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

Fatma Abdelfattah¹*, Nesrin Taha¹, Aya Abdou¹, Nadia Mursi², Laila Emara¹

¹Industrial Pharmacy Laboratory, Medicinal and Pharmaceutical Chemistry Department, Pharmaceutical and Drug Industries Research Institute, National Research Centre (Affiliation ID: 10014618), 33 EL Bohouth St. (Former EL Tahrir st.), Dokki, Giza, P.O.12622, Egypt.
²Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

**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 (R² 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 Cmax 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).

*Corresponding Author
Fatma Abdelfattah, Industrial Pharmacy Laboratory, Medicinal and Pharmaceutical Chemistry Department, Pharmaceutical and Drug Industries Research Institute, National Research Centre (Affiliation ID: 10014618), 33 EL Bohouth St. (Former EL Tahrir st.), Dokki, Giza, 12622, Egypt. E-mail: fatma.m.saied21@gmail.com

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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 Fasshi, 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 silicon 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, t alc, 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 (Milllex, 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 (f1 and f2) (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 f1 evaluates the percentage difference between the two curves; f1 values ranging from 0 to 15 indicate similar dissolution profiles, while values >15 indicate dissimilar profiles, according to the following equation:

\[ f_1 = \frac{\sum_n (R_t - T_t)}{\sum_n R_t} \times 100, \]

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 f2 is a measurement of the similarity of any two dissolution curves according to the following equation:

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

f2 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, f1 and f2 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:

\[ \text{MDT} = \frac{\sum_{j=1}^{n} (t_j \Delta M_j)}{\sum_{j=1}^{n} \Delta M_j}, \]

where j represents sample number, n is the number of dissolution sample times, t_j represents the time at the midpoint between t 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:

\[ \% \text{DE} = \left[ \frac{\text{AUC}_{0-60}}{\text{Q}_{100}} \right] \times 100. \]

Statistical significance was determined for MDT and %DE_{60} 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:

\[ C_{p(t+1)} = \left(2 \times \Delta F_a \times f \times D / V \right) + C_{p(t+1)} \times \left(2 - K_e \times \Delta t\right) \]

\[ / 2 + K_e \times \Delta t, \]

where D is dose, ΔF_a is F_{a(t+1)} - F_{a(0)} and Δt = 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_{64} and C_{max} was calculated according to the following equation:

\[ \% \text{PE} = \left[ \frac{\text{Observed Parameter} - \text{Predicted parameter}}{\text{Observed Parameter}} \right] \times 100. \]

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

Table 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
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 $Q_{60 \text{ minutes}}$ 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 1.** Tablet characterization and content uniformity of IBU commercial products (200 mg/tablet). Data represent mean ± SD ($n = 20$).

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

**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 ($n = 6$).
Abdelfattah et al. / Journal of Applied Pharmaceutical Science 12 (08); 2022: 193-201

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

<table>
<thead>
<tr>
<th>Dissolution model</th>
<th>IBU product</th>
<th>Q$_{5\text{ minutes}}$</th>
<th>Q$_{10\text{ minutes}}$</th>
<th>Q$_{15\text{ minutes}}$</th>
<th>Q$_{30\text{ minutes}}$</th>
<th>Q$_{60\text{ minutes}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP I (basket method)</td>
<td>Brufen</td>
<td>0.01 ± 0.00</td>
<td>0.04 ± 0.00</td>
<td>2.35 ± 1.52</td>
<td>23.17 ± 4.07</td>
<td>44.71 ± 3.48</td>
</tr>
<tr>
<td></td>
<td>Advil</td>
<td>9.83 ± 2.65</td>
<td>47.05 ± 3.56</td>
<td>57.59 ± 3.41</td>
<td>72.56 ± 5.43</td>
<td>76.01 ± 5.82</td>
</tr>
<tr>
<td></td>
<td>Nurofen</td>
<td>3.28 ± 3.43</td>
<td>7.78 ± 3.02</td>
<td>24.67 ± 2.99</td>
<td>55.32 ± 4.91</td>
<td>75.21 ± 6.32</td>
</tr>
<tr>
<td>USP II (paddle method)</td>
<td>Brufen</td>
<td>0.19 ± 0.4</td>
<td>0.23 ± 0.7</td>
<td>8.07 ± 0.53</td>
<td>68.70 ± 0.6</td>
<td>82.39 ± 2.19</td>
</tr>
<tr>
<td></td>
<td>Advil</td>
<td>23.63 ± 1.61</td>
<td>80.86 ± 3.21</td>
<td>81.51 ± 3.11</td>
<td>87.49 ± 3.28</td>
<td>93.39 ± 3.37</td>
</tr>
<tr>
<td></td>
<td>Nurofen</td>
<td>7.63 ± 3.42</td>
<td>27.21 ± 4.55</td>
<td>47.56 ± 2.59</td>
<td>80.69 ± 3.98</td>
<td>86.64 ± 3.19</td>
</tr>
<tr>
<td>USP IV (FTC method)</td>
<td>Brufen</td>
<td>3.56 ± 0.77</td>
<td>19.91 ± 0.99</td>
<td>35.63 ± 1.98</td>
<td>82.06 ± 0.92</td>
<td>98.57 ± 1.67</td>
</tr>
<tr>
<td></td>
<td>Advil</td>
<td>23.25 ± 1.93</td>
<td>44.56 ± 0.78</td>
<td>76.62 ± 0.88</td>
<td>86.54 ± 0.37</td>
<td>98.60 ± 1.55</td>
</tr>
<tr>
<td></td>
<td>Nurofen</td>
<td>4.89 ± 1.3</td>
<td>33.81 ± 1.65</td>
<td>62.74 ± 1.02</td>
<td>95.13 ± 0.68</td>
<td>99.84 ± 0.87</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dissolution model</th>
<th>IBU products$^a$</th>
<th>Fit factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$f_1$</td>
</tr>
<tr>
<td>USP I (basket method)</td>
<td>Advil # Brufen</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Advil # Nurofen</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Nurofen # Brufen</td>
<td>57</td>
</tr>
<tr>
<td>USP II (paddle method)</td>
<td>Advil # Brufen</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Advil # Nurofen</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Nurofen # Brufen</td>
<td>49</td>
</tr>
<tr>
<td>USP IV (FTC method)</td>
<td>Advil # Brufen</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Advil # Nurofen</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Nurofen # Brufen</td>
<td>23</td>
</tr>
</tbody>
</table>

$^a$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$_{60\text{ minutes}}$) mean values for comparing dissolution profiles of IBU products in different dissolution models. Significant differences were found in MDT and %DE$_{60\text{ minutes}}$ 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.
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 ($C_{\text{max}}$) was 24.1±4.10 mg/L. The area under the plasma concentration–time curve $AUC_{0-12}$ and $AUC_{0-\infty}$ 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, $C_{\text{max}}$, $AUC_{0-12}$, and $AUC_{0-\infty}$ and the percentages prediction error (%PE), of the IBU IR products in the studied USP models. In
the USP I dissolution model, the %PE between the actual and predicted $C_{\text{max}}, \text{AUC}_{0-12}$, and $\text{AUC}_{0-\infty}$ 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 $C_{\text{max}}$ values was >20%. However, %PE of $\text{AUC}_{0-12}$ and $\text{AUC}_{0-\infty}$ 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 $\text{AUC}_{0-12}$ and $\text{AUC}_{0-\infty}$, respectively (Table 7).

Yet, upon employing the USP IV model, %PE regarding $C_{\text{max}}$ values were 10%–20%; also, %PE for $\text{AUC}_{0-12}$ and $\text{AUC}_{0-\infty}$ 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.
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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Table 6. The obtained $R^2$, slope, and intercept values for the IVIVC models applied for IBU commercial products.

<table>
<thead>
<tr>
<th>Dissolution model</th>
<th>IBU product</th>
<th>Linear regression parameters for IVIVC models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$R^2$</td>
</tr>
<tr>
<td>USP I (basket method)</td>
<td>Brufen</td>
<td>0.871</td>
</tr>
<tr>
<td></td>
<td>Advil</td>
<td>0.761</td>
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<tr>
<td></td>
<td>Nurofen</td>
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<tr>
<td>USP II (paddle method)</td>
<td>Brufen</td>
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<tr>
<td></td>
<td>Advil</td>
<td>0.992</td>
</tr>
<tr>
<td></td>
<td>Nurofen</td>
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</tr>
<tr>
<td>USP IV (FTC method)</td>
<td>Brufen</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td>Advil</td>
<td>0.995</td>
</tr>
<tr>
<td></td>
<td>Nurofen</td>
<td>0.993</td>
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</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Dissolution model</th>
<th>Predicted $C_{\text{max}}$ (µg/ml)</th>
<th>PE%</th>
<th>Predicted $AUC_{0-12}$ (µg.hour/ml)</th>
<th>PE%</th>
<th>Predicted $AUC_{0-\infty}$ (µg.hour/ml)</th>
<th>PE%</th>
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<tr>
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<td></td>
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<tr>
<td>Brufen</td>
<td>9.35</td>
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<td>43.7</td>
<td>45.1</td>
<td>45.01</td>
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<td>33.48</td>
<td>63.53</td>
<td>20.18</td>
<td>65.08</td>
<td>19.35</td>
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<tr>
<td>Nurofen</td>
<td>15.51</td>
<td>35.64</td>
<td>62.07</td>
<td>22.02</td>
<td>63.69</td>
<td>21.07</td>
</tr>
<tr>
<td>USP II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brufen</td>
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<td>70.13</td>
<td>11.89</td>
<td>72.04</td>
<td>10.72</td>
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<tr>
<td>Advil</td>
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<td>21.86</td>
<td>74.66</td>
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<tr>
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<td>79.8</td>
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<td>81.76</td>
<td>−1.31</td>
</tr>
</tbody>
</table>
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