European Journal of Pharmaceutical Sciences 211 (2025) 107147

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Dumping test: In vitro predictive tool for bioequivalence of Telmisartan formulations

Martha Cossio [a,1], Barbara Sanchez-Dengra [b,1], Alejandro Ruiz-Picazo [b], Mirna Fernandez-Cervera [a], Miguel-Angel Cabrera-Perez [b,c], Marta González-Alvarez [b], Isabel González-Alvarez [b,*], Marival Bermejo [b]

[a] Department of Pharmacy, Farmacia y Alimentos University of Havana, Cuba
[b] Department Engineering Pharmacy Section, Miguel Hernandez University, San Juan de Alicante, 03550, Alicante, Spain
[c] Departamento de Ciencias Farmacéuticas, Facultad de Ciencias, Universidad Católica del Norte, Angamos, 0610 Antofagasta, Chile

ARTICLE INFO

Keywords:
Dumping test
Bioequivalence
IVIVC
Telmisartan

ABSTRACT

Background: The "dumping" test is a simple dynamic dissolution methodology widely studied as a useful tool in bioequivalence trials for class II drug products.
Objective: This study aimed to evaluate the dumping test as an in vitro method to predict the in vivo behavior of Telmisartan formulations. A one-step level A IVIVC was developed for three immediate-release formulations (Micardis® as the reference and two generics, X1 and X2) using this transfer model.
Methods: Dumping tests were performed by placing drug products in 20 mL of HCl 0.01 N and sampling for 20 min at 37 °C in an orbital shaker. The contents were then transferred to a USP 2 apparatus with 480 mL of pH 6.8 phosphate buffer, maintaining 37 °C and 50 rpm stirring. Bioequivalence was assessed using the similarity factor f2.
Results: The f2 values were 46.47 between REF and NBE (non-similar) and 57.43 between REF and BE (similar). The IVIVC study confirmed a level A correlation, supporting the in vitro dissolution results.
Conclusions: The dynamic dissolution dumping test proved to be a valuable tool for studying the complex in vivo dissolution process of Telmisartan immediate-release formulations.

1. Introduction

For drugs to have a therapeutic effect and be clinically successful, they must perform consistently when administered orally, which is the most common and preferred route by patients. Therefore, a crucial step to ensure the greatest possible absorption in the clinical phases is to verify them with in vitro and in silico methodologies to predict the performance of oral products in the development phase. Before any drug in an oral pharmaceutical form is absorbed through the intestinal wall, it must first dissolve in the intestinal fluids.

Gastroenterology and the design of new dissolution methods and strategies have advanced together in recent times, leading to the development of new biorelevant in vivo approaches and in vivo predictive systems (Carapeto et al., 2023; Jiang et al., 2011; Katona et al., 2022; Westerhout et al., 2014). Advances in intestinal physiology are responsible for the emergence of this new area that has abundant applications to improve and accelerate the development of drugs and guarantee the bioequivalence of new formulations.

Biopredictive methods (iPD) can be defined as those that are capable of accurately and precisely predicting, from an in vitro dissolution assay, the behavior of the drug after its administration in vivo. In some of these cases, it is possible to establish an in vitro-in vivo correlation (IVIVC) that corresponds to a mathematical model that describes the relationship between an in vitro property of the formulation (e.g., dissolution rate) and the in vivo response (e.g., plasma concentrations vs. time). There are 4 levels of correlation, the most complex being the one that provides the most information: the A-level correlation is a point-to-point relationship between the fraction dissolved in vitro and the fraction

* Corresponding author at: Dep. Ingeniería. Área Farmacia, Edificio 2, Departamentos, Carretera Alicante Valencia s/n, Campus San Juan de Alicante UMH, 03550, Alicante, Spain.
E-mail address: isabel.gonzalez@umh.es (I. González-Alvarez).
[1] Both authors have contributed equally

https://doi.org/10.1016/j.ejps.2025.107147
Received 3 March 2025; Received in revised form 1 May 2025; Accepted 27 May 2025
Available online 29 May 2025

absorbed of a drug from a pharmaceutical form.

The iPD are classified in static and dynamic models and their main characteristics are based in the complexity of the procedure (modifications in apparatus and dissolution medium) employed. For the static models (SM) USP apparatus proposed by Pharmacopeia is used. Although there are seven apparatuses for dissolution tests, the most employed are USP1 and USP2 due to its simplicity. For dynamic models (DM), several models can be used: the simplest dynamic model is the transfer model by dumping strategy or more sophisticated and complex apparatus with programmable pumps to transfer the content from one compartment to another. Those apparatuses represent the most advanced technology in the research about the predictive dissolution of the API with the simulation of dissolution studies closer to the physiological behavior in the human body (Bermejo, 2019; Culen et al., 2013; Goyanes et al., 2015; Kambayashi et al., 2016).

The main problem with complex systems is that they are expensive and are not useful for the rapid screening of formulations to be tested.

Unlike iPD, which focuses on creating more physiologically relevant in vitro tests, IVIVC establishes mathematical relationships between existing in vitro and in vivo data. An in vitro in vivo correlation is an important tool to predict behavior of the formulations in human. In addition, the development of validated IVIVC is also promoted for ethical reasons because using biopredictive in vitro dissolution data reduces the need for human volunteers, as well as the cost and opening period of the drug market. Due to these facts, the use of IVIVC has been very successful in the development of innovative drug administration systems.

In the last ten years, much work has been carried out on explaining and utilizing IVIVC for dosage forms (Cook, 2012; Gaynor et al., 2009; Nguyen et al., 2017; Takano et al., 2012). All sectors (academia, pharmaceutical industry and regulatory agencies) have been interested in the use of IVIVC to achieve different objectives. In fact, the FDA published in 1997 three regulatory guidelines to set the conditions for the development of IVIVC for immediate release (IR), extended release (ER) and scale-up and post-approval: chemistry, manufacturing and controls, in vitro dissolution testing and documentation of in vivo bioequivalence for IR and ER (FDA, 1997a, 1997b, 1997c).

For low-solubility drugs, bioequivalence must be demonstrated through human studies. To ensure success in human trials, it is necessary to have a prior screening test that perfectly mimics the in vivo behavior of the formulations that are tested.

Using in vitro information to predict in vivo behavior is the main goal of IVIVC. Taking into account the priority to establish IVIVC for different compounds and their advantages it is mandatory to find simplest devices and simplest media that mimic in vivo behavior of the formulations.

For this reason, the objective of this study is to determine whether the simplest method of dynamic dissolution (dumping test), based on a pretreatment in an acid medium and dissolution in the USP 2 apparatus, is capable of replicating the in vivo behavior of different formulations of Telmisartan and compared the results of the developed IVIVC with a previously published one (Ruiz Picazo et al., 2018).

2. Materials and methods

2.1. Drug and formulations

The immediate release Telmisartan formulations (tests and reference) with conventional excipients in customary amounts were purchased for a Spanish Pharmaceutical Company. HPLC liquids and reagents were purchased for Sigma.

Telmisartan is a BCS class II weak acid. Telmisartan is an angiotensin receptor blocker which is used to treat hypertension and cardiovascular risk conditions (Bakheit et al., 2015). Hypertension is one of the major risk factors for the development of cardiovascular disease (CVD) (Chobanian et al., 2003). For this reason, many investigations about the pharmacokinetics (PK) and bioequivalence (BE) of the Telmisartan have been studied.

It is a low-solubility and high-permeability compound (logP = 7.23) with pH dependent solubility, and in this case, dissolution is the limiting process in the absorption rate. For low solubility drugs, BE could be demonstrated by a developed and validated Level A IVIVC (Ruiz Picazo et al., 2018).

2.2. Dissolution procedure

Dynamic dissolution tests were carried out in an orbital shaker set at 37 °C. The drug product was placed in a beaker containing 20 mL of the pretreatment medium (HCl 0.01 N), and samples were taken for 20 min. Subsequently, the contents were poured into the vessels of the USP 2 apparatus containing 480 mL of the selected medium (5 mM pH 6.8 Phosphate Buffer) [2]. The test continued at 37 °C and with a stirring rate of 50 rpm.

Samples (1 mL) at different times were taken and centrifugated immediately. The sample volume was replaced with the same buffer volume to keep the dissolution volume constant throughout the test. This test was performed in six replicates.

Samples were centrifuged to ensure accurate measurement of the drug concentration at specific time points. Centrifugation helps separate any undissolved drug particles or formulation components from the liquid phase. This prevents further dissolution of these particles after sample collection, which could lead to overestimation of the dissolved drug concentration.

Samples were analyzed by HPLC employing a UV detector (Waters® 2487), an X-Bridge® C18 column (3.5 µm, 4.6 × 100 mm) and a mobile phase of 50 % methanol and 50 % acid water (0.05 % v/v TFA in water). The wavelength was set to 225 nm, the flow of the mobile phase to 1 mL/min and the temperature to 30 °C. The accuracy of the method was calculated using five standards and analyzed in triplicate. Precision was calculated as the coefficient of variation of five determinations over the same standards (values <5 %). Linearity was established over the range of concentrations present in the samples (r2 > 0.999). The limit of quantification for telmisartan was 3.4 µg/mL.

2.3. IVIVC

Formally, an in vitro-in vivo correlation is defined as a predictive mathematical model that describes the relationship between a dosage form characteristic and an in vivo response variable (FDA, 1997c). The in vitro characteristic is, normally, the rate of dissolution or release of the drug, while the in vivo response variable corresponds with the plasma levels of the drug or the percentage of drug absorbed at each time.

IVIVC-Level A corresponds to a point-to-point association between in vitro dissolution rate and in vivo absorption rate. In general, correlations are linear but nonlinear correlations, although less common, can also be suitable. With independence of the methodology used to create an IVIVC level A, the model should predict plasma levels from in vitro data

Evaluation of the IVIVC's predictability comes after the IVIVC has been constructed. The prediction error is determined using the observed in vivo parameter (such as AUC and Cmax) and the estimated in vivo parameter is typically used to evaluate the IVIVC.

The comparison between the observed in vivo parameter used to develop the IVIVC and the in vivo parameter predicted from the developed IVIVC allows the evaluation of the prediction error (PE) and results in internal validation. The %PE can be obtained by using the following Eq. (1):

$$\%PE = \frac{(Observed\ Parameter - Predicted\ Parameter)}{Observed\ Parameter} \cdot 100 \quad (1)$$

FDA and EMA guidelines establishes that an IVIVC can be considered as valid if the mean absolute PE for all products is lower than 10 % and

the PE for each product is lower than 15 %

The IVIVC were constructed by one step procedure, i.e., by directly linking in vitro dissolution with plasma levels through a link model.

Dissolution profile was described with a first order model in the case of the in vitro data from USP IV apparatus with the following Eq. (2):

$$Ft = Fmax\cdot\left(1 - e^{-kd\cdot t}\right) \quad (2)$$

Where Fmax is the maximal dissolved percentage and kd the first order dissolution rate constant

Data from the dumping dissolution test were used to fit a double first order model with the following Eq. (3):

$$Ft = \left(Fmax_1\cdot\left(1 - e^{-kd_1\cdot t}\right)\right)\cdot i + \left(Fmax_1\cdot\left(1 - e^{-kd_1\cdot t}\right) + Fmax_2\cdot\left(1 - e^{-kd_2\cdot t}\right)\right)\cdot(1 - i) \quad (3)$$

Where parameters Fmax1 and kd1 describe the first phase of the in vitro dissolution process (previous to dumping) and Fmax2and kd2 describe the second phase of the in vitro dissolution process. The "i" parameter was used as an on/off button to select which part of the equation should be used depending on the moment of the experiment (i = IF $t > 0.333$ h THEN 0 ELSE 1).

First order model was selected due to its simplicity compared with other dissolution models following the parsimony principle as it requires only two parameters

A time scaling linear model was used in both IVIVC (Eq. (4)), as the in vitro dissolution process tends to be faster than the in vivo one:

$$t\_sc = a\cdot t + b \quad (4)$$

Where t_sc corresponds with the in vivo time for the in vitro time (t).

Finally, an extent scaling parameter n was included in the model. N was fixed to 1 in the IVIVC with the dumping test data but fitted in the IVIVC with the USP IV apparatus. This parameter was needed as the dissolution profiles obtained with USP IV did not reach 100 %.

$$\frac{dQc}{dt} = ka\cdot Qdiss_{vivo} - k12\cdot Qc + k21\cdot Qp - k13\cdot Qc \quad (5)$$

As it can be seen in Eq. (5) disposition was described as a two compartment model (k12 and k21 as distribution microconstants) with first order elimination from central compartment (kel) and first order absorption (ka). $Qdiss_{vivo}$ represents the in vivo fraction dissolved obtained after fitting the in vitro dissolution profiles and using the time and extent scaling factors.

3. Results

Two objectives were achieved in this work. One of them, establishing a IVIVC for telmisartan formulations using the simplest dynamic apparatus and the second one compared validation results with IVIVC values using a complex apparatus (USP IV apparatus).

In Table 1 the difference between media conditions, apparatus and pharmacokinetic models established in each IVIVC has been summarized.

Table 1
Media composition and PK model establish in each dissolution apparatus and IVIVC construction.

	USP II with acid pretreatment "Dumping test"	USP IV apparatus
Media conditions	20 mL pH 1.2 → 20 min 480 mL pH 6.8 (5 mM)	pH 1.2 + Tween 80 (0.05 %) → 15 min pH 4.5 + Tween 80 (0.05 %) → 15 min pH 6.8 + Tween 80 (0.05 %)
PK model	Dissolution: Double 1° order Distribution: 2-compartmental model	Dissolution: 1° order Distribution: 2-compartmental model

Table 2 shows the model fitted parameters.

The average dissolved amounts of Telmisartan for the three products are represented in Fig. 1 (dashed lines correspond to the fitted values to the mass transport model). Each point corresponds to the average of four tablets of each formulation. The results for the different dissolution assays that were carried out with both apparatus (A- Values obtained by USP II apparatus with acid pretreat and B- Values obtained by USP IV apparatus) (Ruiz Picazo et al., 2018)

The IVIVC was established and the experimental and simulated plasma profiles are illustrated in Figs. 2 and 3.

The predicted C_{max} and $AUC_{0\text{-}t}$ values were calculated by non-compartmental methods (linear trapezoidal rule). Tables 3 and 4 show the prediction errors of C_{max} and $AUC_{0\text{-}t}$ values.

4. Discussion

Biopredictive dissolution methods have proven to be an excellent development tools in order to ascertain in vivo formulation performance (Al-Gousous et al., 2016; Andreas et al., 2018; Butler et al., 2019; Carapeto et al., 2023; Mann et al., 2017). The relevant factors affecting in vivo dissolution vary across BCS classes and formulation types (Immediate release versus controlled release) and it is important to select those ones to be replicated in the in vitro system. For low solubility weak acid and bases with pKa values within the physiological range the changes in solubility while transiting through the gastrointestinal system is a determinant aspect affecting in vivo dissolution rate. Consequently, biopredictive methods for those compounds may need replicating these dynamic changes in fluid pH and fluid volumes. USP IV apparatus is a compendial device that permits changing the characteristics of the fluid flowing in the dissolution chamber and for that reason it has been used in the development on several IVIVC (Abdelfattah et al., 2022; Prieto-Escolar et al., 2021; Taha and Emara, 2022).

Nevertheless, this apparatus requires higher fluid volumes; thus, drug concentration on samples could be very low, complicating the analytical procedures. It is more complex in its settings and USP II is more extended among pharmaceutical companies due to its use in quality control procedures. In principle, the USP II device does not allow changing pH conditions unless the so-called "dumping" procedure is used. This procedure has several alternatives, as the gastric phase/media could be placed initially in the USP II vessel. Then, the Intestinal media is poured into it to elevate the pH or perform the gastric dissolution phase in a beaker. The fluid is in the USP II vessel already containing the intestinal buffer (Fiolka and Dressman, 2018). In this work, we have attempted to reproduce a previously obtained IVIVC with USP IV and telmisartan products with a simpler dumping method in the USP II apparatus that may mimic the gastric emptying process and the corresponding potential supersaturation and precipitation processes better.

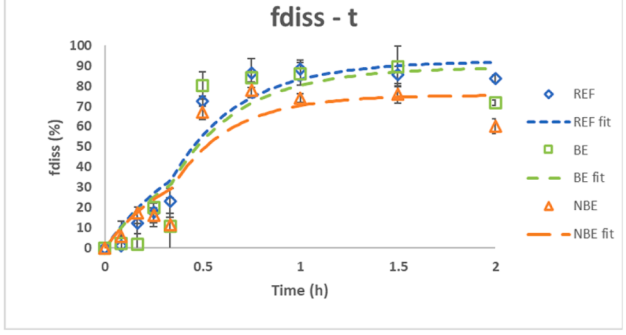
As a weak acid Telmisartan solubility is lower in stomach and higher in the intestinal environment. Supersaturation and precipitation phenomena are usually observed for weak bases for which the dissolved concentrations in the acid gastric fluid are higher and those dissolved concentrations are emptied in a more alkaline fluid on the intestine in which the solubility is much lower leading to the base precipitation. The transition from a low solubility zone to a high solubility environment generally does not causes supersaturation effect for weak acids. Nevertheless, due to the several ionizable groups in Telmisartan moiety, between pH3 and 8 the presence on zwitterionic species has been described and its dimerization causing a supersaturation over the thermodynamic solubility at those pH's (Kádár et al., 2022). In spite of this effect, as the amorphous or supersaturated solubility is lower in acid pH than in alkaline pH, there is no further precipitation and it is not reported that this phenomenon has any influence on Telmisartan absorption (López Mármol et al., 2021).

As it can be seen in the model fitted parameters Table 2, the dissolution rate coefficients in the acidic media (kd1) for all formulations were lower than the ones in the alkaline media(kd2). The asymptotic

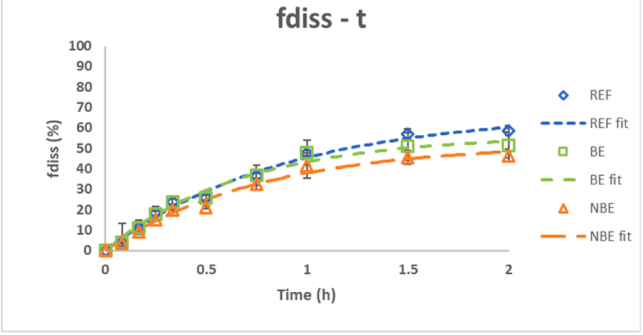
Table 2
Parameters of both models, Dumping test (left) and USP IV (right).

Dumping Test		
Name	**Initial**	**Adjusted**
kd1_REF *	0.76	2.31
kd2_REF *	3.56	3.52
Fmax1_REF *	100.00	61.87
Fmax2_REF *	64.53	100.00
kd1_BE *	0.62	2.30
kd2_BE *	7.12	3.45
Fmax1_BE *	76.12	58.10
Fmax2_BE *	68.64	100.00
kd1_NBE *	10.82	2.84
kd2_NBE *	6.38	3.75
Fmax1_NBE *	15.33	47.17
Fmax2_NBE *	56.65	100.00
a *	1.00	1.55
b *	1.00	-0.23
ka *	0.33	0.78
Vc *	88.00	19.69

USP IV		
Name	**Initial**	**Adjusted**
kd_REF *	1.13	1.13
Fmax_REF *	67.32	67.31
kd_BE *	1.47	1.47
Fmax_BE *	56.47	56.46
kd_NBE *	1.30	1.30
Fmax_NBE *	52.20	52.19
a *	1.00	2.12
b *	1.00	0.00
ka *	0.33	0.78
Vc *	88.00	19.69
n *	1.00	3.24



Data from dynamic dissolution rate tests (Dumping Test) of different Telmisartan formulations.



Data from USP IV dissolution rate tests of different Telmisartan formulations.

Fig. 1. Dissolution rate profiles of three Telmisartan formulations (REF, BE and NBE) in percentage dissolved versus time. On the left, the profiles obtained with the Dumping Test method and on the right, using the USP IV method. Dashed lines correspond to the fitted values to the mass transport model.

values were also lower in the first acidic step than after the dumping

The previously published IVIVC correlation for telmisartan was developed with a two-step procedure by performing Loo-Riegelman deconvolution of in vivo plasma levels and superimposing fractions absorbed and fractions dissolved by mean of time scaling step with a levy plot and an extent scaling factor (Ruiz Picazo et al., 2018). The dissolution data from the USP IV method were used to develop a one-step IVIVC, and the dumping test data were also used to construct a

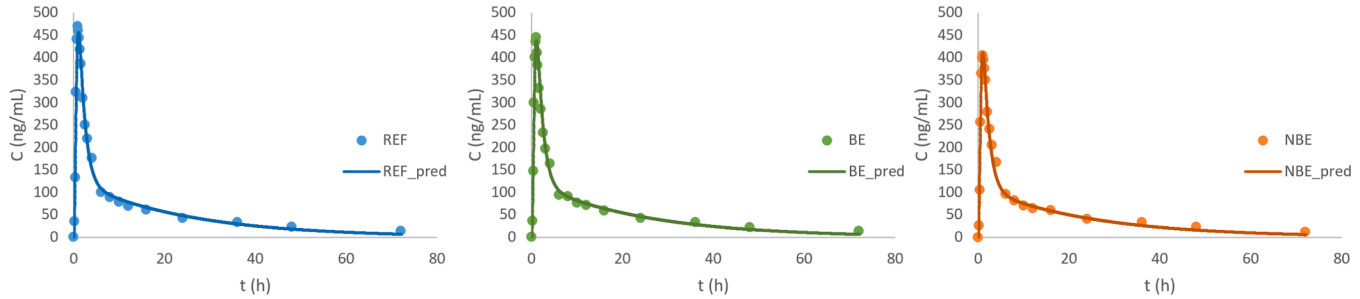


Fig. 2. Experimental (dots) and simulated plasma concentration – time profiles (dashed lines) of Telmisartan in the reference and test products obtained by IVIVC established with USP IV in vitro device.

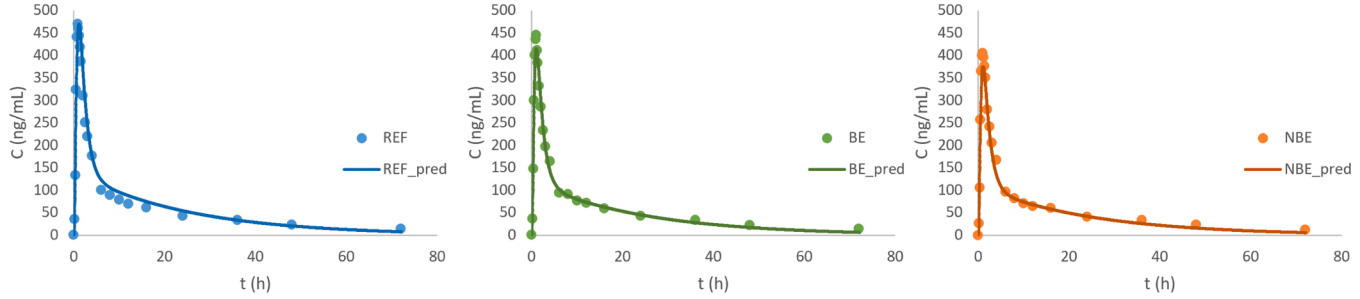


Fig. 3. Experimental (dots) and simulated plasma concentration – time profiles (dashed lines) of Telmisartan in the reference and test products obtained by IVIVC established with dumping test in vitro technique.

Table 3
Prediction errors of the PK parameters of Telmisartan by IVIVC established by dumping test.

Internal validation for IVIVC-dumping test						
	AUC 0→inf (ng/mL·h)			Cmax (ng/mL)		
	EXP	PRED	%EP	EXP	PRED	%EP
1	4166.77	3859.19	7.38	469.75	456.25	2.87
2	4003.42	3697.98	7.63	445.19	436.92	1.86
3	3919.64	3407.68	13.06	404.98	410.08	1.26
Total			9.36			2.00

Table 4
Prediction errors of the PK parameters of Telmisartan by IVIVC established by USP IV apparatus.

Internal validation-USP IV						
	AUC 0→inf (ng/mL·h)			Cmax (ng/mL)		
	EXP	PRED	%EP	EXP	PRED	%EP
1	4166.7	4310.0	3.44	469.7	468.9	0.16
2	4003.4	3615.4	9.69	445.1	415.1	6.75
3	3919.6	3342.1	14.73	404.9	374.9	7.41
Total			9.29			4.77

one-step IVIVC model to compare both in vitro dissolution methods (USP IV versus dumping test) in the same conditions.

From a mathematical point of view, the in vivo pharmacokinetic part of both models was similar as a two-compartment disposition model was used with a first-order absorption input. The disposition parameters were the same in IVIVC, and the intestinal permeability value was parametrized as an absorption rate coefficient.

As the pH change in the USP IV chamber happens as a smooth transition, the cumulative fractions dissolved can be described with a single slope from the beginning to the end (Fig. 1B). Consequently, the first order or Weibull model describes this apparatus's dissolution profiles well. In the Telmisartan products used in this work, a first-order dissolution model that described well all the formulations as previously published (Ruiz Picazo et al., 2018), so this model was used for the in vitro dissolution part of the one step model.

As the pH transition happens more abruptly in the dumping method, dissolution profiles presented a clear transition with different slopes and asymptotic values at the dumping time (Fig. 1A). Consequently, a double first-order model was used to describe the dissolution part. Telmisartan is a weak acid, so its solubility is lower in the gastric phase and increases rapidly after the dumping step.

The time scaling function parameters show a slight difference between the dumping and the UPP IV methods. The USP IV method required a slope close to 2 versus 1.5 in the dumping, indicating a slower dissolution with the USP IV method. On the other hand, the incomplete dissolution from the USP IV method made the use of an extent scaling factor necessary.

Even if, from a mathematical point of view, it is possible to link in vitro data from both dissolution methods with the plasma levels and the predictions errors were within the acceptance limits, the practical convenience of the dumping test, as mentioned previously, could facilitate the use of dissolution as a development tool for formulation selection before an in vivo bioequivalence test. Eventually, the dumping procedure may represent the gastric emptying process and lead to similar super-saturation and precipitation processes.

5. Conclusions

Dynamic dissolution tests, such as the Dumping test, are a useful tool for studying the complex process of in vivo dissolution of Telmisartan formulations. The dumping tests allowed the development of a predictive level A IVIVC with less experimental burden than the previously developed IVIVC with USP IV apparatus.

Funding

This work was supported by grants: #CIAICO/2022/082 funded by

GVA Conselleria de Educación Universidades y Empleo, and # PID2021-123888OB-I00 funded by MCIN/AEI/10.13039/501100011033/ FEDER, UE.

CRediT authorship contribution statement

Martha Cossio: Writing – original draft, Methodology, Investigation, Formal analysis. **Barbara Sanchez-Dengra:** Writing – original draft, Software, Formal analysis, Data curation. **Alejandro Ruiz-Picazo:** Writing – original draft, Validation, Investigation, Formal analysis. **Mirna Fernandez-Cervera:** Writing – original draft, Validation, Supervision, Methodology. **Miguel-Angel Cabrera-Perez:** Writing – review & editing, Validation, Supervision, Data curation. **Marta González-Alvarez:** Writing – review & editing, Validation, Supervision, Funding acquisition, Data curation. **Isabel González-Alvarez:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Data curation, Conceptualization. **Marival Bermejo:** Writing – review & editing, Validation, Supervision, Resources, Data curation, Conceptualization.

Data availability

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

References

Abdelfattah, F., Taha, N., Abdou, A., Mursi, N., Emara, L., 2022. Prediction of in vivo performance of ibuprofen immediate-release products using different dissolution models. J. Appl. Pharm. Sci. 12. https://doi.org/10.7324/JAPS.2022.120820.

Al-Gousous, J., Amidon, G.L., Langguth, P., 2016. Toward biopredictive dissolution for enteric coated dosage forms. Mol. Pharm. 13, 1927–1936. https://doi.org/10.1021/acs.molpharmaceut.6b00077.

Andreas, C.J., Rosenberger, J., Butler, J., Augustijns, P., McAllister, M., Abrahamsson, B., Dressman, J., 2018. Introduction to the OrBiTo decision tree to select the most appropriate in vitro methodology for release testing of solid oral dosage forms during development. Eur. J. Pharmaceut. Biopharmaceut. https://doi.org/10.1016/j.ejpb.2018.07.003.

Bakheit, A.H.H., Abd-Elgalil, A.A., Mustafa, B., Haque, A., Wani, T.A., 2015. Chapter six – telmisartan. Profiles of Drug Substances, Excipients and Related Methodology.

Bermejo, M., 2019. Biofarmacia y Farmacocinética, Pioneras de las fronteras en el viaje de la Píldora Dorada al siglo XXI.

Butler, J., Hens, B., Vertzoni, M., Brouwers, J., Berben, P., Dressman, J., Andreas, C.J., Schaefer, K.J., Mann, J., McAllister, M., Jamei, M., Kostewicz, E., Kesisoglou, F., Langguth, P., Minekus, M., Müllertz, A., Schilderink, R., Koziolek, M., Jedamzik, P., Weitschies, W., Reppas, C., Augustijns, P., 2019. In vitro models for the prediction of in vivo performance of oral dosage forms: recent progress from partnership through the IMI OrBiTo collaboration. Eur. J. Pharmaceut. Biopharmaceut. 136, 70–83. https://doi.org/10.1016/j.ejpb.2018.12.010.

Carapeto, G.V., Duque, M.D., Issa, M.G., Ferraz, H.G., 2023. Development of biopredictive dissolution method for extended-release desvenlafaxine tablets. Pharmaceutics 15. https://doi.org/10.3390/pharmaceutics15051544.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Roccella, E.J., 2003. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. https://doi.org/10.1161/01.HYP.0000107251.49515.c2.

Cook, J.A., 2012. Development strategies for IVIVC in an industrial environment. Biopharm. Drug. Dispos. 33, 349–353. https://doi.org/10.1002/bdd.1791.

Culen, M., Rezacova, A., Jampilek, J., Dohnal, J., 2013. Designing a dynamic dissolution method: a review of instrumental options and corresponding physiology of stomach and small intestine. J. Pharm. Sci. 102. https://doi.org/10.1002/jps.23494.

FDA, 1997a. Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: chemistry, Manufacturing, and Controls. Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.

FDA, 1997b. SUPAC-MR: modified release solid oral dosage forms scale-up and postapproval changes: chemistry, manufacturing, and controls. Vitro Dissolution Testing and In Vivo Bioequivalence Documentation. FDA.

FDA, 1997c. Guidance For Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro In Vivo Correlations.

Fiolka, T., Dressman, J., 2018. Development, current applications and future roles of biorelevant two-stage in vitro testing in drug development. J. Pharm. Pharmacol. https://doi.org/10.1111/jphp.12875.

Gaynor, C., Dunne, A., Davis, J., 2009. The effects of averaging on accuracy of IVIVC model predictions. J. Pharm. Sci. 98. https://doi.org/10.1002/jps.21662.

Goyanes, A., Hatton, G.B., Merchant, H.A., Basit, A.W., 2015. Gastrointestinal release behaviour of modified-release drug products: dynamic dissolution testing of mesalazine formulations. Int. J. Pharm. 484, 103–108. https://doi.org/10.1016/j.ijpharm.2015.02.051.

Jiang, W., Kim, S., Zhang, X., Lionberger, R.A., Davit, B.M., Conner, D.P., Yu, L.X., 2011. The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation. Int. J. Pharm. 418. https://doi.org/10.1016/j.ijpharm.2011.07.024.

Kádár, S., Csicsák, D., Tőzsér, P., Farkas, A., Pálla, T., Mirzahosseini, A., Tóth, B., Tóth, G., Fiser, B., Horváth, P., Madarász, J., Avdeef, A., Takács-Novák, K., Sinkó, B., Borbás, E., Völgyi, G., 2022. Understanding the pH dependence of supersaturation state—a case study of Telmisartan. Pharmaceutics 14. https://doi.org/10.3390/pharmaceutics14081635.

Kambayashi, A., Yasuji, T., Dressman, J.B., 2016. Prediction of the precipitation profiles of weak base drugs in the small intestine using a simplified transfer ("dumping") model coupled with in silico modeling and simulation approach. Eur. J. Pharmaceut. Biopharmaceut. 103, 95–103. https://doi.org/10.1016/j.ejpb.2016.03.020.

Katona, M.T., Kakuk, M., Szabó, R., Tonka-Nagy, P., Takács-Novák, K., Borbás, E., 2022. Towards a better understanding of the post-gastric behavior of enteric-coated formulations. Pharm. Res. 39. https://doi.org/10.1007/s11095-021-03163-0.

López Mármol, Á., Denninger, A., Touzet, A., Dauer, K., Becker, T., Pöstges, F., Pellequer, Y., Lamprecht, A., Wagner, K.G., 2021. The relevance of supersaturation and solubilization in the gastrointestinal tract for oral bioavailability: an in vitro vs. in vivo approach. Int. J. Pharm. 603. https://doi.org/10.1016/j.ijpharm.2021.120648.

Mann, J., Dressman, J., Rosenblatt, K., Ashworth, L., Muenster, U., Frank, K., Hutchins, P., Williams, J., Klumpp, L., Wielockx, K., Berben, P., Augustijns, P., Holm, R., Hofmann, M., Patel, S., Beato, S., Ojala, K., Tomaszewska, I., Bruel, J.-L.L., Butler, J., 2017. Validation of dissolution testing with biorelevant media: an OrBiTo study. Mol. Pharm. 14, 4192–4201. https://doi.org/10.1021/acs.molpharmaceut.7b00198.

Nguyen, M.A., Flanagan, T., Brewster, M., Kesisoglou, F., Beato, S., Biewenga, J., Crison, J., Holm, R., Li, R., Mannaert, E., McAllister, M., Mueller-Zsigmondy, M., Muenster, U., Ojala, K., Page, S., Parr, A., Rossenu, S., Timmins, P., Van Peer, A., Vermeulen, A., Langguth, P., 2017. A survey on IVIVC/IVIVR development in the pharmaceutical industry – past experience and current perspectives. Eur. J. Pharmaceut. Sci. https://doi.org/10.1016/j.ejps.2017.02.029.

Prieto-Escolar, M., Torrado, J.J., Álvarez, C., Ruiz-Picazo, A., Simón-Vázquez, M., Govantes, C., Frias, J., García-Arieta, A., Gonzalez-Alvarez, I., Bermejo, M., 2021. One and two-step in vitro-in vivo correlations based on usp iv dynamic dissolution applied to four sodium montelukast products. Pharmaceutics 13. https://doi.org/10.3390/pharmaceutics13050690.

Ruiz Picazo, A., Martinez-Martinez, M.T.T., Colón-Useche, S., Iriarte, R., Sánchez-Dengra, B., González-Álvarez, M., García-Arieta, A., González-Álvarez, I., Bermejo, M., 2018. Vitro dissolution as a tool for formulation selection: Telmisartan two-step IVIVC. Mol. Pharm. 15, 2307–2315. https://doi.org/10.1021/acs.molpharmaceut.8b00153.

Taha, N.F., Emara, L.H., 2022. Convolution- and deconvolution-based approaches for prediction of pharmacokinetic parameters of diltiazem extended-release products in flow-through cell dissolution tester. AAPS PharmSciTech 23. https://doi.org/10.1208/s12249-022-02361-2.

Takano, R., Kataoka, M., Yamashita, S., 2012. Integrating drug permeability with dissolution profile to develop IVIVC. Biopharm. Drug. Dispos. 33, 354–365. https://doi.org/10.1002/bdd.1792.

Westerhout, J., Van De Steeg, E., Grossouw, D., Zeijdner, E.E., Krul, C.A.M., Verwei, M., Wortelboer, H.M., 2014. A new approach to predict human intestinal absorption using porcine intestinal tissue and biorelevant matrices. Eur. J. Pharmaceut. Sci. 63. https://doi.org/10.1016/j.ejps.2014.07.003.