Iranian Journal of Pharmaceutical Sciences
2025: 21 (1): 461- 469
https://journals.sbmu.ac.ir/IJPS

Research Article

OPEN ACCESS

Hypothetical In-vivo Behavior of Pediatric Dosage Forms: Ibuprofen Oral Suspensions

Stephanie Marlen Reyes-Castillo, Felipe Dino Reyes-Ramírez, Luis Antonio Cedillo-Díaz, Juan Manuel Contreras-Jiménez, José Raúl Medina-López*

Departamento Sistemas Biológicos, Universidad Autónoma Metropolitana-Xochimilco, Mexico City, Mexico.

Received: January 18, 2025 **Last Revision:** October 14, 2025 **Accepted:** November 8, 2025 **Available online:** December 21, 2025.

Abstract

The hypothetical plasma concentration-time profiles of ibuprofen pediatric formulations using in-vitro release data of the mini-paddle apparatus and the USP apparatus were proposed. Dissolution conditions were as follows: a mini-paddle apparatus at 75 rpm, 200 mL of medium, a USP apparatus 4 laminar flow at 16 mL/min, and phosphate buffer (pH 6.8). Five commercial formulations (reference and four multi-source drug products) were used. Samples were taken at previously established times for up to 60 minutes. The dissolved drug was quantified by UV derivative spectrophotometric analysis. Profiles were compared with different approaches, and dissolution data were fitted with several mathematical equations. Predicted in vivo behavior was calculated using dissolution data from both apparatuses and published pharmacokinetic information through a convolution approach. Validation of the results was carried out by calculating the prediction error (PE) for the hypothetical peak plasma level (Cmax) as well as the area under the curve from zero to infinity ($AUC_{0\text{-}inf}$). Calculations are valid if PE is equal to or less than 10%. Considering the f_2 value, similar in-vitro release curves of all suspensions were found using data from the USP apparatus 4 ($f_2 > 50$). No statistically significant differences were calculated for the release parameters of B and C drug products, respectively, using data from the USP apparatus 4. PE < 10% for C_{max} and $AUC_{0\text{-}inf}$ in the same formulation was only found with R, B, and C drug products, based on data from the USP apparatus 4. This apparatus appears to be the appropriate choice for assessing the biopharmaceutical quality of pediatric ibuprofen formulations.

Keywords: Convolution; Ibuprofen; Inverse Release Function; Prediction Error; Suspension; USP Apparatus 4.

1. Introduction

Ibuprofen is an anti-inflammatory compound that belongs to the class of non-steroidal anti-inflammatory drugs. In children, ibuprofen suspension is an option for treating fever, and it is also used by patients who have difficulty swallowing. This drug is widely available in generic or multi-source formulations (solid and liquid) and is part of the World Health Organization's Model List of Essential Medicines [1]. To determine if generic formulations are safely interchangeable with the reference drug product, in-vivo absorption studies are necessary. With the available scientific information, a biowaiver monograph for ibuprofen tablets has been published to suggest replacing human studies with in-

*** Corresponding Author**:
José Raúl Medina-López, Departamento Sistemas Biológicos, Universidad Autónoma Metropolitana-Xochimilco, Calz. del Hueso 1100 Col. Villa Quietud Alcaldía Coyoacán Mexico City, Mexico. E-mail: rmlopez@correo.xoc.uam.mx.

Cite this article as: Reyes-Castillo S.M., Reyes-Ramirez F. D., Cedillo-Diaz L.A., Contreras-Jimenez J.M., Medina-López J. R. Hypothetical In-vivo Behavior of Pediatric Dosage Forms: Ibuprofen Oral Suspensions. Iran. J. Pharm. Sci., 2025, 21 (1): 461- 469.

DOI: https://doi.org/10.22037/ijps.v21i1.47326

vitro release studies [2]; however, no biowaiver monograph for ibuprofen suspensions, nor for any other dosage form other than solid, is available.

The pharmacopeial dissolution quality control test for ibuprofen oral suspension is suggested in the United States Pharmacopeia (USP) [3]. The method considers the paddle apparatus (USP apparatus 2) at 50 rpm and 900 ml of phosphate buffer (pH 7.2). At 60 min, not less than 80% of the labelled amount should be dissolved. Chromatographic determination is also recommended. The analytical determinations of drug mixtures by UV derivative spectroscopy are a common practice. This procedure allows for the simultaneous determination of each compound in the mixture without mutual interference and with the same results as chromatographic analysis [4].

The in-vitro release experiments with the standard paddle apparatus require large volumes of test media; however, a mini-paddle system is now available to use less dissolution media. Different types of mini-paddle apparatus reflect everything but a miniaturized reproduction of the USP paddle method. Due to the possibility of working with smaller samples and volumes, the mini-paddle apparatus offers advantages in terms of substance, analytical, and material cost savings when evaluating release mechanisms [5]. Other authors have stated that the USP apparatus 2, with its small volume and paddle, has gained much acceptance due to its ease of use, research efficiency, and suitability for dosage forms related to pediatric populations [6].

It is known that the USP apparatus 4 (flow-through cell method) better simulates the environment of the gastrointestinal tract. It has a nonstop extraction of the drug, producing an intermittent flow into the place where the formulation is positioned. This system is open, allowing for easy changes to the medium with varying pH levels. The USP apparatus 4 has shown a better discriminative capacity. On the other hand, some authors have established the possibility of predicting in-vivo behavior of ibuprofen tablets and soft gelatin capsules with mathematical models and dissolution data generated by the USP apparatus 4 [7, 8].

The objective of this research was to propose plasma concentration-time profiles of ibuprofen pediatric suspensions using in-vitro release data of the mini-paddle apparatus and USP apparatus 4. Published ibuprofen pharmacokinetic information, including half-life, volume of distribution, and a numerical convolution approach, was considered. This information could be useful for the design of better ibuprofen oral dosage forms (for children's use).

2. Materials and Methods

2.1. Formulations and Chemicals

The used formulations were: ibuprofen reference suspension (coded as R, a drug product) (Advil 100 mg/5 mL, GlaxoSmithKline Consumer Healthcare México, S. de R.L. de C.V., Mexico) and four multi-source drug products commercially available to the public (randomly coded as A, B, C, and D formulations). Methanol, sodium hydroxide, and sodium phosphate monobasic crystals were provided by J.T.Baker-Mexico (Xalostoc, Mexico). Ibuprofen, the standard compound, was supplied by Sigma-Aldrich Co. (St. Louis, MO, USA).

2.2. Ibuprofen Determination

The UV derivative determination of ibuprofen in a mixture of ibuprofen + caffeine was developed by our research group [9]. In this study, the UV derivative methodology has been used to eliminate the interference of excipients. It is important to note that the ibuprofen drug products used in the present work contained only ibuprofen as the active pharmaceutical ingredient, and caffeine was added as part of the analytical method. A UV/Vis spectrophotometer (PerkinElmer Lambda 35, Waltham, MA, USA) was used. The analytical procedure considers the second-derivative mode (D^2), scan speed 240 nm/min, slit width 2.0 nm, and sampling interval 1.0 nm. Five standard solutions of ibuprofen (10 – 50 µg/ml) diluted in phosphate buffer (pH 6.8) and one solution of caffeine (15 µg/ml) in the same medium were used. The zero-order spectra from 230 to 240 nm were recorded and stored. Quartz cells of 1 cm were used. To determine ibuprofen, the zero-order spectra were transformed into D_2 spectra, and a zero-crossing method was used to quantify ibuprofen from the standard solutions or diluted dissolution samples (at 235.5 nm).

2.3. Method Validation

The spectrophotometric analysis was validated in accordance with the guidelines of the International

Conference on Harmonization (ICH). Parameters such as linearity, accuracy, precision, filter influence, and short-term stability were evaluated.

2.3.1. Linearity

Three ibuprofen standard calibration curves were determined, and linear regressions were performed. The proportionality of ibuprofen and analytical response was tested using the relative standard deviation (RSD), calculated as (standard deviation/mean) × 100.

2.3.2. Accuracy and Precision

Matrix effects were removed using the added standard method. Quantities of ibuprofen standard compound (5 mg) plus a volume of ibuprofen suspension equivalent to doses of 80, 100, and 120% were added to 200 ml of dissolution medium. The mini-paddle method at 75 rpm was operated, and after 60 minutes, the dissolved ibuprofen was calculated (n = 3, over 3 days). The relative error (RE) = ((found-added)/found) × 100 was taken as a measure of accuracy, and RSD as a measure of precision.

2.3.3. Stability

Two ibuprofen solutions (15 and 45 µg/mL) in phosphate buffer (pH 6.8) were analyzed at 0, 24, and 48 hours after storage at 4 °C. Then, the absolute difference (AD) = ((initial-final)/initial) × 100 was determined.

2.4. In-vitro Release Performance

Dissolution profiles of ibuprofen were obtained using the mini-paddle apparatus (Sotax AT-7 Smart Model, Switzerland) at 75 rpm and 200 ml of phosphate buffer (pH 6.8). The USP apparatus 4 (Sotax CE6 Model, Switzerland) with laminar flow at 16 ml/min was operated. Dissolution medium was used at 37.0 ± 0.5 °C. A suspension sample containing 10 mg of ibuprofen was tested. 5 ml of dissolution samples were taken at 10-, 20-, 30-, 45-, and 60-minute intervals, and they were filtered with nitrocellulose filters (Millipore). After the samples were taken, 5 mL of pre-warmed medium was added to each mini-vessel. To quantify ibuprofen, the zero-order spectra of diluted dissolution samples were registered. Finally, the D^2 UV spectra of ibuprofen from dissolution samples and standard solutions of known concentration were considered.

2.5. Dissolution Data Analysis

Dissolution profiles of ibuprofen multi-source suspensions compared to the reference were related to different approaches. The f_1 difference factor, f_2 similarity factor, dissolution efficiency (DE), and mean dissolution time (MDT) were computed using the Excel add-in DDSolver [10]. Suppose $f_1 = 0 – 15$, no difference between profiles was considered, while if $f_2 = 50 – 100$, similar dissolution profiles were found. In-vitro release data were fitted with the hyperbola model described in **Table 1** using the Sigmaplot program (Version 11.0). With hyperbola parameters, the times to release 50% ($t_{50\%}$), 63.2% ($t_{63.2\%}$), and 80% ($t_{80\%}$) of the drug were calculated. Comparisons were performed using a one-way ANOVA and a post hoc Dunnett's multiple comparisons test. If $p < 0.05$, statistically significant differences were considered. This is a statistical procedure for comparing the means of multiple experimental treatment groups against a single control group. The percentage of released drug was fitted with some mathematical models. The following equations were used: Korsmeyer-Peppas, Makoid-Banakar, Peppas-Sahlin, Logistic, and Weibull (**Table 1**). The best-fit model was chosen based on the highest adjusted determination coefficient ($R^2_{adjusted}$) and the lowest Akaike Information Criterion (AIC).

Table 1. Mathematical models.

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

2.6. Prediction of In-vivo Behavior

The hypothetical ibuprofen plasma concentration-time profiles were computed using the in-vitro release data obtained with the mini-paddle apparatus and USP

apparatus 4, as well as the Inverse Release Function methodology [11]. This procedure was used to adjust the time scale of the dissolution profile as described in detail in the aforementioned publication. Once the new timescale was calculated, the hypothetical in-vivo behavior was simulated using a numerical convolution approach [12]. This calculation considers published ibuprofen pharmacokinetic data, including volume of distribution (Vd), bioavailability factor (F), and elimination rate constant (ke) [2, 13]. Calculations were performed as detailed below [12].

The in-vitro dissolution profile was divided into separate parts where the amount of drug (mg) dissolved within each sampling interval was estimated (X = drug dissolved / strength × 100). After that, the latter was corrected for F, and the observed amount of drug in blood was calculated ($X_{corrected}$ = amount of drug [mg] released within sampling interval × F). Finally, blood concentrations (µg/ml) equivalent to the total amount of ibuprofen in blood at different times after ingestion of suspension were calculated using **Eq. 1**.

$$\frac{Total\ amount\ of\ drug\ in\ blood\ after\ absorption\ at\ time\ t}{V_d \times body\ weigth} \times 100 \quad \textbf{Eq. [1]}$$

After calculating the ibuprofen plasma concentration-time profiles, the peak plasma level (C_{max}) and area under the concentration-time curve from zero time to infinity ($AUC_{0\text{-}inf}$) were calculated using the Excel add-in PKSolver. To evaluate the predictability of the convolution methodology, published pharmacokinetic information from an ibuprofen bioequivalence study (400 mg tablets) was slightly modified by our used dose (10 mg) and applied [14]. The computation of the percentage of prediction error (%PE) for pharmacokinetic parameters C_{max} and $AUC_{0\text{-}inf}$ was made considering **Eq. 2** (a PE value less than 10% is optimal) [15].

$$(\%PE) = \frac{(observed\ value - predicted\ value)}{observed\ value} \times 100 \quad \textbf{Eq. [2]}$$

3. Results and Discussion

3.1. Method Validation

3.1.1. Linearity and Stability

The mean regression equation was described as y = 0.0373x + 0.0448 (R^2 > 0.999 with a p < 0.05). The RSD of the response factor was less than 2.0%. The AD values for the 15 µg/ml solution at 24 and 48 h were -8.64% and -12.59%, respectively. The AD values for the 45 µg/ml solution at 24 and 48 h were -3.61% and -7.24% respectively. The results suggest storing the dissolution samples at 4°C for no more than 24 hours.

3.1.2. Accuracy and Precision

Accuracy and precision of ibuprofen solutions are depicted in **Table 2**. The RSD was 0.36 – 1.15% and the RE was < 0.49%. No interferences of excipient were found.

Inter-day precision evaluates the variability of results when assays are conducted on different days. In contrast, intra-day precision focuses on the variation of results when tests are performed multiple times within the same day. Both measures are essential for ensuring the reliability of the analytical method and the accuracy of the results obtained from the assays.

Table 2. Accuracy and precision to determine ibuprofen in pediatric suspension by D^2 derivative spectrophotometry.

		Intra-day (n = 3)			**Inter-day (n = 9)**		
Dose (%)	Added (mg)	Found (mg)	RSD (%)	RE (%)	Found (mg)	RSD (%)	RE (%)
80	8.00	8.00	0.96	-0.05	8.02	1.15	0.19
100	10.00	10.05	0.64	0.49	10.01	1.04	0.05
120	12.00	12.03	0.36	0.23	12.01	0.78	0.05

3.2. In-vitro Release

The direct UV determination of ibuprofen from suspension was complicated by interference from excipients (some of which are dyes), making drug identification difficult (data not shown). In the present work, the spectrophotometric D^2 method for quantifying ibuprofen in pediatric suspensions was successfully applied. Dissolution profiles of ibuprofen multi-source formulations and the R drug product are shown in **Figure 1**. The plot shows a difference in the effect of the hydrodynamic environment on both dissolution apparatuses, as the dissolution rate of multi-source formulations differed from that of the R drug product, especially with the mini-paddle apparatus. Model-independent and model-dependent parameters calculated for comparison of dissolution profiles are presented in **Table 3**.

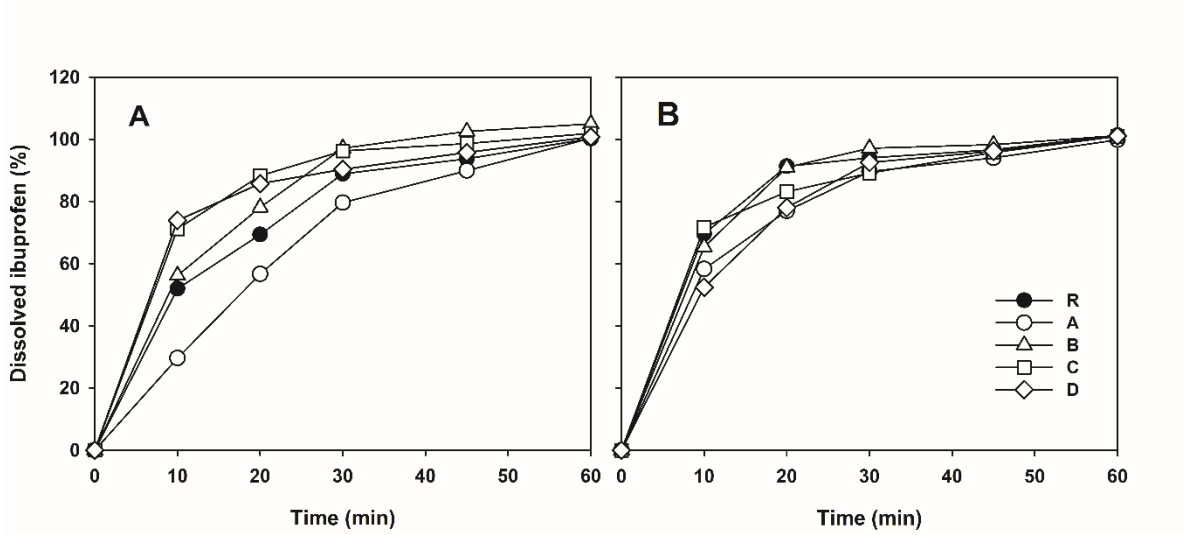

Figure 1. Ibuprofen profiles A) Mini-paddle apparatus and B) USP apparatus 4. Reference (R) and multi-source drug products (A-D). Mean, n = 12.

Table 3. Parameters of ibuprofen suspensions. Reference formulations (R) and multi-source products (A-D). Mean ± SEM, n = 12. *p < 0.05.

Parameter	R	A	B	C	D
Mini-paddle apparatus					
f_1	-	11.93	8.60	12.90	10.51
f_2	-	47.37	58.75	46.66	47.35
Q_{60} (%)	100.21±0.79	100.31±0.35	104.91±0.21*	101.88±0.46	100.78±0.36
MDT (min)	15.28±0.49	20.54±0.08*	13.48±0.09*	10.53±0.14*	11.21±0.18*
DE (%)	74.65±0.88	65.95±0.17*	81.33±0.19*	83.98±0.29*	81.94±0.19*
$t_{50\%}$ (min)	7.71±0.26	15.92±0.30*	7.77±0.06	4.83±0.10*	3.93±0.05*
$t_{63.2\%}$ (min)	11.88±0.40	22.59±0.42*	11.83±0.10	7.73±0.15*	6.49±0.07*
$t_{80\%}$ (min)	20.86±0.68	33.89±0.63*	20.25±0.22	14.80±0.29*	13.47±0.20*
USP apparatus 4					
f_1	-	7.54	2.08	3.61	7.22
f_2	-	55.28	80.51	69.22	52.41
Q_{60} (%)	101.30±0.57	99.84±0.69	101.21±1.07	101.02±0.43	101.03±0.41
MDT (min)	10.68±0.22	13.59±0.19*	10.44±0.39	11.91±0.16*	13.85±0.20*
DE (%)	83.22±0.16	77.19±0.27*	83.52±0.51	80.95±0.20*	77.69±0.27*
$t_{50\%}$ (min)	4.79±0.10	7.21±0.10*	5.47±0.25*	4.85±0.08	7.97±0.16*
$t_{63.2\%}$ (min)	7.71±0.15	11.38±0.19*	8.82±0.42*	7.91±0.12	12.32±0.23*
$t_{80\%}$ (min)	15.00±0.26	21.12±0.52*	17.30±0.95*	15.97±0.35	21.75±0.31*

A similarity factor (f_2) between 50 and 100 was found for the B formulation, considering data from the mini-paddle apparatus, and for all formulations using the USP apparatus 4. In these cases, similar dissolution profiles were considered. No differences were observed between MDT and DE of the B formulation using the USP apparatus 4 ($p > 0.05$). Similar findings were computed with $t_{50\%}$, $t_{63.2\%}$, and $t_{80\%}$ of B formulation using dissolution data of the mini-paddle apparatus and C formulation using data from USP apparatus 4 ($p > 0.05$). In practically all comparisons, statistically significant differences were found ($p < 0.05$). MDT and DE are suitable values for establishing in-vitro/in-vivo correlations (IVIVC). In IVIVC level B, the MDT parameter is used. The MDT is defined as the time to dissolve 63.2% of the dose. To establish IVIVC level C, the DE parameter is considered.

Considering the diversity, the release behavior of ibuprofen from used drug products can be mathematically explained by different equations. As the

number of parameters in different models varied, instead of the coefficient of regression, the R^2 Adjusted and AIC were selected as the statistical criteria to evaluate the best-fit model. The formula for $R^2_{adjusted}$ is $R^2_{adjusted} = 1 - [(1 - R^2) * (n - 1) / (n - k - 1)]$, where R^2 is the original R^2 value, n is the total number of observations, and k is the number of independent variables in the model. The formula for AIC is $AIC = 2k - 2\ln(L)$, where k is the number of independent variables (or parameters) in the model, and 'ln(L)' is the natural logarithm of the maximum value of the likelihood function for the model. Both parameters were calculated with the Excel add-in DDSolver [10].

The results of the data fitting are depicted in **Table 4**. Makoid-Banakar, Weibull, and Korsmeyer-Peppas better explained the ibuprofen release mechanism from R, C, and D formulation, respectively (with data from the mini-paddle apparatus). On the other hand, the Weibull function was suitable for R, B, and D formulations, and the Korsmeyer-Peppas model for C formulation, using dissolution data from the USP apparatus 4. The exact release mechanism was observed in both dissolution apparatuses for the A formulation.

The release of the R drug product was described using the Makoid-Banakar model with data from the mini-paddle apparatus. At the same time, the Weibull function was the best equation to fit the data from the USP apparatus 4. 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 curve [16]. In contrast, the Weibull function is more useful for comparing the release profiles of matrix-type drug delivery, and the equation includes the Td parameter, which represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form [17].

When a new solid dosage form is developed, it is crucial to investigate drug release. The quantitative analysis of values obtained in dissolution or release rates is easier when mathematical formulae are used to describe the process. Mathematical modeling helps optimize the design of a therapeutic device to yield information on the efficacy of various release models [17]. The dissolution data adjustment with several mathematical models was made without any physiological implications. The aim of using these models was to facilitate easy analysis of the results.

3.3. Estimation of Plasma Concentration-Time Profiles

The used convolution approach was able to generate hypothetical in-vivo performance similar to that reported in the scientific literature. To confirm this procedure, predicted C_{max} and $AUC_{0\text{-}inf}$ and their respective PE values are shown in **Table 5**. Only PE < 10% for both pharmacokinetic parameters was found with R, B, and C formulations using dissolution data generated by the USP apparatus 4.

Table 4. $R^2_{adjusted}$/AIC values. Mean, n = 12.

Model	R	A	B	C	D
Mini-paddle apparatus					
Korsmeyer-Peppas	0.9155/26.68	0.9276/29.66	0.8832/28.82	0.8809/23.31	0.9583/16.74
Makoid-Banakar	0.9521/23.61	0.9821/21.30	0.9796/19.77	0.9707/14.53	0.9558/17.03
Peppas-Sahlin	0.9509/23.86	0.9749/23.40	0.9720/19.97	0.9697/14.61	0.9560/17.05
Logistic	0.9147/26.63	0.9691/25.27	0.8912/28.57	0.9522/18.05	0.9016/20.94
Weibull	0.9242/23.89	0.9751/20.49	0.9756/19.02	0.9806/10.66	0.9276/18.05
USP apparatus 4					
Korsmeyer-Peppas	0.8077/26.24	0.9295/24.02	0.7426/29.29	0.9840/10.48	0.8686/28.99
Makoid-Banakar	0.8887/23.41	0.9765/18.02	0.9263/22.72	0.9803/10.76	0.9760/20.03
Peppas-Sahlin	0.8867/23.51	0.9755/18.28	0.9127/23.72	0.9807/10.65	0.9681/21.52
Logistic	0.9659/17.01	0.9557/20.53	0.9677/18.52	0.8949/22.34	0.9738/20.86
Weibull	0.9667/14.23	0.9712/16.84	0.9784/12.82	0.9700/11.21	0.9811/17.20

Table 5. Predicted C_{max} and $AUC_{0\text{-}inf}$ of ibuprofen suspensions and their corresponding PE values.

Code	Predicted C_{max} (µg/ml)	PE for C_{max} (%)	Predicted $AUC_{0\text{-}inf}$ (µgh/ml)	PE for $AUC_{0\text{-}inf}$ (%)
Mini-paddle apparatus				
R	0.33	27.04	1.73	16.42
A	0.31	32.00	1.57	24.15
B	0.34	23.78	1.69	18.35
C	0.46	-1.65	2.28	-10.14
D	0.46	-2.41	2.35	-13.52
USP apparatus 4				
R	0.48	-5.61	2.19	-5.79
A	0.35	22.26	1.83	11.59
B	0.41	9.47	2.00	3.38
C	0.44	3.05	2.24	-8.21
D	0.33	26.18	1.78	14.00

Observed C_{max} = 0.45 µg/ml [14]
Observed $AUC_{0\text{-}inf}$ = 2.07 µgh/ml [14]

Several authors have investigated the release of ibuprofen from suspensions. A group of researchers conducted experiments using the paddle method at 25 and 50 rpm, with 900 ml of buffer (pH 7.2, pH 6.8, and pH 4.5) and 0.1 M HCl. Direct UV determination was performed at 221 nm. The released drug using pH 6.8 and 25 rpm was 66% at 60 min, while using 50 rpm, more than 100% (± 120%) at 30 min was found. Additionally, first-order kinetics provided a better explanation of the release mechanism at pH 6.8, although only this model and zero-order kinetics were tested [18].

On the other hand, and intending to improve convenience and compliance among elderly and pediatric patients, several authors have proposed and tested 10 formulations of ibuprofen oral suspensions. Excipients, such as poloxamer, polyvinylpyrrolidone, and polyvinyl alcohol, were used in a sodium carboxymethyl cellulose dispersing medium. Attention was given to the selection of suitable taste masking agents. Dissolution studies were conducted using the USP paddle method at 50 rpm and with 900 mL of phosphate buffer (pH 7.2). UV determination at 221 nm was considered. At 60 min, a range of dissolved drugs of 47.33 – 104.78% was found. The zero-order and first-order kinetics were chosen to explain the ibuprofen release of these proposed formulations [19].

In our study, the USP apparatus 4 at 16 ml/min and buffer (pH 6.8) were the suitable settings to evaluate the dissolution mechanism of ibuprofen pediatric formulations, as these dissolution conditions generated an in-vivo behavior similar to that found in a bioavailability study for the R formulation. PE data < 10% for pharmacokinetic parameters C_{max} and $AUC_{0\text{-}inf}$ were computed under these conditions. To achieve comparable biopharmaceutical quality among all ibuprofen drug products, multi-source formulations should have similar dissolution profiles to the R drug product. In this regard, the concept of a bio-predictive dissolution tool can estimate the drug pharmacokinetics in humans and support formulation design [20]. On the other hand, no hypothetical PE values less than 10% for C_{max} and $AUC_{0\text{-}inf}$ were achieved in the same formulation with in-vitro data from the mini-paddle apparatus. Therefore, apparently, in this case, the mini-paddle apparatus was not capable of generating in-vitro release data that can be mathematically transformed into hypothetical ibuprofen concentrations like those reported in an in-vivo study.

The mathematical treatment of dissolution data using a numerical convolution approach is straightforward. It provides a simple method for designing bioequivalent drug products during the development stage, facilitating multi-source formulations with improved in-vivo performance. A convolution-based approach benefits from fewer experimental animal or human resources for in-vivo studies, which is ideal [21]. The convolution method is a tool for designing and selecting formulations before animal or human studies, as well as for predicting

human plasma profiles. The application of convolution includes, but is not limited to, predicting drug product performance, developing and validating IVIVC, rational drug development, defining safe spaces, SUPAC, among many other possibilities [22]. This method has been successfully applied in examples of IVIVC and the prediction of plasma concentration profiles [21-23]. Using dissolution data from the USP apparatus, four previous reports demonstrated a good prediction of pharmacokinetic parameters for non-steroidal anti-inflammatory drugs (oral dosage forms) [7]. Hypothetical human performance of extender-release formulations and the USP apparatus 4 has also been documented [21].

In another approach, a pilot study identifies an excessive use of ibuprofen (OTC formulations), suggesting a need for pharmacovigilance studies. Generic or multi-source formulations are equivalent to the reference if they contain the same active pharmaceutical ingredient, dosage form, and therapeutic indications. However, the bioequivalence and the role of excipients may be clarified regarding their impact on clinical effectiveness during interchangeability (generic vs. reference). To increase purchase intentions, generic formulations should have positive perceptions. Health authorities should work on policies and promote industrialization, commercialization, and widespread access to multi-source drug products [24]. Simulation approaches could be used to incorporate the adult population and to adjust data for different groups (children or elderly) [25].

4. Conclusion

Dissolution behavior of ibuprofen pediatric suspensions was evaluated using a mini-paddle apparatus and the flow-through cell method. The USP 4 apparatus is designed better to reveal similarities between multi-source formulations and the reference. Hypothetical in-vivo plasma concentration-time profiles were calculated using a numerical convolution method and in-vitro release data of both dissolution apparatuses. Proposed pharmacokinetic parameters C_{max} and $AUC_{0\text{-}inf}$ of some formulations showed PE values less than 10%. The USP apparatus 4 at 16 ml/min and phosphate buffer (pH 6.8) were suitable settings to evaluate ibuprofen multi-source drug products, as these dissolution conditions generated, with reference to the formulation, an in-vivo behavior similar to that found in an ibuprofen bioavailability study. Based on the obtained findings, the use of USP apparatus 4 is suggested for testing ibuprofen pediatric dosage forms. To corroborate the results, human studies using the formulated products are necessary.

Acknowledgment

The authors express their cordial gratitude to QFB Elias Villegas for providing technical support in mini-paddle apparatus.

Conflict of interest

The authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Authors Contributions

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Authors Orcid numbers:

Stephanie Marlen Reyes-Castillo: 0009-0000-9754-6541
Felipe Dino Reyes-Ramírez: 0009-0009-6876-9223
Luis Antonio Cedillo-Díaz: 0009-0008-4724-2548
Juan Manuel Contreras-Jiménez: 0000-0002-9844-8676
José Raúl Medina-López: 0000-0002-4159-8403

Funding

No funding agency is involved in the present study.

Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

References

1. WHO Model List of Essential Medicines – 23rd List (2023). http://chrome-

extension://efaidnbmnnnibpcajpcglclefindmkaj/https://iris.who.int/server/api/core/bitstreams/289a875c-cc89-4914-90ad-eb3c578ebaf6/content (Accessed Oct 5, 2025).
2. Potthast *et al*. Biowaiver monographs for immediate release solid oral dosage forms: ibuprofen. J. Pharm. Sci. (2005) 94 (10): 2121–2131.
3. United States Pharmacopeia and national formulary USP43-NF38; The United States pharmacopeial convention. Rockville, MD: Inc; 2021.
4. Medina-López JR, Pacheco JG, Rojas PA, Castro N. Derivatives of the ratio spectra for determination of acetylsalicylic acid, acetaminophen, and caffeine in fixed-dose combination formulations: application to dissolution studies. Int. J. App. Pharm. (2020) 12 (6): 253–257.
5. Klein S, Shah VP. A standardized mini paddle apparatus as an alternative to the standard paddle. AAPS PharmSciTech. (2008) 9 (4): 1179–1184.
6. Mohammadi A, Moghaddas JS. Experimental and computational study on hydrodynamic of a downscaled mini vessel USP dissolution test apparatus II. Iranian J. Chem. Engineering. (2019) 16 (3): 3–22.
7. Abdelfattah F, Taha N, Abdou A, Mursi N and Emara L. Prediction of in-vivo performance of ibuprofen immediate-release products using different dissolution models. J. App. Pharm. Sci. (2022) 12 (8): 193–201.
8. Medina-López JR, Ríos-López A, Reyes-Ramírez FD. Convolution approach to estimate the in-vivo behavior of ibuprofen soft gelatin capsules from in vitro release data of USP Apparatus 4. Int. J. Res. Pharm. Sci. (2024) 15 (4): 88–94.
9. Medina-López JR, Soto-Juha JA, Contreras-Jiménez JM. Rapid and simple determination of ibuprofen and caffeine in fixed-dose combination formulations: application to dissolution studies. Int. J. Appl. Pharm. (2021) 13 (3): 242–246.
10. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J. (2010) 12 (3): 263–271.
11. Cardot JM, Lukas JC, Muniz P. Time scaling for in vitro-in-vivo correlation: the inverse release function (IRF) approach. AAPS J. (2018) 20 (6): 95.
12. Qureshi SA. In vitro–in-vivo correlation (IVIVC) and determining drug concentrations in blood from dissolution testing – a simple and practical approach. Open Drug Deliv. J. (2010) 4: 38–47.
13. Poveda Andrés JL, García Robles AA, Pérez Huertas P. Farmacología del ibuprofeno intravenoso. Rev. Soc. Esp. Dolor (2016) 23 (Supl. I): 3–12.
14. Villalva-Rojas O, Grande-Ortíz M, Ortiz J, Isasi J, Yantas D, Fiestas V. Estudio de bioequivalencia del ibuprofeno 400 mg tabletas. Rev. Peru. Med. Exp. Salud Publica. (2007) 24 (4): 356–362.
15. Rastogi V, Yadav P, Lal N, Rastogi P, Singh BK, Verma N, Verma A. Mathematical prediction of pharmacokinetic parameters-an *in-vitro* approach for investigating pharmaceutical products for IVIVC. Future J. Pharm. Sci. (2018) 4 (2): 175–184.
16. Ilango KB, Kavimani S. A systematic review of mathematical models of pharmaceutical dosage forms. Int. J. Curr. Pharm. Rev. Res. (2015) 6 (1): 59-70.
17. Ramteke KH, Dighe PA, Kharat AR, Patil SV. Mathematical models of drug dissolution: a review. Sch. Acad. J. Pharm. (2014) 3 (5): 388-396.
18. Rivera-Leyva JC, García-Flores M, Valladares-Méndez A, Orozco-Castellanos M, Martínez-Alfaro M. Comparative studies of the dissolution profiles of oral ibuprofen suspension and commercial tablets using Biopharmaceutical Classification System Criteria. Indian J. Pharm. Sci. (2012) 74 (4): 312–318.
19. Sudhir M, Divya Ch, Lakshmi Prasanti N, Liakhat Ali Sk, Fridepaul Ch, Jyothi N. Formulation and characterization of oral suspension containing ibuprofen. Asian J. Pharm. Technol. Inn. (2016) 4 (21): 23–32.
20. Xu J, Zhang L, Shao X. Application of bio-predictive dissolution tools for the development of solid oral dosage forms: current industrial experience. Drug Dev. Ind. Pharm. (2022) 48 (3): 79–97.
21. Taha NF, Emara LH. Convolution- and deconvolution-based approaches for prediction of pharmacokinetic parameters of diltiazem extended-release products in flow-through cell dissolution tester. AAPS PharmSciTech. (2022) 23 (6): 202.
22. García MA, González PM, Aceituno A, Al-Gousous J. Novel analytical solutions for convolution in compartmental pharmacokinetic models and application to non-bioequivalent formulations. Eur. J. Pharm. Sci. (2024) 202: 106892.
23. Sánchez-Dengra B, González-García I, González-Álvarez M, González-Álvarez I, Bermejo M. Two-step in vitro-in-vivo correlations: deconvolution and convolution methods, which one gives the best predictability? Comparison with one-step approach. Eur. J. Pharmaceut. Biopharmaceut. (2021) 158: 185–197.
24. Arcaro R, Rereira da Veiga CR, Vieira da Silva W, Pereira da Veiga C. Attitude and purchase intention to generic drugs. Int. J. Environ. Res. Public Health (2021) 18: 4579.
25. Illamola SM, Birnbaum AK, Sherwin CM. Generic drug products in paediatrics: where are the data?. Br. J. Clin. Pharmacol. (2019) 85: 1871–1873.