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Application of physiologically based absorption and pharmacokinetic modeling in the development process of oral modified release generic products

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ABSTRACT

Physiologically based pharmacokinetic (PBPK) modeling for biopharmaceutics applications holds great promise as modelling and simulation tool in the field of modern oral modified release (MR) products. Understanding of gastro-intestinal absorption related processes is crucial to ensure the successful development of complex oral drug generic products. In the recent years, PBPK approach has been gradually influencing decision making ability of pharmaceutical industry as well as regulatory agencies. However, there is a gap in understanding its contribution in the field of oral modified release products. In this review, we have collected different recent research articles illustrating the significant contribution of PBPK to the research and development process of oral MR products, with special emphasis on generic drug products. Concretely, literature examples on the utility of PBPK formulation development, for *in vitro- in vivo* correlations (IVIVC) and prediction of oral bioavailability, and for *in-silico* food effect predictions were included in the review.

1. Introduction

Based on U.S. Food and Drug Administration (FDA), generic drugs are products that are comparable to a reference drug product (branded drug) with respect to the dosage form, strength, route of administration, quality, safety, performance characteristics and intended use [1]. With the advancement of pharmaceutical technology, drug products have increased in complexity. This also applies to the generic drug products industry that needs to do higher investment on formulation development and analytical methods. One example is oral modified release (MR) products such as delayed release (DR), extended release (ER), and other targeted release products (e.g., biphasic release). These MR products are also known by several names in the marketed formulations such as sustained release (SR), long-action (XL, XR), sustained-action, targeted drug delivery, prolonged-action, and slow-release (CD) [2,3]. ER formulations can steadily deliver the active pharmaceutical ingredient (API) in the human body over a period, unlike the DR products, which release the drug at a time other than the administration time. Inherent benefits to using the ER formulations include maintenance of therapeutic concentrations over prolonged periods for drugs with short half-lives, reduction of dosing frequency and improved adherence to therapy, minimization of fluctuation in plasma concentration (Cp) profiles, reduction of toxicities associated with peak Cp, and limiting healthcare costs. Various formulation strategies are available for the development of MR products such as the use of matrix systems of release controlling polymers and osmotic pump formulations. Despite several advantages, MR formulations also have several drawbacks. When orally administered, the release is prone to food effect, in some dosage forms higher size results in difficulty in ingestion and movement through the gastrointestinal tract (GIT), and higher cost of manufacturing. In vitro dissolution studies are frequently used during the development of generic drug products to test similarity between the reference and test formulations. However, the development of predictive dissolution methods is dependent on the matrix and/or technology used to modify

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the rate of drug release. Generic drug products, often used release mechanisms different to that of the branded drug and, thus, it is rare that one dissolution method is useful to predict the *in vivo* release of both the reference and test products [4]. Moreover, different release mechanisms can be translated in similar *in vitro* dissolution profiles in non-biorelevant media complicating the prediction of the *in vivo* release and dissolution and thus leading to poor predictions of the *in vivo* absorption. Many biopharmaceutics conferences have emphasized the role of innovative predictive tools in the systematic approach to the development of oral pharmaceutical products [5,6]. Modeling and simulation (M&S) have gained prominence in drug development and regulatory evaluation in recent years because they can save time and development costs. Mechanistic and empirical models have the potential to be used in the different development stages of oral generic drug products, including MR formulations.

Fig. 1 depicts several M&S strategies and their potential role along the different stages and challenges encountered in the development process of generic products. Empirical models are primarily important to describe the data with few assumptions on the mechanism involved in drug/formulation behavior, whereas mechanistic models consider known factors of the biological system surrounding the data and specify the assumptions in an attempt to describe the data. Preclinical *in-vitro* absorption modeling such as modeling of intestinal absorption [7] process in an *in-vitro* cell-based system to study drug or formulation related parameters such as drug permeability and the role of transporters could be informative towards building PBPK models Empirical modeling strategies could be applied during generic product development with different purposes including to perform *in vitro- in vivo* correlations (IVIVC), select more promising batches for clinical trials, improve the understanding of factors affecting the variability in the pharmacokinetics (PK), and design clinical trials. Additionally, tools like virtual bioequivalence clinical trial simulation could be of tremendous prospective application to evaluate the probability of success before the actual human clinical study and to support regulatory decision making [8]. Also, post-marketing surveillance drug analysis could be used for monitoring the safety of approved generic products. However, these techniques are still under development and not yet fully implemented in the drug development and approval cycle. A variety of useful mechanistic and empirical modeling approaches listed in Fig. 1 are also available to aid in decision making, starting from pre-formulation, formulation optimization, and generic product approval. Although this figure is in general for the development of oral generic drug products, can also be specifically applied to MR generic drug products. The advancement of creativity and innovation can improve the utilization of these approaches in the generic drug development process. The integration of anatomical and physiological parameters of animal, humans, physiochemical and formulation properties of drugs through mathematical modeling is known as physiologically based pharmacokinetic (PBPK) modeling. This enables improved understanding of *in vivo* absorption, distribution, metabolism and excretion (ADME) processes. The mechanistic modeling of the absorption phase is known as physiologically based absorption modeling (PBAM). Among the various challenges faced by the pharmaceutical industry, the development of mechanistic relationship between the *in vitro* release as well as physiological drug absorption to translate the *in vitro* findings still stands as a major challenge for some drugs and complex formulations. Due to widely spread application of PBPK to improve the development of oral drug products, other terms can also be found in the literature such as physiologically based biopharmaceutics modeling (PBBM) and PBPK modeling for biopharmaceutics applications. In line with the FDA guidance, we will used the term of PBPK modeling for biopharmaceutics applications to emphasize the focus on the understanding of the interaction of the products attributes with physiology to affect *in vivo* drug performance [9]. Increased interest in PBPK modeling for biopharmaceutics application has successfully grown their application in i) development of IVIVC, ii) *in silico* prediction of food effect, iii) establishment of properties of active pharmaceutical ingredient (API) to predict the failure in the later development stage. In this review, we have collected different recent research articles illustrating the significant contribution of PBPK modeling for biopharmaceutics application to the research and development process of oral MR products, with especial emphasis on oral MR generic products.

2. Physiologically based pharmacokinetic modeling for MR formulations: Generalities

Absorption is a very critical process for obtaining the desired drug exposure after the administration of a formulation orally. The drug in the MR formulation has to experience and overcome a number of barriers (e.g., release of drug from the dosage form at appropriate site, dissolution of the drug in the gastrointestinal (GI) fluid, etc.) to reach the systemic circulation and finally making its way to the site of action. Additionally, several physiological processes can be contributing to the variability of the drug absorption through the GI tract (GIT), such as, pre-systemic metabolism in the liver and the gut wall or the effect of influx and efflux transporters. These factors, could affect differently to

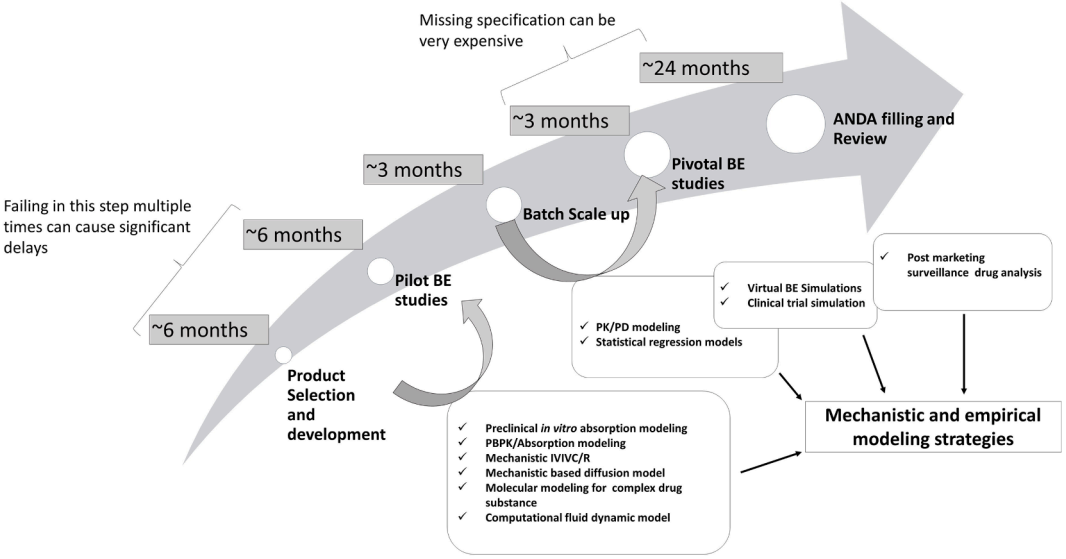

Fig. 1. Potential utility of different modeling platforms along the stages of development of generic drug development process.

the test and reference products if there are regional differences in the release of the product in the GIT. In addition, testing of the effect of all these processes and barriers in *in vitro* setting is very complex and time and resources consuming. Computational tools, such as PBPK modeling for biopharmaceutics application, have been successfully applied to model the high variable *in vivo* absorption process by accounting for the available knowledge on the biological system, and drug and formulation related properties. The development of PBPK models for the test and reference MR drug product, could help to increase the knowledge on the differences and similarities in the *in vivo* release, dissolution and absorption between these two products, and anticipate the effect of different factors such as food or alcohol ingestion on systemic exposure. As such, they could be used to take informed go/no-go decisions and expedite the research and development of oral MR generic drug products.

During the process of drug development, pharmaceutical scientist faces common challenges related to, among others, low oral bioavailability of active pharmaceutical ingredients (API) and several formulation specific challenges such as unclear *in vitro- in vivo* relationships (IVIVR) and the effect of food on drug release, dissolution and absorption. The clarification of IVIVR and the establishment of quantitative IVIVR with adequate predictive capacity is a complex process. Computational PBPK modeling integrating physiological- and drug-related factors aimed to characterize the oral absorption process can be helpful to understand the overall interplay of the different processes and factors that occur in the GIT and contribute to the variability in absorption and ease the drug development process [10,11]. The available information on the drug (API and formulation characteristics, physicochemical properties, *in vitro* assays, clinical information) are used to train the model to predict the PK characteristics in the human body.

The most common oral PBPK models are based on assuming the GIT as a series of compartments through which the drug can transit. These models are valuable resources to predict the oral PK of drug candidates in different scenarios such as compounds moving to clinical research, predicting the species difference in PK and aiding in prediction made on basis of *in vitro* assays. While most of the *in vitro* assays are not able to fully predict the process of absorption, the absorption modeling incorporates several crucial factors and help in making informed decisions. Early simpler mathematical models considered mainly two primary process such as solubility and permeability. Equations like Absorption Potential (AP) and Maximum Absorbable Dose (MAD) were widely used to predict the extent of absorption in a more static conditions such as estimation of fraction absorbed of a given dose [12], and maximum amount of drug which can be absorbed within 6 h period[13]. For example, the AP could be defined by the equation adapted from [12,13].

$$AP = log\left(P^{*}Fnon^{*}\left(\mathrm{So}^{*}\frac{VL}{X0}\right)\right)$$

$$MAD = S^{*}Ka^{*}\mathrm{Vt}.$$

Where P is the 1-octanol-water partition coefficient, So is the intrinsic solubility (aqueous solubility of the nonionized species at 37″C),X0 is the dose administered, Fnon is the fraction in nonionized form at pH 6.5, and VL is the volume of the luminal contents, S is drug solubility, Ka is transintestinal absorption rate constant, Vt is the volume of fluid in the gastrointestinal tract at any time (t). These models were simple and incorporated key factors and variables playing a role in oral absorption. Nevertheless these models were unable to integrate more complex phenomenon such as pH-dependent absorption and effect of food on absorption.

Integrating dissolution and permeation in models such as mixing tank model [14], GIT was treated as single well-stirred compartment in which the amount of drug inputted was mixed instantaneously and output was governed by intestinal transit time. This model was among the first few models which incorporated dissolution rate-limited absorption. Nevertheless, the groundbreaking on the prediction of oral drug absorption and for the biopharmaceutics field occurred in 1993 with the publication of the microscopic tube model by Amidon et al. The model proposed “dissolution”, “dose” and “absorption” numbers, as essential parameters to control the extent of oral drug absorption [15]. However, these early models lacked the phenomena such as metabolism in gut wall, liver first-pass metabolism, and drug chemical stability and ignored the heterogeneity along the GIT. Later, compartmental absorption and transit model (CAT) was proposed [16]. This model considers different sections of small intestine as a series of seven compartments and the movement of drug through the small intestine controlled by transit rate constant. Eventually, seven compartments were added to differentiate undissolved and dissolved drug compartments. This enabled CAT model to capture dissolution rate-limited absorption [17]. Expansion of CAT model with new compartments of different drug states (unreleased drug in formulation, undissolved drug, and dissolved drug) led to the development of advanced compartment absorption and transit model (ACAT) [18]. There are multiple addition benefits of the ACAT model such as investigation of dissolution-rate limited absorption, study of effect of formulation release rate on PK, investigation of gastric emptying, and incorporation colonic absorption. Eventually, GIT heterogeneity (gastric pH, transporter expression and GIT transit time), gut and hepatic metabolism were incorporated leading to significant improvement in predictions [19–21]. Several other models were also developed with slight difference. Advanced Dissolution Absorption metabolism (ADAM) is the most notable [22]. The ADAM model represents the GIT as nine compartments from the stomach to the colon and the absorption of drug in each segment is expressed as a function of release from the dosage form, dissolution, precipitation, luminal degradation, metabolism, transport and inter-segmental transit [23]. Above mechanistic absorption models can be further linked to the whole body PBPK model. Fig. 2 show the general steps needed to build a PBPK model for biopharmaceutics applications.

Recently, the US Food and Drug Administration (FDA) published recommendations for adopting the PBPK models for biopharmaceutical application for the oral drug products which include the oral MR products [24]. The guidelines mention details for development, evaluation and use of PBPK models for biopharmaceutical analysis. Also, highlighted the recommended steps for PBPK model development which include: 1.) identification of the main objective of the model, 2.) development of the model with appropriate structure, parameter and assumptions, 3.) validation of the developed model, and finally 4.) application of the model for the desired purpose [24]. Some generalities of the approach includes the integration of drug related and system related parameter from experimental findings to inform the whole body PBPK model. It is also suggested to use of *in vitro* dissolution profiles to inform the release of drug from the dosage forms. The agency also advised sponsors to consider relevant dissolution acceptance criteria, in order to identify and reject drug product batches that are not bioequivalent to the main drug product. A clinically relevant dissolution acceptance criterion can be wider than the average dissolution data of main clinical batches, i.e, a variation range of beyond plus or minus 10% for an extended-release drug product [25]. The initial step in the PBPK model development is providing the product quality issue(s) or question (s) to be addressed by type of modeling. The model structure should account for different mechanisms representing the *in vivo* drug absorption process and inclusive of the relevant product quality attribute(s) that affect drug dissolution and absorption. The assumptions used in the processes (drug disintegration, dissolution, precipitation, degradation, transport, first-pass effect, distribution, and clearance) should be scientifically justified [18]. Also, the selection of parameter inputs should rationalized and clearly justified. The model-based predictive performance should be validated for its intended objective. The amount and type of data needed for model validation may varies depending on the clinical risk and purpose of the model. In order to evaluate the model predicitons, independent datasets not used in the model building process

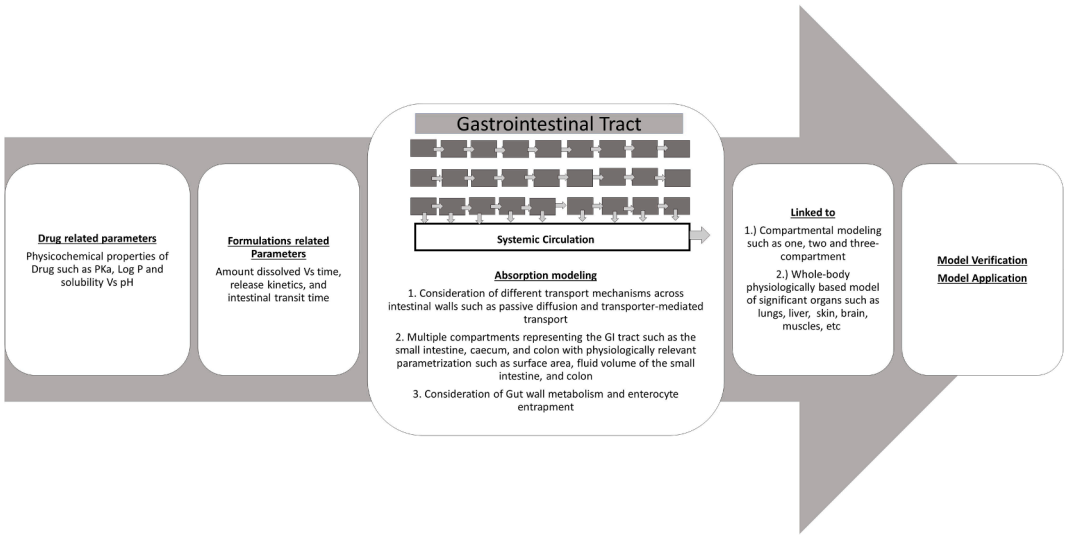

Fig. 2. Schematic to depict the steps to build a physiologically based absorption model.

should be used. However, the approach involves several challenges such as inadequate *in vitro* and *in vivo* experimental data to inform different aspects of the models including model development, verification, and validation, and integration of complexity of product formulations. In future, well verified and validated models can be used to support formulation development, establish clinically relevant product specification, quality risk assessment, drug product life cycle management, reduce the *in vivo* BA/BE studies.

3. Utility of physiologically based pharmacokinetic modeling in the development of oral MR generic products

3.1. Utility of PBPK in the development of generic MR formulations

Generally, formulation development for generic MR products is challenging. Formulation development and design are essential steps in the drug development process which require exhaustive and expensive laboratory work [26]. Although the application of PBPK modeling to MR products could be of high utility to optimize formulation development, there are few reports stating their application to inform product development. This could be related with the fact that the strategies forMR product development are more focused on conventional dissolution studies along with preclinical and clinical studies. Kesisoglou et al. 2016 [27] demonstrated the utility of PBPK modeling approach to bolster formulation development of gaboxadol. Although the drug is a BCS I compound formulating it into a MR formulation could be challenging due to the region-dependent absorption as low colonic absorption was expected for the drug. A PBPK developed based on preclinical information in dogs was used to forecast the absorption behavior of two matrix-based MR formulations of gaboxadol, which were successfully evaluated by comparing the model predictions with the outcome of minipig studies using these two formulations with different release rates. The given study demonstrated the prospective application of PBPK models for early MR formulation development without much PK data available in the clinical scenario. Similar approaches can be applied to compare test and reference formulations/batches during the development of generic drug products and select those to be moved forward to clinical phases. An interesting aspect related with the development of generic MR drug products is that by the time of starting the development of this new dosage form, there is usually a huge amount of information already available for the drug itself, the reference formulation and in many cases on conventional IR formulations. All this knowledge can be integrated together via PBPK modeling before even starting any formulation development work, to anticipate the best mechanism of release for the test product to reproduce the systemic exposure of the reference product, and design bio-relevant dissolution media. Lucakova et al., 2009, illustrated this very insightfully using two different drugs: adinazolam and metoprolol. PBPK models for adinazolam and metoprolol were developed after intravenous and IR oral formulations [28]. The model for adinazolam was further linked to a pharmacodynamic model using sedation scores and applied to design a new MR formulation with desired onset and duration of action. Additionally, the metoprolol PBPK model was used to gain insight and to explain the *in vivo* behaviors of MR formulations, and to select *in vitro* dissolution conditions that best matched the *in vivo* release of MR products. The value of mechanistic simulations in gaining insight into the behaviors of MR formulations *in vivo* has a huge potential that can also be used to optimize the development of generic drug products. As an example, Farhan et al., 2021, developed a PBPK model to investigate formulation factors influencing the generic substitution of dabigatran etexilate [29]. Although these authors were not referring to MR products, the example is still valid to depict the potential of this tool in formulation development in the field of generic drug products.

PBPK enables studying the dissolution profiles in the physiological scenario and check the predictability of the dissolution profiles with respect to the clinical PK data. Abend et al. 2018 [30] summarized some of the contributions of PBPK and its role in the patient centri drug development. PBPK empowers the dissolution testing specifications by establishing boundaries to enable formulation to be accepted or rejected. Hence, the understanding of whether PBPK alone can be used for approval of biowaivers and to provide wider product acceptance criteria to regulatory agencies. Currently, major emphasis is placed on using such approaches to support the regulatory application in order to increase the overall knowledge and understanding of the drug product. Sandra Suarez-Sharp et al. 2018 [31] have provided the decision tree in highlighting risks associated in using PBPK in supporting biowaiver request(s). Moreover, the report summarized some of the key points which need to be tackled in the field of application of PBPK for biopharmaceutics applications in regulatory decisions such as building high confidence around model verification and validation, case-by-case examination of each scenario due high complexities, consideration of big picture including formulation differences and purpose of the model along with assumptions should be adequately justified. Cristofoletti et al. 2019 [32] reported evidence that suggested the self-buffering effect, dynamic intraluminal pH, GI variability (e.g., gastric emptying time, fluid volume, etc.), and product specific particle distribution should be considered when trying to establish *in vitro* to *in vivo* relevance for drug products containing ionizable compounds such as ibuprofen.

Pepsin et al. 2021 [33] summarized the current state and future expectations surrounding translational modeling and its implementation in drug product development. This report highlights certain shortcoming such as typical input of PBPK models only account for limited properties of the formulation selected like particle size**.** Therefore, it is challenging to predict influence of several changes on the performance and systemic exposure.

3.2. Development of IVIVC and prediction of oral bioavailability

The generics industries share a common goal to optimize formulations based on the reference product, before it reaches the regulatory approval. However, a huge percentage of these formulations do not make it to the market resulting into tremendous loss of resources, time and funding. To overcome these challenges several M&S tools have been proposed/developed. One of such tool is IVIVC which refers to establishing an *in vitro-in vivo* link started early in drug development process [34]. Data from first-in human studies can be used to understand the *in vivo* absorption rates from a formulation and to relate this with the *in vitro* data. Throughout the development program, there are several opportunities where the performance of IVIVC can be evaluated with development of new formulations [35]. Therefore, poor prediction adequacy result in development of new IVIVC strategies and more predictive dissolution conditions. Moreover, the traditional deconvolution/ convolution method is more appropriate for compounds with linear pharmacokinetics which are well-absorbed throughout the GI tract. Model adjustments, such as the use of time scaling/time-shifting and absorption time cut-offs can be further added to the conventional methods, However, for compounds with more complex absorption patterns, additional validation steps would be needed [36,37]. As the PBPK modeling-based IVIVC allows the incorporation of physiological processes involved in absorption (regional dependent absorption due to either physicochemical properties or transporter involvement) as well as saturable metabolic components. There is currently lack of M&S approach in the Abbreviated New Drug Application (ANDA) submissions [38]. Additionally, generic drug applications go through an average of three review cycles taking several years, before being approved. The first review cycle begins with acceptance of ANDA application and ends when marketing authorities make a first decision. If an application is not approved in the first decision, it has to go through subsequent cycles to get approval. This procedure delays the arrival of the generic drug to the market. It has been reported that the FDA approved 12% generic drug applications in the first review cycle and several factors such as sufficiency of the application, deficiencies in drug quality, and type of drug e.g., formulation and complexity [39]. Proper validated PBPK M&Ss could expedite the previously mentioned preliminary cycle of approval of generic formulations by serving as alternatives or complementary approach to *in vitro and in vivo studies*. So far, PBPK M&S approach has been used for particle size optimization [10,40], salt selection [41], to estimate effect of food [42,43], effect of pH and prediction of oral bioavailability (BA) in different conditions [44]. The PBPK-based IVIVC offers several advantages such as i) more mechanistic correlation with accommodation of more complex absorption processes, and ii) model can be expanded to improve understanding by incorporation of information from different studies [45]. Jung et al. [46] established IVIVC using the PBPK platform to compare two biorelevant *in vitro* release methods for nanotherapeutics, flurbiprofen served as a model drug. The approach could successfully demonstrate the utility of the PBAM platform based model to predict the impact of these *in vitro* methods on the *in vivo* PK changes. Otsuka et al.[47] established the PBPK absorption model for the IR tablets and MR capsules by incorporating the biorelevant dissolution testing results to account for key factors influencing the absorption process of furosemide. The sensitivity analysis suggested gastric emptying, absorption rate and release rate in the small intestine have an important influence on the plasma concentration profile. Olivares-morales et al. [48] developed a minimal segmented transit and absorption model and expanded it to predict the oral bioavailability for modified release OROS® formulation of Oxybutynin. The following study demonstrated increased intestinal availability due to decreased intestinal first pass metabolism in the distal regions (decreased abundance of CYP enzymes) as the main factor responsible for the higher bioavailability of the OROS formulation compared to IR counterpart. Kesisoglou et al. [37] established and compared the traditional deconvolution/ convolution method and via PBPK absorption modeling for two different formulations (matrix type and multi-particulate tablets) of MK-0941. The PBPK regiospecific absorption approach could complement traditional IVIVC approaches and could be used for future formulation development. Basu et al. [49] also illustrated the use of PBPK absorption modeling to investigate the influence of drug and formulation-related properties on the oral absorption and bioequivalence of brand and generic ER formulation of metoprolol products. The result reported that sensitivity analysis indicated dissolution as highly sensitive to changes in the properties of the release-controlling polymer, HPMC (Hydroxypropyl methyl cellulose). Also, dissolution and BE are very sensitive to changes in N (hybrid release exponent summarizing factors such as polymer type, grade and molecular weight). Current bioequivalence assessments largely geared towards APIs leaving excipient effects usually neglected. However, the absorption of the API may be affected by the excipients. This could be thus important to predict the absorption of formulation containing different modulating excipients [50].

3.3. Study the properties of API to detect the failure in the later development stage

Improved understanding of the API properties earlier in the generic product development process reduces the chances of extensive monetary loss due to poor product performance, to the pharmaceutical industry. Parrott et al. [51] studied changes in the oral PK of bitopertin using PBPK absorption modeling, due to difference in particle size and dosage form (capsules, tablets or aqueous suspension). Melillo et al. [52] demonstrated the application of global sensitivity analysis methodology to improve the understanding of PBPK absorption models and in guiding the choice of model input parameters (drug/formulation related parameters) to study its influence on the output results (drug exposure and PK properties). Hansmann et al. [53] showed the importance of coupling *in vitro* results with the *in silico* PBPK models to better understand the *in vivo* behavior of weakly basic drug such as ciprofloxacin in several different patient population. Some examples include IR formulations to bring forth utility of the methodology, which could be applied to MR formulations. Ding et al. [54] integrated PBPK modeling in the development processes to effectively design ER clinical products for an ester prodrug LY545694. The accurate prediction of the performance of these optimized ER products was confirmed by the third clinical trial. Therefore, PBPK M&S can guide the development of formulation development and can be used to simulate the clinical impact of formulation related properties. This, allows the simulation of clinical trial outputs after the administration of formulations containing different API properties and choose those with higher probability of success minimizing failure rates in late development stages.

3.4. In silico prediction of food effect

Prediction of food effect and mechanisms responsible for food effect during early stages of drug and formulation development, can offer valuable insight on the expected clinical PK profile. FDA recommends that all oral MR products should be tested for bioavailability under fasted and fed conditions, for filling abbreviated new drug applications (ANDAs), bioequivalence studies in fasting and in fed conditions are required [55]. Also, food effect studies can show possibility of dose dumping which may result in safety concerns for study subjects [55]. Therefore, more informed formulation development can be helpful in

reducing the food effect and *in vivo* dog studies designed carefully can be insightful. In addition, majority of food effect studies done in animals struggle to be translated in humans. Several strategies have been adopted to integrate the biopharmaceutical knowledge and *in vitro* data such as solubility and dissolution testing using *in silico* modeling approach. These models need to account for the influence of food on the GI tract environment, physiology, drug dissolution, permeation, etc. Positive food effects are observed in lipophilic drugs due to higher bile salt and lipid concentrations. Whereas, negative food effect is usually observed for hydrophilic drugs, low permeability drugs. Several factors might contribute to observing negative food effect in drugs such as luminal degradation [56], and complexation to metal ions [57]. Also, in the fed state the drug concentration and diffusion change due to increased viscosity [58]. Moreover, the amount of mechanical stress the MR formulation especially matrix tablets, are exposed in the GIT, does influence whether the originator and generic formulation are bioequivalent under fasting and fed conditions. Danielak et al. [59] reported the importance biorelevant dissolution testing inclusive of stress modulation, led to the successful development of a pharmaceutically equivalent generic trazodone ER formulation to the originator under fed conditions. Therefore, PBPK models could be very supportive in the formulation development process, if they could capture stress induced dissolution changes in the generic formulations. Jones et al. [60] developed mathematical models illustrating fed and fasted physiologies together with biorelevant solubility, dissolution rates and degradation data to show food effect for six Roche compounds. The compounds were all lipophilic with log P values ranging from 2.3 to 6.5. These studies report accurately the significant food effects (two compounds) and mild food effects (four compounds). The simulation well captured the magnitude of food effect and correctly predicted the plasma exposure under fasted ad fed condition for the different compounds. Thus, the probable reason for food effect would be enhanced solubility/dissolution and conversely, for some compound it might be due to decreased solubility and increased degradation. Patel et al [61] investigated the food effect of BCS class II drug nifedipine IR and OROS formulation incorporating the population variability using the physiologically based ADAM model. This study demonstrates that anticipation of food effect in advance of *in vivo* studies. Andreas et al. [62] investigated the negative food effect of MR formulation of zolpidem resulting into decrease of Cmax and AUC. This study demonstrated the utility of combining dissolution testing and absorption modeling to improve the understanding of absorption process of 12.5 mg modified release Ambien® CR and 10 mg IR product. The *in vitro* biorelevant dissolution profiles of the MR formulations were used to check the prediction ability of the *in vitro* dissolution profile in both GastroPlus ™ and Simcyp ® software. The strategies such as deconvolution and PBPK modeling employed suggests incomplete drug release from the formulation resulted in reduction in fraction absorbed, thereby, contributing to negative food effect observed *in vivo*. However, the model suggested much future work for characterizing the drug release in the complex environments such as fed state.

4. Conclusions

PBPK has extensive applications in the field of biopharmaceutics. Nevertheless, this review found an under-utilization of this tool in the field of generic drug products in general, and more specifically for MR generic drug products. There is growing interest in the field of complex generic products [63]. In general, the field faces several challenges such as selection of input parameters, appropriate assumptions, lack of *in vitro* testing in biorelevant specifications, well rationalized optimization, model verification, gap in biopharmaceutical knowledge, incomplete understanding of *in vivo* influence of formulation excipients and inclusion of regulatory expectations. Above mentioned challenges result in underutilization of this tool in generic industry. With the growing confidence in PBPK modeling, there is growing opportunity of inclusion of different MR formulation categories to increase the utility of this approach in pharmaceutical regulatory applications. Few post- approval case studies suggest the application of PBPK modeling for rapidly dissolving immediate release (IR) products of BCS Class 1 and Class IV compounds used to justification or extension of biowaivers respectively [64,65]. Also, software tools such as DDDPlus® and Simcyp *in vitro* data analysis (SIVA) toolkit could help in highlighting formulation related risk factors which might have prominent impact on the bioequivalence and bioavailability study [32,49]. This field is still under research and continuous advancement. Hence, robust guidelines and well-defined regulatory expectations will result in better decision making in future applications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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