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New mathematical model from dynamic dissolution rate tests

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ABSTRACT

In vitro dissolution experiments are becoming increasingly complex attempting to replicate in vivo behavior. The objective of these new methods is to explore the behavior of low-solubility drugs. This is more relevant for drugs classified in subclasses 2a, 2b and 2c of the BCS, considering their pH-dependent solubility and dissolution characteristics.

A novel mathematical approach using a modified double Weibull equation is proposed to model the dissolution and precipitation kinetics observed in two-stage and transfer dissolution experiments (dumping test). This approach demonstrates a high level of accuracy in fitting experimental data for two drugs BCS class 2a and two BCS class 2b, providing valuable insights into their dissolution behavior under different conditions.

The results highlight the versatility of the proposed model in capturing complex dissolution phenomena, including rapid dissolution, precipitation, and redissolution. The ease of implementation in Excel, using the Solver tool, makes it a practical and accessible tool for pharmaceutical researchers.

Overall, the study contributes to the development of more effective in vitro dissolution testing methods, facilitating the formulation and optimization of pharmaceutical products and potentially aiding in the establishment of *in vitro-in vivo* correlations (IVIVC).

1. Introduction

The absorption of a drug from a solid dosage form following oral administration is limited upon the release of the medicinal substance from the product, dissolution, or solubilization of the drug under physiological conditions, and permeability through the gastrointestinal system. Given the critical nature of these initial two steps, in vitro dissolution is relevant for predicting in vivo performance. In accordance with this overarching consideration, in vitro dissolution tests are employed for solid oral dosage forms, such as tablets and capsules (Fda et al., 2018).

Dissolution rate tests are conducted using apparatus approved by the United States Pharmacopeia (USP). The basket apparatus (USP I) and paddle apparatus (USP II) were initially introduced in the United States Pharmacopeia in the 1970s to assess the dissolution characteristics of oral medications (Dokoumetzidis and Macheras, 2006). They have primarily been used as a quality control function, testing a variety of oral dosage forms and providing a substantial volume for a dosage form to dissolve in a well-agitated environment (McAllister, 2010). Dissolution tests employing either the USP I or USP II apparatus are carried out under various parameters and conditions, including variations in hydrodynamics, the type, and volume of the dissolution medium (Dressman et al., 2005).

The most common approach to represent data obtained through these methods is with a graph of Percentage Dissolved vs. Time. Dissolution kinetics can be characterized by a multitude of different equations. The most classical is the first-order kinetics, but the Weibull function is also widely used due to its versatility and flexibility. The choice between them depends on the data; for instance, Korsmeyer-Peppas or zero-order kinetics may be employed for controlled release data (Bermejo et al., 2020; Gao, 2011).

On one hand, the transfer process from the stomach through various parts of the intestine is not taken into account when using the compendial dissolution methods USP I and USP II.

Permeability and solubility are the primary factors determining the oral absorption of drugs. Biopharmaceutical classification system established in 1995 four classes according to those parameters (Amidon et al., 1995). In that classification acid or basic nature of the compound was not taken into account, so some years later the same group established a subcategory for drug with low solubility due to the dissolution of drugs belonging to classes 2 and 4 is largely dependent on the acidic or basic nature of the drug and the characteristics of the intestinal

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lumen. In 2014, Tsume et al. (Tsume et al., 2014) published a subclassification for classes 2 and 4 of the BCS, considering whether the drug is acidic, basic, or neutral and the physiological pH range (pH < 7.5).

In class 2a, weak acids with a pKa less than 5 are included. This type of compound exhibits greater solubility at basic pH, thus, their solubility are almost negligible in stomach and, therefore, absorption percentage will be higher in distal segments of the gastrointestinal tract such as the ileum and colon. Due to the extended residence time that any molecule shows in the large intestine, drugs belonging to class 2a have enough time for complete dissolution and absorption, making their behavior similar to those classified in BCS class 1 (Tsume et al., 2014, 2012).

Within class 2b are weak bases with a pKa greater than 6. Their solubility increases at acidic pH, so, in stomach their solubility is the highest solubility of the drug and this fact provide them with greater absorption in proximal segments such as the duodenum. The more basic pH in the small intestine could lead to their precipitation, resulting in a relatively short residence time for optimal absorption (Higashino et al., 2023; Tsume et al., 2018).

Class 2c consists of neutral compounds, and their solubility is unaffected by pH changes along the gastrointestinal tract. They are absorbed more slowly; thus exhibiting a high degree of absorption in the colon and making them ideal for controlled-release formulations (Tsume et al., 2014).

Currently, drug supersaturation or apparent precipitation in vivo is assessed directly in human luminal fluid or indirectly using plasma profiles (from humans or animals), *ex vivo* or in vitro methods. Human luminal studies provide the best source of information regarding supersaturation or precipitation of different compounds(Hens et al., 2016a, 2016b; Kourentas et al., 2016; Psachoulias et al., 2011; Rubbens et al., 2016). Despite the valuable information obtained from luminal and in vivo methods in humans, as well as *ex vivo* studies, (Bevernage et al., 2012) they are considered costly, time-consuming, and may involve ethical concerns.

A broad range of gastrointestinal systems has been designed to study the fate of orally ingested substances, ranging from single to multicompartmental apparatus and statics or dynamic systems. In comparison to static models, dynamic models include physical-chemical and mechanical processes, as well as temporal changes in luminal conditions that occur in vivo. Dynamic systems are a dissolution assay in which the medium is pumped into a flow cell, allowing for a change in the medium surrounding the formulation over time. This enables differentiation between different subclasses drugs: BCS class 2a drug will dissolve more rapidly after the switch to a basic medium; Class 2b drug will dissolve faster in acidic medium and for a class 2c drug the pumped medium will not influence the dissolution rate.

These types of curves can be characterized using a different equation for each segment, distinguished by the change in the pumped medium.

There are several apparatuses to describe the in vivo behavior of BCS subclasses, as the flow-through cell apparatus (USP IV). In this assay, samples are taken from the volume at the exit of the flow cell, containing the dissolved drug. The possible precipitation process of BCS class 2b drugs will not be observed.

Another adequate technique is two-stage and transfer dissolution experiments (Dumping Test assay). It describes a multi-step in vitro test configuration, consisting of two consecutive experimental test levels, to assess the behavior of substances or drug formulations when exposed to a change from gastric to intestinal conditions. As oral dosage forms undergo a similar process during their passage through the upper gastrointestinal tract, two-stage tests provide an opportunity to evaluate drug performance in this area of the gastrointestinal tract (Fiolka and Dressman, 2018a).

Gastrointestinal Simulator apparatus is more sophisticated technique to describe the behavior of Class IIa and IIb BCS drug. GIS enables the evaluation of pharmaceutical products in a manner that effectively measures dissolution under conditions that mimic the physiological environment. These conditions include pH levels, buffer concentrations, formulation additives, and variations in gastrointestinal factors such as pH, buffer concentrations, secretions, stomach emptying rate, residence time in the GI tract, and luminal volume. In order to anticipate drug dissolution within the GIS, a validated hierarchical mass transport model was employed, which was supported by in vitro experimental data (Kuminek et al., 2023).

Methodologies for evaluating drug supersaturation or precipitation in vitro allow understanding and predicting the behavior of a formulation and can facilitate the development of more effective and safer pharmaceutical products for patients. Assessing the supersaturation and precipitation kinetics of a compound is crucial in the early stages of product development, prior to human studies, as well as in the later stages of formulation development.

The results of these experiments can lead to two situations. If dealing with a BCS class 2a, the drug will dissolve better in a basic medium after the pH increase but it will be conditioned by volume of the compartment which experiment is performed. Conversely, if dealing with a BCS class 2b, drug precipitation will be observed, due to the pH increase but the volume of both compartments (stomach and duodenum chamber) have a crucial participation.

The aim of this work is focus on characterizing this type of curves with the proposed equation (Modified double Weibull), which given its versatility, should be able to describe all phenomena (negligible dissolution, dissolution and precipitation) regardless the system or the volume used.

In the existing literature, no previous attempts have been made to characterize data from two-stage dissolution rate tests independently of the process involved. That is, redissolution has been characterized with one model and precipitation with another model. Typically, data from each phase are characterized separately, following procedures analogous to those used in classical dissolution tests (Pathak et al., 2019). This approach requires selecting different models depending on whether the active ingredient undergoes redissolution or precipitation. The methodology proposed in this work seeks to simplify this decision-making process by employing a single equation capable of fitting the diverse range of results that can emerge from the two-stage dissolution rate technique.

The proposed equation arises from the need to characterize the results of two-stage dissolution tests. It was constructed from two Weibull equations because this equation can be successfully applied to almost all kinds of dissolution curves and is commonly used in these studies (Costa and Sousa Lobo, 2001).

2. Materials and methods

2.1. Chemicals

Etoricoxib (MW= 358.842 g/mol; logP= 2.79 and pKa: 4.96) ("Chemicalize - Instant Cheminformatics Solutions," n.d) is a reference pharmaceutical product were kindly provided by a pharmaceutical company. This product consists of immediate release 120 mg Etoricoxib and it was commercialized in Europe as Arcoxia®.

Ibuprofen (MW= 206.29 g/mol; logP= 3.84 and pKa: 4.87 ("Ibuprofen - Drug Bank," n.d.)). The reference product (Nurofen® cold and flu from Reckitt Benckiser Healthcare (UK) Ltd.). was brought from a local Spanish pharmacy.

Telmisartan (MW = 514.64 g/mol; logP= 7.7 pKa: 3.62–5.83 ("Telmisartan - Drug Bank," n.d.)) was given by a pharmaceutical company. It was commercialized in Europe as Micardis® and it contains 80 mg of telmisartan.

Dipyridamole (MW= 504.626 g/mol; logP= 3.92 and pKa: 14.97 ("Dipyridamole - Drug Bank," n.d.)) The product (Persantin® from Glenwood GMBH Pharmazeutische Erzeugnisse) was brought from a local Spanish pharmacy.

Acetonitrile and methanol were purchased from Sigma (Barcelona, Spain). NaOH, NaCl, and NaH2PO4.H2O were received from Sigma-

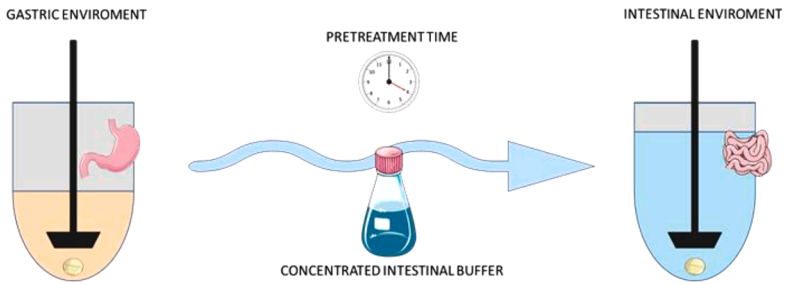

Fig. 1. Diagram of the Dumping Test in USP II.

Aldrich (St. Louis, MO, USA). Purified water (i.e., filtrated and deionized) was used in the analysis methods and in dissolution studies to prepare the dissolution media (Millipore, Billerica, MA, USA).

2.2. Methods

The conducted assay is a two-stage and transfer dissolution experiments known as 'Dumping Test.' This is a multicompartment dissolution system has been developed by modifying a conventional six-vessel USP dissolution system (USP II or paddle apparatus (Pharma-Test PT-DT70)) to include a "gastric" compartment, an "intestinal" compartment. In this case, the procedure starts with a volume (20 or 250 mL) of an acidic medium (HCl 0.1 M pH=1.2). After a specified time (20 min), the intestinal content is transferred to the system, for small gastric volumes (480 or 250 mL) that contains buffer phosphate 5 mM pH 6.5. The resulting medium resembles the intestinal lumen, and the volume is the sum of the two volumes used. The gastric dissolution phase can be performed using two different apparatuses depending on the volume (Cámara-Martinez et al., 2022). For small volumes (<250 mL), a beaker and a temperature-controlled orbital shaker set at 37 °C will be employed. For larger volumes, the USP II apparatus can be used, conforming to the scheme depicted in Fig. 1.

The condition of the experiments is summarized in Table 1 and Fig. 2.

The pharmaceutical form will be administered to the beaker at time 0, and samples will be taken to characterize the dissolution in the gastric medium. After 20 min, the beakers will be emptied into the USP II. In the case of starting with small volumes in the gastric phase, the beaker with the gastric medium and the dissolved pharmaceutical form will be poured onto the USP II beaker with the concentrated intestinal medium. If already in the USP II, the beaker with the concentrated intestinal medium will be poured onto the beaker of the gastric phase. Sampling points in gastric phase were 5, 10, 15 and 20 min.

Immediately after removing the 20 min sample, dump the acidic media into the phosphate buffer media and adjusted to achieve the desired conditions: a final volume of ~500 mL, buffer concentration 5 mM and a pH of ~6.5. Samples will continue to be taken at subsequent times after pouring to characterize both dissolution and precipitation phenomena Samples, in the mixed media, are collected then removed at 30, 45, 60, 90 and 120 min (equivalent to 10, 25, 40, 70 and 100 min post media change). Samples will be centrifuged for 5 min at 8000 rpm in a centrifuge. The supernatant will be taken and diluted in the appropriate medium to prevent precipitation outside the assay.

The samples will be analyzed using HPLC with a stationary phase Nova (C18 4.0 μm, 3.9 × 150 mm) or a spectrophotometer, depending on the compound being tested.

All methods were validated and demonstrated to be adequate regarding linearity ($r^2 > 0.999$), accuracy (relative error <5%) and precision or repeatability (SD ≤ 2%) (Table 2).

2.3. Mathematical approach

In order to model the data from duping tests experiments, it has to be considered, that the expected profiles will be very different in shape depending on the drug type. Drugs that are weak bases will dissolve quickly and completely in the gastric pretreatment, while when they pass into the intestinal environment they will precipitate at a certain rate. On the other hand, drugs that are weak acids will hardly dissolve during pretreatment, but will dissolve rapidly upon dumping of gastric contents into the intestinal environment.

Among the numerous models available for characterizing the dissolution process, the Weibull equation is the most suitable for this type of data (Costa and Sousa Lobo, 2001). This suitability stems from the equation's significant versatility. As an empirical equation, it can be adjusted to fit various curve types. Such versatility is crucial for handling the data from the intestinal phase. After the dumping phase, the dissolved percentage may increase almost instantaneously or precipitate drastically, necessitating a model capable of fitting these extreme values.

To treat this type of data indistinctly, a two-step approach is proposed that will be able to adjust the experimental data for both weak acids and weak bases.

The equations would be the following:

Dissolution during the pretreatment in gastric medium (Weibull equation):

$$\%Diss_{gt}^{0} = Fmax_1 \cdot \left(1 - e^{-\left(\frac{t}{\alpha_1}\right)^{\beta_1}}\right) \quad (1)$$

Dissolution in the intestinal medium (Modified double Weibull equation):

$$\%Diss_{\infty}^{gt} = \left(\left(Fmax_2 - \left(Fmax_1 \cdot \left(1 - e^{-\left(\frac{gt}{\alpha_1}\right)^{\beta_1}}\right)\right)\right) \cdot \left(1 - e^{-\left(\frac{t-gt}{\alpha_2}\right)^{\beta_2}}\right)\right) \quad (2)$$

Overall dissolution process during the whole experiment

$$\%Diss_{\infty}^{0} = Fmax_1 \cdot \left(1 - e^{-\left(\frac{gt}{\alpha_1}\right)^{\beta_1}}\right) + \left(\left(Fmax_2 - \left(Fmax_1 \cdot \left(1 - e^{-\left(\frac{gt}{\alpha_1}\right)^{\beta_1}}\right)\right)\right) \cdot \left(1 - e^{-\left(\frac{t-gt}{\alpha_2}\right)^{\beta_2}}\right)\right) \quad (3)$$

Table 1
Two-stage and transfer dissolution conditions of telmisartan, etoricoxib, ibuprofen and dypiridamole.

Formulation	Pretreatment time (min)	Gastric media	Gastric Volume (mL)	Intestinal media	Intestinal Volume (mL)	Final Volume (mL)	BCS Classification
Micardis® Telmisartan 80mg	20	HCl pH 1.2 0.1 M	20 250	Phosphate pH 6.5 5 mM	480 250	500	BCS 2a
Arcoxia® Etoricoxib 120mg	20	HCl pH 1.2 0.1 M	20 250	Phosphate pH 6.5 5 mM	480 250	500	BCS 2b
Nurofen® Ibuprofen 200 mg	20	HCl pH 1.2 0.1 M	20 250	Phosphate pH 6.5 5 mM	480 250	500	BCS 2a
Persantin® Dipyridamole 100mg	20	HCl pH 1.2 0.1 M	20 250	Phosphate pH 6.5 5 mM	480 250	900	BCS 2b

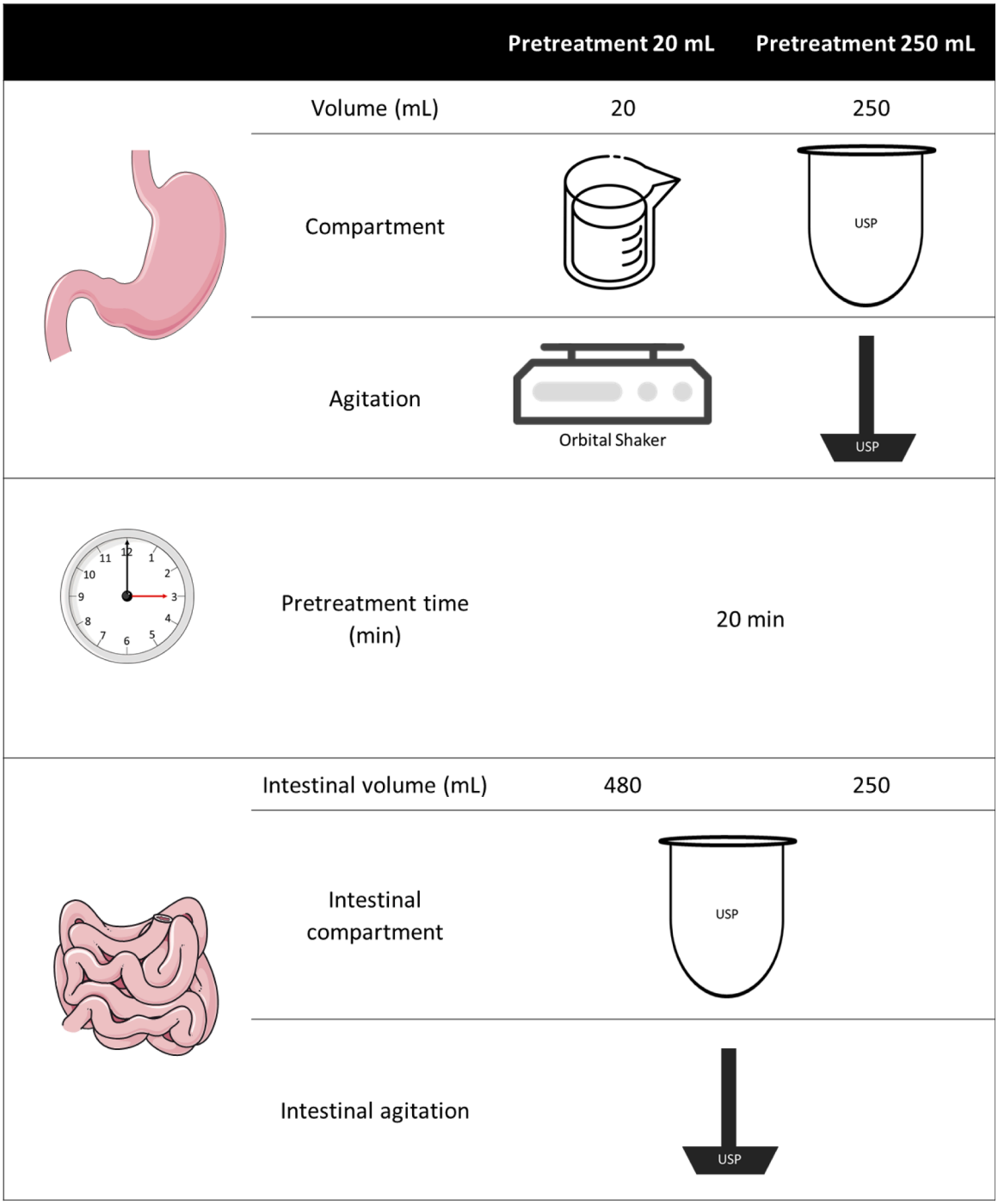

Fig. 2. Diagram of the material used in both protocols performed.

Table 2
Analysis conditions.

Analysis conditions						
Compound	Apparatus	nm	Movil phase	Flow (mL/min)	Retention time (min)	Injection volumen (μL)
Telmisartan	HPLC	250	80:10:10 MeOH:H2Oac:ACN	1	1.98	50
Etoricoxib	HPLC	245	30:70 H2Oac:ACN	1	2.34	25
Ibuprofen	HPLC	229	30:70 H2O:ACN	1	2.32	25
Dypiridamole	Spectrometer	450	–	–	–	–

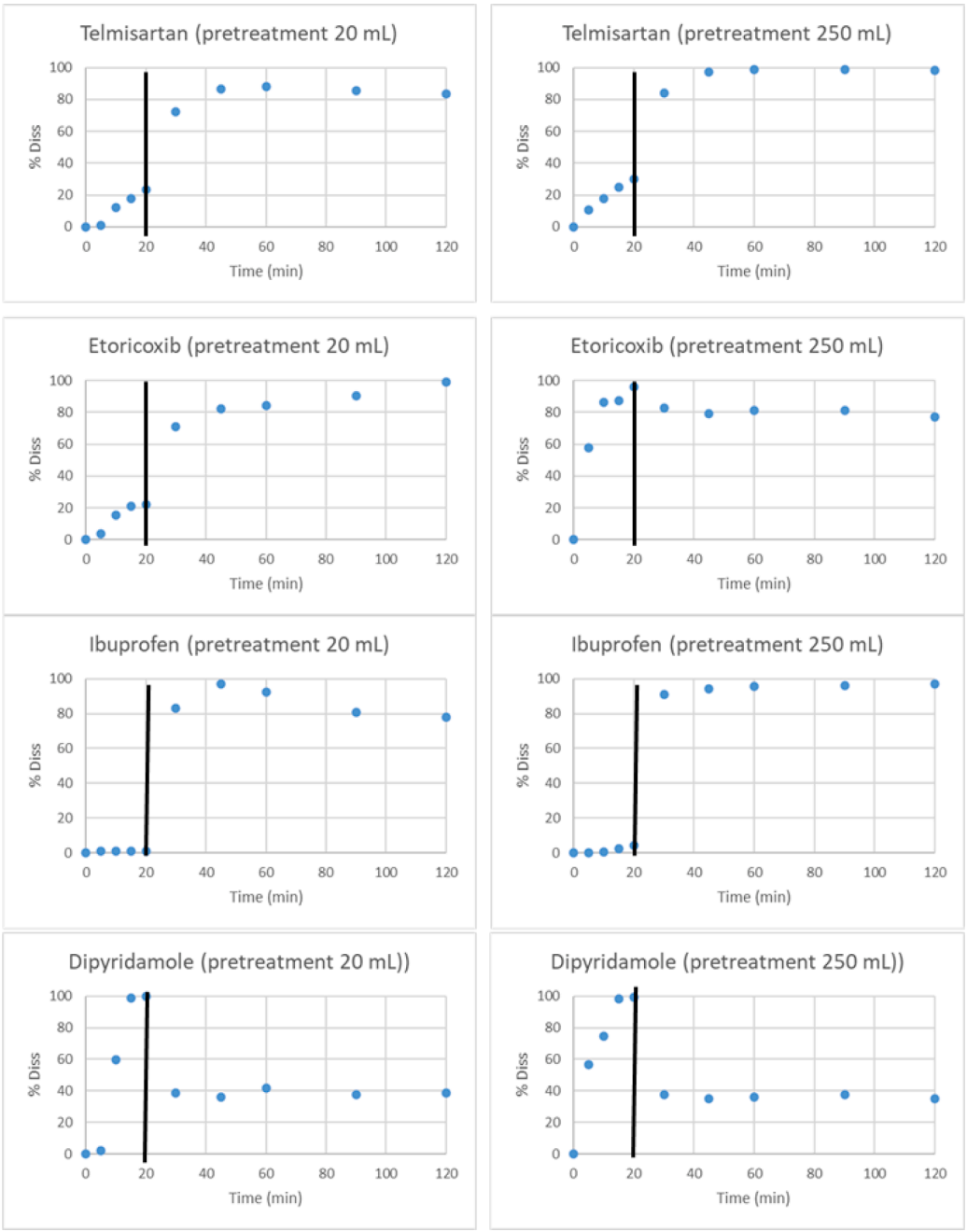

Fig. 3. Experimental data from Dumping test experiments of telmisartan, etoricoxib, ibuprofen and dipyridamole in two different pretreatment methods; 20 mL of gastric volume (left), or 250 of gastric volume (right). Solid black line represents Dumping moment.

$Fmax_1$ and $Fmax_2$ are the maximum dissolved percentages in each phase of the experiment (due to solubility and volume; are restricted to be a number between 0 and 100), α and β the Weibull parameters for each phase, and gt the gastric pretreatment time.

If $Fmax_2$ is greater than $Fmax_1$, de drug will dissolve better in the intestinal phase. If the case is the opposite, $Fmax_2$ is smaller than $Fmax_1$, the concentrations that will be obtained after the pretreatment will be lower due to the precipitation process.

There are considerations when using these equations to fit data from a dumping test:

If $Fmax_1$ is reached during pretreatment, Eq. (2) can be simplified to Eq. (4):

$$\%Diss_{\infty}^{0} = Fmax_1 \cdot + \left((Fmax_2 - Fmax_1 \cdot) \cdot \left(1 - e^{-\left(\frac{t-gt}{\alpha_2}\right)^{\beta_2}} \right) \right) \quad (4)$$

If the precipitation or dissolution after gastric pretreatment is immediate, the second exponential will be 0, so $Fmax_2$ will become the constant that allows the equation to give the same value throughout its range.

The mathematical approach was made completely in Excel software, using solver complement to optimize the objective function and to estimate the model parameters.

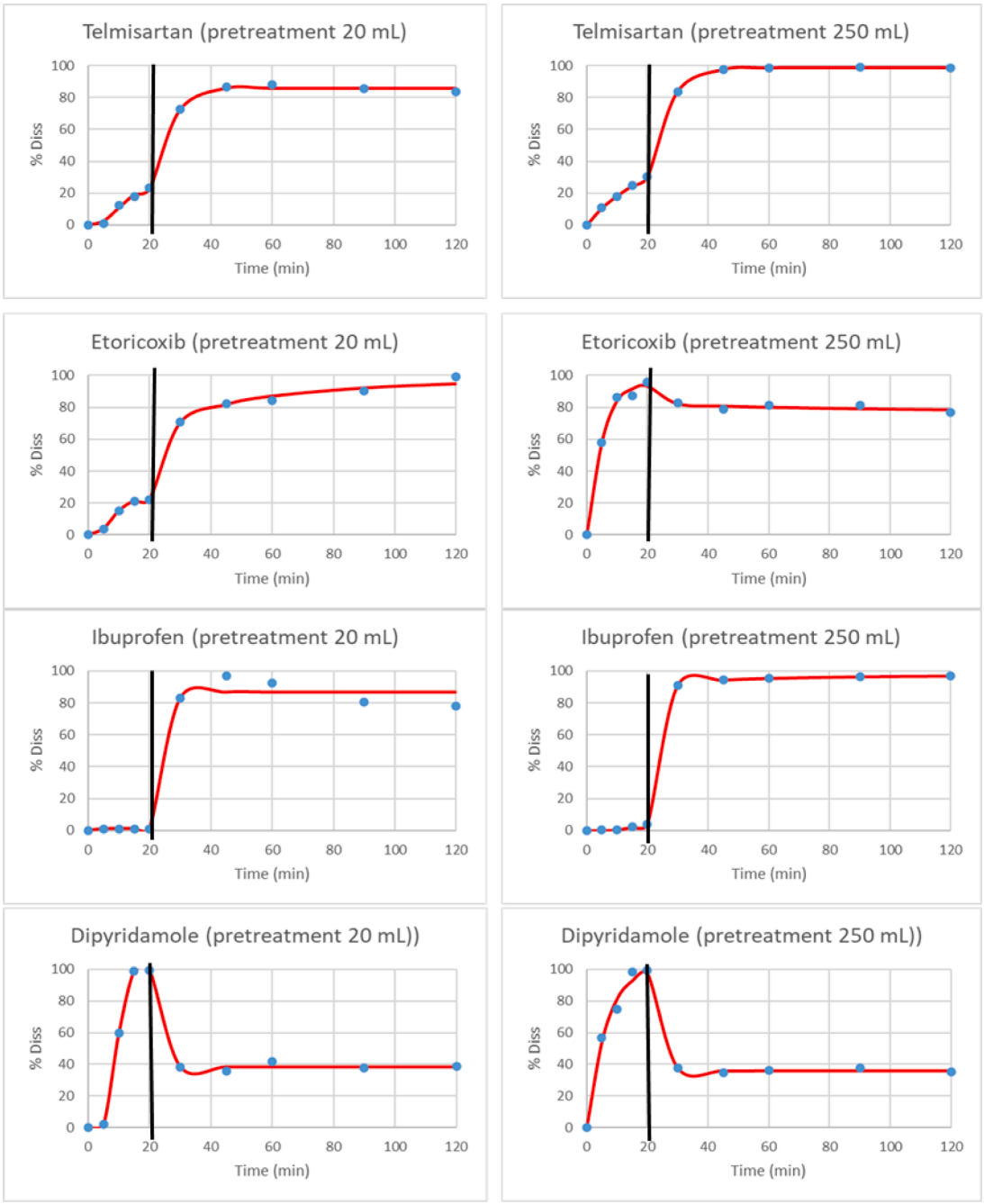

Fig. 4. Experimental data (blue dots) and mathematical adjustment (red line) from Dumping test experiments of telmisartan, etoricoxib, ibuprofen and dipyridamole in two different pretreatment methods; 20 mL of gastric volume (left), or 250 of gastric volume (right). Solid black line represents Dumping moment.

Table 3
Modified double Weibull fit parameters.

Parameters	Telmisartan		Etoricoxib		Ibuprofen		Dypiridamole	
	20 mL	250 mL	20 mL	250 mL	20 mL	250 mL	20 mL	250 mL
α_1	12.19	67.88	9.46	5.13	1.08	16.26	10.15	6.23
β_1	2.43	0.84	2.54	1.25	0.47	4.61	5.37	1.10
α_2	8.23	6.74	10.81	10,441.60	5.97	0.17	0.85	4.12
β_2	2.24	1.08	0.44	0.16	2.21	0.23	1.85	1.47
$Fmax_1$	23.60	100.00	22.10	93.76	1.11	4.43	99.29	100.00
$Fmax_2$	86.78	98.64	100.00	54.78	86.92	97.95	38.50	35.82
r^2 (exp vs pred)	0.998	0.999	0.997	0.952	0.984	0.999	0.997	0.985

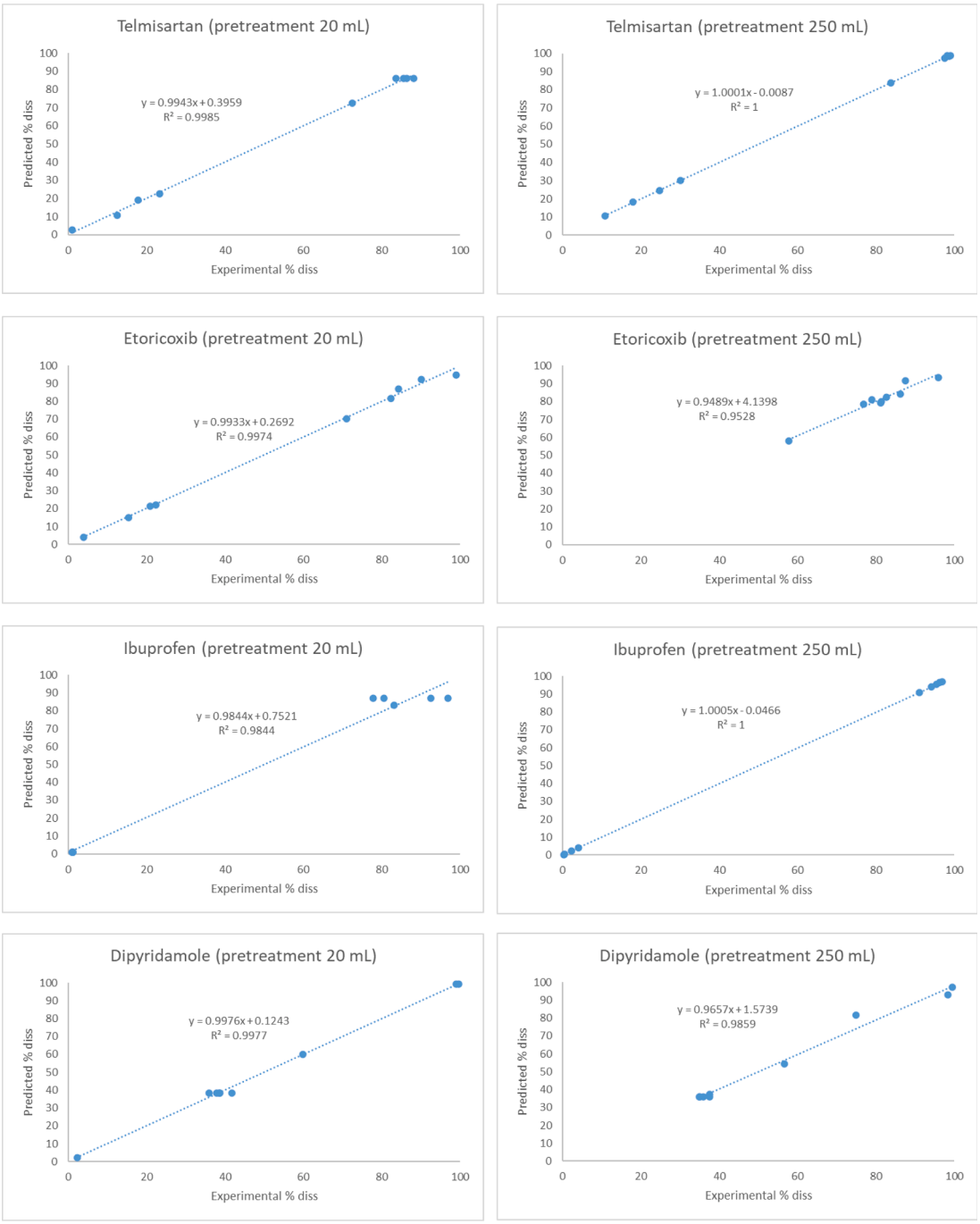

Fig. 5. Experimental% diss (X axis) VS Predicted% diss (Y axis) of individual fits.

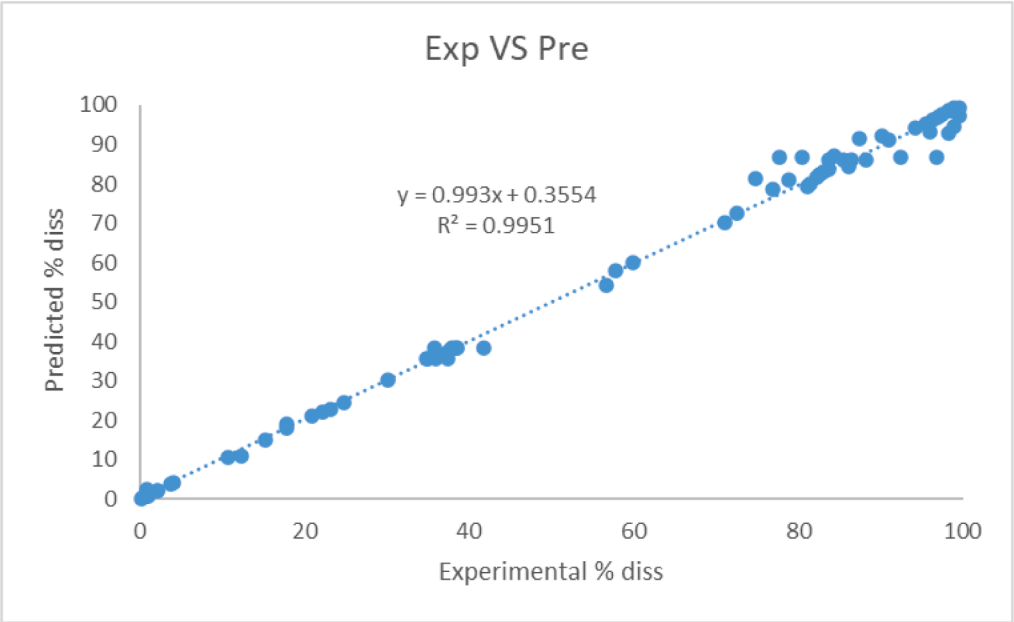

Fig. 6. Experimental% diss (X axis) VS Predicted% diss (Y axis) of all experiments carried out.

3. Results

The results of Dumping test of the formulations of telmisartan, etoricoxib, ibuprofen and dipyridamole are presented in Fig. 3.

Fig. 4 represents the mathematical approach using the modified double Weibull equation.

Model Parameters are summarized in Table 3.

To evaluate the goodness of fit, the correlation coefficient r2 was calculated for both the individual results (Table 3 and Fig. 5) and for all predictions combined (Fig. 6).

In Fig. 5, the experimental data are shown against the predicted data from the different experiments. For each dataset, a linear fit was performed to calculate the correlation coefficient r2. In Fig. 6, the experimental data are compared with the predicted data from all the experiments conducted.

Another comparison that would reflect the drug available for absorption in the gastrointestinal tract is the mathematical comparison of the AUCs (Area under the curve). To compare the predicted versus experimental dissolution profiles, the AUCs were calculated using the trapezoidal method for both experimental concentrations and mathematically adjusted concentrations. Subsequently, the percentage error (PE%= 100* (experimental value-predicted value) /experimental value) was calculated and summarized in Table 4.

4. Discussion

Nowadays, there is a huge interest in the development of in vitro tools to predict the in vivo behavior of pharmaceutical formulations. The main problem is that the more complex the in vitro tool is, the more complex the data processing is and, therefore, more complex and expensive computer programs are required.

Two-stage testing plays a crucial role in analyzing the dissolution process of BCS class 2 drugs, which are characterized by being poorly soluble but highly permeable. These drugs often face challenges related to their dissolution behavior, which can significantly impact their bioavailability and therapeutic effectiveness. By simulating the transition of these drugs from gastric to intestinal conditions in a controlled experimental setup, two-stage testing allows for a comprehensive evaluation of factors influencing drug dissolution, such as supersaturation and precipitation tendencies. This approach provides valuable insights into the performance of BCS class 2 drugs in the gastrointestinal tract, aiding in the formulation and development of effective drug delivery systems (Fiolka and Dressman, 2018b).

Telmisartan is a weakly acidic, poorly water-soluble API with pH-dependent solubility. Additionally, telmisartan is highly ionizable (pKa 4.45 ± 0.09) and shows pH-dependent solubility behavior, i.e., sparingly soluble in strongly acidic media but readily soluble at strong alkaline conditions (Giri et al., 2021; Thompson et al., 2022). This coincides with the results obtained in the two-stage dissolution test where the maximum percentage dissolved in gastric conditions reaches 20–30%. The difference between the pretreatments may be due to the disintegration process. The increase in volume and the increase in pH when moving to intestinal conditions cause the dissolved percentage of telmisartan to increase significantly, reaching more than 80% for the 20 mL pretreatment and 100% in the case of the 250 mL pretreatment.

Etoricoxib is a basic compound, with high solubility at acidic pHs (25.1 mg/mL at pH 2) and lower solubility at basic pHs (0.05 mg/mL at pH 6.9) (Mitra et al., 2014). The fact that it does not completely dissolve in the 20 mL pretreatment may be due to the disintegration process. Then, with increasing volume, a redissolution occurs in the case of the 20 mL pretreatment and a small precipitation for the 250 mL pretreatment data. On the one hand, this can be explained because the increase in volume and the change in hydrodynamic properties (change from the beaker to the spherical bottom glass of USP 2) help the disintegration of the tablet. On the other hand, in the case of complete dissolution during pretreatment with 250 mL, the pH change after dumping predominates and precipitation occurs.

Ibuprofen is an acid compound as has a low solubility at acidic pHs

Table 4
AUC Percentage Error (PE) of experimental data vs mathematical approach.

Drug	Gastric Volume (mL)	AUC PE%
Telmisartan (BCS IIa)	20	0.092
	250	0.057
Etoricoxib (BCS IIb)	20	0.426
	250	0.477
Ibuprofen (BCS IIa)	20	0.657
	250	0.003
Dypiridamol (BCS IIb)	20	0.301
	250	0.891

(0.05 mg/ml at pH 1.2) and higher solubility at basic pHs (2.18 mg/ml at pH 6.8) (Pali et al., 2020). Both treatments have similar behavior. The increase in pH accompanies the increase in volume, which means that if it does not dissolve during pretreatment, it becomes completely dissolved after dumping.

Dipyridamole is a basic compound. Due to its weakly basic nature (pKa of 6.4), dipyridamole has a pH dependent solubility and low aqueous solubility of 5 μg/ml at pH 7.0 at body temperature, but dissolves readily in acidic environment and precipitates at basic pH (Xi et al., 2019). In both pretreatments, dipyridamole precipitates after dumping, even after increasing volume, which corroborates its nature as a basic compound.

The model proposed (Modified double Weibull equation) can be implemented in Excel tool and it can be execute using Solver tool. Solver is a Microsoft Excel add-in program you can use for what-if analysis. Use Solver to find an optimal (maximum or minimum) value for a formula in one cell — called the objective cell — subject to constraints, or limits, on the values of other formula cells on a worksheet.

The results show that the modified double Weibull equation is capable of fitting both redissolution and precipitation data. For BCS class 2a drugs, the equation can fit to the new dissolution rate, as observed in instances of telmisartan and ibuprofen. For telmisartan, both dissolution processes could be observed and well characterized by the equation, for Ibuprofen, the percentage dissolved after the pretreatment time shows an instant redissolution.

For a BCS class 2b drugs, the equation has proven capable of fitting the precipitation process. In the case of dipyridamole, the drastic drop after dumping has been characterized by extreme values of the α and β constants of the second process. If α tends to zero or if β tends to infinity, the exponential will tend to 0.

The etoricoxib data are relevant because the different form between pretreatment conditions data. For a pretreatment of 20 mL the $Fmax_1$ is 22% and $Fmax_2$ is 100%. For a 250 mL pretreatment $Fmax_1$ is 93.75%, this is because the relation between Fmax, solubility and volume, and $Fmax_2$ is 54.77%. In this case the initial volume is key to determine the behavior of the second process; for 20 mL the second process is a redissolution and for 250 mL it is a precipitation.

The data from ibuprofen and 20 mL of pretreatment shows a limitation of this approach. The experimental data shows a rapid dissolution after dumping and a trend to precipitate after that. Although the fit shows a very small error for this case (AUC PE = 0.657%), the equation cannot fit this type of behavior.

The results obtained are promising, but several considerations must be taken into account. Regarding the two-stage dissolution test, the tendency to crystallize represents a "worst case scenario" because the API is not being removed by permeation as it would be in vivo. When permeation is slow, these tests can effectively discriminate for resistance to precipitation and sustainment of the permeable API. However, when permeation is known to be rapid, it may be appropriate to use a dissolution test that includes a permeation step (Grass, 2017).

Regarding to the Weibull equation, it is an empirical equation, without direct pharmacokinetic implications. This means that there is not any single parameter related with the intrinsic dissolution rate of the drug, nevertheless the equation is still useful for establishing in vivo/ in vitro correlations as its parameters can be modelled as a function of some formulation characteristics (Cámara-Martinez et al., 2022).

Despite the promising results showing the model's versatility, it is true that data from only two BCS class 2a drugs and two BCS class 2b drugs were fitted. Therefore, it is necessary to conduct further tests with a larger variety of drugs from both classes to more comprehensively evaluate the proposed tool's value.

Having a tool like this, capable of characterizing such data, is highly useful for the development of *in vitro-in vivo* correlations (IVIVC). These experiments are designed to simulate the in vivo dissolution process in the gastrointestinal tract, making it desirable to use the results in IVIVC development.

5. Conclusion

The modified double Weibull equation has proven to be an useful tool to model data obtained with two-stage and transfer dissolution experiments, achieving very small error percentages in all the cases studied (<1%). This tool can be run easily in Excel tool and can be very useful for another purposes as establishing a new in vitro in vivo correlation (IVIVC).

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CRediT authorship contribution statement

A Ruiz-Picazo: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **I Gonzalez-Alvarez:** Writing – review & editing, Supervision, Software, Methodology, Funding acquisition, Data curation, Conceptualization. **M Bermejo:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **M Gonzalez-Alvarez:** Writing – review & editing, Validation, Supervision, Funding acquisition, Formal analysis.

Data availability

No data was used for the research described in the article.

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