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Review Article

BIPHASIC DISSOLUTION MODEL: NOVEL STRATEGY FOR DEVELOPING DISCRIMINATORY *IN VIVO* PREDICTIVE DISSOLUTION MODEL FOR BCS CLASS II DRUGS

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ABSTRACT

In vitro dissolution study should ideally be designed to predict *in vivo* performance precisely, providing key information on the bioavailability and establishing IVIVC. Development of discriminatory *in vivo* predictive dissolution model and the establishment of IVIVC is difficult to achieve with BCS Class 2 drugs as they exhibit variable absorption along the GI tract owing to pH-dependent solubility, especially for Classes IIa and IIb. In this context, the biphasic dissolution model is a powerful technique for investigating the interplay between dissolution, precipitation and partitioning of various poorly soluble molecules. The dissolution test medium comprising of immiscible aqueous and organic phases enables maintenance of sink conditions and easy quantification of poorly soluble drug partitioning into the organic phase. In the review, novel efforts have been taken to provide comprehensive information on challenges associated with the establishment of IVIVC for BCS Class II drugs, various approaches being adopted for developing discriminatory *in vivo* predictive dissolution model, significant outcomes of studies on biphasic dissolution model to predict the *in vivo* dissolution behaviour of BCS Class II drugs and the problems with the use of biphasic dissolution model including the status of FDA on the same.

Keywords: BCS, Biorelevant dissolution medium, Biphasic dissolution model, IVIVC, *In vivo* predictive dissolution

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INTRODUCTION

Pharmaceutical industry, in recent years, has attempted and adopted several integrated and multidisciplinary approaches to achieve a more logical and assertive development flow with a new drug molecule [1-3]. For many decades, poor aqueous solubility of therapeutically active molecules is one of the most critical issues in the pharmaceutical industry [4-6].

For biopharmaceutics classification system (BCS) Class II drugs, adequate dissolution in an aqueous environment is difficult to achieve at physiological pH [7-9]. BCS Class IIa drugs which are usually weak acids, behave like BCS Class I molecules and dissolve rapidly in the small intestine [10]. On the other hand, BCS class IIb drugs exhibit high solubility and dissolution rates in the acidic environment of the stomach but may precipitate in the small intestine [11]. Solubility of BCS Class IIc drugs has been observed to be pH-independent [10]. However, surfactants and lipids present in the biological milieu play a significant role in the dissolution of BCS Class IIc drugs [12].

Dissolution testing is being employed routinely as the primary tool for evaluating the potential ability of a dosage form to deliver a drug and make it bioavailable [13]. It is an important tool for guiding formulation development, monitoring stability, studying drug-release mechanisms, ensuring batch-to-batch consistency and demonstrating bioequivalence [7, 14, 15]. For compounds with poor aqueous solubility, maintaining the sink condition during the dissolution study, an essential criterion to obtain reproducible, meaningful data can be challenging complete rendering dissolution characterization difficult [16]. *In vivo* predictive dissolution (IPD) methods will be considerably different from and more complex than USP quality control (QC) methodologies [17]. IPD is considered as a surrogate to forecast the *in vivo* drug release and potentially reduces the number of bioavailability/bioequivalence studies required.

In vitro in vivo correlations (IVIVC) play an important role in the drug development process and optimization of the formulation [7, 18, 19]. The main objective of an IVIVC is to serve as a surrogate for *in vivo* bioavailability studies [20, 21]. Establishment of an IVIVC is highly dependent on the ability of *in vitro* tests to predict *in vivo* absorption, wherein IPD methodology can be beneficial. In the last two decades, great efforts have been employed to develop dissolution tests with biorelevant media (e. g. FaSSIF, FeSSIF, SGF, etc.) to characterize immediate release dosage forms of poorly water-soluble drugs in order to simulate the dissolution and absorption processes in the GI tract [22]. However, establishing IVIVC of BCS Class II drugs from immediate-release (IR) dosage forms is a difficult task to achieve [23-25]. Table 1 has been framed to provide an overview on the status of *in vivo* studies and establishment of IVIVC with immediate-release (IR)/sustained-release (SR) formulations of BCS Class II drugs in last 5 y. For the purpose and also for writing the review, a systematic search of PubMed and Web of Science databases was conducted in the period October 2021 to January 2022 to retrieve all articles reporting studies on BCS Class II drugs since 1990 till date. Search terms included '*in vivo* predictive dissolution model', 'BCS Class II', '*in vitro* drug release study', '*in vivo* study', 'pharmacokinetic parameters', 'IVIVC', 'biphasic dissolution model' combined with the Boolean operator "AND", were applied for all database fields. Restrictions were applied to the article language (only in English).

Since conventional dissolution tests fail to fulfil the objectives of IPD due to the lack of biorelevance, more physiologically relevant dissolution methods have been developed to predict *in vivo* performance [19, 38]. Examples are artificial stomach-duodenum models, physical stress models, dissolution-permeation models, digestion model, biphasic dissolution model etc [39-43]. A biphasic dissolution system is one attractive technique, expected to be particularly applicable in studying the *in vitro* dissolution and predicting *in vivo* behaviour of both IR and modified-release formulations of BCS Class II compounds [4, 13, 22, 44].

The present review focuses on challenges in establishing IVIVC of BCS Class II drugs approaches for developing discriminatory *in vivo* predictive dissolution model for BCS Class II drugs with special emphasis on the biphasic dissolution model. No previous attempt has been made till date to highlight the significance of the biphasic dissolution model in predicting *in vivo* dissolution behaviour of BCS Class II drugs.

Table 1: Update on studies to establish IVIVC with IR/SR formulations of BCS Class II drugs in 2016-2021

Drug	Formulation	*In vitro* drug release study	*In vivo* studies	IVIVC	Remarks	Reference
Etoricoxib	Tablets	Computer-controlled multicompartmental device (GIS) equipped with 3 dissolution chambers representing stomach, duodenum, and jejunum. Dissolution media: SGF (pH 2.0), phosphate buffer (5 mmol, pH6.5)	Data obtained from BE cross-over studies in healthy subjects and *in silico* simulation to predict pharmacokinetic profile	Not done	GIS able to detect dissolution differences between formulations in SGF -Impact of excipients on *in vivo* duodenal and jejunal behaviour observed	[26]
Fenofibrate	Microemulsion	USP Type II; Dissolution media: Buffers of pH 1.2, 4.5, and 6.8	Not done. Permeability studies done using biomimetic artificial membrane and everted gut sac technique	-	Permeability determined by everted gut sac technique was of higher magnitude than that determined using artificial membrane	[27]
Oxcarbazepine	Microfibres pressed into tablets	USP Type II; Dissolution medium: Phosphate buffer (pH 6.8)	In healthy human volunteers	Not done	*In vitro* dissolution was>90% within 2 min which is 5 times faster than that of pure drug, improvement in Cmax, Tmax, AUC	[28]
Atorvastatin calcium	Gelatin nanoparticles	Dialysis bag diffusion technique	In Sprague-dawley rats	Not done	Cmax and AUC 0-24 of nanoparticles 4-fold and 11-fold higher than that of pure drug suspension	[29]
Sorafenib tosylate	Self-nano emulsifying drug delivery system (SNEDDS)	Done. Details could not be obtained	Done. Details could not be obtained	Not done	Cmax of optimized SNEDDS higher than pure suspension and the AUC 0-∞ of optimized SNEDDS increased by 5 times than pure drug	[30]
Telmisartan	Nanosuspension	USP Type II; 0.1N HCl	Not done	NA	-	[31]
Ezetimibe	Liquisolid compacts	USP Type II; Dissolution media: 0.5% SLS, 0.05 M acetate buffer (pH4.5)	Not done	-	Better drug release compared to marketed tablet	[32]
Sildenafil	IR and SR tablets	USP Type II; Dissolution media: 0.1N HCl (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8)	In beagle dogs. Non-compartmental pharmacokinetic parameters determined such as t1/2, AUC, Vd, CL, Cmax, tmax	Population pharmacokinetics for establishing IVIVC. Level A IVIVC	Unusual patterns in complex, pH/site-dependent solubility and dissolution explained by population pharmacokinetics	[33]
Gliclazide	Tablets with cyclodextrin complex	USP Type I; Dissolution medium: phosphate buffer (pH 6.8)	Not done	-	Dissolution rate enhanced by complexation	[34]
Carvedilol	Marketed tablets	USP Type II; Dissolution media: 0.7% HCl (USP 38, pH 1.45), SGF *sans pepsin* (pH1.2), FaSSGF (pH 1.6), FeSSGF (pH 5.0), SIF *sans pancreatin* (pH 6.8), 0.05M phosphate buffer (pH 6.8), acetate buffer (pH 4.5), FaSSIF (pH 6.5), FeSSIF (pH 5.0), phosphate buffer (pH 6.8, 7.2, 7.8, 6.25, 12.5, 25, 50, 100 mmol)	Not done	NA	Dissolution of carvedilol completed within 60 min in SGF (pH 1.2-5.0) relatively low within 240 min in SIF (pH 6.5-7.8)	[35]
Efavirenz	IR suspension, modified-	USP Type II (Minipaddle) for IR suspension;	Done in rats. Cubosome *in vivo* data fit two-	Levy plots done and r2	Rate of absorption not dramatically	[36]

Drug	Formulation	*In vitro* drug release study	*In vivo* studies	IVIVC	Remarks	Reference
	release cubosomes	Dialysis method using Minipaddle for cubosomes; Dissolution media: FaSSIF, FeSSIF, phosphate buffer (pH 6.8, 7.4), water with 0.5, 1.0, or 2.0% SLS, SGF, SGF *sans pepsin*, lipolytic medium, water, 0.1N HCl	compartment model and IR suspension followed one-compartment model after extravascular administration. PK parameters evaluated. Cmax, AUC, Ke, tmax, t1/2, the fraction of dose absorbed at each time point evaluated	values for all media were calculated. Level A IVIVC obtained with 0.5% SLS in water for cubosomes and FaSSIF for IR suspension	different for cubosomes and suspension but difference in the extent of absorption	
Nifedipine	IR capsules	USP Type II; Dissolution medium: FaSSGF	In healthy human volunteers	Not done	Effect of administration of large volumes of water with capsules on pharmacokinetic parameters studied	[37]

FaSSIF: Fasted-state simulated intestinal fluid; FeSSIF: Fed State Simulated Intestinal Fluid; FaSSGF: Fasted State Simulated Gastric Fluid; FeSSGF: Fed State Simulated Gastric Fluid; SLS: Sodium lauryl sulphate; SGF: simulated gastric fluid; GIS: Gastrointestinal Simulation

Challenges in establishing IVIVC of BCS class II drugs

BCS Class II drugs are characterized by aberrant biopharmaceutical properties. Dissolution of BCS Class IIa and Class IIb drugs is highly dependent on drug pKa, its solubility, formulation variables, in addition to the *in vivo* luminal environment [10, 45]. Gastric content with food and orally administered drug gradually enters the small intestine, where bile and the pancreatic juice are secreted to neutralize the gastric content, and the drug ultimately gets absorbed into the systemic circulation across the intestinal membrane [46, 47]. Some BCS Class IIa weak acids, particularly the small molecule nonsteroidal anti-inflammatory drugs (NSAIDs), are reported to dissolve quickly and behave like BCS Class I drugs in the small intestine, even though they exhibit low solubility at acidic gastric pH. Weakly basic drugs with poor intrinsic solubility (BCS Class IIb) quickly dissolve and are minimally absorbed in gastric pH owing to ionization but may precipitate upon entry in the upper small intestine due to the pH shift to the higher side [26, 48]. Therefore, dissolved BCS Class IIb drugs may be present in a supersaturated state [46]. While BCS Class II weak acids and bases demonstrate pH-dependent solubility in environments of varying pH in the human GI tract, the solubility of BCS Class IIc drugs would not be affected by this *in vivo* pH change. However, for BCS Class IIc drug products, surfactants and lipids present in the biological environment play a significant but difficult to predict role in drug dissolution.

IVIVC development becomes thus challenging owing to complexities in the phenomena of drug dissolution and absorption from the dosage forms of BCS Class IIa and IIb drugs, especially [12]. Various factors that usually determine the feasibility and success of IVIVC include physicochemical, biological, and pharmacokinetic properties of a drug substance, formulation design, *in vitro* and *in vivo* study designs for characterizing dosage form performance, modeling methodology, and level of understanding of the inter-relationship among the variables involved in the *in vivo* processes of release and absorption [12, 49].

Approaches for developing discriminatory *in vivo* predictive dissolution model

For developing a discriminatory *in vivo* predictive dissolution model, empirical and first-principles-based approaches have been documented for a range of intended purposes. Combinations of these two, such as the use of empirical model-derived parameters as inputs for the first principles and vice versa, are also common [50]. Based on the type of model used for decision-making, modeling approaches have been categorized, regardless of the input source.

First-principles approach

Early in drug product development, with a lack of data, first-principles-based models are created to aid in formulation development and process screening. With increased data and knowledge, these models mature into data-driven predictive models to enable real-time release testing (RTRt) and QC testing [51]. The first-principles study of dissolution profiles of drugs has been initiated by Arthur Noyes and Willis Whitney in 1897 [52]. The first-of-its-kind study characterized dissolution as a first-order rate process, dependent only on a rate parameter k and the material solubility. At sink conditions, this model further reduces to a zero-order one. This 0^{th}- and 1st-order kinetics are the most basic mechanistic descriptions of dissolution [50].

Empirical approach

An empirically predictive *in vitro* dissolution model is dependent upon a traditional dissolution method due to the nature of the empirical approach that is used to forecast the dissolution profiles either directly (i.e., release level at specific time points or time to reach a specified release) or through predicting values of coefficients for fit to functional forms of dissolution profiles [50, 53, 54]. Exploring the formulation and process knowledge space provides an opportunity to understand the impact of various formulation and process variables on dissolution, which also establishes a foundation for the subsequent model-building exercise [53, 54].

To predict *in vivo* performance, there are more physiologically relevant dissolution methods other than the above-mentioned approaches. Examples are artificial stomach-duodenum models, physical stress models, dissolution-permeation models, digestion models, etc [19].

Artificial stomach-duodenum (ASD) model

This *in vitro* model mimics the functions of parts of the human digestive system (particularly stomach and duodenum), thus enabling scientists to understand how food and drug formulations are dissolved and transported within the GI tract [55, 56]. Also, it allows studying the influence of physical properties of drugs such as solubility and wettability on drug absorption, assuming that duodenal drug concentration is proportionally related to absorption [56, 57]. ASD modeling provides an important dynamic tool for the investigation of transient effects. This type of model has been successfully used to improve the dynamic *in vitro* assessment of antacid-induced resistance to stomach acidification and measure their activity in the duodenal milieu as well as in evaluating the effect of proteins and magnesium oxide in neutralizing stomach pH [57, 58].

Physical stress model

The novel dissolution stress test device, developed by Garbacz and Weitschies, exposes the dosage forms to physiological mechanical

stress as an arbitrary sequence of movements, pressure waves, and phases of rest in the manner they may occur under *in vivo* conditions during passage of the dosage form through GI tract in a fasted state [41, 59]. Moreover, it enables the simulation of an intermittent contact of the dosage form with the dissolution medium [60].

Dynamic gastric model (DGM)

To address the need for a model, DGM was developed at the Institute of Food Research (Norwich, UK) that could simulate both the biochemical and mechanical processes occurring during human gastric digestion in a physiologically relevant manner [61]. It mimics the mechanical stress of mixing and the gastric fluid secretion depends on the volume of gastric content. Its close simulation of physiological conditions has enabled the application of DGM in the pharmaceutical industry as an *in vitro* tool to study the effect of food matrices on the disintegration and dissolution of dosage forms and the drug delivery profile to the duodenum [61, 62].

GastroPlus simulation

GastroPlus is a mechanistically based simulation software package that simulates absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals, following several routes of administration [63, 64]. The PBPK Plus™ Module in GastroPlus is the top-ranked physiologically based pharmacokinetic (PBPK) software for IVIVEs, pre-first-in-human (FIH) predictions, pediatric dose selection, and formulation optimization. In the convolution technique, a set of *in vitro* data from different dissolution scenarios are used as input functions to estimate the expected drug plasma concentration-time profile. In deconvolution, *in vivo* dissolution profiles created by GastroPlus are plotted against *in vitro* obtained dissolution profiles so that "bio-performance" dissolution conditions can be identified [64]. GastroPlus offers several advantages in predicting *in vivo* dissolution and absorption behavior in both fasted and fed conditions. Based on known solubility at a particular pH and drug pKa, GastroPlus enables the calculation of regional solubility on the basis of the fraction of drug ionized at each compartmental pH from the Henderson-Hasselbach equation. It can predict the effect of bile salt on *in vivo* drug solubility and dissolution. GastroPlus is capable of modeling the possible precipitation of poorly soluble weak bases when moving from stomach to small intestine [40].

pH-stat lipolysis

One way to overcome the solubility limitations of emerging drug candidates is through the use of lipid-based formulations (LBFs) [65-69]. The current *in vitro* setups to assess the performance of LBFs have limitations and often produce results that are quite different from the *in vivo* performance [70-72]. This lack of predictive and high throughput *in vitro* tests hampers the efficient development of LBFs. Commonly, LBFs are tested for their dispersibility, micellar size, and behavior upon digestion, in line with the lipidic formulation classification system [73-77]. The pH-stat lipolysis method is the most widespread standard method for *in vitro* assessment of LBFs [78-80]. It typically involves the dispersion of LBF in a medium representing the fasted intestinal environment with the addition of digestive lipases while controlling pH throughout the experiment by the addition of NaOH solution [5, 81, 82].

Biphasic dissolution model

A biphasic dissolution study is expected to be particularly suitable to study the *in vitro* dissolution and predict *in vivo* behavior of formulations of BCS Class II compounds. It involves the use of two immiscible liquid layers, an organic phase and an aqueous one [83, 84].

Biphasic dissolution model

Biphasic dissolution test medium consists of immiscible aqueous and organic phases, where maintenance of sink condition is possible due to continuous partitioning of drug into the organic phase, depending on its distribution coefficient [13, 15, 85]. The basis for the biphasic dissolution model was first reported by Levy, who proposed that the presence of an upper organic phase within the dissolution medium could act as a reservoir or sink for the dissolved drug. Sink conditions are conventionally maintained in dissolution tests by means of surfactants, a large volume of dissolution medium, or cosolvents, but they have no physiological relevance [4, 86]. Combined dissolution and partition kinetics in biphasic dissolution models provide a discriminative power to dissolution tests for formulations of BCS Class II drugs [15, 44, 85]. In biphasic dissolution, 1-octanol is used for generating distribution or absorption-sink conditions due to its physicochemical properties and its application in logP determination [14, 16, 44].

The biphasic dissolution system is simple, easy to implement, and uses commonly available equipment [44, 87]. The advantage of this system lies in its single-step likeness to *in vivo* release, dissolution, and absorption of therapeutically active molecules in the gastrointestinal tract. Moreover, in the biphasic dissolution test, quantification of the drug concentration in the organic phase avoids the analytical challenges of measuring the free drug concentration in the aqueous phase [44]. Reliable and accurate determination of the free drug concentration belonging to BCS Class II becomes difficult due to the presence of precipitated drug particles in the aqueous phase under a non-sink condition. In contrast, the drug concentration in the organic phase can be reliably and accurately determined. Particle movement into the organic phase by the process of partition effectively acts as an analytical "filter" [88, 89].

Biphasic dissolution models: Past studies and significant outcomes

Anishetty *et. al* performed an experiment to assess the dissolution behavior of tablets with meloxicam nanoparticles in the biphasic medium of octanol-buffer of varying pH and it was concluded that excipients play a major role in the release behavior of drug with lactose as diluent promoting rapid wetting of drug particles by dissolution medium than dicalcium phosphate [90].

In an experiment to develop a biphasic dissolution test for deferasirox dispersible tablets and its application in establishing an *in vitro-in vivo* correlation, flow-through apparatus and the USP paddle apparatus were employed as dissolution apparatuses and octanol-phosphate buffer (pH 6.8) was used as biphasic dissolution medium and level-A IVIVC correlation was successfully established. Level A IVIVC was obtained with both dissolution apparatuses and the system was demonstrated to be superior to the single-phase system with respect to its ability to discriminate between different formulations [13].

In another study, an absorptive compartment (biphasic system) was introduced to a gastrointestinal simulator (GIS) and USP dissolution apparatus II for the assessment of *in vivo* prediction from immediate-release dosage forms for BCS Class IIc drugs, donepezil and danazol. Donepezil exhibited complete dissolution with the presence of an absorptive phase at 180 min (10 % in simulated intestinal fluid+90% in 1-octanol). Danazol also exhibited a 2-fold improvement in its dissolution with a distinct absorptive phase at 180 min [83].

It was difficult to establish IVIVC for different polymorphic forms of carbamazepine using single-phase dissolution. The difference between the anhydrous and dihydrate forms could be noted under non-sink conditions but it failed to establish meaningful IVIVC. However, when a biphasic *in vitro* dissolution test was employed with USP Type II apparatus as dissolution apparatus and phosphate buffer pH 6.8 containing octanol as dissolution medium, satisfactory discriminative power could be observed for the different polymorphic forms (form III>form I>dihydrate form) [21].

Gastrointestinal simulator (GIS) with biphasic platform proved beneficial in predicting *in vivo* dissolution profiles for BCS Class IIb drugs, ketoconazole, and raloxifene, including supersaturation and precipitation as well as mass transport analysis. In the study, sodium phosphate buffer (pH 6.5)-octanol was employed as the dissolution medium [11].

In a study to ascertain the application of a biphasic dissolution model as a discriminating tool for HPMC matrices containing BCS Class II drug, nifedipine, several combinations of aqueous and organic phases were investigated, which included SIF, HCl, sodium dodecyl sulfate (SDS), and sodium phosphate-buffer as aqueous phase whereas chloroform, ethyl acetate, cyclohexene/octanol, and

nonanol/octanol as the organic phase. From the study, it was concluded that a biphasic dissolution medium consisting of an optimized deionized water/octanol system exhibited discriminatory power in revealing differences among nifedipine formulations with different HPMC percentages [7].

Biphasic dissolution model in establishing IVIVC

IVIVC has been defined by the FDA as "a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and an *in vivo* response". Generally; the *in vitro* property is the rate or extent of drug dissolution or release, while the *in vivo* response is the plasma drug concentration or amount of drug absorbed. The United States Pharmacopoeia (USP) also defines IVIVC as "the establishment of a relationship between a biological property, and a parameter derived from a biological property produced from a dosage form, and a physicochemical property of the same dosage form" [18, 20, 91].

The basic requirements for establishing IVIVC are: Data obtained from human studies are essential for regulatory consideration of the correlation, two or more drug product formulations with different release rates are compared by employing an appropriate *in vitro* dissolution method, the development of IVIVC enables the standardization of the same dissolution method for all the formulations, and plasma concentration data from a bioavailability study for each of the formulations [22, 92].

In order to establish quantitative IVIVC with the biphasic test, an optimal hydrodynamic condition coupled with the use of biorelevant media is required. *In vivo* absorption profile is analogous to the drug concentration-time profile in the organic phase due to the presence of an "absorptive" phase in the biphasic dissolution model [22, 49].

Challenges with biphasic dissolution model

The biphasic dissolution model cannot be used as a regulatory test without the approval of the FDA, although it can act as a valuable bio relevant dissolution strategy enabling prediction of the outcome of bioequivalence studies and assisting in formulation selection [16]. The sampling of biphasic systems is associated with several analytical problems. The use of an automated sampling unit in standard USP I/II dissolution vessels with a medium such as octanol may block the sampling lines. In the biphasic dissolution model, the switch from gastric to intestinal conditions occurs very rapidly, whereas the process of gastric emptying is usually more gradual *in vivo*. Rapid pH transition may lead to an overestimation of the precipitation rate [5].

CONCLUSION

Dissolution testing is employed for *in vitro* assessment and prediction of the *in vivo* behavior of a pharmaceutical dosage form. Various approaches are being adopted in order to develop the discriminatory *in vivo* predictive dissolution model, which includes the First-Principles approach and the Empirical approach. There are several other models such as artificial stomach-duodenum models, physical stress models, dissolution-permeation models, digestion models, etc. In order to overcome the challenges associated with the development of a discriminatory *in vivo* predictive dissolution model and the establishment of IVIVC for BCS Class II drugs, the biphasic dissolution model has been reported to be very effective as discussed in the review with case studies on BCS Class IIa and IIb drugs. Although the model shows promise, limitations do exist regarding quantification and rapid pH transition, and also FDA approval with respect to its use for regulatory purposes is still awaited. Further studies in this direction will establish the biphasic dissolution model as an extremely beneficial tool in IVIVC studies.

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AUTHORS CONTRIBUTIONS

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CONFLICT OF INTERESTS

No conflict of interest by authors.

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