

The Case for Physiologically Based Biopharmaceutics Modelling (PBBM): What do Dissolution Scientists Need to Know?

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ABSTRACT

The purpose of this article is to inform the dissolution scientist of a powerful emerging tool that provides in vivo linkage to dissolution methods. This tool is physiologically based biopharmaceutics modelling (PBBM). Dissolution scientists are mostly concerned with analytical sections of drug development, so exposure to modeling and other pharmacokinetics and biopharmaceutic concepts may be uncommon. PBBM is an in-silico model that focuses on the interactions between the in vivo physiology and the formulation and drug characteristics. The principles behind PBBM is that all mechanisms related to drug release, dissolution, and diffusion from the site of administration to the site of action can be described in a mechanistic way or semi-empirical way. The integration of in vitro dissolution data in PBBM is described, including examples of software and modeling applications. The expertise needed to use the software and appropriate training is discussed. The key inputs that are expected from the dissolution scientist include an understanding of the aqueous solubility across the physiological pH range, impact of in vivo relevant bile salts and phospholipids on solubilization, and the impact of surface pH on dissolution rate. An example of an advanced in vitro system, TNO intestinal model (TIM-1), will be discussed and its importance in establishing a biorelevant understanding of dissolution behavior. PBBM can evaluate the clinical relevance of a dissolution method and justify specifications and ultimately provide an approval advantage to the sponsor. A well-supported dissolution method that provides clinically relevant drug product specifications (CRDPS) will be viewed with favor by the regulators. Therefore, the partnering of a dissolution scientist and biopharmaceutics scientist to develop PBBM is clearly an important step forward in drug development.

KEYWORDS: Dissolution, physiologically based biopharmaceutics modelling (PBBM), mechanistic

INTRODUCTION

The purpose of this article is to inform the dissolution scientist of a powerful emerging tool that provides in vivo linkage to dissolution methods. This tool is physiologically based biopharmaceutics modelling (PBBM). Dissolution scientists are mostly concerned with analytical sections of drug development, so exposure to modeling and other pharmacokinetics and biopharmaceutic concepts may be uncommon.

PBBM is an in silico model that focuses on the interactions between the physiology and the formulation and drug characteristics (1). This term encompasses all fields of biopharmaceutics. PBBM can be applied to orally administered drugs where absorption is desired or used to model drugs that are not designed to be absorbed.

For instance, drugs designed to exert a local action in the gastrointestinal (GI) tract or via intra-articular or intra-tumoral routes can be modelled using PBBM (2). The principles behind PBBM is that the mechanisms related to drug release, dissolution, and diffusion from the site of administration to the site of action can be described in a mechanistic way or semi-empirical way. These mechanisms for an orally dosed drug with targeted systemic action are illustrated in Figure 1. Several of these mechanisms can be measured in vitro and included directly or after data manipulation in PBBM platforms.

The PBBM can simulate all the mechanisms shown in Figure 1 from first principles or based on semi-empirical models. The model also adds a dynamic level, where the system parameters (i.e., those related to the physiology)

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can be varied over time as the product transits along the GI tract, for example. In addition, saturable mechanisms such as those related to drug metabolism or active transport can be included, which makes their prediction a function of local drug concentration. With regards to dissolution method development, the inclusion of dissolution data in PBBM for verification against clinical data obtained with various formulation variants is useful to assess whether the dissolution method is clinically relevant or over- or under-discriminating. Once the PBBM is built and verified using clinical data, it can be used to justify the specifications for the product critical quality attributes (CQA) and define the size of the “clinical safe space,” i.e., the product quality attribute ranges where all manufactured products are anticipated to be bioequivalent to the pivotal clinical trial batch(es). The PBBM can then be used with virtual bioequivalence studies to support changes within the safe space for products that would fail statistical comparison of dissolution profiles, for instance.

The dissolution method has evolved over many years. It began as a one-point quality control (QC) tool designed to profile and support bioequivalence testing and present where discriminatory and clinically relevant methods are expected (3–6). Provided in the literature are recommendations and strategies on how to develop dissolution methods (7, 8). If development is performed with a close eye on the in vivo performance and aligned with the biopharmaceutic risk assessment, the dissolution method could lead to clinically relevant drug products specifications (CRDPS). The present state

of dissolution methods includes robust challenges to show discriminatory power for CQA (9). A discriminating method is useful, especially for a QC tool, but it could lead to specifications that may not be considered clinically relevant. CRDPS are able to distinguish between bioequivalent and bio-inequivalent batches. Therefore, dissolution testing is not only to pass or fail a batch based on a predetermined value but to develop product specifications that will ensure bioequivalence of future batches manufactured within the limits of acceptable dissolution specifications.

To achieve CRDPS, regulators are strongly urging that methods have an in vivo link. This linkage, ideally, would be actual in vivo data in humans, as in the case of in vitro and in vivo correlations (IVIVC), or through modeling based on biopharmaceutical information (10, 11). Modeling in addition to supporting the dissolution method and hence specifications, has other uses, as assisting in Quality by Design (QbD), bioequivalence (BE), and formulation development (12–14).

Examples of Pharmacokinetic Data That Can Be Used to Build Mechanistic Dissolution Understanding

The gold standard for a developing a clinically relevant dissolution method is when a relative bioavailability study is conducted using deliberate formulation and process variants to show meaningful differences in dissolution performance (15). The combination of dissolution data and in vivo exposure data can verify if the dissolution method is clinically relevant, which enables identification of CRDPS and safe space, use of a traditional IVIVC,

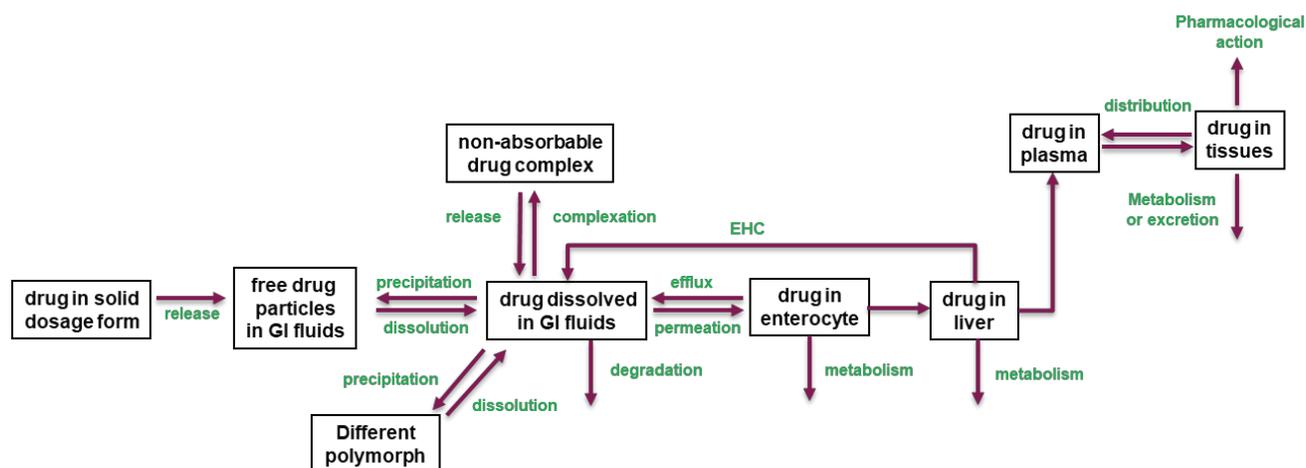


Figure 1. Mechanisms determining drug pharmacological action from an orally administered solid oral dosage form. EHC: Entero-hepatic circulation, GI: Gastrointestinal.

or application of PBBM to justify specification and interpolate the size of the safe space (Fig. 2).

Conducting such a relative bioavailability study may not always be possible due to financial constraints, ethical considerations regarding patient populations (e.g., some oncology drugs cannot be dosed to healthy volunteers, so the barrier to dosing variants in patients is higher), or time constraints (e.g., product is in-licensed late in development, so there is no time to run a variant study prior to submission). Even then, it may still be advantageous to run an in vivo variant study to determine if the chosen QC method using the traditional approach may be clinically relevant as much of the advantage of building the link between in vivo and in vitro comes when changes to the product are needed post approval.

Plans for establishing clinical relevance should ideally start early in development, and the benefits for particular products should be outlined to key stakeholders. This allows development of a coherent clinically relevant method and specification story to be available at time of first submission. Although it may not be possible to perform a variant study in vivo, Pepin et al. have shown that a validated PBBM model can be produced without the use of a variant study by simply looking across the entire span of in vivo data, which, in this example, included dosing with early and late formulations, dosing with and

without acid reducing agents, dosing varying batches of the late formulation, and dosing with orange drink/ grapefruit juice (16). By utilizing the wealth of clinical data, it was possible to predict the outcome of 16 different clinical scenarios with a good level of accuracy. This model was then used to support the establishment of the drug substance particle size. Supporting the drug substance particle size and drug product dissolution specifications for submission is a key role in the use of PBBM.

CURRENT WAYS TO INTEGRATE DISSOLUTION DATA IN THE PBBM MODEL

The integration of in vitro dissolution data in a PBBM can be done in a variety of ways. The more mechanistic the interpretation of the in vitro data is, the better the outcome of the model. There are many parameters that can influence drug dissolution in vivo, such as the local and varying conditions of pH, liquid volume, hydrodynamics, bile salt concentration, permeability, and transit time (Fig. 1). A QC dissolution method cannot reproduce all these parameters, and it is recommended to evaluate which are the most important parameters controlling in vivo dissolution. Since PBBM comprises most of the mechanisms described in Figure 1, a sensitivity analysis is useful to run early during product development to evaluate which parameter is most likely to influence in vivo dissolution. This parameter can then be varied in

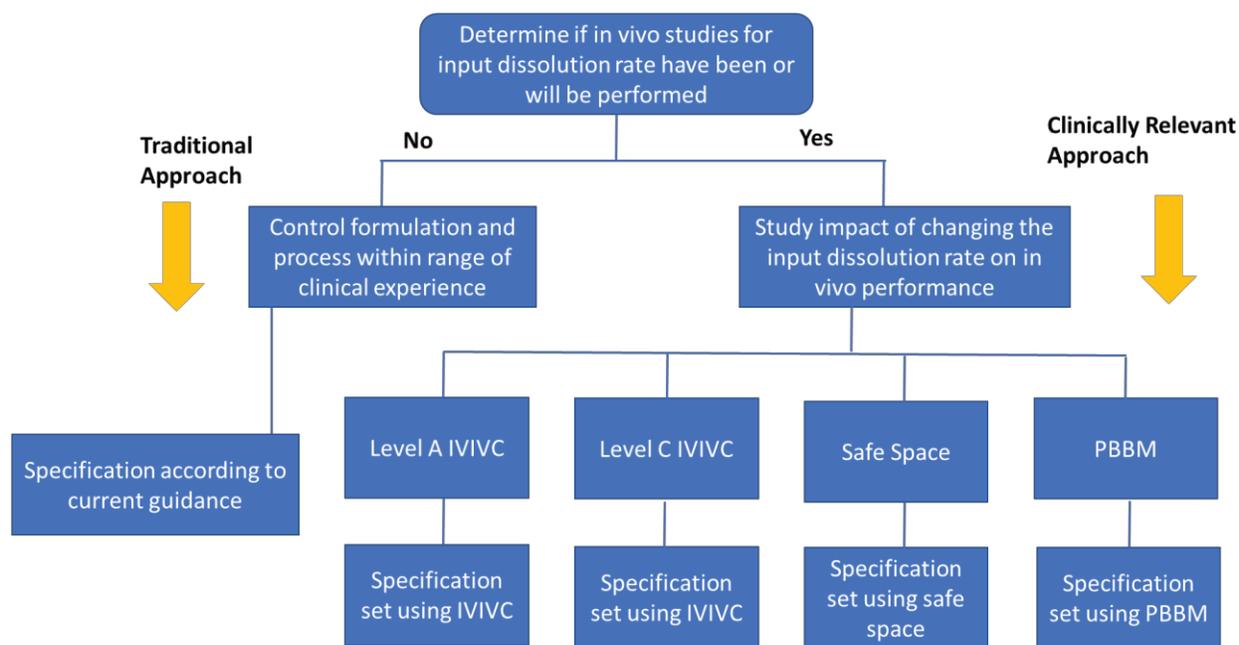


Figure 2. Approaches for setting dissolution specifications. IVIVC: In vitro in vivo correlation; PBBM: physiologically based biopharmaceutics model.

Adapted from Ref 70: Hermans, A. et al. Approaches for Establishing Clinically Relevant Dissolution Specifications for Immediate Release Solid Oral Dosage Forms. AAPS J 19, 1537–1549 (2017). Used under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

in vitro to generate relevant in vitro data to feed the model or to guide certain aspects of in vitro dissolution testing.

Mechanistic or Non-Mechanistic Integration

Currently, several methods are available to integrate dissolution data in a PBBM model. Examples of non-mechanistic integration of dissolution data are tabulated measurement of the dissolution profile over time or use of a Weibull equation or any other mathematical equation to plot drug release versus time and use that function as an input to the PBBM. Mechanistic examples for integration of dissolution including fitting a Z -factor to the dissolution data as proposed by Takano et al. or the product-particle size distribution (P-PSD) approach as proposed by Pepin et al. (15, 17, 18). Both parameters can be fitted to drug substance or drug product dissolution data. The Z -factor ($\text{volume.mass}^{-1}.\text{time}^{-1}$) is a hybrid parameter function of the drug diffusion coefficient, true crystal density, thickness of the unstirred water layer, and initial particle radius. The P-PSD is a 10-bin PSD fitted to drug product dissolution data in given conditions using a modified Nernst-Brunner equation to differentiate the impact of micelles on the drug dissolution rate and define different unstirred water layer thicknesses for the free drug and micelles (17). Both the z -factor and P-PSD approaches are able to predict other dissolution conditions and therefore are independent from the dose, volume, pH, and solubility of the drug. The Z -factor cannot be used easily with micelle-containing media and typically only predicts first-order type of dissolution rates, whereas the P-PSD approach allows prediction of dissolution rates resulting from the dissolution of faster and slower dissolving particles. This is often the case for polydisperse particle sizes or for a drug that is more or less accessible in a formulation, for example, which will take time to wet or be hidden in slowly disintegrating granules.

Current mechanistic approaches to dissolution are shown to integrate the impact of pH, volume, micelles, dose, and transit on in vivo product dissolution. Although theoretically the impact of drug substance particle size on in vivo dissolution can also be integrated mechanistically, such as through the use of a scaling factor for the diffusion layer model (in Simcyp), there are several aspects to check before using drug substance particle size as a direct input in PBBM (19, 20). The assumption of spherical shape for the particles, the potential particle aggregation, and differential wettability according to size may lead to disconnects between drug substance particle size and drug product dissolution (16). In addition, some process parameters may influence dissolution of

immediate-release products regardless of the formulation components. In this case, the current way to integrate dissolution of such products in the most mechanistic way is to adopt the P-PSD approach (15).

Immediate-Release Products

For immediate-release products, determination of dissolution under discriminating conditions is needed to establish the link between product dissolution and drug substance particle size. This link is important to ascertain, as the surface area developed by drug substance batches may be significantly higher than calculated by PBBM due to the use of laser diffraction data, which assume spherical particle morphology. Product batch specific dissolution data should be compared with particle size data of the drug substance used for product manufacture, because the manufacturing process and excipients may lead to changes in the drug substance surface available for dissolution. For a simple drug substance suspension it may be appropriate to utilize just the drug substance PSD as an input to the PBBM if it adequately describes the surface area, but some authors have found a disconnect between the measured PSD and the observed dissolution performance and accounted for it prior to inputting a particle size into PBBM (16, 17, 21). This has been described by Pepin et al with the P-PSD approach by utilizing a PSD that describes the dissolution performance of a specific batch of product, which takes into account formulation-related dissolution rate phenomena such as wetting, disintegration, capsule rupture, and deagglomeration and integrates process parameters such as compression force or granulation time, thus providing a more accurate input to PBBM (15, 17).

Adaptations to current PBBM are required in some situations. These mainly include the use of surface pH in the compartments of the GI tract where the drug is reactive and the use of physiological fluid volumes in the lumen of the GI tract. For a weak base where the maximum basic pK_a is less than 6, only the stomach is concerned with pH adjustment. For stronger bases, if the basic pK_a is higher than 6, pH adaptations in more or all the GI tract segments may be needed.

Modified-Release Products

For modified-release (MR) products, there is a clear advantage of using PBBM versus a classical IVIVC because, for instance, first pass gut extraction can be increased by a slower drug release along the GI tract, which is easily modeled with PBBM. For MR products, whether they contain amorphous drug or crystalline drug, the dissolution rate is generally controlled by the excipients

of the matrix or the coating applied to the formulation, and the link between *in vitro* dissolution and particle size surface area is usually lost. For prolonged release formulations where the drug is amorphous, the concept of mechanistic dissolution based on a surface area of a solid suspension is far from the formulation reality. However, if the dissolution is relatively fast, the use of amorphous solubility and a low particle size as an input can be relevant to the *in vivo* exposure, as shown by Mitra et al. (22).

For prolonged release products comprising Biopharmaceutics Classification System (BCS) class I drugs, the volume available for dissolution may not be influential on the *in vivo* dissolution, hence the use of a QC dissolution method may be appropriate to predict the *in vivo* dissolution rate (23, 24). For this reason, the authors

recommend for MR formulations, to fit a mathematical model to dissolution data obtained in sink conditions such as a one or two-phase Weibull model (23). When Weibull functions are used as an input in PBBM, the dissolution rate will be that of the mathematical model versus time, irrespective of solubility, volume, or pH in the GI tract. A prerequisite to this approach is to check the independence of drug release from the MR formulation to conditions of pH and volume *in vitro*. In case pH or volume impact drug release from the MR formulation, a Z-factor may be useful if it is region specific or pH specific in the PBBM (18). Further validation and application are needed to understand the limitation of this approach.

Based on the arguments detailed above, the authors propose a decision tree for integration of dissolution data in PBBM (Fig. 3).

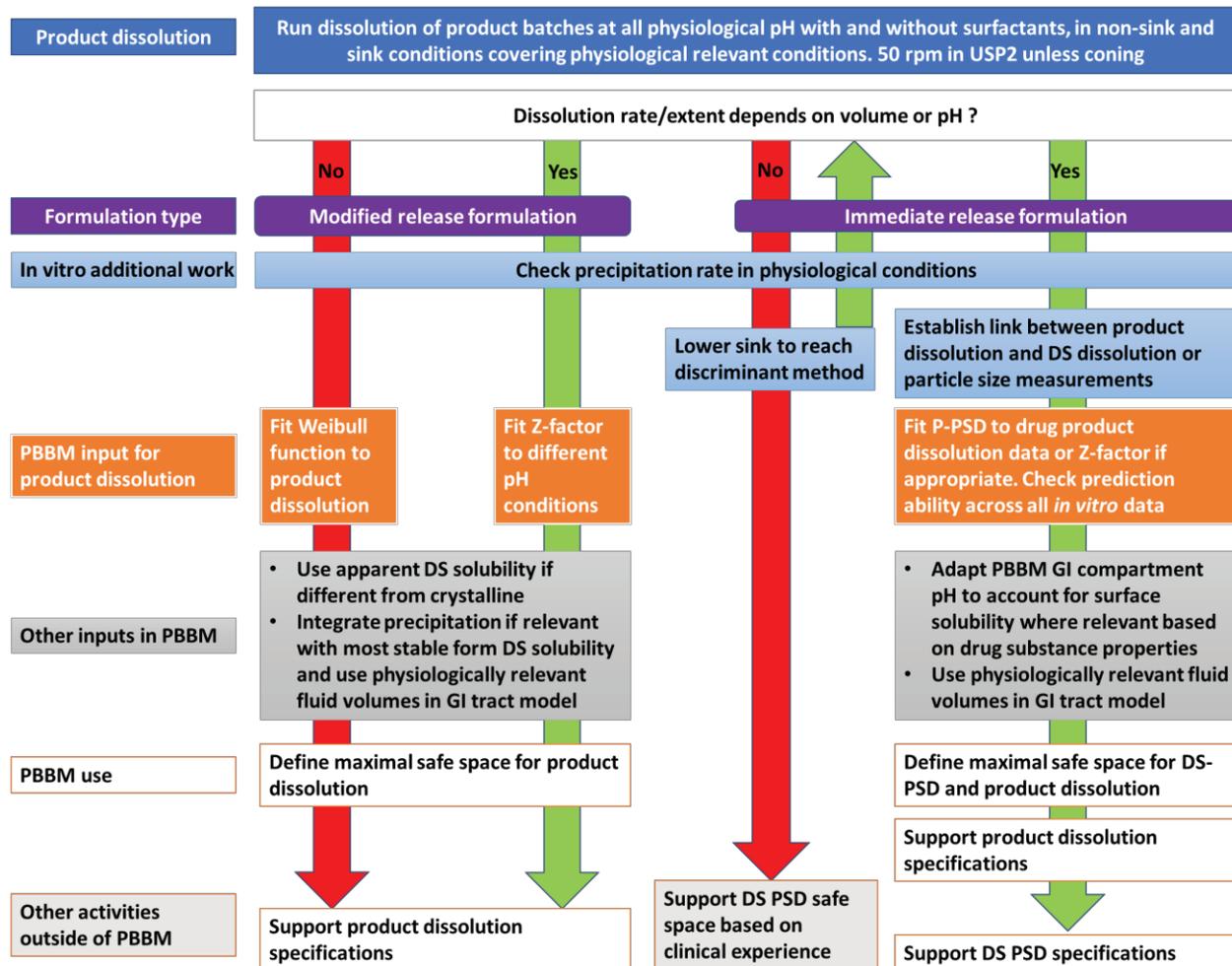


Figure 3. Integration of drug product dissolution data in PBBM. DS: drug substance, PSD: particle size distribution, PBBM: physiologically based biopharmaceutics model; GI: gastrointestinal; USP2: United States Pharmacopeia apparatus 2

Gaps in PBBM

Another area considered to be a gap in PBBM is the current description of liquid volumes along the GI tract, with regard to the distribution of the formulation or its released particles (1). To describe the GI tract, current PBBM assumes a series of well-stirred compartments linked to one another in series, where the drug distributes according to predefined transit functions. The default liquid volume in these compartments, depending on the PBBM platform selected, can be quite different from the physiological reality, and the drug dissolution is hypothesized to only happen in the lumen. The in vivo dissolution rate is calculated based on derivatives from the Nernst Brunner equation, where a bulk drug concentration will eventually limit dissolution. Recent insights about the volume available in the entire intestine from magnetic resonance imaging (MRI) show that approximately 80 to 100 mL fluid is available in the lumen of the entire small intestine, whereas 10 mL only is available in the colon lumen. This water is not found in a single compartment but as separate drops with an average volume of 6 mL (25, 26). This observation together with the formulation dispersion along the GI tract for disintegrating formulations or multi-particulates goes against the notion of bulk drug concentration in vivo. In addition, despite its small thickness, the volume of water available in the mucus lining the small intestine is approximately 5 times that of the lumen and 10 times that of the lumen for the colon. This mucus acts as a barrier towards particles above approximately 200 nm with an added impact of wettability and charge, and the diffusion of free drug in the mucus is not a simple function of hydrodynamic radius (27–30). The secretions from the GI membrane are also ignored in how dissolution is currently calculated. There needs to be a fundamental change in how dissolution is calculated in the GI tract of the PBBM to be able to evaluate dissolution in a more mechanistic way for all types of particle sizes.

Models need to be developed for predicting the impact of hydrodynamics on in vivo release for immediate-release and MR products, especially to predict the impact of different prandial states (31–33). Polymer-rich matrix systems that ensure prolonged release or protect amorphous drugs are sensitive to hydrodynamics. To our knowledge, no commercial model currently integrates the impact of hydrodynamics on the dissolution of matrix formulations. From Simcyp v15 (Certara), the impact of hydrodynamics is accounted for immediate-release formulations but has not received full validation from independent groups and will not apply to MR.

In the future, the impact of in vivo and in vitro agitation on drug release from matrix systems, whether erosion-based or diffusion-based, may open up new avenues to a more mechanistic integration in PBBM platforms. For hydroxypropyl methylcellulose (HPMC) matrices, Guiastron et al. recently derived a semi-empirical model for in vitro and in vivo release and calculated United States Pharmacopoeia (USP) apparatus 2--equivalent agitation rates throughout the GI tract (34). Further work is needed to define the appropriate in vitro tools to investigate biorelevant release mechanisms and get formulation dependent understanding of the impact of agitation on drug release from matrixes to allow meaningful integration in PBBM. Region-specific compression due to peristaltic movements in the GI tract may be useful to reproduce in silico to calculate in vivo dissolution from matrixes in a more biorelevant way, and be able to predict the multiple drug absorption phases sometimes seen from individual pharmacokinetic data (35–37). The TIM model described below could be used for this purpose.

PBBM SOFTWARE

Several software platforms can be used to build a PBBM; from open source PK-SIM (Open Systems Pharmacology) to commercial products such as Simcyp (Certara) or GastroPlus (SimulationsPlus). Some companies have developed their own tools such as GI-Sim in AstraZeneca and current regulatory guidance documents do not prescribe to use a specific tool to establish a PBBM (38, 39).

Software licenses range from no cost for open sources to approximately \$100k USD per year, depending on the provider and options selected.

Examples of Modeling Applications

PBBM can be used for a variety of purposes. Recent publication following a PBBM workshop at the FDA in 2019 highlighted the various application of PBBM amongst the workshop survey participants. There is an even spread of PBBM applications to support justification of product specifications (dissolution, particle size) during development, but also to support many post-approval changes on composition, dissolution specification, manufacturing site, or process (1) (Fig. 4).

In addition, since PBBM is mechanistic, it can help scientists understand the reasons behind within-subject and between-subject variability in pharmacokinetics, which can lead to strategies to improve product performance during development or as a life cycle

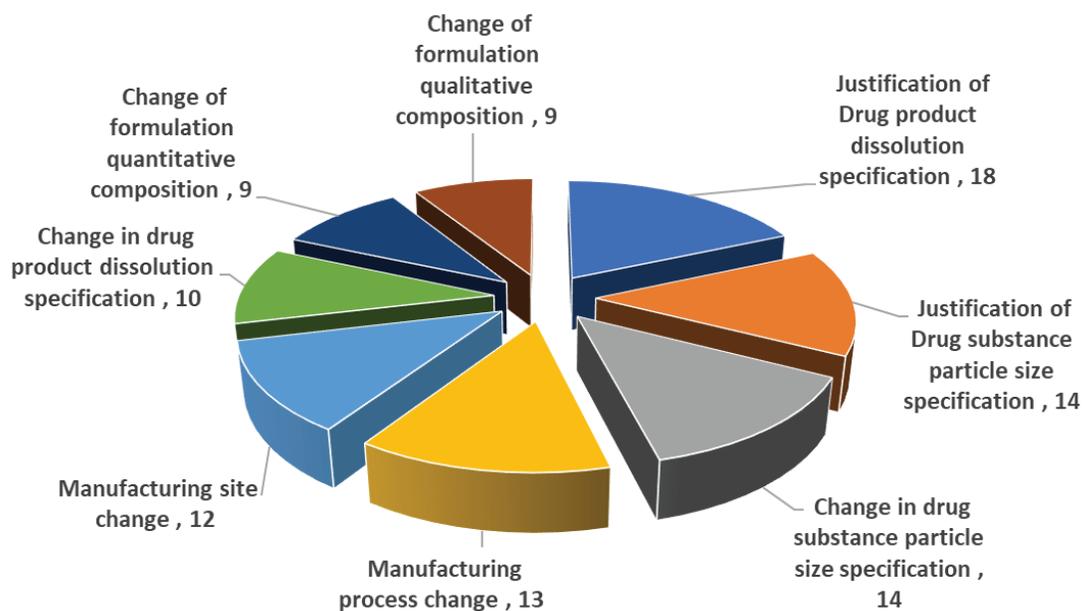


Figure 4: Applications of PBBM in drug development and post approval. Numbers are percentages (total is 99% due to rounding). PBBM: physiologically based biopharmaceutics model.

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management product. Chemists, analysts, formulators, and biopharmaceutics scientists work as a team to understand and improve the product performance through the use of predictive science.

Expertise Needed to Use the Software

The use of PBBM platforms requires some knowledge of physico-chemical chemistry, human or animal physiology, and pharmacokinetics. Depending on the organization, various functions will utilize the PBBM tool, including biopharmaceutics experts, pharmacokineticists, or pharmacometricians. These experts may have a different focus depending on the specific modelling aspect. Biopharmaceutics experts would use PBBM to support the quality aspects of products. If expertise is missing, a team effort is usually required to achieve optimal integration of in vitro and in vivo data in the PBBM.

Training

Training can be done by commercial software providers in the form of webinars, conferences, and specific support to customers. Additional resources are available through communities of practitioners or user groups that are publicly available. Being confident in using a software requires several years of practice on different types of project examples, as shown by a recent blind modelling exercise conducted through the IMI OrBiTo project that

showed prediction error reduced with the number of years of experience in modelling and simulation (40).

IN VITRO DATA NEEDED FOR PBBM

A dissolution scientist is tasked with providing some of the most key inputs to the PBBM. These include an understanding of the aqueous solubility across the physiological pH range, impact of in vivo relevant bile salts and phospholipids on solubilization, and the impact of surface pH on dissolution rate.

It is also important to determine the most mechanistic way to integrate dissolution into the PBBM. Building an understanding of product dissolution across a series of changes in pH, surfactant conditions, and hydrodynamic conditions is a key step in verifying the inputs. It is also key to understand and differentiate between true changes in performance and those that are related to in vitro artifacts.

Solubility Experiments

It is important to determine the intrinsic solubility of the compound and accurate experimentally determined pKa values to make predictions based on the Henderson-Hasselbalch equation. Once the prediction is in place, it should be confirmed by conducting traditional shake flask equilibrium solubility experiments to validate the

prediction and ensure there is no unusual solution behavior that could impact the prediction, such as in-situ salt formation or aggregation (41). It is also important to confirm the measured pH at the end of the experiment to allow an accurate check of where on the prediction you should look, and a confirmation of the solid state is needed to ensure no form changes have occurred. If deviations to the predicted solubility profile occurs, an assessment on the impact in vivo should take place, as it may be that the conditions needed for the deviation may not be present in vivo. When the drug is present in the product as a higher energy polymorph compared to the most stable thermodynamic form in the medium, or if the drug is a salt of the most stable form, a measurement of the critical supersaturation (i.e., drug concentration above which precipitation is observed) is recommended in addition to the precipitation rate in conditions relevant to the dose administered for the target population. For salts, the dissociation constant and surface pH in the physiological pH range need to be measured. For amorphous materials, the amorphous intrinsic solubility should be measured. All these parameters are used as inputs to the PBBM.

It is also necessary to understand the impact of in vivo relevant surfactants on solubility. The solubility of the compound in fasted state simulated intestinal fluid (the authors recommend V2) and fed state simulated intestinal fluid (authors recommend V1) alongside the blank buffers minus the bile salts and phospholipid should be measured (42, 43). Depending on the PBBM platform used, a simple model using the approach proposed by Mithani et al. or the fit of two partitioning coefficients for the ionized and unionized drug can be applied (17, 19, 44). It can also be useful to understand the apparent affinity of the drug to synthetic surfactants, as being able to predict the drug dissolution in the presence and absence of synthetic micelles is an additional verification of a mechanistic understanding of the drug dissolution. If this is done the solubility in the presence of several levels of commonly used dissolution surfactants like sodium dodecyl sulfate and polysorbate 80 should be performed. It is also necessary to measure the micelle size of the surfactants to accurately predict the dissolution performance in surfactant-containing media, which typically can be measured using dynamic light scattering or obtained from the literature, if available (17, 45).

For ionizable drugs where acid-base reactions take place at the surface, there are often differences between the bulk pH of the medium and the pH directly at the crystal surface of the dissolving active pharmaceutical ingredient

(API). This 'surface pH' and the related solubility at this pH are key for mechanistically understanding the dissolution (46–48). This issue is especially important for weak bases under gastric conditions, where the protons from the gastric juice will be consumed, raising the surface pH and lowering the driver for dissolution. It is important to understand the impact of this effect, as most modelling programs do not yet account for this well-known phenomenon. The surface pH is easily approximated by a simple concentrated slurry method, as described by Serajuddin et al. using various concentrations of hydrochloric acid (HCl) and sodium hydroxide (NaOH) (49). When the drug is in its neutral form, the bulk pH should be equal to the surface pH as no acid-base reactions are occurring. When correctly incorporated into the PBBM, the surface pH effect will improve the prediction capability of the model (16, 49).

Dissolution Data for Modelling

To build a mechanistic understanding of the dissolution of drug product it is important to test the impact of a change in experimental conditions on the dissolution performance. The most common change particularly for ionizable drugs is to test under different medium conditions while maintaining the apparatus and rotation speed (17). For example, a test could be conducted on a batch of a weakly basic drug product while the drug is neutral and expected to have poorer solubility and then measured again at lower pHs, where the performance is expected to improve. A consideration of the expected results achieved when considering the solubility, surface pH of the API should be made. If deviations from the expected results are observed, then an assessment of the root cause should be made, for instance, to determine if there are influences on the dissolution from the excipients, such as coning or pH modification from the excipients that are impacting the predictions (50, 51). This validation of dissolution performance is particularly important when using the P-PSD approach.

If excipients are present that may alter the solubility, then a simple surface pH experiment can be conducted on the blend or the granule to understand the impact and account for that in the comparison of predicted in vitro versus experimental values. If coning is present, it may be necessary to alter the hydrodynamics by increasing the rotation speed to remove the in vitro artifacts.

It is also important to assess the risk of in vitro precipitation for drug products that will solubilize under gastric conditions and then may precipitate as they travel into the higher pH intestinal conditions. Advanced in vitro

tools such as the TIM-1 system (TNO Nutrition and Food Research, Zeist, The Netherlands) can provide a useful indication along with simpler biorelevant dissolution experiments known as pH shift methods. Recent OrBiTo papers described a simple biorelevant pH shift method, for which there are variations used widely in the industry (52, 53). Once the extent of precipitation in vivo is assessed, the modeler can incorporate the findings. For example, longer precipitation times may be set if supersaturation was maintained for several hours after the pH shift from gastric to intestinal conditions for a weakly basic compound. When precipitation is measured with this simple procedure, there tends to be an over-prediction of in vivo precipitation because there is no absorptive sink (54, 55). Integration of precipitation rate in PBBM as a first-order precipitation rate can improve model prediction for situations where drugs are in supersaturation, but this may be dependent on the in vitro model and PBBM platform used (19, 54, 56, 57). The integration of precipitation with a mechanistic model such as the one proposed by Lindfors et al. is still not fully validated, and there has been no consensus on how to integrate drug precipitation in PBBM (58, 59).

USE OF ADVANCED IN-VITRO TOOLS FOR PBBM

The TNO intestinal model (TIM-1) system has been previously described in detail in the literature and can be used as an important tool in the testing cascade for building mechanistic understanding of the in vitro product performance and demonstrating the clinical relevance of the selected in vitro method (60).

The TIM-1 system is a multicompartamental, dynamic system that makes use of in-vivo relevant media, volumes, pH, and hydrodynamics to mimic the conditions found in the upper GI tract of an adult human. The system also mimics absorptive sink by means of hollow fiber ultrafiltration. Volumes, media composition, emptying rates, temperature, and pH are all dynamically computer controlled, allowing the definition of various subject physiologies, such as fasted, fed, or other various more complex disease states, essentially allowing the user to recreate the GI conditions of any patient group for which there are known physiological parameters.

The model has seen its main use in the nutritional science area (61, 62). The TIM-1 system has been suggested as a suitable tool for developing in vivo relevant in vitro dissolution and absorption methodologies (63, 64). The TIM-1 system is used by some members of the pharmaceutical industry as a part of evaluating

pre-absorption processes of drug candidates and their formulations in a more in-vivo relevant setting. Typical applications include but are not limited to:

- Formulation selection and relative bioavailability
- Food effect determination
- Dose linearity
- Formulation performance in disease state
- Exploration of physiological parameter ranges on formulation performance
- Life cycle management
- Clinical relevance of specifications of critical material attributes (CMAs) and critical process parameters (CPPs) (e.g., particle size, polymorphic form, process parameters)

Advantages of a More Complex System

The traditional one-compartment systems such as USP apparatus 1 and 2, though useful for developing clinically relevant dissolution methods, have limitations in how in vivo-relevant they can be. For example, drug and formulation specific factors, such as pKa(s), the selected formulation technology, and solubility-limited doses mean that each dissolution methodology must be carefully chosen to best represent clinical relevance. When more evolved methods are applied, such as pH shift dissolution, biphasic dissolution, or the use of more complex fluids, these methods still do not completely recreate the conditions found in the GI tract (54, 65, 66). As a result, there is no one size fits all dissolution method suitable for all products, a fact evidenced by the huge number of available methods and medias.

The TNO TIM-1 system utilizes a range of complex biological media, including the use of porcine bile, porcine pancreatin, and various enzymes. Combined with a large catalogue of patient physiologies that are available, the TNO TIM-1 system specifically aims to address some of the shortcomings of traditional methods by being as in vivo-relevant as possible. For example, pH shift dissolution may use a bolus addition of buffer to affect the pH shift, whereas in the GI tract and TIM-1 system, the rate of pH shift is controlled by the emptying of the stomach into the duodenum. This is of particular importance for the most commonly developed solid oral products which are poorly soluble weak bases. Where the supersaturation, precipitation, and redissolution kinetics are much more in vivo-relevant in TIM-1 than USP methods and these

factors critical for product performance, such as gastric emptying rate, media composition, buffering capacity, micelle concentration and volumes are much closer to that found in the human GI-tract than in USP methods. This may aid in decision making when studying the importance of particle size or polymorphic form. This increased understanding of precipitation kinetics under in vivo-relevant conditions can also be used to support PBBM parameters.

The TNO TIM-1 system also mimics the absorptive sink found in the GI tract via means of two hollow fiber ultrafiltration modules. This provides a potential benefit over traditional methods by providing for the constant removal of solubilized drug, bypassing the need for more complex media use (such as surfactants) to artificially boost solubility, thus potentially increasing the dynamic range of detectable differences between drug product variants. In addition, this filtration rate can also be altered to more closely mimic the in vivo permeability value, allowing for a closer approximation of product performance where that performance is permeability driven.

Another aspect where TIM-1 might be useful in making risk-based decisions is food effects. TIM-1 is capable of being dosed with a real United States Food and Drug Administration (FDA) breakfast and can mimic the clinical dosing scenario as closely as possible, because the physiology of the TIM-1 system can be altered to mimic a fed state in human. This involves factors such as prolonged gastric emptying, higher bile and enzyme concentrations, etc. This has important implications when considering the impact of elements such as enzymatic degradation of the API or formulation components, such as capsule shells, or complexation with digestion products from the meal itself. Researchers are evaluating the impact of other meal types typically used in clinical studies (such as a light European-style breakfast), as well as coping mechanisms (such as juices and yogurts) typically used as suspending or taste-masking agents in pediatric studies.

Disadvantages of a More Complex System

There are, of course, disadvantages to the application of such a technology. Disadvantages with more complex systems are typically related to throughput; TIM-1 cannot compete with more traditional methods, although efforts are underway to partially close this gap with the development of the “Benchtop TIM” by the TIM Company (Zeist, The Netherlands). This system aims to be a simplified, more automated variant of the full-scale TIM-1 system, allowing for higher throughput and less

user intervention. Benchtop TIM would sit ahead of a full-scale TIM-1 system in the testing cascade.

Because the system uses ultrafiltration, it only provides rank order information, not bioavailability data. This is because the system is unable to recreate the processes influencing drug absorption that happens at or beyond the gut wall, such as efflux. Due to this, the scientist must know something about the permeability of the molecule before embarking on a TIM-1 study.

It is important to remember that devices such as the TNO TIM-1 system are only one of a suite of tools available to pharmaceutical scientists. The favored approach to the deployment of TIM-1 is as a replacement for post-tox dog studies (60).

Linking TIM data to PBBM

The original TIM-1 was designed primarily for studying nutritional products, and as such, was only equipped with a simplistic stomach model with rudimentary mixing. Although this worked well enough for homogeneous doses such as solutions or suspensions, it was not well optimized for studying inhomogeneous doses. AstraZeneca worked with the manufacturer to develop a new stomach module that had more in vivo-relevant geometry and hydrodynamics, and this combined module is called the TIM-1 advanced gastric compartment (AGC) (TNO). A detailed description of the development and use of the AGC, including the development of a computational fluid dynamics (CFD) model of the TIM-1 AGC is detailed in the literature (67).

As TIM-1 AGC is now regularly deployed across all areas of the pharmaceutical development process, the range of products it is used to develop and test has expanded into complex oral products including but not limited to eroding matrices, fixed-dose combinations, enteric-coated products, and gastro-retentive devices. The use of a model with more in vivo relevant hydrodynamics is crucial to the rapid and accurate development of these complex products. In particular, because of the mode of operation of the TIM-1 AGC, the system could be used to determine the drug release rate from an MR matrix as a function of varying mechanical stress. A semi-empirical drug release model, as a function of time and applied stress, could be developed from the TIM-1 data and could be integrated in the PBBM. Using existing databases on in vivo pressure events along the GI tract, such as those recorded with a Smartpill (Medtronic, Herts, UK), the PBBM could calculate in vivo-relevant dissolution in the fasted and fed states. This approach would be a great

improvement compared to non-mechanistic models, such as the Weibull function.

CONCLUSIONS

The global acceptance of PBBM by regulators is still unknown. Contrary to the BCS classification that took 25 years to be fully recognized, from the first publication by Amidon et al. to the acceptance by International Conference Harmonization (ICH) countries in late 2019, there is hope that the process will be quicker for PBBM through conferences, publications, and general advocacy (68, 69). The current workshop held at the FDA in 2019 paves the way towards greater scientific collaboration to improve the PBBM tools and their acceptance worldwide (1). The clinical evaluation of formulation variants that represent commercial formulation and processes to vary the most relevant CQAs to support PBBM can only be beneficial. If bioequivalence is demonstrated for the variants tested, in the absence of any modelling, the results can be used to define a clinical safe space where post-approval product changes can be managed (11). If variants show differences in vivo, PBBM can help interpolate the edge of failure of the safe space and help justify the proposed specifications (15).

Current PBBM tools have shown their utility to support the demonstration of the clinical relevance of a dissolution method, to justify specifications, or even be able to obtain regulatory flexibility in changing a specification after approval or during the review period if the products are demonstrated to be in a safe space. There are some gaps in these tools but ways forward to improve the mechanistic approach to integration of dissolution, namely to review the dissolution equations to handle more physiologically relevant transit functions and water distribution along the GI tract, and to integrate hydrodynamics and compression forces for immediate-release and MR formulations.

Virtual bioequivalence studies hold the promise to support changes in products currently requiring human evaluation and therefore reduce the number of unnecessary clinical trials and expedite development to bring quality medicines to patients.

Ultimately the use of modeling will provide an approval advantage to the sponsor. A well-supported dissolution method that provides CRDPS will be viewed with favor by the regulators. Therefore, the use of PBBM by research teams and partnering with a dissolution scientist is clearly an important step forward in the drug development path.

CONFLICT OF INTEREST

James Mann, Richard Barker, and Xavier J.H. Pepin are employees of AstraZeneca, and this work was conducted as part of their employment. Vivian Gray disclosed no conflicts of interest related to this article.

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