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Research Article

PREDICTION OF PLASMA CONCENTRATIONS FROM FIXED-DOSE COMBINATION FORMULATIONS: IBUPROFEN/PARACETAMOL DRUG PRODUCTS

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ABSTRACT

Objectives: To predict the *in vivo* performance of ibuprofen and paracetamol (suspension and tablets) using dissolution data of mini-vessels, standard-vessels, United States Pharmacopeia (USP) apparatus IV, and a convolution approach.

Methods: The reference suspension was tested with mini-vessels (200 mL of dissolution medium), USP standard-vessels (900 mL at 75 rpm), and USP apparatus IV (laminar flow at 16 mL/min). The reference and a generic formulation (tablets) were tested with USP apparatus II and IV. Both drugs were quantified by an ultraviolet derivative method. Dissolution efficiency, mean dissolution time, $t_{50\%}$, and $t_{80\%}$of tablets were calculated and statistically compared (Student's t-test). Predicted drug plasma concentrations were calculated. Hypothetical C_{max} and area under the concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$) were compared with real pharmacokinetic values through the calculation of prediction error (PE). PE values should not exceed 10%.

Results: Suspension released a range of 94.51–101.07% of ibuprofen and 94.96–101.28% of paracetamol at 60 min among different dissolution methods. Similar profiles between reference and generic tablets were found with the USP apparatus IV (f_2=75.51 for ibuprofen and 79.07 for paracetamol). Significant differences were found with all dissolution parameters of the standard-vessels (*p<0.05). The PE values for C_{max} of ibuprofen and paracetamol were 7.47 and –8.96%, and for $AUC_{0\text{-}inf}$ –0.16 and 0.29% from suspension using the mini-vessels and –1.17 and 1.11% for C_{max} and –7.91 and –7.14% for $AUC_{0\text{-}inf}$ from reference tablets using the USP apparatus IV.

Conclusion: Better predictions were found with the mini-vessels method using dissolution data of suspension and the USP apparatus IV using data from tablets.

Keywords: Convolution, Ibuprofen, Mini-vessels method, Paracetamol, United States Pharmacopeia apparatus IV.

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INTRODUCTION

Simulation of plasma concentration-time profiles using dissolution data has been previously reported [1,2]. Dissolution and published pharmacokinetic information of drugs are basic elements to apply the convolution methodology through which it is possible to propose hypothetical plasma concentration-time profiles from fixed-dose combination formulations [3]. Prediction of drug plasma concentrations is a powerful tool to propose a bioequivalent formulation [4]. Virtual bioequivalence takes computational simulation techniques to assess the similarity of test product and reference [5]. However, no scientific information is currently available on the prediction of ibuprofen/paracetamol plasma concentration-time profiles from fixed-dose combination formulations through a convolution approach.

Pharmaceutical formulations with drug mixtures are available as fixed-dose products. Some advantages of these drug products are (1) improved medication concordance, (2) reduced risk of adverse reactions relative to higher dose monotherapy, (3) lower overall costs, and (4) greater efficacy compared with higher dose monotherapy [6]. Ibuprofen mixed with paracetamol (acetaminophen) is widely available as over-the-counter formulations, suspensions, and tablets are commercially available. Ibuprofen is a non-steroidal anti-inflammatory drug with analgesic, anti-inflammatory, and antipyretic properties [7], while paracetamol has antipyretic, analgesic, and weak anti-inflammatory actions. It is sparingly soluble in water [3]. Considering its low solubility/high permeability, ibuprofen is a Class II drug of the Biopharmaceutical Classification System (BCS) [7], while due to its high solubility/low permeability, paracetamol is considered a Class III drug [8].

Dissolution studies are carried out with the United States Pharmacopeia (USP) apparatus I or II (basket or paddle apparatus, respectively). The dissolution working conditions using 1000 mL vessels are well established. However, limitations such as analytical sensitivity or the amount of available material, among others, may warrant the use of non-pharmacopeial analytical methods. To overcome these problems, the concept of small-volume dissolution arose with the possibility of using smaller volumes of dissolution media. This offers advantages in terms of substance and material consumption [4]. *In vitro* release studies using mini-vessels with 250 mL of dissolution medium have been reported [9]. The mini-vessel is a scaled-down version of the USP standard vessel with 1/3 of the dimension of the pharmacopeial vessel. On the other hand, the USP apparatus IV (flow-through cell method) is a dissolution apparatus that has been proposed to test the dissolution behavior of water poorly-soluble drugs. The flow-through cell method works under sink conditions due to the constant addition of the dissolution medium to the dosage form. This method is a suitable option to test small samples of suspensions.

Pharmacopeial dissolution tests for ibuprofen and paracetamol suspensions and tablets, and for paracetamol tablets, are described in the USP [10]. To date, no pharmacopeial dissolution test for ibuprofen/paracetamol manufactured in fixed-dose formulations is available. Based on the published information on ibuprofen and paracetamol, both drugs are candidates to waiver *in vivo* studies [7,8]. However, only fixed-dose combination formulations with BCS class I (high solubility/high permeability), or class III, or a combination of class I and class III drugs may be candidates for a biowaiver [11]. Hence, this approach for ibuprofen/paracetamol formulations is not applicable. In addition,

biowaiver dissolution conditions include dissolution media of pH 1.2, 4.5, and 6.8. Ibuprofen has limited dissolution at acidic pHs; hence, pH 6.8 phosphate buffer is a suitable medium to test ibuprofen/paracetamol formulations.

Considering the importance of a biopharmaceutical evaluation that ensures the suitable *in vitro* release performance of fixed-dose combination formulations, the objective of this study was to simulate the plasma concentration-time profiles of ibuprofen and paracetamol from fixed-dose formulations through dissolution data obtained with a mini-vessel apparatus, USP apparatus II and IV, a convolution methodology and published pharmacokinetic information of each drug. The results of the reference drug product will provide information on the *in vitro* conditions necessary to evaluate the release of test formulations through mathematical simulations and already available pharmacokinetic data. This estimates the clinical impact of fixed-dose combination formulations manufactured with ibuprofen and paracetamol through simple dissolution studies.

METHODS

Chemicals

Ibuprofen and paracetamol standards were acquired from Sigma-Aldrich Co. (St. Louis, MO, USA). AR methanol, sodium hydroxide, and monobasic potassium phosphate were obtained from J.T. Baker-Mexico (Xalostoc-Mexico). Three ibuprofen/paracetamol fixed-dose commercial formulations were used. The reference suspension (100 mg/125 mg/5 mL), tablets (200 mg/500 mg), and generic tablets, were used. The Mexican health agency has established the Acciogen® brand (Laboratorios Silanes, S.A. de C.V.) as the reference drug product [12]. The R and G letters were assigned to reference and generic tablets, respectively.

Spectrophotometric determination

Ibuprofen and paracetamol were simultaneously determined by a published ultraviolet (UV) derivative spectrophotometric method [13]. A double-beam UV/visible spectrophotometer was used (Perkin Elmer Lambda 35 Model, Waltham, MA, USA). The operating conditions were first-derivative mode (^{1}D), slit width 2 nm, scan speed 240 nm/min, and sampling interval 1 nm. Ibuprofen and paracetamol were determined at 216.20 and 222.18 nm, respectively.

Standard calibration curves

Stock solutions of ibuprofen and paracetamol in pH 6.8 phosphate buffer were separately prepared. Five standard solutions of each drug in pH 6.8 phosphate buffer were prepared. The concentration range of ibuprofen and paracetamol suspension and tablets was 10–50 µg/mL (for both drugs) and 100–500 µg/mL (for both drugs), respectively. Then, the zero-order spectra taken from 210 to 230 nm were recorded and stored. Quartz cells of 10 mm and 1 mm were used for suspension and tablets, respectively. With zero-order spectra, the ^{1}D of each solution was calculated.

In vitro release studies

USP apparatus II

Dissolution profiles of ibuprofen/paracetamol suspension were determined with the USP paddle apparatus (Sotax AT-7 Smart Model, Switzerland) using mini-vessels (0.4 mL of suspension) and USP standard-vessels (1.8 mL of suspension). The agitation rate was 75 rpm. A volume of 200 mL (mini-vessels) or 900 mL (USP standard vessels) of pH 6.8 phosphate buffer at 37.0±0.5°C were used. Before use, the dissolution medium was degassed by vacuum and transferred into the dissolution vessels. Mini-vessels and USP standard-vessels have different capacities, and the volume of added suspension maintains the theoretical concentration when the dissolved drug is 100%. A sample of 3 mL was withdrawn at 10, 20, 30, 45, and 60 min, and it was filtered with 0.45 µm nitrocellulose filters (Millipore®). Dissolution curves of ibuprofen/paracetamol tablets were determined with the USP apparatus II (USP standard vessels) and 900 mL of pH 6.8 phosphate buffer. A sample of 3 mL was withdrawn at 10, 20, 30, 45, and 60 min, and it was filtered with 0.45 µm nitrocellulose filters (Millipore®) n=12. In all cases, the withdrawn dissolution medium was replaced with a new and warm medium. The amounts of dissolved ibuprofen and paracetamol were determined with the support of standard solutions.

USP apparatus IV

Dissolution profiles of ibuprofen/paracetamol suspension and tablets were obtained using the USP apparatus IV (Sotax CE6, Sotax AG, Switzerland) with laminar flow and 22.6 mm cells (i.d.). The degassed dissolution medium was pumped at the flow rate of 16 mL/min. A sample of 3 ml was withdrawn at 10, 20, 30, 45, and 60 min, and it was filtered with nitrocellulose filters (n=12).

Processing of dissolution data

Due to ibuprofen/paracetamol reference suspension being the only drug product commercially available, dissolution parameters such as mean dissolution time (MDT) and dissolution efficiency (DE) were calculated. On the other hand, dissolution curves of ibuprofen/paracetamol tablets from R and G formulations were compared with the f_2 similarity factor and with the statistical comparison of DE and MDT values (Student's t-test, Sigmaplot software, version 11.0). Similar dissolution profiles were considered if f_2=50–100. After conducting the Student's t-test, statistically significant differences were found if *p<0.05.

All *in vitro* release data were fitted with the hyperbola equation, and with a and b parameters, the time at which formulations released 50 and 80% of the dose ($t_{50\%}$ and $t_{80\%}$, respectively) were calculated. In addition, *in vitro* release data were fitted to First-order, Hopfenberg, Makoid-Banakar, Peppas-Sahlin, and Weibull models [14]. All mathematical models are shown in Table 1. The equation with the highest adjusted determination coefficient ($R^2_{adjusted}$) and lowest Akaike information criterion (AIC) was chosen as the best-fit model [15]. Data treatment was carried out using the Excel add-in DD Solver [14].

Prediction of ibuprofen and paracetamol plasma concentrations

Ibuprofen and paracetamol plasma concentration-time profiles were calculated using the inverse release function methodology [16]. Using this method, the time scale of the dissolution profile was adjusted to facilitate the establishment of a meaningful *in vitro*/*in vivo* correlation. Once the new time scale of the dissolution curve was computed, the simulated drug levels were calculated with a simple numerical convolution approach [17]. All calculations were performed using MS Excel spreadsheets. The convolution approach contemplates published drug pharmacokinetic information such as the elimination rate constant (ke), bioavailability factor (f), and volume of distribution (Vd) of ibuprofen [7,18] and paracetamol [8]. After ibuprofen and paracetamol plasma concentration-time profiles were calculated, they were fitted with a compartment pharmacokinetic model using the Excel add-in PK Solver [19]. Predicted peak plasma concentrations (C_{max}) and area under the concentration-time curve from zero to infinity ($AUC_{0\text{-inf}}$) were compared with published *in vivo* pharmacokinetic data of ibuprofen [20] and paracetamol [21] by the percent of prediction error (%PE) that was calculated by Equation 1. The PE should not exceed 10% [22].

Table 1: Mathematical models

Model	Equation
Hyperbola	$y=\frac{ax}{b+x}$
First-order	$F=100\cdot(1-e^{-k_1\cdot t})$
Hopfenberg	$F=100\cdot(1-[1-k_{HB}\cdot t]^n)$
Makoid-Banakar	$F=k_{MB}\cdot t^n\cdot e^{-k\cdot t}$
Peppas-Sahlin	$F=k_1\cdot t^m+k_2\cdot t^{2m}$
Weibull	$F=F_{max}\cdot\left[1-e^{\frac{(t-Ti)^\beta}{\alpha}}\right]$

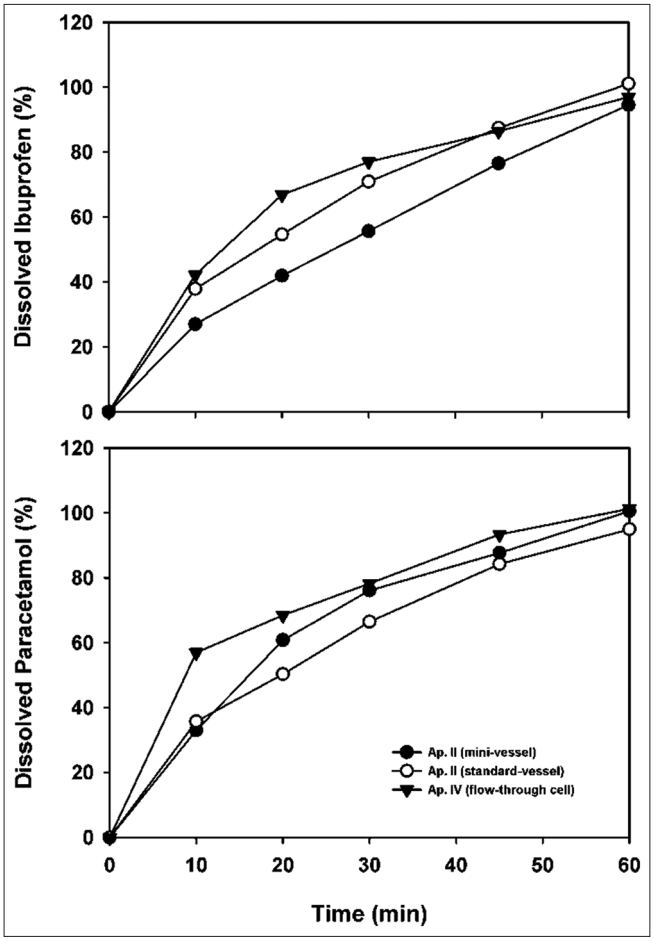

Fig. 1: Dissolution profiles of ibuprofen/paracetamol suspension. Mean, n=12

$$PE = \frac{(Observed\ parameter - Estimated\ parameter)}{Observed\ parameter} \times 100 \quad \text{Eq. 1}$$

RESULTS AND DISCUSSION

Dissolution profiles

Dissolution curves of ibuprofen/paracetamol suspension using mini-vessels, USP standard-vessels, and USP apparatus IV are shown in Fig. 1. Dissolution profiles of ibuprofen/paracetamol tablets obtained with the USP apparatus II and IV are shown in Fig. 2. In all cases, an extent of more than 80% of both drugs was released at 60 min. Tablets meet the pharmacopeial Q criterion. Ibuprofen Q_{80} is at 60 min, and paracetamol Q_{80} is at 30 min, which means that commercial solid dosage forms maintain the quality standard determined in the manufacturing process. Dissolution data of Q_{60}, DE, MDT, $t_{50\%}$, and $t_{80\%}$of suspension are shown in Table 2, whereas the same dissolution parameters from tablets are shown in Table 3. From suspension, a fast dissolution rate of ibuprofen and paracetamol was found using the USP apparatus IV. As a result of the comparison of dissolution parameters from tablets, no similar dissolution profiles between G formulation and R were found (*$p<0.05$), while similar profiles of both drugs were only found with the USP apparatus IV ($f_2>50$).

The result of the kinetic modeling of *in vitro* data of suspension is shown in Table 4, and kinetic modeling from tablets is shown in Table 5. The models were compared using their $R^2_{adjusted}$ and AIC values. The best-fit mathematical model based on $R^2_{adjusted}$ and AIC values is highlighted in bold.

For suspension, the influence of the USP apparatus is a key factor in explaining the *in vitro* release mechanism of each drug since the ranking of adjusted dissolution data for ibuprofen was Makoid-Banakar > Weibull while for paracetamol Weibull > Makoid-Banakar. In no case does the release mechanism match. In other words, for the suspension, the *in vitro* release performance of each drug is dependent on the hydrodynamic environment generated by each dissolution apparatus. The results of the tablets are different; ibuprofen and paracetamol from

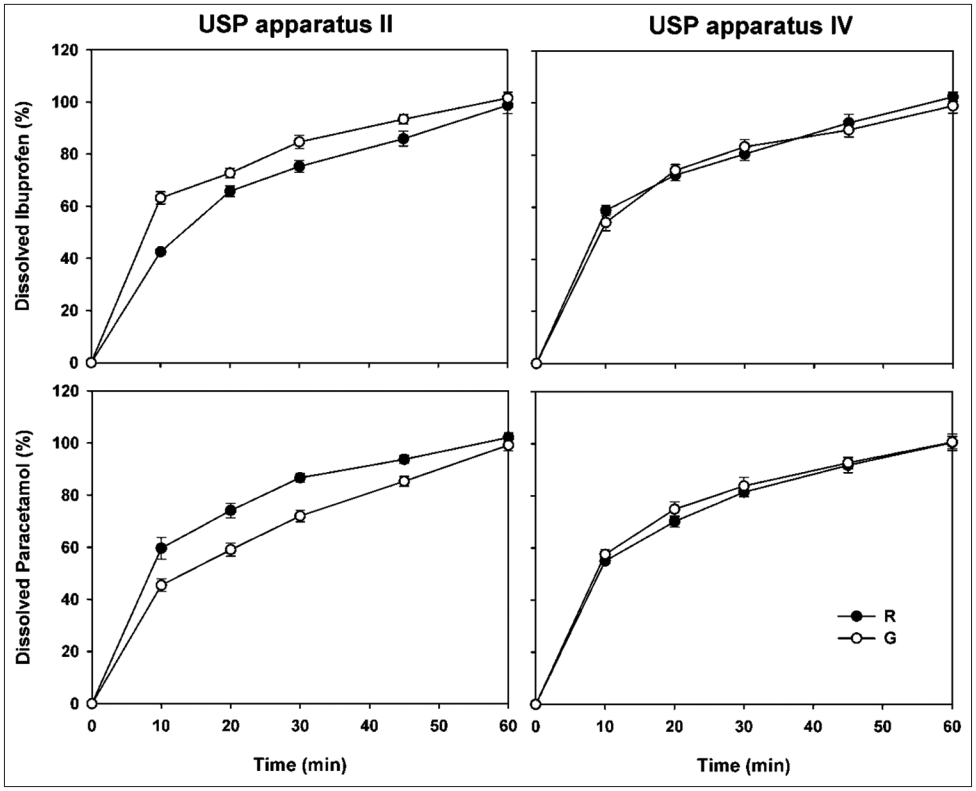

Fig. 2: Dissolution profiles of ibuprofen/paracetamol tablets. Mean±Standard deviation, n=12

the reference formulation showed the same release behavior only using the USP apparatus II (Makoid-Banakar). The Makoid-Banakar model becomes identical to that of Korsmeyer-Peppas when the parameter k is zero. It follows the sole diffusion mechanism. The "n" function governs the shape of the dissolution profile, while the Weibull distribution emphasizes the S-shape or sigmoidal dissolution profile [23].

Table 2: Dissolution parameters of ibuprofen/paracetamol suspension

USP method	Parameter	Ibuprofen	Paracetamol
Ap. II (mini-vessel)	Q_{60} (%)	94.51±0.58	100.55±0.88
	DE (%)	54.00±0.23	65.99±0.44
	MDT (min)	25.70±0.18	20.60±0.33
	$t_{50\%}$ (min)	26.63±1.26	16.53±0.72
	$t_{80\%}$ (min)	42.60±2.02	26.45±1.15
Ap. II (standard-vessel)	Q_{60} (%)	101.07±0.83	94.96±0.66
	DE (%)	64.66±0.42	61.13±0.48
	MDT (min)	24.59±0.27	21.37±0.21
	$t_{50\%}$ (min)	16.28±0.22	19.02±0.33
	$t_{80\%}$ (min)	26.04±0.36	30.55±0.54
Ap. IV (flow-through cell)	Q_{60} (%)	96.94±0.76	101.28±0.77
	DE (%)	67.94±0.45	73.22±0.39
	MDT (min)	17.92±0.36	16.60±0.34
	$t_{50\%}$ (min)	13.98±0.39	8.84±0.35
	$t_{80\%}$ (min)	22.37±0.63	14.15±0.56

Mean±SEM, n=12. USP: United States Pharmacopeia, DE: Dissolution efficiency, MDT: Mean dissolution time

Table 3: Dissolution parameters of ibuprofen/paracetamol tablets

USP method	Parameter	Ibuprofen	Paracetamol
	Reference		
Ap. II (standard-vessel)	Q_{60} (%)	98.76±0.90	102.15±0.50
	DE (%)	67.56±0.38	76.54±0.38
	MDT (min)	18.93±0.30	15.03±0.50
	$t_{50\%}$ (min)	13.57±0.52	7.94±0.37
	$t_{80\%}$ (min)	21.71±0.84	12.70±0.60
Ap. IV (flow-through cell)	Q_{60} (%)	102.30±0.50	100.46±0.68
	DE (%)	74.44±0.37	73.31±0.21
	MDT (min)	16.33±0.29	16.20±0.29
	$t_{50\%}$ (min)	8.41±0.26	9.79±0.35
	$t_{80\%}$ (min)	13.45±0.42	15.67±0.57
	Generic		
Ap. II (standard-vessel)	f_2	49.41	47.91
	Q_{60} (%)	101.49±0.63*	99.20±0.61*
	DE (%)	76.33±0.30*	66.15±0.43*
	MDT (min)	14.86±0.28*	19.99±0.18*
	$t_{50\%}$ (min)	7.82±0.24*	14.33±0.28*
	$t_{80\%}$ (min)	12.51±0.38*	22.93±0.45*
Ap. IV (flow-through cell)	f_2	75.51	79.07
	Q_{60} (%)	98.87±0.82*	100.62±0.92
	DE (%)	73.44±0.42	75.26±0.33*
	MDT (min)	15.41±0.36*	15.09±0.31
	$t_{50\%}$ (min)	8.90±0.26	8.60±0.20*
	$t_{80\%}$ (min)	14.25±0.42*	13.76±0.32*

Mean±SEM, n=12. *p<0.05. USP: United States Pharmacopeia, DE: Dissolution efficiency, MDT: Mean dissolution time

Previous reports showed the results of *in vitro* release studies of ibuprofen (as the only active pharmaceutical ingredient [API]) suspensions using the USP apparatus II (at 50 rpm), flow-through cell method (at 16 mL/min), and pH 7.2 phosphate buffer as dissolution medium [24]. Ibuprofen/paracetamol tablets were also tested with USP apparatus II (at 75 rpm), USP apparatus IV (16 mL/min), and 0.1 M phosphate buffer pH 7.4 as dissolution medium [13]. In both cases, the Weibull function explained the *in vitro* release profile from these dosage forms. On the other hand, several authors have tested ibuprofen pellets with different designs of the USP apparatus IV to select the optimum hydrodynamic conditions to discriminate between different preparations [25], while enhancement of the immediate release of paracetamol from alginate beads has been tested with dissolution media of pH 1.2 and 6.8 [26].

Estimation of ibuprofen and paracetamol concentrations

Using pharmacokinetic information of both drugs and the *in vitro* release data from mini-vessels, USP standard-vessels, and flow-through cell method, plasma concentrations were predicted as described above. For the prediction of plasma levels with dissolution data of pediatric suspension, as an example, children with a body weight of 16 kg were considered, and with data of tablets, adolescents with 50–55 kg were considered. Then, hypothetical C_{max} and $AUC_{0\text{-}inf}$ were calculated, as well as their corresponding PE% values. The results of suspension are shown in Table 6, and the results of tablets are shown in Table 7.

As an example, hypothetical plasma concentration-time profiles of ibuprofen and paracetamol of suspension (using mini-vessels method) are shown in Fig. 3. The plasma concentration-time profiles of ibuprofen and paracetamol from tablets (using USP apparatus IV) are shown in Fig. 4.

The PE values <10% for the pharmacokinetic parameters C_{max} and $AUC_{0\text{-}inf}$ of ibuprofen and paracetamol suspension were achieved only with plasma concentration-time profiles generated with dissolution data of mini-vessels method. On the other hand, PE <10% for both pharmacokinetic parameters was found for reference and generic tablets using dissolution data of USP apparatus IV. Considering these results, the best conditions for evaluating the *in vitro* release behavior of ibuprofen/paracetamol in fixed-dose formulations are the mini-paddle apparatus for suspensions, and the USP apparatus IV for tablets since both hydrodynamic environments generate dissolution data that can be mathematically transformed into plasma profiles comparable to those found in an *in vivo* study.

Our findings agree with previous reports where the USP apparatus IV is a suitable option to predict the *in vivo* behavior of ibuprofen as the only API from soft gelatin capsules [27] and the mini-vessels method to simulate the ibuprofen plasma concentrations from suspensions [9]. Several authors have suggested the USP apparatus IV as a predictive tool for *in vivo* performances of ibuprofen immediate-release products

Table 4: $R^2_{adjusted}$/AIC values after adjusting dissolution data of suspension

USP method	First-order	Hopfenberg	Makoid-Banakar	Peppas-Sahlin	Weibull
	Ibuprofen				
Ap. II (mini-vessel)	0.9453/27.01	0.9766/21.92	**0.9958/10.56**	0.9928/13.73	0.9897/13.16
Ap. II (standard-vessel)	0.9537/25.37	0.9583/21.86	**0.9907/14.24**	0.9906/14.08	0.9846/15.83
Ap. IV (flow-through cell)	0.9693/21.03	0.9591/23.02	0.9620/22.27	0.9598/22.39	**0.9788/19.04**
	Paracetamol				
Ap. II (mini-vessel)	0.9683/23.90	0.9803/21.57	0.9758/21.47	0.9723/22.72	**0.9818/14.90**
Ap. II (standard-vessel)	0.9630/24.01	0.9620/24.47	0.9782/20.04	0.9786/19.98	**0.9796/19.48**
Ap. IV (flow-through cell)	0.8363/28.14	0.7816/30.15	**0.9579/19.93**	0.9426/23.02	0.9218/22.95

Mean, n=12. USP: United States pharmacopeia, AIC: Akaike information criterion

Table 5: $R^2_{adjusted}$/AIC values after adjusting dissolution data of tablets

USP method	First-order	Hopfenberg	Makoid-Banakar	Peppas-Sahlin	Weibull
Reference					
	Ibuprofen				
Ap. II (standard-vessel)	0.9632/21.96	0.9513/23.89	**0.9704/21.41**	0.9698/21.52	0.9640/29.66
Ap. IV (flow-through cell)	0.8389/27.64	0.7850/29.64	**0.9879/12.71**	0.9769/15.71	0.9718/14.95
	Paracetamol				
Ap. II (standard-vessel)	0.9063/24.46	0.8749/26.47	**0.9834/13.93**	0.9827/14.23	0.9700/15.03
Ap. IV (flow-through cell)	0.9139/25.19	0.8851/27.19	0.9839/15.14	0.9831/15.17	**0.9831/13.00**
Generic					
	Ibuprofen				
Ap. II (standard-vessel)	0.7992/27.89	0.7321/29.89	**0.9767/16.69**	0.9654/18.34	0.9577/17.12
Ap. IV (flow-through cell)	0.9095/23.55	0.8792/25.55	**0.9639/19.17**	0.9639/19.30	0.9574/19.26
	Paracetamol				
Ap. II (standard-vessel)	0.9321/25.75	0.9094/27.76	**0.9925/14.60**	0.9880/17.11	0.9853/15.12
Ap. IV (flow-through cell)	0.9038/24.98	0.8717/26.98	0.9702/18.59	0.9701/18.54	0.9598/18.45

Mean, n=12. USP: United States Pharmacopeia, AIC: Akaike information criterion

Table 6: Values of predicted C_{max} and $AUC_{0\text{-}inf}$ and their corresponding %PE for ibuprofen/paracetamol suspension

USP method	Parameter	Ibuprofen	Paracetamol
Ap. II (mini-vessel)	C_{max} (µg/mL)	0.33	0.24
	PE of C_{max} (%)	7.47	−8.96
	$AUC_{0\text{-}inf}$ (µgh/mL)	1.65	0.63
	PE of $AUC_{0\text{-}inf}$ (%)	−0.16	−0.29
Ap. II (standard-vessel)	C_{max} (µg/mL)	1.56	1.10
	PE of C_{max} (%)	3.75	−11.51
	$AUC_{0\text{-}inf}$ (µgh/mL)	7.48	3.66
	PE of $AUC_{0\text{-}inf}$ (%)	−0.44	−26.11
Ap. IV (flow-through cell)	C_{max} (µg/mL)	0.36	0.26
	PE of C_{max} (%)	1.12	−24.92
	$AUC_{0\text{-}inf}$ (µgh/mL)	1.82	0.59
	PE of $AUC_{0\text{-}inf}$ (%)	−10.37	6.06

USP: United States Pharmacopeia, PE: Prediction error, $AU_{C0\text{-}inf}$: Area under the concentration-time curve from zero to infinity

Table 7: Values of predicted C_{max} and $AUC_{0\text{-}inf}$ and their corresponding% PE for ibuprofen/paracetamol tablets

USP Method	Parameter	Ibuprofen	Paracetamol
Reference			
Ap. II (standard-vessel)	C_{max} (µg/mL)	8.17	9.53
	PE of C_{max} (%)	9.71	0.31
	$AUC_{0\text{-}inf}$ (µgh/mL)	39.95	33.08
	PE of $AUC_{0\text{-}inf}$ (%)	3.51	−9.60
Ap. IV (flow-through cell)	C_{max} (µg/mL)	9.16	9.45
	PE of C_{max} (%)	−1.17	1.11
	$AUC_{0\text{-}inf}$ (µgh/mL)	44.67	32.34
	PE of $AUC_{0\text{-}inf}$ (%)	−7.91	−7.14
Generic			
Ap. II (standard-vessel)	C_{max} (µg/mL)	9.70	9.39
	PE of C_{max} (%)	−7.14	1.82
	$AUC_{0\text{-}inf}$ (µgh/mL)	49.13	31.66
	PE of $AUC_{0\text{-}inf}$ (%)	−18.67	−4.92
Ap. IV (flow-through cell)	C_{max} (µg/mL)	8.79	9.46
	PE of C_{max} (%)	2.86	0.99
	$AUC_{0\text{-}inf}$ (µgh/mL)	44.22	32.47
	PE of $AUC_{0\text{-}inf}$ (%)	−6.81	−7.59

USP: United States Pharmacopeia, PE: Prediction error, $AUC_{0\text{-}inf}$: Area under the concentration-time curve from zero to infinity

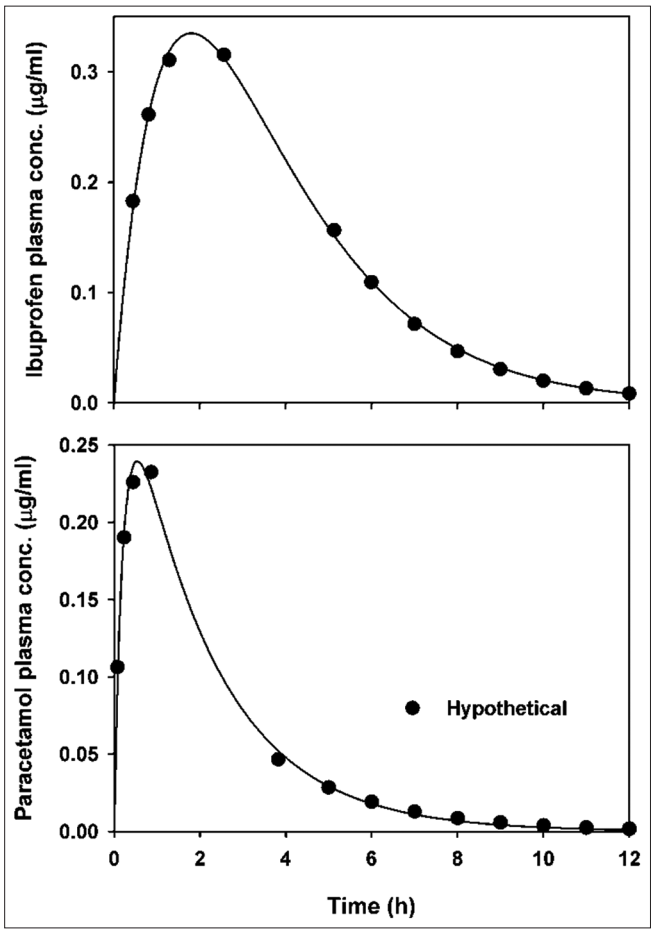

Fig. 3: Hypothetical plasma concentrations of ibuprofen/paracetamol suspension tested with the mini-vessel method

(tablets), especially during early product development, and, hence, might be adopted as a surrogate for conducting clinical bioequivalence studies given that suitable PE% values for C_{max} and AUCs were achieved after comparison of different dissolution models [2]. Suitable *in vivo* predictions for paracetamol in solid oral fixed-dose formulations (acetylsalicylic acid/acetaminophen/caffeine) using the USP apparatus IV were previously reported [3].

It is important to consider that both drugs in the same pharmaceutical dosage form must have PE values <10% to ensure safe interchangeability

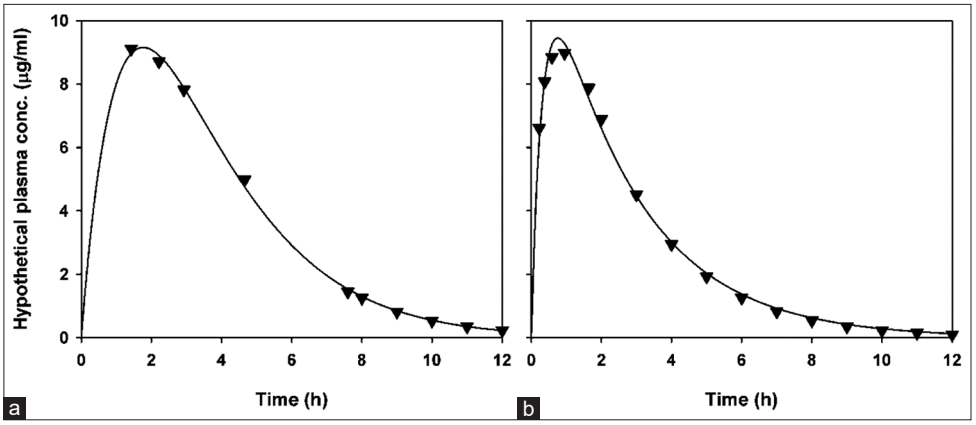

Fig. 4: Hypothetical plasma concentrations of ibuprofen (a) and paracetamol (b) tablets tested with the United States Pharmacopeia apparatus IV

between generic formulations and the reference drug product. In this way, the documented therapeutic effect of the reference formulation is maintained, and the objective of having safe and efficient medicines with a lower cost for the population is fulfilled. Even though commercial drug products are manufactured with high-quality standards, post-marketing surveillance is always recommended [28,29], but in the case of the development of new drug products, the use of predictive *in vitro-in silico* studies to simulate the *in vivo* behavior is needed [30].

The methodology to predict plasma drug levels through *in vitro* release studies can present advantages such as the use of a variety of dissolution data obtained by different conditions (dissolution media, dissolution equipment, agitation rate, etc.) and avoid costly human studies, whereas disadvantages such as limited *in vivo* information available in healthy volunteers generate inaccurate or unreliable predictions so it is advisable to take precautions when using this approach. In addition, the obtained results provide scientific evidence of the usefulness of the mini-paddle method and USP apparatus IV for evaluating ibuprofen and paracetamol reference suspensions and tablets, respectively, through dissolution studies. By determining the *in vitro* conditions that generate results that can be mathematically transformed into plasma concentrations similar to those observed in an *in vivo* study, the appropriate methodology is obtained for comparing test formulations and ensuring that they have a high probability of subsequently being classified as interchangeable drugs. This represents savings for different sectors, especially for the population, which will have access to cheaper medications with the same therapeutic efficacy and safety as the reference drug product. The work described in this paper can be considered an option to evaluate analgesic fixed-dose combination formulations beyond simple dissolution studies. It is important to complement the *in vitro* studies by considering bio-relevant dissolution media to better simulate the environment of the gastrointestinal tract and other drug combinations to treat different diseases.

CONCLUSION

In this study, fixed-dose combination formulations of ibuprofen/paracetamol were tested with the hydrodynamic environment that the mini-vessels method, USP standard-vessels, and the USP apparatus IV generate. The reference suspension and tablets, as well as a generic formulation, were used. Comparable dissolution profiles between the generic formulation and reference (tablets) were found only with the USP apparatus IV (f_2>50), whereas Makoid-Banakar and Weibull functions were the mathematical models that better explained the *in vitro* release performance of both drugs. With dissolution data, simulated plasma profiles were established and compared with real pharmacokinetic information. Better predictions were found with the mini-vessels method using dissolution data of suspension and with the USP apparatus IV using data from tablets. In both dissolution methods, PE for C_{max} and $AUC_{0\text{-}inf}$ was <10%; therefore, it is considered that the predicted parameters are very similar to those observed in a real *in vivo* study. The current study is an option to test the quality of ibuprofen/paracetamol fixed-dose combination formulations beyond simple dissolution studies. More research in this field is necessary, considering biorelevant media and other drug combinations.

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AUTHORS' CONTRIBUTIONS

JR Medina-López: Conceptualization, Reviewing, Editing, and Supervision. JC Ruiz-Segura Writing-original draft, statistical analysis, and Editing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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