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Hypothetical *in vivo* behavior of semisolid dosage forms: indomethacin suppositories

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ABSTRACT

This study aimed to simulate the *in vivo* behavior of indomethacin suppositories (reference and a generic formulation) using *in vitro* dissolution data and a numerical convolution method. The United States Pharmacopeia (USP) basket apparatus (USP apparatus I) at 100 rpm and the flow-through cell method (USP apparatus IV) with laminar flow at 16 ml/min were used. The dissolution medium phosphate buffer (0.1 M, pH 7.4) with or without 1% sodium dodecyl sulfate (SDS) was used. The dissolution profiles were compared with model-dependent and independent methods. For the reference drug product, tested with the USP apparatus IV and without 1% SDS, predicted C_{max} and AUC_{0-inf} were 2.39 and 8.46 µgh/ml, respectively; for the generic formulation, same medium but with the USP apparatus I, values of 0.73 and 3.11 µgh/ml were calculated. When comparing predicted pharmacokinetic parameters with *in vivo* data prediction errors <10% for C_{max} and AUC_{0-inf} were only found with the reference drug product and the flow-through cell method. USP apparatus IV and phosphate buffer (0.1 M, pH 7.4) without 1% SDS were the ideal dissolution conditions to test multisource formulations and generate hypothetical *in vivo* behavior. To confirm these results, human studies using indomethacin suppositories should be conducted.

INTRODUCTION

The nonsteroidal anti-inflammatory drug indomethacin is used to treat known diseases or for medical procedures. Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic joint inflammation. The incidence among women is 2–3 times higher than that in men. Traditional drug therapy for this disease has many disadvantages like poor bioavailability and degradation by gastrointestinal enzymes [1]. On the other hand, endoscopic retrograde cholangiopancreatography (ERCP) is a widely used medical procedure for the diagnosis of liver, bile duct, and pancreatic problems. Indomethacin is a drug of choice for the prevention of post-ERCP pancreatitis [2,3].

According to the biopharmaceutical classification system, indomethacin belongs to Class II drugs [4]; hence, it exhibits a fast absorption rate but lacks good solubility. The mechanism of action of indomethacin is well documented, and it is known that indomethacin acts as a non-selective cyclooxygenase (COX) inhibitor. Inhibition occurs in COX-1 and COX-2 isoforms. The COX-2 isoform is activated at inflammation sites, whereas the COX-1 isoform is constitutive and regulates normal body functions [5].

Rectal administration is recommended for patients who are unconscious, hesitate, vomit, or difficult to swallow. This route of administration avoids the first-pass effect or presystemic metabolism. However, low/variable absorption due to high interindividual variability has been documented [6]. An absolute bioavailability factor $f = 0.8$ was reported for rectal indomethacin administration [7].

To ensure acceptable biopharmaceutical quality in the post-marketing evaluation, dissolution studies are an adequate option to reveal differences in the release rate, which may prevent therapeutic failure. Some authors have reported the preparation of rectal formulations and their evaluation with *in vitro* release studies to improve drug absorption and therapeutic

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effects [8,9]. Indomethacin suppositories are commercially available as over-the-counter drugs.

The indomethacin suppository pharmacopeial dissolution test established a USP paddle apparatus (USP apparatus II) at an agitation rate of 50 rpm and 900 ml of phosphate buffer (0.1 M, pH 7.2). At 60 minutes, not less than 75% of the labeled amount is dissolved [10]. In addition, the mathematical management of dissolution data are a valuable tool for simulating plasma concentration-time profiles. Convolution is a well-known model-independent approach that helps simulate human performance. The hypothetical values of C_{max} and AUC_{0-inf} were calculated using *in vitro* data (as input functions) as well as pharmacokinetic parameter values of innovator drug products (as a weighted function) [11].

To date, no hypothetical plasma levels of indomethacin suppositories from dissolution data generated by the USP basket apparatus and flow-through cell method (USP apparatus IV) have been reported. The USP apparatus IV is a special device for testing rectal formulations manufactured with poorly water-soluble drugs. Some studies have shown good *in vitro*/*in vivo* correlation with dissolution data generated by the flow-through cell method [12,13]. Therefore, it is important to document the usefulness of this USP apparatus for simulating indomethacin *in vivo* performance using semisolid formulations.

The objective of this study was to predict the indomethacin plasma levels of all available suppositories from the local market. Hypothetical *in vivo* performance was calculated using the percentage of indomethacin dissolved obtained using USP apparatuses I and IV as well as pharmacokinetic parameters (elimination rate constant, volume of distribution, and bioavailability factor *f*) using a numerical convolution method. Results could be important in proposing better semisolid rectal formulations manufactured with indomethacin.

MATERIAL AND METHODS

Chemicals

Only two indomethacin semisolid rectal dosage forms (suppositories, 100 mg) available in the local market were used. The reference (classified as R drug product) and generic formulation (classified as G formulation) were tested. J.T.Baker High Performance Liquid Chromatography methanol (≥99.9%), AR sodium hydroxide (≥98%), AR sodium phosphate monobasic crystals (98%–102%), and sodium dodecyl sulfate (SDS) (≥99%) were acquired from a local supplier (Mexico). The indomethacin reference compound was acquired from Sigma-Aldrich Co. (purity 98.5%–100.5%, St. Louis, MO). In each experiment, five indomethacin solutions of known concentration (3.12–50 µg/ml) in phosphate buffer (0.1 M, pH 7.4) were prepared.

USP basket apparatus

The dissolution profiles of indomethacin suppositories were obtained using USP apparatus I (Sotax AT-7 Smart Model, Switzerland) at an agitation rate of 100 rpm. To quantify released indomethacin, spectrophotometric analysis was considered (Perkin Elmer spectrophotometer Lambda 35 Model, USA). The dissolved drug was calculated using a calibration curve with indomethacin standard solutions and UV absorbance determination at 318 nm. The formulations were added to 750 ml of phosphate buffer (0.1 M, pH 7.4). To improve *in vitro* release, the same medium was added with 1% SDS. The temperature of the dissolution medium was 37.0°C ± 0.5°C. The percentage of dissolved indomethacin was calculated every 5 over 60 minutes ($n = 12$) with the support of standard solutions (with or without 1% SDS).

Flow-through cell method

Indomethacin suppositories were tested using United States Pharmacopeia (USP) apparatus IV with specific dual chamber suppository cells (Sotax CE6 Model, Switzerland). As dissolution medium, phosphate buffer (0.1 M, pH 7.4) or phosphate buffer (0.1 M, pH 7.4) was added with 1% SDS and pumped at 16 ml/min. Dissolved indomethacin was calculated spectrophotometrically at the same sampling times as in the USP apparatus I experiments.

Data treatment

The dissolution profiles of indomethacin in the formulations were compared with model-independent and model-dependent methods. According to Equation 1, similarity factor f_2 was calculated. An f_2 value between 50–100 has been established to ensure the sameness of the two *in vitro* release curves [14]. In addition, the dissolution efficiency (DE), dissolved indomethacin level at 60 minutes (Q_{60}), and mean dissolution time (MDT) were determined. The f_2, MDT, and DE values were computed with the support of the add-in DDSolver [15]. Results were analyzed using Student's *t*-test. The mechanism of indomethacin release from suppositories was determined by fitting dissolution data with several mathematical equations. The following models were used: First-order, Makoid–Banakar, Korsmeyer–Peppas, Peppas–Sahlin, and Weibull. Fittings were computed using the add-in DDSolver [15]. To mathematically explain the *in vitro* release mechanism, the model that showed the highest adjusted determination coefficient ($R^2_{adjusted}$) and the lowest akaike information criterion (AIC) was selected as the best-fit model [16].

$$f_2 = 50 \cdot log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (1)$$

Here, n is the number of time points, and R_t and T_t are the dissolution values of the reference and test product at time t, respectively [14].

Hypothetical *in vivo* behavior

Dissolution profiles generated by both USP apparatuses and published pharmacokinetic information [7] were used to predict indomethacin *in vivo* behavior. A simple numerical convolution method was used [17]. The predicted plasma concentrations were fitted with a two-compartment open model using the add-in PKSolver [18]. Peak plasma concentration (C_{max}) and area under the curve from zero time to infinity (AUC_{0-inf}) were computed and related to observed pharmacokinetic parameters. The observed C_{max} (2.36 µg/ml) and AUC_{0-inf} (9.08 µgh/ml) were calculated after adjusting indomethacin

in vivo data [7]. The predictability of the convolution method was tested using the percentage of prediction error (%PE) for C_{max} and AUC_{0-inf}. The %PE was calculated using Equation 2 (suitable values should not exceed 10%) [19]. All calculations were performed using an Excel spreadsheet.

$$\%PE = \frac{(\text{observed value-predicted value})}{\text{observed value}} \times 100 \quad \textbf{(2)}$$

RESULTS AND DISCUSSION

Standard calibration curve

Indomethacin standard calibration curves in phosphate buffer (0.1 M, pH 7.4) with and without the addition of 1% SDS were linear in the range of 3.12–50 µg/ml. The linear regression results are shown in Figure 1. Both linear regressions were significant ($p < 0.05$).

In vitro release data

The indomethacin dissolution profiles of the R and G formulations are depicted in Figure 2. Both drug products exhibited different *in vitro* release performances. The release pattern of the R drug product remained consistent, regardless of the dissolution conditions. The G formulation showed high sensitivity to the hydrodynamic environment of both dissolution apparatuses, and a faster *in vitro* release was observed using the flow-through cell method. The addition of a surfactant did not appear to modify the release of indomethacin. The f_2 values are given in Table 1. In all cases, no similarity in dissolution profiles between the G and R formulations was observed ($f_2 < 50$).

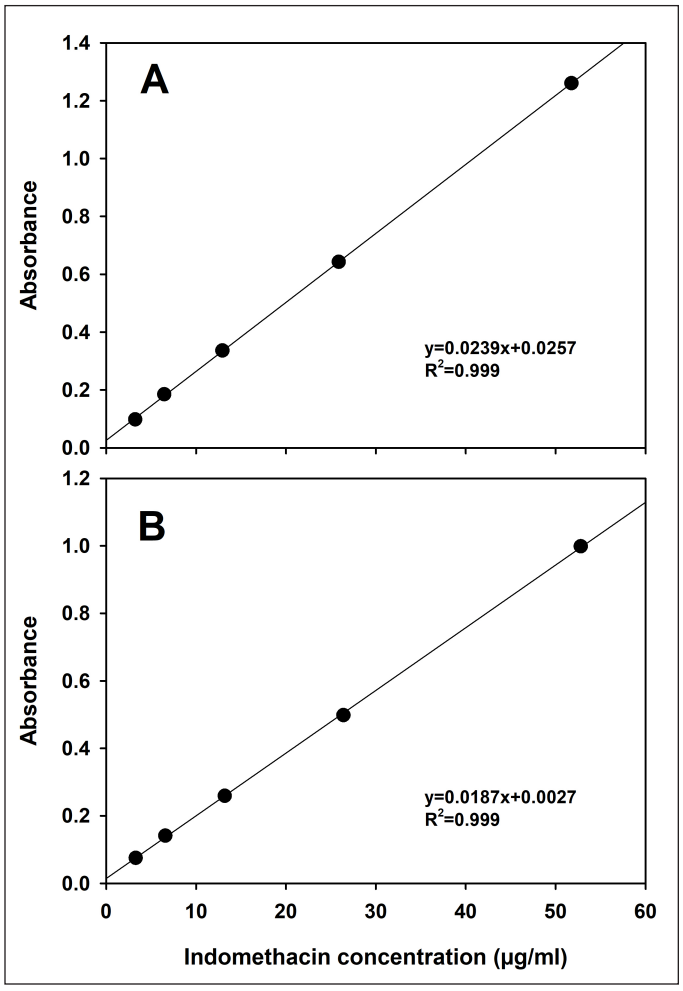

Figure 1. Standard calibration curves in phosphate buffer (0.1 M, pH 7.4) (A) without 1% SDS and (B) added with 1% SDS. Mean, $n = 3$.

Considering the use of surfactants, some authors have shown that three mechanisms are involved in the increase of drug release: improved wetting, solubilization, and the dissolution of soluble surfactants to form pores in the matrix [20]. On the other hand, several authors have found that indomethacin dissolution is faster in hydrophilic than in lipophilic suppositories. The distinction was more evident when the flow-through cell method was used [21]. Other authors stated that conventional USP apparatus I, paddle (II), or IV seem to be adequate for testing hydrophilic suppositories, while modified basket, modified paddle, or modified flow-through cell have been recommended for use with lipophilic suppositories [22]. In this study, only two commercially available pharmaceutical drug products were used, and information on the nature of the excipients or the manufacturing process is unknown. Both drug products showed a total difference in the *in vitro* release rate of the active ingredient, which suggests that one formulation is prepared with a hydrophilic base while the other with a lipophilic base. This assumption allows manufacturers to evaluate the impact of the nature of the drug based on indomethacin release and its repercussions on *in vivo* performance.

Results of dissolved indomethacin at the last sampling time (Q_{60}), MDT data, and DE values are presented in Table 1. All Q_{60}, DE, and MDT values of the G formulation differed significantly from the parameters of the R drug product in both USP dissolution apparatuses ($p < 0.05$). Considering the *in vitro* release behavior shown in Figure 2, these results were expected. Dissolution profile comparison using MDT data is a common approach and has been previously considered [23].

Our results are comparable with those of a study on sustained release of indomethacin suppositories. Experiments were carried out with USP apparatus I at 100 rpm and 900 ml of phosphate buffer (0.2 M, pH 7.2) as the dissolution medium. Control conventional suppositories released 98.43% ± 0.01% at 30 minutes [9], whereas in our work, the R drug product in the same USP apparatus but with dissolution media added with 1% SDS achieved 95.92 % at 60 minutes.

A study in which a continuous flow-through bead bed dissolution apparatus and rotating paddle method were used to test indomethacin suppositories (100 mg) from fatty and water-soluble bases was reported by some authors [24]. Polyethylene glycol water-soluble bases gave faster drug release rates compared to fatty bases, whereas the drug release rate from fatty bases increased significantly when a surface-active agent was present. On the other hand, the authors stated that the rotating paddle technique may be considered a suitable method for routine dissolution testing, but the continuous flow-through bead bed dissolution apparatus is more suitable for the experimental study of suppositories as this equipment

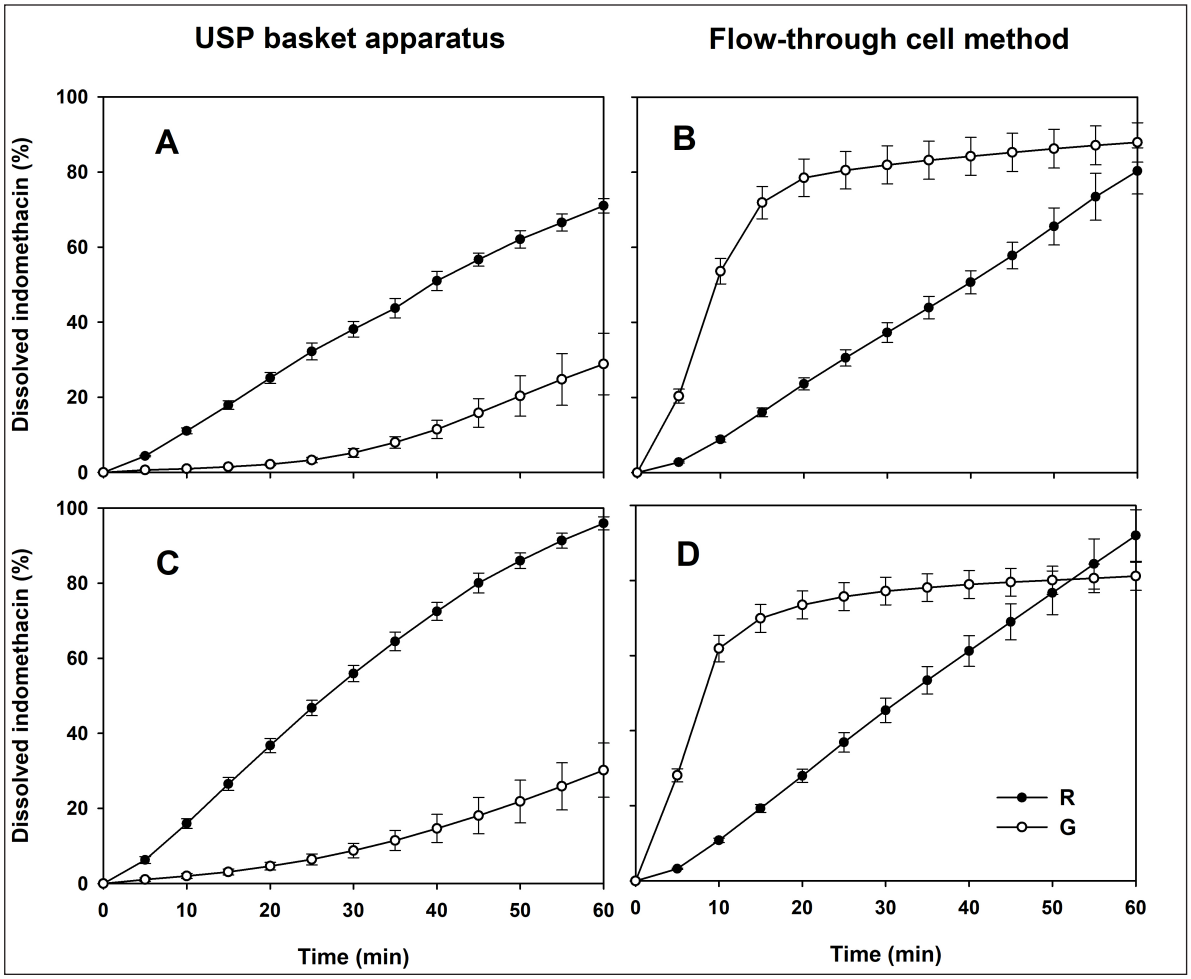

Figure 2. Dissolution profiles of indomethacin suppositories with phosphate buffer (0.1 M, pH 7.4). (A and B) Profiles where no 1% SDS was added. (C and D) Profiles with 1% SDS in dissolution medium. Reference (R) and generic (G) formulation. Mean ± SD, $n = 12$.

Table 1. Similarity factor f_2 and dissolution parameters. Mean ± SE medium, $n = 12$. *$p < 0.05$.

	USP basket apparatus		Flow-through cell method	
1% SDS	No	Yes	No	Yes
Reference drug product				
Q_{60} (%)	71.00 ± 0.55	95.92 ± 0.50	80.33 ± 1.77	91.99 ± 1.99
DE (%)	37.02 ± 0.42	52.53 ± 0.48	37.55 ± 0.61	44.53 ± 0.87
MDT (min)	28.72 ± 0.14	27.51 ± 0.17	31.89 ± 0.38	30.94 ± 0.17
Generic formulation				
f_2	25.32	16.53	22.06	26.26
Q_{60} (%)	28.85 ± 2.37*	30.19 ± 2.08*	87.92 ± 1.51*	81.14 ± 1.08*
DE (%)	9.04 ± 0.59*	11.08 ± 0.74*	71.40 ± 1.24*	68.67 ± 0.95*
MDT (min)	40.84 ± 0.51*	37.86 ± 0.55*	11.27 ± 0.11*	9.22 ± 0.23*

significantly prolongs the drug release rate from suppositories and with this method, a better correlation may be obtained with the *in vivo* absorption.

To document the mechanism of indomethacin release from suppositories, the dissolution data of both drug products were fitted with common mathematical models as previously described. Results of $R^2_{adjusted}$ and AIC are presented in Table 2.

All data generated by the R drug product in both hydrodynamic environments (with and without 1% SDS) and G formulation in the flow-through cell (with and without 1% SDS) were adjusted to the Weibull function. Data for G formulation of USP apparatus I (with and without 1% SDS) adjusted to Makoid–Banakar model. Adjustment of the dissolution data to the Weibull function emphasizes the S-shape of the dissolution profile while the Makoid–Banakar model becomes identical to the Korsmeyer–Peppas model when parameter k is zero. It follows the sole diffusion mechanism. The "n" function governs the shape of the dissolution curve [25].

The flow-through cell has shown better discriminatory capacity than other dissolution apparatuses in determining the *in vitro* release rate of drugs with limited solubility [26], so it is necessary to evaluate dissolution conditions like those observed in the human gastrointestinal tract. Several authors have found a meaningful correlation with data obtained using USP apparatus IV [13,27], and it is important to consider the details that led them to this conclusion, such as the physicochemical information of each active ingredient as well as data mathematical handling.

Table 2. Values of $R^2_{adjusted}$/AIC.

	USP basket apparatus		Flow-through cell method	
Buffer 0.1 M pH 7.4 + 1% SDS	No	Yes	No	Yes
Reference drug product				
First-order	0.9714/70	0.9419/88	0.9269/84	0.9183/90
Makoid-Banakar	0.9981/19	0.9996/11	0.9979/36	0.9993/28
Korsmeyer-Peppas	0.9951/47	0.9919/63	0.9967/43	0.9971/47
Peppas-Sahlin	0.9975/33	0.9975/47	0.9981/36	0.9996/20
Weibull	0.9980/18	0.9996/10	0.9980/34	0.9996/18
Generic formulation				
First-order	0.7882/72	0.8803/65	0.9175/86	0.7815/97
Makoid-Banakar	0.9963/19	0.9984/9	0.9632/79	0.9628/76
Korsmeyer-Peppas	0.9946/22	0.9959/17	0.8873/93	0.9044/87
Peppas-Sahlin	0.9945/23	0.9971/13	0.9530/82	0.9577/77
Weibull	0.9942/25	0.9894/29	0.9975/44	0.9999/–3

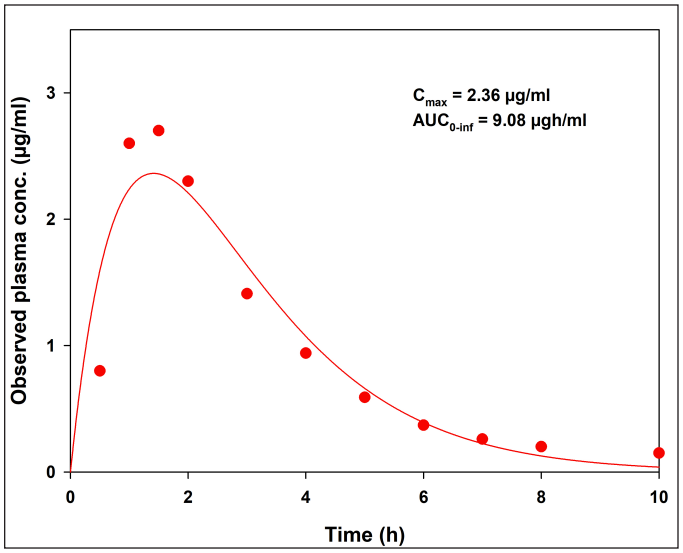

Figure 3. Indomethacin plasma concentrations fitted to a two-compartment open model with the add-in PKSolver. Observed data previously reported [7].

Training human resources in the collection of data obtained using the flow-through cell method and in the handling of the information generated by this equipment is necessary.

Simulation of plasma concentrations

To compare our results, data from an *in vivo* study [7] are presented in Figure 3. Indomethacin plasma concentrations were fitted to a two-compartment open model using the add-in PKSolver [18]. The observed C_{max} and $AUC_{0–inf}$ values are described in the same plot. After applying a convolution approach with, *in vitro* release data from both USP apparatuses and published pharmacokinetic information, the hypothetical *in vivo* behavior of indomethacin suppositories is shown in Figure 4.

Predicted human performances reflect the *in vitro* release behaviors generated by the hydrodynamic environment of both dissolution apparatus types. Values of predicted C_{max} and $AUC_{0–inf}$ are shown in Table 3. As comparative data, some authors have studied the bioavailability of indomethacin suppositories (100 mg). Four formulations were administered to healthy volunteers, and drug levels were quantified. The reported C_{max} and $AUC_{0–12h}$ for Indocid® formulation was 3.08 ± 0.96 (2.18–4.35) and 9.51 ± 4.06 (4.98–14.18) µgh/ml, respectively [28]. The PE values calculated to validate the convolution of dissolution data are presented in Table 3.

Only PE data <10% for the pharmacokinetic parameters C_{max} and $AUC_{0–inf}$ of the R drug product was achieved using the flow-through cell method. Since this USP apparatus generates a hydrodynamic environment similar to that found in the gastrointestinal tract, the mathematical transformation of the dissolution data of R formulation adequately simulates drug absorption and generates C_{max} and $AUC_{0–inf}$ values similar to an *in vivo* study (Fig. 3). If the R formulation of the reported human study has been manufactured without significantly changing the excipients or the manufacturing process, the PE values generated by the current *in vitro* data will be less than 10%. Appropriate conditions for evaluating the quality of indomethacin suppositories appear to be the use of USP apparatus IV at a flow rate of 16 ml/min and phosphate buffer (0.1 M, pH 7.4) without 1% SDS. To achieve comparable biopharmaceutical quality, multisource formulations should have dissolution profiles similar to those of R drug products under previously described *in vitro* conditions. In this regard, the concept of a bio-predictive dissolution tool can be used to estimate the human pharmacokinetic and support formulation design [29].

No hypothetical pharmacokinetic parameters calculated using dissolution data for the G formulation generated by the USP basket apparatus achieved PE values less than 10% (with or without 1% SDS). Therefore, in this case, USP apparatus I was not capable of generating *in vitro* release data that can be mathematically transformed into hypothetical concentrations like those reported in an *in vivo* study. These differences between the R and G formulations cannot be attributed to the convolution method, since it was applied in the same way to all data, nor to experimental variability, since the dissolution data comply with the variability allowed by international standards (coefficient of variation <20% at the earlier time points and <10% at other time points) [30]. The difference in the prediction of the drug's performance in the G formulation, considering the PE values of both pharmacokinetic parameters, agrees with the evident difference in the rate and extent of drug release from the pharmaceutical dosage form that contains it.

Some advantages of using USP apparatus IV as an alternative method to the vessels apparatuses (USP I and II) are: 1) it is possible to use it as an open system that can operate under *sink* conditions which facilitates the dissolution of poorly water-soluble drugs as well as changing the dissolution medium within a range of physiological pH throughout the test [31]. 2) The flow-through cell method has a continuous extraction of the drug, simulating the absorption

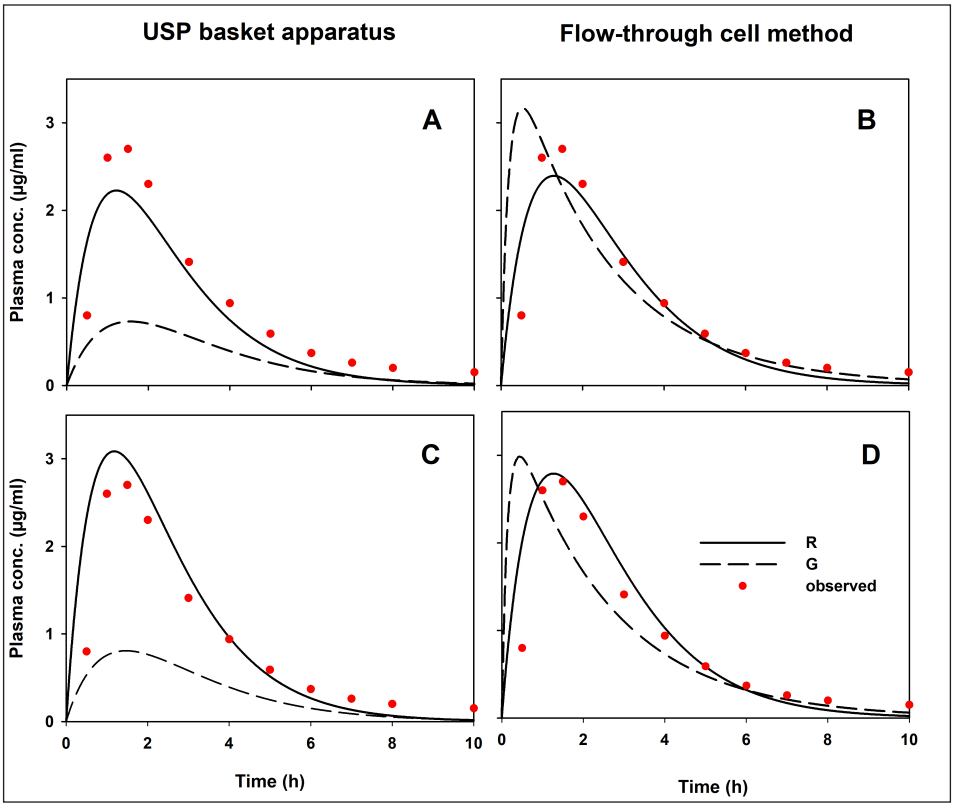

Figure 4. Hypothetical indomethacin plasma concentration-time profiles. (A and B) Profiles where no 1% SDS was added. (C and D) Profiles with 1% SDS in dissolution medium. Reference (R) and generic (G) formulation. Observed data previously reported [7].

Table 3. Hypothetical C_{max} and $AUC_{0\text{-}inf}$ values and PE for each parameter calculated with indomethacin dissolution data and published pharmacokinetic information.

	USP basket apparatus		Flow-through cell method	
1% SDS	No	Yes	No	Yes
Reference drug product				
C_{max} (µg/ml)	2.23	3.09	2.39	2.79
PE for C_{max} (%)	5.75	–30.61	–1.32	–18.18
$AUC_{0\text{-}inf}$ (µgh/ml)	7.39	9.92	8.46	9.67
PE for $AUC_{0\text{-}inf}$ (%)	18.66	–9.15	6.91	–6.41
Generic formulation				
C_{max} (µg/ml)	0.73	0.81	3.17	2.99
PE for C_{max} (%)	69.09	65.83	–34.16	–26.45
$AUC_{0\text{-}inf}$ (µgh/ml)	3.11	3.22	9.37	8.68
PE for $AUC_{0\text{-}inf}$ (%)	65.80	64.52	–3.19	4.47

into the systemic circulation generating an intermittent flow of the dissolution medium into the cell where the dosage form is placed [32] and 3) USP apparatus IV better simulates the hydrodynamic environment that is found inside the gastrointestinal tract [33].

The flow-through cell generally gives better results than the membrane-type dissolution apparatus; therefore, the flow-through cell could be useful for predicting *in vivo* concentration curves from *in vitro* dissolution curves [21]. The mathematical treatment of dissolution data by numerical convolution is simple and offers an easy way to design bioequivalent drug products in the development stage [11], facilitating the development of multi-source formulations with better *in vivo* performance. The use of a USP apparatus IV is suggested to test the *in vitro* release behavior of indomethacin in rectal dosage forms.

The rectal route of administration is recommended for unconscious patients, those who have difficulty swallowing a solid dosage form, and for small children. Post-marketing *in vitro* dissolution studies of rectal formulations are essential to monitor the main quality attributes of the pharmaceutical drug product because different storage conditions can modify the *in vitro* release rate and, therefore, the absorption and the timely manifestation of the therapeutic effect. In addition, previous reports have shown a good prediction of the pharmacokinetic parameters of drugs with solubility problems (oral dosage forms) using dissolution data from the USP apparatus IV [34,35].

Dissolution studies are currently available *in vitro* laboratory resources that allow the determination of the release process of the drug from the formulation to be administered. These resources have some advantages, such as the ease of obtaining data under circumstances similar to those of the body, as well as avoiding expenses for *in vivo* absorption studies. Some disadvantages of *in vivo* performance predictions from

dissolution data through mathematical calculations lie in inaccuracies due to variations in the pharmacokinetic data with which the calculations are generated or the scarcity of plasma data from a study in humans that allows validating the proposed predictions. In our study, no actual human data were freely available. In addition, the lack of training in data processing limits the widespread use of this type of prediction. One of the repercussions of this approach in humans is that these predictions do not consider the physiological conditions modified by diseases previously detected in patients; however, all changes in the formulations are made to improve absorption and promote the timely manifestation of the therapeutic effect.

The proposed simulations allow us to determine the appropriate *in vitro* conditions for evaluating the biopharmaceutical quality of indomethacin multisource rectal formulations through dissolution studies. Thus, these formulations can be safely interchangeable with reference drug products and can promote the development of therapeutic regimens at a low cost for patients.

CONCLUSION

Dissolution profiles of indomethacin rectal formulations were obtained in the hydrodynamic environment of USP apparatuses I and IV. After the experiments, similar *in vitro* release performance, regardless of the dissolution apparatus used and the addition of surfactant, was only obtained for the R drug product. For this formulation, values between 71% and 95% of the released drug were observed at 60 minutes. The best mathematical model to explain the drug-release mechanism is the Weibull function. On the other hand, the G formulation was more sensitive to the changes generated by the hydrodynamic environment and the addition of a surfactant. At 60 minutes, less than 29% of the dissolved drug (USP apparatus I without 1% SDS) and more than 81% (flow-through cell method with 1% SDS) were detected. The *in vitro* release of this formulation was better explained by the Makoid–Banakar model (USP apparatus I) and Weibull function (USP apparatus IV). Hypothetical plasma concentration-time profiles calculated with dissolution data of R drug product and a convolution approach produced C_{max} and AUC_{0-inf} values (2.39 and 8.46 µgh/ml, respectively), similar to those found in an *in vivo* study. Validation of this kind of prediction gave PE < 10% for both pharmacokinetic parameters. The flow-through cell method at 16 ml/min and phosphate buffer (0.1 M, pH 7.4) without 1% SDS were the best *in vitro* conditions to test multisource formulations given that dissolution data of R formulation and the convolution approach generated *in vivo* behavior as previously reported. Due to several characteristics of the flow-through cell method, especially hydrodynamic environment like that found in the gastrointestinal tract (generated by laminar flow and the design of the cell where the dosage form is placed), the production of *in vitro* data and their mathematical transformation in hypothetical *in vivo* behavior was easy to establish. Human studies with indomethacin suppositories are needed to confirm these findings.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the concept and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the revision to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declared that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript. No images were manipulated using AI.

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