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Prediction of *in vivo* performance of ibuprofen immediate-release products using different dissolution models

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ABSTRACT

This study explored the role of different compendial dissolution apparatuses in predicting the pharmacokinetic performance of ibuprofen (IBU) immediate-release (IR) commercial products. Dissolution studies of 200 mg IBU IR tablets of Brufen® (Abbott, Egypt), Nurofen® (Reckitt Benckiser Healthcare, Belgium), and Advil® (Pfizer, USA) were carried out employing the United States Pharmacopeia (USP) I, II, and IV models. Comparison of dissolution profiles was carried out using fit factors, mean dissolution time, and dissolution efficiency. Prediction of *in vivo* plasma concentration–time profile from *in vitro* data was carried out by back-calculation of the Wagner–Nelson approach. *In vitro/in vivo* correlation (IVIVC) was verified between the predicted and actual pharmacokinetic parameters with an estimation of prediction error (PE%). USP II and IV met the accepted dissolution criterion (80% of the label dissolved in 60 minutes) for all IBU IR products, while USP I failed. All commercial tablets showed dissimilar dissolution profiles in all studied models, except Advil versus Nurofen in USP IV. The best IVIVC (R^2 values ≥ 0.99 and intercept values close to zero) were observed for Advil in USP II and IV as well as Brufen and Nurofen in USP IV. Accepted PE% values in terms of C_{max} and AUCs were achieved for all products in USP IV. The USP IV dissolution model was utilized as a predictive tool for *in vivo* performances of IBU IR products especially during early product development and, hence, might be adopted as a surrogate for conducting clinical bioequivalence studies.

INTRODUCTION

Dissolution testing of oral solid dosage forms has been employed for several decades for developing new drug products and formulation and/or process development and ensuring batch-to-batch quality, consistency, and final product performance (Bredael *et al*., 2015). Moreover, it serves as a tool for determining long-term stability, shelf life, and impact of postapproval changes during the manufacturing process of a specific drug product (Khan *et al*., 2013).

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In vitro dissolution testing serves as a powerful means to predict *in vivo* behavior of drug products. The procedures of connecting *in vitro/in vivo* release profiles are regularly recognized as *in vitro/in vivo* correlation (IVIVC). The main goal of an IVIVC is to help as a surrogate for *in vivo* bioavailability and/or to support biowaiver (Emara *et al*., 2000; Taha *et al*., 2020). Hence, instead of costly and time-consuming *in vivo* trials, a suggestive dissolution methodology could be a safe alternative to predict whether pharmaceutical dosage forms are equivalent or not (Hashem *et al*., 2019).

The correlation of dissolution results with bioavailability data remains a subject of debate, with intense activity in the pharmaceutical field being considered for establishing satisfactory quantitative correlations. Several drugs were tested for successful IVIVC, e.g., ibuprofen (IBU). (Tamilvanan and Sa, 2006), domperidone (Bose and Wui, 2013), aprepitant and donepezil (Chakraborty *et al*., 2014), and glyburide (Wei and Löbenberg, 2006). The ability of a certain dissolution testing model to estimate

actual *in vivo* behavior is quite complex, and further investigations on a case-by-case basis are needed to confirm the robustness of the suggested *in vitro* approach.

In the 1970s, the basket method [United States Pharmacopeia (USP) apparatus I] and paddle method (USP apparatus II) were adopted as official quality control (QC) dissolution tests. These dissolution models usually employ simple experimental conditions, which do not reflect the actual *in vivo* situation. However, in the 1990s, the flow-through cell dissolution model (FTC) was introduced as the official USP apparatus IV (Todaro *et al*., 2017). The FTC method has gained recent acceptance into the dissolution world for its advantages over traditional methods (basket and paddle). It is possible to maintain sink conditions; the intraluminal hydrodynamics are more efficiently simulated, making the development of IVIVC easier, especially for poorly soluble drugs. Therefore, FTC is more reliable, reproducible, and discriminative than other methods (Emara *et al*., 2009, 2014b; Forrest *et al*., 2018).

IBU, a chiral nonsteroidal anti-inflammatory drug, is recommended to treat moderate and acute pain. It probably ranks after acetaminophen and paracetamol as nonprescriptive over-the-counter drugs. The normal daily (IR) oral dose ranges from 200 to 600 mg every 6 hours. IBU bioavailability is over 80% after oral administration (Higgins *et al*., 2001), and its biological half-life is 2 hours (Rainsford, 2009). IBU is classified according to the Biopharmaceutics Classification System as a Class II drug, which exhibits low solubility and good permeability characteristics; thus, its absorption depends on dissolution (Reddy and Karunakar, 2011). Therefore, employing a well-designed *in vitro* dissolution test that mimics the gastrointestinal physiology allows for a reliable IVIVC (Emara *et al*., 2000).

The USP recommends performing dissolution testing for IBU IR tablets in a compendial paddle apparatus (USP II) at 50 rpm, using 900 mL of phosphate buffer media of pH 7.2 (USP-32, 2009), with few studies published in the literature assessing the dissolution performance of IBU products worldwide (Chevalier *et al*., 2009; Medina *et al*., 2017; Lu and Fassihi, 2017).

The main objective of the present investigation was to assess the importance of different *in vitro* compendial dissolution models in developing IVIVC for IBU IR commercial products (tablets) obtained from Egyptian (Brufen®, Abbott), European (Nurofen®, Reckitt Benckiser Healthcare), and American (Advil®, Pfizer) markets. In order to figure out the early dissolution of IBU, a multipoint sampling scheme was conducted, instead of a single point analysis stated by USP, using the USP I, II, and IV models. The deconvolution approach, employing the back-calculation of the Wagner–Nelson (WN) method, was utilized for estimating the *in vivo* pharmacokinetic parameters. The predicted drug plasma concentration–time profiles calculated from dissolution results were compared with the actual C_{max} and AUCs parameters obtained from well-authenticated published literature to come to terms with the ideal USP model which could accurately predict IBU *in vivo* performance.

MATERIALS AND METHODS

Materials

Pure IBU powder was donated by Sigma Pharma, Egypt. Potassium dihydrogen orthophosphate and sodium hydroxide pellets were obtained from Rasayan Laboratories, India. Methanol and acetonitrile (HPLC grade, Prolabo, France) were used for the preparation of stock solutions. Purified Milli-Q water (Millipore Corp., Billerica, MA) was used for the preparation of the dissolution medium.

IBU IR commercial products (each contains 200 mg IBU/tablet):

Brufen® tablets (Abbott, Egypt) (Batch No. 04228), excipients composition, as listed: "starch corn, magnesium stearate, opaglos regular (NA-7150), acacia, sucrose, calcium sulfate, sodium CMC, opalux pink as-1537, hard paraffin, talcum powder, and opacode S-1-2779 black."

Advil® tablets (Pfizer, USA) (Batch No. CJ3334), excipients composition, as listed: "acetylated monoglycerides, colloidal silicone dioxide, corn starch, croscarmellose sodium, methylparaben, microcrystalline cellulose, pharmaceutical glaze, pharmaceutical ink, povidone, pregelatinized starch, propylparaben, sodium benzoate, sodium lauryl sulfate, stearic acid, sucrose, synthetic iron oxide, titanium dioxide, and white wax."

Nurofen® tablets (Reckitt Benckiser Healthcare, Belgium) (Batch No. JJ060), excipients composition, as listed: "sucrose, sodium citrate, talc, croscarmellose sodium, stearic acid, titanium dioxide, silicon dioxide, acacia, carmellose sodium, sodium lauryl sulfate, marcogol, and black ink [contains shellac, iron oxide black (E172), and propylene glycol]."

Methods

Characterization of IBU IR commercial products

Full tablet characterization was carried out using a 3-in-1 hardness, diameter, and thickness tablet tester (Sotax-MT 50 MultiTest 50, Switzerland). The uniformity of weight for each product was calculated using electric balance. The mean of 20 tablets for each product was calculated.

Content uniformity

The assay of IBU in different IR commercial products was assessed by the UV spectrophotometric method (DU–650 UV-Vis Spectrophotometer, Beckman, USA) at λ_{max} of 221 nm (Emara *et al*., 2014a). Briefly, 20 tablets of each product were weighed and ground, and the weight equivalent to one tablet was dissolved in methanol, then vortexed, and filtered (Millex, 0.45 um). The filtrate was diluted with phosphate buffer of pH 7.2 and analyzed for drug content.

Comparative in vitro dissolution studies of IBU products

In vitro dissolution (n = 6) of IBU IR commercial products (200 mg IBU/tablet) was carried out in filtered, degassed 900 mL phosphate buffer of pH 7.2 (as recommended by USP, USP-32, 2009) at 37°C ± 0.2°C employing the three compendial dissolution apparatuses as described below:

USP I (basket) and USP II (paddle, pharmacopeial) methods

IBU dissolution profiles were determined in an automated dissolution USP apparatus I (basket method) and USP apparatus II (paddle method) dissolution tester (AT8-Xtend, Sotax, Switzerland), with a rotation speed of 50 rpm and an autocontrolled multichannel pump employed.

USP IV (flow-through cell) method

IBU dissolution profiles were carried out in the FTC, USP apparatus IV (Dissotest CE-6 equipped with a CY 7-50 piston pump, Sotax, Switzerland). In all experiments, a tablet was loaded in the 22.6 mm dissolution cell, with a ruby bead located at the cone entry and no glass beads present to ensure a turbulent flow pattern. Built-in filtration of 0.7 µm Whatman glass microfiber, followed by GF/F and GF/D and then glass wool, was employed, with pump speed set at 8 ± 0.2 ml/minute.

For all dissolution testing, samples were withdrawn from dissolution media at predetermined time intervals and replaced with fresh media. Collected samples were analyzed spectrophotometrically at λ_{max} of 221 nm against a blank buffer (Emara *et al*., 2014a).

Comparison and analysis of in vitro dissolution data

An independent model was applied for comparison among different dissolution profiles of IBU IR commercial products.

The model-independent approaches provide a direct comparison of dissolution profiles. Fit factors (f_1 and f_2) (Moore and Flanner, 1996), mean dissolution time (MDT) (Costa and Lobo, 2001), and dissolution efficiency (DE) (Emara *et al*., 2014b) were employed.

Fit factors

The difference factor f_1 evaluates the percentage difference between the two curves: f_1 values ranging from 0 to 15 indicate similar dissolution profiles, while values >15 indicate dissimilar profiles, according to the following equation:

$$f_1 = \sum_{t=1}^{n} [R_t - T_t] / \sum_{t=1}^{n} R_t] \times 100,$$

where R_t and T_t represent the percent of drug dissolved for reference and test, respectively, at each sample point t and n is the number of time intervals.

On the other hand, the similarity factor f_2 is a measurement of the similarity of any two dissolution curves according to the following equation:

$$f_2 = 50 \times \log \{[1 + (1/n \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}.$$

f_2 values ranging from 50 to 100 indicate similar dissolution profiles, while values ≤50 indicate dissimilar dissolution profiles (Costa and Lobo, 2001; Moore and Flanner, 1996; Shah *et al*., 1997). As stated by the FDA guidelines, f_1 and f_2 values of ≤15 and ≥50, respectively, ensure equivalence in the dissolution profiles (Shah *et al*., 1997).

Mean dissolution time (MDT)

MDT was calculated, as described by Costa and Lobo (2001), as follows:

$$MDT = \sum_{j=1}^{n} [t^{\wedge}_{j} \Delta M_j] / \sum_{j=1}^{n} \Delta M_j,$$

where j represents sample number, n is the number of dissolution sample times, $t^{\wedge}_{j}$ represents the time at the midpoint between t_j and t_{j-1}, and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1}.

Dissolution efficiency (DE)

Percent dissolution efficiency (%DE) was also calculated to evaluate the relative performance of IBU IR commercial products (Emara *et al*., 2014b). The value of %DE at 60 minutes ($\%DE_{60}$) for each tablet was quantified as % ratio of area under the dissolution curve till 60 minutes relative to the area of the rectangle defined by 100% dissolution at the same time, as follows:

$$\%DE = [AUC_{0\text{-}60} / Q_{100.t}] \times 100.$$

Statistical significance was determined for MDT and $\%DE_{60\ minutes}$ using Student's t-test in the comparison between means of two groups. Data analysis was carried out using SPSS software (version 17.0). Differences were considered significant when $p < 0.05$.

Prediction of in vivo plasma response

The deconvolution approach was employed for the prediction of IBU *in vivo* plasma response. The *in vitro* dissolution data of different IBU IR commercial products, in different USP apparatuses, were converted into predicted plasma concentration–time curves, based on the back-calculation of the WN equation (Ostrowski *et al*., 2010), according to the following equation:

$$C_{(t+1)} = [(2 \times \Delta F_{\alpha} \times f \times D / V_d) + C_{(t+1)} \times (2 - K_e \times \Delta t)] / 2 + K_e \times \Delta t$$

where D is dose, $\Delta F_a = F_{a(t+1)} - F_{a(t)}$, and $\Delta t = t_{(t+1)} - t_{(t)}$.

Validity of prediction

FDA guidance specifies the importance of assessment of internal and/or external predictability/validity as a requirement for the employment of IVIVC models for official regulatory submissions (Ostrowski *et al*., 2010).

The %prediction error (PE%) for $AUC_{0\text{-}t}$ and C_{max} was calculated according to the following equation:

%PE = [Observed Parameter – Predicted parameter) / Observed Parameter] × 100.

The IVIVC model is assumed to be valid if %PE is equal to or less than 10, while %PE between 10% and 20% suggests inconclusive predictability, which requires additional data. %PE greater than 20% indicates inadequate or lack of predictability/ validity of the IVIVC model (Ostrowski *et al*., 2010).

RESULTS AND DISCUSSION

Tablet characterization

Table 1 shows the tablet characterization and drug content for IBU products. The three IBU products (200 mg IBU/ tablet) under investigation showed acceptable weight variations, thickness, diameter, and hardness characteristics. The content uniformity of all IBU products met the assay specifications in the

Table 1. Tablet characterization and content uniformity of IBU commercial products (200 mg/tablet). Data represent mean ± SD (n = 20).

IBU product	Average weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Drug content (%)
Brufen (Abbott, Egypt)	470.46 ± 9.48	5.96 ± 0.13	11.21 ± 0.02	48 ± 1.73	96.26 ± 1.73
Advil (Pfizer, USA)	476.46 ± 2.32	6.06 ± 0.05	11.29 ± 0.01	50 ± 3.00	98.6 ± 0.66
Nurofen (Reckitt Benckiser Healthcare, Belgium)	421.56 ± 10.51	5.66 ± 0.08	10.41 ± 0.03	58.33 ± 2.08	97.83 ± 0.50

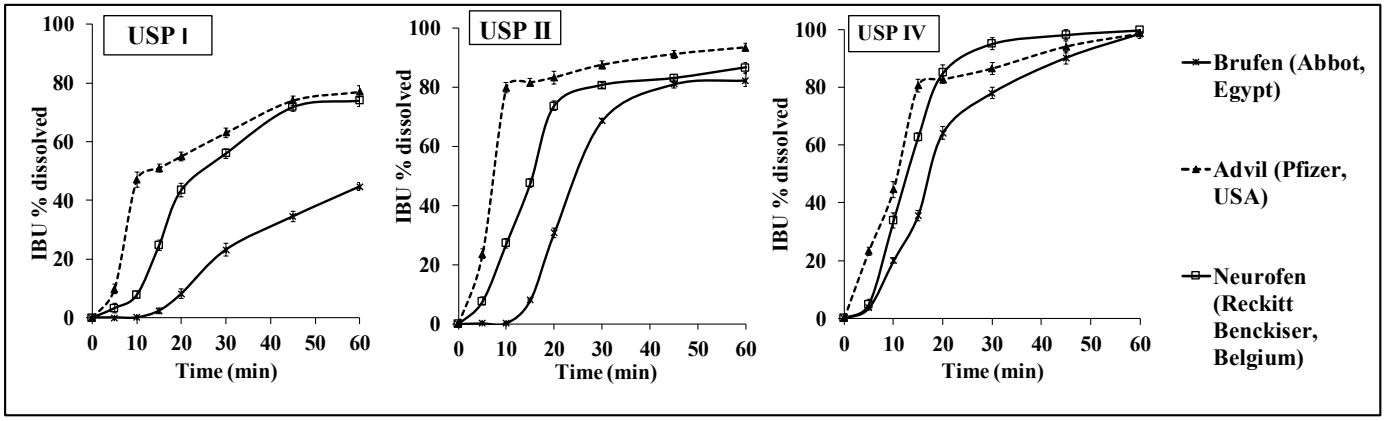

Figure 1. Dissolution profiles of IBU IR commercial products (200 mg) employing different USP models in phosphate buffer of pH 7.2 at 37°C. Data represent mean ± SD (n = 6).

USP, where the percentages of IBU were between 90 and 110% (USP-32, 2009).

In vitro dissolution results

Figure 1 shows the dissolution profiles of IBU products using different dissolution models (USP I, USP II, and USP IV). Table 2 presents IBU multipoints percent dissolved along the 60-minutes dissolution.

As evident from Figure 1 and Table 2, the dissolution of IBU was highly influenced by different dissolution models employed and the manufacturing sites and/or excipient compositions exhibited by various IBU products.

As shown in Figure 1, upon employing the USP I model (basket method), all products showed the lowest percentage of IBU dissolved. Table 2 shows that $Q_{60\ minutes}$ ranged from 45% to 76%.

However, upon employing the USP II model (paddle method, the official dissolution model), all IBU products complied with the pharmacopeial dissolution criterion [not less than 80% (Q) of IBU dissolved within 60 minutes] (USP-32, 2009). As observed in Table 2, Advil showed the fastest dissolution profile [80% (Q) in 10 minutes], followed by Nurofen [80% (Q) in 30 minutes], which might result in a rapid onset of action (Emam *et al*., 2020).

These vast differences in the dissolution patterns among IBU IR products in USP I and USP II could be attributed to the fact that the hydrodynamic environment below the basket in USP I is not as well mixed as that of the paddle in USP II (Todaro *et al*., 2017), which might cause the product to stick to the basket mesh, hence affecting the dissolution uniformity. In addition, the high agitation force exhibited by the paddle shaft in USP II could cause the higher dissolution of IBU in this model when compared to USP I (Hashem *et al*., 2019).

On the other hand, Figure 1 and Table 2 show that upon using the USP IV model (FTC method), all IBU products gave fast dissolution results, where more than 80% of IBU dissolved at 30 minutes with the lowest SD values indicating higher reproducibility and uniformity. Previously (Yoshida *et al*., 2016), the FTC method proved to mimic ideal hydrodynamic conditions for homogenous and mild agitation in contrast to other dissolution models (basket and paddle). FTC uses a piston pump that produces a sinusoidal or semisinusoidal flow, which in turns allows a continuous, uniform flow of the dissolution medium around the dosage form that mimics the natural environment in the GIT (Medina *et al*., 2017), in addition to maintaining perfect sink conditions which is important for the *in vitro* dissolution study of poorly soluble drugs such as IBU (Emara *et al*., 2014b; Forrest *et al*., 2018).

A previous study compared the *in vitro* dissolution performance of two IBU generic suspensions available in Mexico against the reference (Advil® suspension, 2 g/100 ml), employing both the USP II and IV models (Medina *et al*., 2017). They concluded that the FTC method under the proposed setup (i.e., open system, 22.6 mm cells, laminar flow pattern at a flow rate of 16 ml/min) was suitable for studying the *in vitro* dissolution of

Table 2 Percent IBU dissolved after 5 ($Q_{5\ minutes}$), 10 ($Q_{10\ minutes}$), 15 ($Q_{15\ minutes}$), 30 ($Q_{30\ minutes}$), and 60 ($Q_{60\ minutes}$) minutes from IR products in different dissolution models. Data represent mean ± SD (n = 6).

Dissolution model	IBU product	% IBU dissolved				
		$Q_{5\ minutes}$	$Q_{10\ minutes}$	$Q_{15\ minutes}$	$Q_{30\ minutes}$	$Q_{60\ minutes}$
USP I (basket method)	Brufen	0.01 ± 0.00	0.04 ± 0.00	2.35 ± 1.52	23.17 ± 4.07	44.71 ± 3.48
	Advil	9.83 ± 2.65	47.05 ± 3.56	57.59 ± 3.41	72.56 ± 5.43	76.01 ± 5.82
	Nurofen	3.28 ± 3.43	7.78 ± 3.02	24.67 ± 2.99	55.32 ± 4.91	75.21 ± 6.32
USP II (paddle method)	Brufen	0.19 ± 0.4	0.23 ± 0.7	8.07 ± 0.53	68.70 ± 0.6	82.39 ± 2.19
	Advil	23.63 ± 1.61	80.86 ± 3.21	81.51 ± 3.11	87.49 ± 3.28	93.39 ± 3.37
	Nurofen	7.63 ± 3.42	27.21 ± 4.55	47.56 ± 2.59	80.69 ± 3.98	86.64 ± 3.19
USP IV (FTC method)	Brufen	3.56 ± 0.77	19.91 ± 0.99	35.63 ± 1.98	82.06 ± 0.92	98.57 ± 1.67
	Advil	23.25 ± 1.9	44.56 ± 0.78	76.62 ± 0.88	86.54 ± 0.37	98.60 ± 1.55
	Nurofen	4.89 ± 1.3	33.81 ± 1.65	62.74 ± 1.02	95.13 ± 0.68	99.84 ± 0.87

Table 3. Fit factors' values comparing the dissolution profiles of IBU commercial products in each dissolution model.

Dissolution model	IBU products[a]	Fit factors	
		f_1	f_2
USP I (basket method)	Advil # Brufen	79	11
	Advil # Nurofen	57	30
	Nurofen # Brufen	57	31
USP II (paddle method)	Advil # Brufen	50	18
	Advil # Nurofen	25	31
	Nurofen # Brufen	49	32
USP IV (FTC method)	Advil # Brufen	29	35
	Advil # Nurofen	11	50
	Nurofen # Brufen	23	42

[a]Advil tablets (Pfizer, USA), Brufen tablets (Abbott, Egypt) and Nurofen tablets (Reckitt Benckiser Healthcare, Belgium).

IBU suspensions. They recommended carrying out future *in vivo* studies to estimate the proposed dissolution methodology (Medina *et al*., 2017).

Lu and Fassihi studied the dissolution of commercial IBU IR 200 mg tablets available in the United States using both apparatuses (USP I and II) in phosphate buffer pH 7.2 at rotation speeds of 50 and 100. Their results confirmed comparable dissolution profiles among the studied IBU products in both USP models, proposing the capability of apparatus interchangeability (Lu and Fassihi, 2017).

Comparative evaluation of *in vitro* dissolution data

Table 3 shows the fit factor values (f_1 and f_2) upon comparing the dissolution profiles of IBU products with each other in each dissolution model. Fit factors data showed dissimilar dissolution profiles of IBU products employing USP I and II models. For USP IV, only Advil and Nurofen exhibited similar dissolution profiles (with f_1 and f_2 values of 11 and 50, respectively).

From another perspective, Table 4 shows the values of the fit factors comparing the dissolution profiles of each IBU product upon employing different dissolution models with each other. Fit factors' data revealed dissimilar dissolution profiles for each IBU product among the three USP methods.

Overall results concluded from Tables 3 and 4 emphasize that varying the *in vitro* dissolution testing model, and variations related to changes in the manufacturing sites and/or formulation differences within the tested products, led to the changes in dissolution profiles of IBU products.

In addition to fit factors, Table 5 presents the MDT and DE at 60 minutes (%$DE_{60\ minutes}$) mean values for comparing dissolution profiles of IBU products in different dissolution models. Significant differences were found in MDT and %$DE_{60\ minutes}$ values ($p< 0.05$) for all IBU products using the USP I, II, and IV models.

Prediction of IBU *in vivo* plasma concentration-time profile from *in vitro* data

Inspection of the above dissolution results showed the possibilities of generating IVIVC for the three commercial products due to the effect seen upon changing the dissolution model employed as well as product manufacturing site and/or formulation variables.

Table 4. Fit factors' values comparing dissolution profiles of each IBU commercial product using different dissolution models.

IBU product	USP dissolution models[a]	Fit factors	
		f_1	f_2
Brufen (Pfizer, USA)	I # II	58	28
	I # IV	71	19
	II # IV	30	37
Advil (Abbott, Egypt)	I # II	31	37
	I # IV	20	42
	II # IV	9	45
Nurofen (Reckitt Benckiser Healthcare, Belgium)	I # II	43	37
	I # IV	41	27
	II # IV	16	47

[a]USP I: basket method; USP II: paddle method; USP IV: FTC method.

Table 5. Dissolution parameters calculated with mean dissolution time (MDT) and dissolution efficiency at 60 minutes ($\%DE_{60\ minutes}$). Data represent mean ± SD (n = 6).

Dissolution model	IBU product	$\%DE_{60\ minutes}$	MDT (minute)
USP I (basket method)	Brufen	20.26 ± 0.7	32.81 ± 0.2
	Advil	62.87 ± 0.1	12.53 ± 0.8
	Nurofen	44.89 ± 0.5	25.38 ± 0.5
USP II (paddle method)	Brufen	49.44 ± 0.2	24.02 ± 0.7
	Advil	78.5 ± 0.1	9.57 ± 0.4
	Nurofen	64.2 ± 0.2	15.53 ± 0.3
USP IV (FTC method)	Brufen	64.09 ± 0.8	20.99 ± 0.7
	Advil	76.14 ± 0.8	13.38 ± 0.7
	Nurofen	75.94 ± 0.1	14.37 ± 0.4

For the establishment of the IVIVC approach, simple spreadsheet software was employed for data calculation and conversion, with the *in vitro* dissolution data used as the input function. The actual PK data of the IBU IR commercial product (200 mg) were obtained from a previously published study (Shin *et al*., 2017), where the bioavailability of the IBU IR tablet (Brufen, 200 mg) was investigated in 36 healthy human volunteers under fasting conditions. The maximum observed plasma concentration (C_{max}) was 24.1±4.10 mg/L. The area under the plasma concentration–time curve $AUC_{0\text{-}12}$ and $AUC_{0\text{-}\infty}$ were 79.60 ± 13.90 and 80.70 ± 15 mg.hour/L, respectively. These data were used for IVIVC purposes.

Figure 2 shows the corresponding predicted IBU plasma concentrations for the three commercial products in the USP I, II, and IV apparatuses. The observed results indicated that drug *in vitro* input data variations were well reflected on the predicted *in vivo* profiles. The observed high predicted plasma profiles for the IBU commercial products in USP II and IV were well reflected with their corresponding *in vitro* results, where more than 80% of the drug was dissolved within 60 minutes (Figures 1 and 2). On the other hand, USP I represented a scenario in which less than 80% of the drug dissolved (Figure 1), which was well reflected in the *in vivo* results (Figure 2).

Figure 3 shows IVIVC models plotted between the predicted plasma concentrations in different dissolution apparatuses against actual plasma concentrations obtained from (Shin *et al*., 2017) to determine which USP model provided the best correlation with the *in vivo* results. The suggested *in vitro/in vivo* relationships are described by linear regression and presented by R^2, slope, and intercept, with the results tabulated in Table 6.

Good correlation, with R^2 values ≥ 0.96, could be observed for all IBU products in the USP II and IV models (Figure 3 and Table 6). The best IVIVC models with R^2 values ≥ 0.99 and intercept values close to zero were observed in the following cases: Advil product in the USP II and IV models as well as Brufen and Nurofen in the USP IV model.

Validation of the IVIVC

Table 7 presents predicted pharmacokinetic parameters, C_{max}, $AUC_{0\text{-}12}$, and $AUC_{0\text{-}\infty}$ and the percentages prediction error (%PE), of the IBU IR products in the studied USP models. In

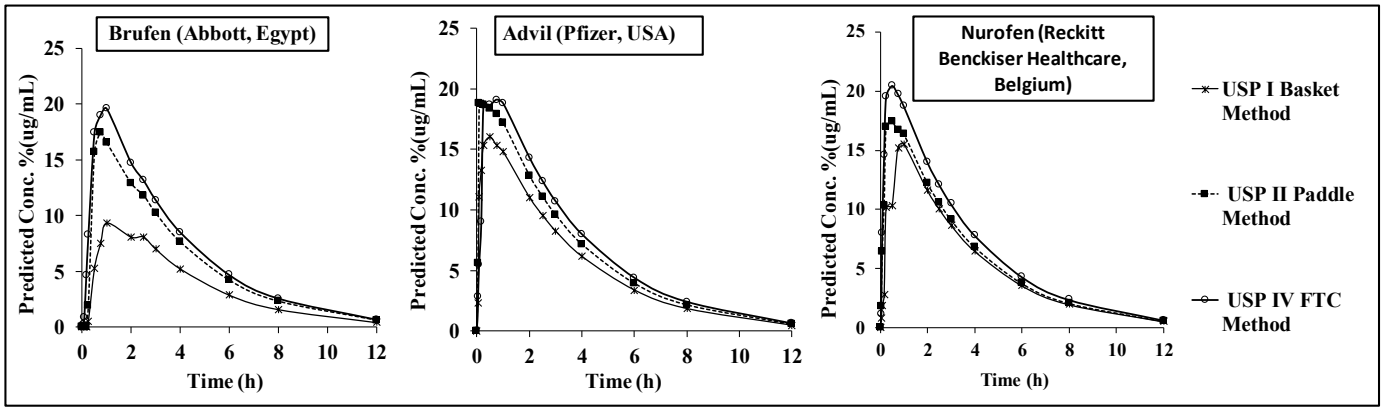

Figure 2. Plasma profiles of IBU IR commercial products in different dissolution models predicted by back-calculation of the Wagner-Nelson method. Results are presented as mean ± SD (n = 6).

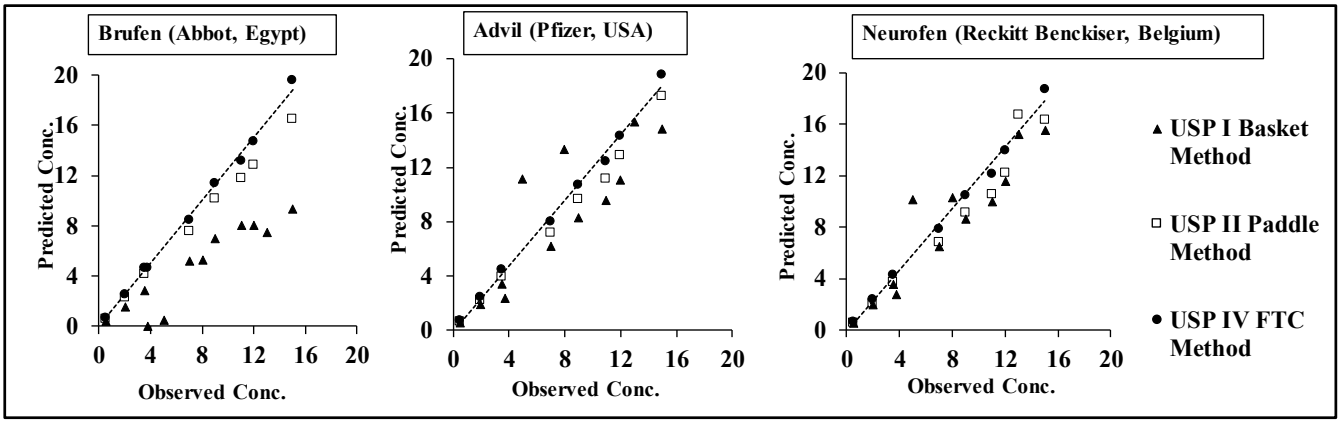

Figure 3. Predicted concentration against observed concentration for IBU IR commercial products using deconvolution approach, dotted lines represent the best linear regression for each IBU product.

the USP I dissolution model, the %PE between the actual and predicted C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$ values were >20% for the three commercial products (Table 7), which is indicative of the lack of validity of the suggested IVIVC model (Ostrowski *et al*., 2010).

On the other hand, in the USP II dissolution model, %PE regarding C_{max} values was >20%. However, %PE of AUC_{0-12} and $AUC_{0-\infty}$ values for Brufen and Nurofen ranged from 10.72 to 13.03%, indicating inconclusive validation, and hence, additional data is preferably needed. Only the Advil product exhibited %PE values of 6.21% and 5.22% for AUC_{0-12} and $AUC_{0-\infty,}$ respectively (Table 7).

Yet, upon employing the USP IV model, %PE regarding C_{max} values were 10%–20%; also, %PE for AUC_{0-12} and $AUC_{0-\infty}$ were ≤10%, which met the US-FDA acceptance limit (i.e., the ideal IVIVC model is assumed if %PE equals or is less than 10) (Ostrowski *et al*., 2010). Low prediction error values observed for the USP IV dissolution model strongly confirm the validity of the IVIVC model and its predictive ability to estimate IBU *in vivo* performance from IR commercial products.

It is worth mentioning that the FDA requirements for IR products focus on a single-point sampling approach, where a single sample at one specified time point (60 minutes) is required to meet an acceptance criterion (≥80% Q). This approach is usually employed for QC purposes. Yet, such an approach is not appropriate during product and/or method development stages or minor changes of excipients after product approval, which should be better reflected by the multipoint sampling approach (Zhang *et al*., 2007). Hence, for a more discriminating dissolution method and reducing the incidence of unexpected results, multiple sampling time points and sample withdrawals are preferred (Zhang *et al*., 2007).

The present study outlined the differences observed among commercially available IBU products during the early, mid, and late stages of dissolution employing different USP dissolution models. Both USP II and IV succeeded as single-point dissolution assays in yielding around 80% of IBU dissolved in 60 minutes. However, actual differences related to formulation variables or changing manufacturing sites were better explained by sampling at several discrete time points.

Table 6. The obtained R^2, slope, and intercept values for the IVIVC models applied for IBU commercial products.

Dissolution model	IBU product	Linear regression parameters for IVIVC models		
		R^2	Slope	Intercept
USP I (basket method)	Brufen	0.871	0.688	−0.479
	Advil	0.761	0.982	0.801
	Nurofen	0.873	1.009	0.505
USP II (paddle method)	Brufen	0.999	1.077	0.19
	Advil	0.992	1.098	−0.154
	Nurofen	0.964	1.119	−0.391
USP IV (FTC method)	Brufen	0.996	1.257	−0.019
	Advil	0.995	1.209	−0.103
	Nurofen	0.993	1.195	−0.168

Table 7. Predicted pharmacokinetics parameters and percentage prediction error (%PE) of IBU IR commercial product (200 mg) in different USP dissolution models. Actual PK parameters were obtained from Shin *et al*. (2017).

	Predicted PK parameters					
	C_{max} (µg/ml)		AUC_{0-12} (µg.hour/ml)		$AUC_{0-\infty}$ (µg.hour/ml)	
Dissolution model	Predicted C_{max}	PE%	Predicted AUC_{0-12}	PE%	Predicted $AUC_{0-\infty}$	PE%
USP I						
Brufen	9.35	61.2	43.7	45.1	45.01	44.21
Advil	16.03	33.48	63.53	20.18	65.08	19.35
Nurofen	15.51	35.64	62.07	22.02	63.69	21.07
USP II						
Brufen	17.44	27.63	70.13	11.89	72.04	10.72
Advil	18.83	21.86	74.66	6.2	76.48	5.22
Nurofen	17.38	27.88	69.23	13.02	70.94	12.08
USP IV						
Brufen	19.99	17.05	80.56	−1.2	82.69	−2.47
Advil	19.11	20.7	79.88	−0.35	81.88	−1.47
Nurofen	20.45	15.14	79.8	−0.25	81.76	−1.31

To date, the ability of a certain dissolution model to predict the bioavailability of commercial products is still under investigation. The present study pointed out the ability of the FTC model (USP IV) to simulate more adequately the *in vivo* performance of IBU and hence could reflect the bioavailability of the drug from IR tablets. The effective use of such a simple predictive approach could support in saving valuable resources in terms of budgets and increased costs associated with drug development within pharmaceutical industries.

CONCLUSION

The discriminatory power of different compendial dissolution models on IBU release behavior from IR commercially available products was established, with dissolution curves comparison carried out using a model-independent approach. Also, the back-calculation of the Wagner–Nelson method was tested for establishing the IVIVC between IBU *in vitro* data in different dissolution models and previously well-authenticated drug *in vivo* performance. Based on the results, the dissolution of IBU tablets (200 mg) was highly influenced by different dissolution models employed and the manufacturing sites and/or formulation variables among IR products available in different markets. The FTC method (USP IV) provided the highest IVIVC with *in vivo* pharmacokinetic data of the IBU IR commercial products. The dissolution criteria suggested could be utilized to develop an *in vitro* approach that would be predictive of drug products *in vivo* behavior and hence might serve as a surrogate for carrying out clinical bioequivalence studies for IBU IR tablets.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception 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

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