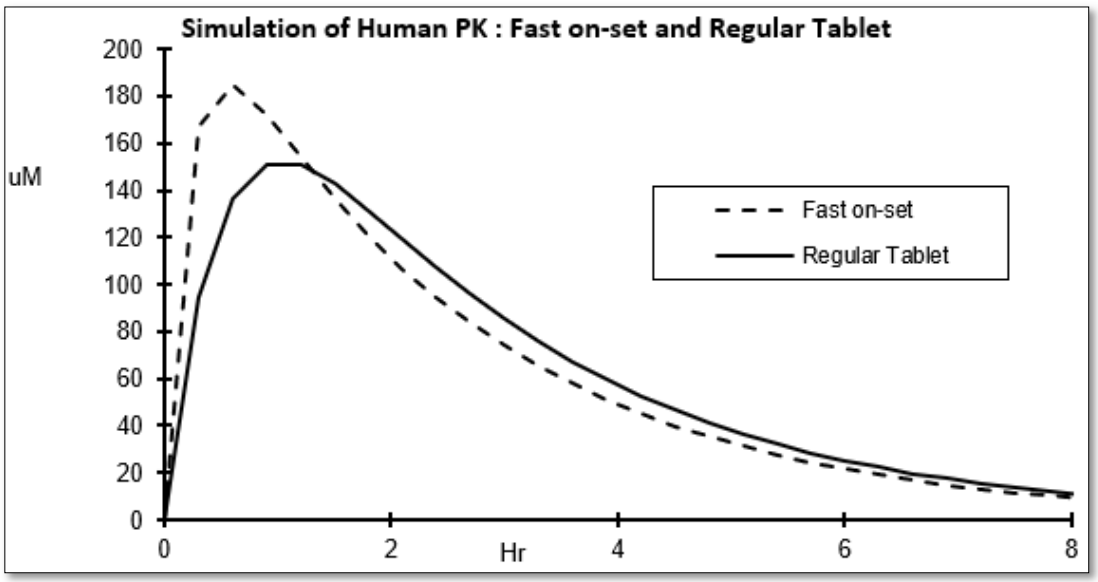

Figure 3. An example of simulated ibuprofen human oral exposure of a fast on-set formulation (i.e. liquid filled soft gel) versus a regular tablet.

CONCLUSION

Following the continued research that was conducted in the past two decades, applications of PBPK modeling to support our understanding and prediction of oral absorption have become more widely used and versatile. These techniques are capable of providing important insights on the key factors influencing oral absorption and providing critical information for guiding drug product development. Because of that, PBPK modeling has quickly gained popularity within the pharmaceutical industry. The application of PBPK modeling has been proved to be highly valuable at all stages of drug discovery and development. It is believed that PBPK modeling and simulation will continue to increase its influence. Hence, the progression of model research and enhancement will need to be continued to improve accuracy and precision, particularly in the case of more complex or challenging ADME properties. For example, accurate prediction of in vivo precipitation and/or super saturation will be a very useful tool for the future development of modeling

and simulation, and efforts to improve our understanding and ability to predict these properties cannot be overemphasized.

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