Dissolution Performance of Verapamil-HCl Tablets Using USP Apparatus 2 and 4: Prediction of In Vivo Plasma Profiles

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ABSTRACT

This study aimed to examine the in vitro dissolution performance of verapamil-HCl reference tablets using USP apparatus 2 (paddle), apparatus 4 (flow-through cell), and media of physiological relevance, and to estimate plasma levels using a convolution approach. The study used apparatus 2 at 50 rpm and apparatus 4 at 16 mL/min. Solutions of 0.1 N HCl, acetate buffer (pH 4.5), and phosphate buffer (pH 6.8) were used as dissolution media. UV quantification of the drug at 278 and 300 nm was registered after 30 min of dissolution. In vitro release was evaluated by model-independent and model-dependent methods. Mean dissolution time (MDT), dissolution efficiency (DE), t_{50%}, and t_{63.2%} were calculated and statistically compared. The percent of dissolved drug was fitted with first-order, Korsmeyer-Peppas, Makoid-Banakar, Weibull, Logistic, and Gompertz models; Makoid-Banakar and Gompertz were the best-fit equations used to explain drug release. In vivo performance of verapamil-HCl tablets was predicted using apparatus 4 to mimic in vivo plasma concentrations of the drug in humans.

KEYWORDS: Convolution, flow-through cell, USP apparatus 2, USP apparatus 4, verapamil-HCl, dissolution

INTRODUCTION

Verapamil is a derivative of papaverine, belonging to a class of medications known as calcium channel blockers (1). It is prescribed to treat arrhythmia and high blood pressure and to control angina pectoris (2). Verapamil works by dilating blood vessels, increasing blood flow and oxygenation to the heart, and decreasing the electrical activity of the heart to control heart rate (3). It is a highly absorbed drug, with more than 90% of an orally administered dose absorbed (4). Despite this, its bioavailability is only 20–30% due to its extensive first-pass metabolism (5). It is also a highly variable drug; its apparent volume of distribution is about 2.5 L/kg, peak plasma concentrations are reached within 1–2 h following oral administration, and it has a relatively short half-life (2.8–5 h) (5–7).

Information about verapamil-HCl solubility, permeability, pKa, pharmacokinetic properties, and other property data has been collected, but discrepancies exist (7). Verapamil-HCl has been classified as a class I drug, but some authors have placed it on a list of compounds with inconclusive data (class I/II drug) (4, 8). High (82–11 mg/mL) or low (0.44–0.025 mg/mL) solubility has also been reported depending on the degree of acidity of the surrounding environment (7).

The official dissolution test for verapamil-HCl tablets is described in the United States Pharmacopoeia (USP) (9). The method indicates the use of USP apparatus 2 (paddle) at 50 rpm with 900 mL of 0.01 N HCl at 37.0 ± 0.5 °C as dissolution medium (Q not less than 75% at 30 min). To date, no in vitro/in vivo correlation (IVIVC) has been reported that considers pharmacopeial conditions. On the other hand, the biowaiver monograph for verapamil-HCl tablets provides guidelines for carrying out in vitro studies that allow in vivo studies to be avoided (7).
To suggest a biowaiver based on the Biopharmaceutics Classification System (BSC) for class I drugs, several conditions must be fulfilled; in particular, the drug (test and reference) must rapidly dissolve and the product must not contain any excipient that will affect the rate or extent of absorption (10). An immediate-release product is considered rapidly dissolving when a mean of 85% or more of the drug dissolves within 30 min when using apparatus 2 at 50 rpm in 900 mL at pH 1.2, 4.5, and 6.8 (10).

USP apparatus 1 (basket) and apparatus 2 (paddle) are currently the most popular methods to carry out dissolution studies. Both apparatus operate under closed finite sink conditions; however, they cannot mimic the hydrodynamic environment of the gastrointestinal (GI) tract (11). Because of its characteristics, USP apparatus 4 (flow-through cell) is better suited to estimate the in vivo performance of certain formulations (12, 13). Comparative in vitro dissolution studies of verapamil-HCl tablets using apparatus 4 vs. apparatus 1 or 2 are scarce.

This study aimed to evaluate the in vitro dissolution of verapamil-HCl reference tablets under the hydrodynamic environments generated by apparatus 2 and 4 at pH 1.2 (0.1 N HCl), pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer). Additionally, the dissolution results will be used to predict in vivo plasma profiles of verapamil-HCl utilizing a convolution strategy to assess which method is most promising for mimicking the in vivo performance of verapamil in humans.

MATERIALS AND METHODS
Reagents and Chemicals
Verapamil-HCl tablets (Dilacoran 40 mg, Abbott Laboratories, Mexico City, Mexico) were used. Mexican health authorities have established this commercial brand as the reference product for dissolution and bioequivalence studies (14). HCl, CH₃OH, CH₃COONa, H₂PO₄⁻ and HPO₄²⁻ were acquired from J. T. Baker-Mexico (Xalostoc, Mexico). Verapamil-HCl standard was acquired from Sigma-Aldrich Co. (St. Louis, MO, USA).

Absorption Spectrum
To verify the maximum dissolution of verapamil-HCl in pH 1.2 (0.1 N HCl), pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer), a drug solution of 50 µg/mL was prepared in each medium, and an ultraviolet (UV) spectrophotometer (Lambda 35, Perkin Elmer, USA) was used to measure the absorbance at 200–350 nm.

Validation
Linearity
According to ICH guidelines, three standard curves of verapamil-HCl were prepared in each solution (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) (15). From a methanol stock solution (1 mg/mL), standard solutions of 10, 30, 50, 75, and 100 µg/mL of the drug were prepared at each pH. Absorbances measured at 278 and 300 nm were recorded, and differences in absorbance (278–300 nm) were fitted vs. drug concentration by linear regression. Absorbance differences at these wavelengths have been suggested by the USP 42 (9).

Accuracy and Precision
Twenty tablets were accurately weighed and crushed in a mortar. Powdered verapamil-HCl tablets were added to a quantity of verapamil-HCl standard (10 mg) to give the equivalent of 80, 100, and 120% of the dose, which was dissolved in 900 mL of 0.1 N HCl acid at 37.0 ± 0.5 °C. USP Apparatus 2 was used at 50 rpm to dissolve the drug. After 30 min, the amount of verapamil-HCl dissolved in each vessel (n = 3) was calculated with the standard calibration curve in 0.1 N HCl. The relative error (%RE) was used as a measure of accuracy and the relative standard deviation (%RSD) was used as a measure of precision.

Solution Stability
Solution stability was evaluated using two solutions of verapamil-HCl in 0.1 N HCl (20 and 80 µg/mL). The solutions were analyzed at 0 h at 25 °C and 24 and 48 h after storage at either 4 or 25 °C. At each temperature after 24 and 48 h, the absolute difference (%AD) was calculated.

Uniformity of Dosage Units and Assay
Uniformity of dosage units and assay were performed according to the procedures described in the USP 42 (9).

Dissolution Profiles
Dissolution profiles of verapamil-HCl tablets were obtained using a paddle apparatus 2 (Sotax AT7-Smart, Sotax AG, Switzerland) at 50 rpm with 900 mL of 0.1 N HCl, pH 4.5 acetate buffer, or pH 6.8 phosphate buffer at 37.0 ± 0.5 °C (n = 6). Additionally, verapamil-HCl tablets were tested with a flow-through cell apparatus 4 (Sotax CE6, Sotax AG) at a flow rate of 16 mL/min using 22.6 mm cells (internal diameter). Laminar flow was used. Dissolution samples were taken at 5, 10, 15, 20, and 30 mins using glass fiber filters (1.0 µm, Millipore). The amount of verapamil-HCl dissolved was determined by UV spectrophotometry at 278 and 300 nm.

Data Analysis
Dissolution profiles of verapamil-HCl in apparatus 2 vs 4 were evaluated using different comparison methods. For model-independent comparisons, the in vitro release at 30 min (Q₃₀), the area under the cumulative dissolution
curve (AUCC), percent of dissolution efficiency (%DE), and mean dissolution time (MDT) were calculated and statistically compared with a student’s t-test. Significant differences were defined as $p < 0.05$. For model-dependent comparisons, in vitro results were adjusted to the hyperbola model. With $a$ and $b$ parameters, $t_{50\%}$ and $t_{63.2\%}$ values were obtained. Dissolution data were adjusted to different mathematical equations (first-order, Korsmeyer-Peppas, Makoid-Banakar, Weibull, logistic, and Gompertz). The model with the highest determination coefficient ($R_2^2$) and the lowest Akaike information criterion (AIC) was chosen as the best-fit model (16). Data analysis was carried out using the Excel add-in, DDSolver program (17).

**Prediction of In Vivo Plasma Profiles**

In vitro dissolution data can be manipulated to predict the in vivo behavior of verapamil-HCl in humans through a simple numerical convolution method created by Qureshi using an MS Excel spreadsheet (18). The method uses reported pharmacokinetic parameters of verapamil such as bioavailability factor ($F$), elimination rate constant ($k_e$), and volume of distribution ($V_d$) to construct plasma drug concentration-time profiles (7, 19). Using this, pharmacokinetic parameters such as peak concentration ($C_{max}$), time to reach peak concentration ($T_{max}$), and area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) were predicted and calculated from profiles by a non-compartmental method (20). Detailed calculations were performed as detailed below (18).

The in vitro dissolution profile was divided into separate parts where the amount of drug (mg) dissolved within each sampling interval was estimated ($X = \text{drug dissolved/ strength } \times 100$). After that, the latter was corrected for $F$, and the observed amount of drug in blood was calculated ($X_{\text{corrected}} = \text{amount of drug [mg] released within sampling interval } \times F$). Finally, blood concentrations (ng/mL) equivalent to the total amount of verapamil-HCl in blood at different times after ingestion of a tablet were calculated using Equation 1.

\[
\text{Total amount of drug in blood after absorption at time } t = \frac{X_{\text{corrected}}}{V_d \times \text{body weight}} \times 100 \quad \text{Eq. (1)}
\]

The reported data for the concentration-time profile and pharmacokinetic parameters of the reference drug product Isoptin (80-mg verapamil-HCl) were used to establish the predictability of the convolution method, which was established by the calculation of the mean absolute percent of prediction error (%PE) for $C_{max}$ and $AUC_{0-\infty}$ according to Equation 2 (where %PE should not exceed 15%) (19, 21–23).

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

**RESULTS AND DISCUSSION**

**Ultraviolet Spectra**

The UV spectra of verapamil-HCl dissolved in 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer were very similar, with maximum measurement found at 278 nm in all cases; at 300 nm, a very small measurement was found (almost zero).

**Validation Linearity**

The equations of standard solutions of verapamil-HCl in 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer were $y = 0.0111x + 0.019$ ($R^2 = 0.9997, p < 0.05$), $y = 0.0115x - 0.0038$ ($R^2 = 0.9996, p < 0.05$), and $y = 0.0119x + 0.005$ ($R^2 = 0.9999, p < 0.05$), respectively.

**Accuracy and Precision**

After 3 days of experiments, the %RSD was found to range from 0.36% to 0.91%, and the %RE was lower than 1.3%.

**Solution Stability**

At 4 °C and 25 °C, the %AD values were less than 0.86% after 24 h and 48 h of storage, suggesting good stability of verapamil-HCl in solution under all tested storage conditions.

**Uniformity of Dosage Units and Assay**

Verapamil-HCl tablets were within USP limits. The average ± %RSD of 10 verapamil-HCl tablets in uniformity of dosage unit tests was 101.04 ± 2.31% (85–115% is the USP limit); in assay test with three samples the result was 99.81 ± 0.22% (90–110% being the USP limit) (9).

**Dissolution Profiles**

Dissolution profiles of verapamil-HCl tablets are shown in Figure 1, and profile comparisons are given in Table 1. Verapamil-HCl tablets were more than 85% dissolved within 15 min using both dissolution apparatuses when 0.1 N HCl was used as the dissolution medium. This indicates a very rapid in vitro release of the drug at pH 1.2 regardless of the apparatus used; however, use of the flow-through cell (apparatus 4) affected the rate and extent of verapamil-HCl dissolution, as the drug dissolved considerably slower. When the paddle method (apparatus 2) was used, MDT, $t_{50\%}$, and $t_{63.2\%}$ were significantly lower compared with the flow-through cell ($p < 0.05$); the extent of drug dissolution, represented by $Q_{30}$ and AUCC, was also significantly less ($p < 0.05$). For apparatus 4, $Q_{30}$ and
AUCC values were 89.45% and 2285.0%·min, respectively, compared to 94.14% and 2339.9%·min with apparatus 2, respectively; additionally, the overall DE was slightly lower in the flow-through cell compared to the paddle apparatus ($p < 0.05$).

Drug dissolution in pH 4.5 acetate buffer was faster when using the flow-through cell compared to the paddle. The reference tablets released 96.12% of drug within 30 min compared to 75.6% with the paddle method ($p < 0.05$). This was further confirmed by AUCC values (Table 1). The rate of drug dissolution was faster for apparatus 4 as indicated by $t_{63.2\%}$ at 4:12 min:sec vs 7:10 for apparatus 2. A significantly higher overall DE was found with apparatus 4 at pH 4.5 compared to apparatus 2.

Given the limited solubility of verapamil-HCl at higher pH, dissolution testing at pH 6.8 was more discriminative, as the solubility of the drug is only 11 mg/mL (7). Release of verapamil-HCl from reference tablets was less than 85% at 30 mins in both dissolution apparatuses; only 78.93% and 82.53% of the drug dissolved with apparatus 2 and 4, respectively. The flow-through cell method resulted in significantly slower dissolution of verapamil-HCl compared to the paddle method.

Overall, significant differences in dissolution parameters were found beyond MDT and $t_{50\%}$ at pH 4.5 and $Q_{30}$ at pH 6.8. At least 85% of the drug dissolved within 15 min in both dissolution apparatuses at pH 1.2, but only with the apparatus 4 at pH 4.5. When pH 6.8 phosphate buffer was used, less than 85% of drug was released at 30 mins in both apparatuses. Therefore, verapamil-HCl reference tablets do not meet the biowaiver criterion established for class I drugs. The dissolution rate of verapamil-HCl was lowered by increased pH in the flow-through cell, whereas the opposite was true in the paddle apparatus; this may be attributed to the different hydrodynamic conditions generated by each apparatus.

### Table 1. Dissolution Parameters of Verapamil-HCl Tablets

<table>
<thead>
<tr>
<th>pH</th>
<th>Parameter</th>
<th>USP Apparatus 2</th>
<th>USP Apparatus 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUCC (%·min)</td>
<td>2339.9 ± 19.0</td>
<td>2285.0 ± 12.5*</td>
</tr>
<tr>
<td>1.2</td>
<td>DE (%)</td>
<td>78.00 ± 0.63</td>
<td>76.17 ± 0.42*</td>
</tr>
<tr>
<td></td>
<td>MDT (min:sec)</td>
<td>5:08 ± 0:12</td>
<td>4:27 ± 0:06*</td>
</tr>
<tr>
<td></td>
<td>$t_{50%}$ (min:sec)</td>
<td>2:17 ± 0:09</td>
<td>1:40 ± 0:08*</td>
</tr>
<tr>
<td></td>
<td>$t_{63.2%}$ (min:sec)</td>
<td>3:540 ± 0:15</td>
<td>3:02 ± 0:13*</td>
</tr>
<tr>
<td>4.5</td>
<td>AUCC (%·min)</td>
<td>1904.6 ± 52.2</td>
<td>2427.1 ± 52.0*</td>
</tr>
<tr>
<td></td>
<td>DE (%)</td>
<td>63.49 ± 1.74</td>
<td>80.91 ± 1.73*</td>
</tr>
<tr>
<td></td>
<td>MDT (min:sec)</td>
<td>4:48 ± 0:10</td>
<td>4:43 ± 0:42</td>
</tr>
<tr>
<td></td>
<td>$t_{50%}$ (min:sec)</td>
<td>4:25 ± 0:16</td>
<td>3:26 ± 0:24</td>
</tr>
<tr>
<td></td>
<td>$t_{63.2%}$ (min:sec)</td>
<td>7:10 ± 1:06</td>
<td>4:12 ± 0:37*</td>
</tr>
<tr>
<td>6.8</td>
<td>AUCC (%·min)</td>
<td>2043.6 ± 64.1</td>
<td>1844.1 ± 19.2*</td>
</tr>
<tr>
<td></td>
<td>DE (%)</td>
<td>68.12 ± 2.13</td>
<td>61.47 ± 0.64*</td>
</tr>
<tr>
<td></td>
<td>MDT (min:sec)</td>
<td>4:06 ± 0:24</td>
<td>7:39 ± 0:12*</td>
</tr>
<tr>
<td></td>
<td>$t_{50%}$ (min:sec)</td>
<td>1:26 ± 0:22</td>
<td>6:03 ± 0:12*</td>
</tr>
<tr>
<td></td>
<td>$t_{63.2%}$ (min:sec)</td>
<td>3:32 ± 1:01</td>
<td>10:50 ± 0:21*</td>
</tr>
</tbody>
</table>

Values are shown as the mean value ± standard error medium, n = 6.

*: Significant difference ($p < 0.05$) compared to apparatus 2; ++: at least 85% dissolved within 15 min (very rapidly dissolving); +: at least 80% dissolved within 30 min; -: less than 80% dissolved within 30 min.

Results of the adjustment to the mathematical models are shown in Table 2. The data were well-fit to the Makoid-Banakar model using apparatus 2 at all pH levels and using apparatus 4 at pH 4.5 and 6.8. To compare dissolution profiles at pH 4.5 and pH 6.8 with a model-dependent approach, a student’s t-test was carried out with kMB.
and k parameters; when this was performed, differences were found ($p < 0.05$). At pH 1.2, the dissolution data of apparatus 2 and 4 were best fitted with the Makoid-Banakar and Gompertz models, respectively. As different mathematical equations explained the in vitro dissolution performance of verapamil-HCl at pH 1.2, no comparison was made.

From the obtained results, the dissolution behavior of verapamil-HCl differs between the paddle method and flow-through cell method; however, the different hydrodynamic environments that each piece of equipment generates over the solid dosage means that these differences were expected. To identify the apparatus that generates the most accurate data, the MDT (as a model-independent parameter) and $t_{63.2\%}$ (as a model-dependent parameter) were plotted for each dissolution apparatus. Both parameters represent the time at which the same extent of verapamil-HCl dissolves (Fig. 2).

Only data obtained with apparatus 4 gave a significant linear regression ($p < 0.05$). MDT and $t_{63.2\%}$ obtained by different methods maintained linearity only with data produced by apparatus 4. This indicated that the in vitro dissolution performance of verapamil-HCl tablets in apparatus 4 was more accurate than the dissolution behavior in apparatus 2, regardless of the dissolution media pH (pH 1.2–6.8).

Some authors have studied the effect of the hydrodynamic environment surrounding solid dosage forms. Wu et al. studied the rate underlying tablet dissolution to better understand the role of external hydrodynamic conditions on mass transfer rate and film thickness during in vitro dissolution tests (24). Gao explained that apparatus 1 and

### Table 2. Results of Dissolution Data Adjustment.

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>pH</th>
<th>First-Order</th>
<th>Korsmeyer-Peppas</th>
<th>Weibull</th>
<th>Logistic</th>
<th>Gompertz</th>
<th>Makoid-Banakar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$R^2$</td>
<td>AIC</td>
<td>$R^2$</td>
<td>AIC</td>
<td>$R^2$</td>
<td>AIC</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>0.9700</td>
<td>12.52</td>
<td>0.9456</td>
<td>16.20</td>
<td>0.9907</td>
<td>6.79</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>0.9405</td>
<td>6.68</td>
<td>0.9718</td>
<td>7.71</td>
<td>0.9722</td>
<td>6.39</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>0.9243</td>
<td>6.23</td>
<td>0.9302</td>
<td>4.75</td>
<td>0.9164</td>
<td>5.59</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>0.6319</td>
<td>23.78</td>
<td>0.7081</td>
<td>22.56</td>
<td>0.7695</td>
<td>21.22</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>0.9458</td>
<td>14.95</td>
<td>0.7214</td>
<td>26.44</td>
<td>0.9333</td>
<td>15.49</td>
</tr>
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<td></td>
<td>6.8</td>
<td>0.9662</td>
<td>16.45</td>
<td>0.9685</td>
<td>15.16</td>
<td>0.9742</td>
<td>16.04</td>
</tr>
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</table>

Mean value, $n = 6$. *: Significant difference compared to apparatus 2 ($p < 0.05$). AIC: Akaike information criterion.

Figure 2. Association between $t_{63.2\%}$ and mean dissolution time (MDT ± SE, $n = 6$) at pH 1.2 (1), 4.5 (2), and 6.8 (3) in USP apparatus 2 and 4.
2 work under closed finite sink conditions and cannot mimic the hydrodynamic conditions of the GI tract (11). Butler and Bateman found that the flow-through cell method showed less variation compared to apparatus 2 and was less dependent on hydrodynamics and the amount of substance tested (25).

Apparatus 4 has gained recent acceptance due to its versatility in testing dosage forms where conventional dissolution apparatuses have failed (26). The results of this comparative dissolution study for verapamil-HCl tablets agree with those reported by other authors — apparatus 4 was more accurate than USP Apparatus 2. Details of the successful association of MDT and model-dependent parameters of naproxen tablets, ibuprofen suspensions, and fixed-dose combination formulations of acetaminophen and ibuprofen have been reported (27–29).

The adjustment to kinetic models was carried out without any physiological meaning to establish a model that describes the dissolution performance of verapamil-HCl tablets under the hydrodynamics of both apparatuses. The aim of adjusting dissolution data is to simplify the analysis and interpretation of drug release as a function of parameters that can be compared by simple statistical tests (30).

**Prediction of In Vivo Concentration-Time Profile of Verapamil-HCl in Humans**

Prediction of in vivo performance of drugs from in vitro dissolution data is essential during drug development. To identify whether the conditions for the flow-through cell reflect the in vivo performance of the drug in humans, it was necessary to predict the in vivo pharmacokinetics and plasma concentration-time profiles of verapamil-HCl from the in vitro dissolution data. A simple convolution method was chosen, utilizing the reported pharmacokinetic parameters of verapamil-HCl (7, 18, 19). The predicted plasma concentrations of verapamil-HCl were plotted against the actual published concentrations of Isoptin (Reference) (Fig. 3) (19). Pharmacokinetic parameters calculated from the predicted plasma concentrations are listed in Table 3.

![Figure 3. Mean plasma drug concentration-time profiles of verapamil-HCl at pH 1.2 (A), 4.5 (B), and 6.8 (C) (n = 6). R: Reported data from Haeri et al (19).](image)

<table>
<thead>
<tr>
<th>pH</th>
<th>USP 2</th>
<th>USP 4</th>
<th>USP 2</th>
<th>USP 4</th>
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<tbody>
<tr>
<td>1.2</td>
<td>0.50</td>
<td>0.73</td>
<td>25.0</td>
<td>25.0</td>
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<tr>
<td>4.5</td>
<td>0.78</td>
<td>27.48</td>
<td>8.92</td>
<td>8.92</td>
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<tr>
<td>6.8</td>
<td>78.6</td>
<td>82.51</td>
<td>27.48</td>
<td>23.93</td>
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Table 3. Predicted Pharmacokinetic Parameters of Verapamil-HCl in Humans

<table>
<thead>
<tr>
<th>Parameter</th>
<th>pH</th>
<th>Apparatus</th>
<th>Tmax (h)</th>
<th>Cmax (ng/mL)</th>
<th>PE for Cmax (%)</th>
<th>AUC0→∞ (ng·h/mL)</th>
<th>PE for AUC0→∞ (%)</th>
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</thead>
<tbody>
<tr>
<td>Reported data†</td>
<td>1.2</td>
<td>USP 2</td>
<td>0.50</td>
<td>108.4</td>
<td>-</td>
<td>515.8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>USP 4</td>
<td>0.25</td>
<td>93.7 (1.0)</td>
<td>13.59</td>
<td>552.2 (5.8)</td>
<td>-7.03</td>
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<tr>
<td></td>
<td>4.5</td>
<td>USP 2</td>
<td>0.50</td>
<td>74.8 (4.2)</td>
<td>31.03</td>
<td>441.6 (25.5)</td>
<td>14.39</td>
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<tr>
<td></td>
<td>4.5</td>
<td>USP 4</td>
<td>0.38</td>
<td>98.7 (2.8)</td>
<td>8.92</td>
<td>574.7 (17.1)</td>
<td>-11.41</td>
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<tr>
<td></td>
<td>6.8</td>
<td>USP 2</td>
<td>0.50</td>
<td>78.6 (5.4)</td>
<td>27.48</td>
<td>460.2 (31.8)</td>
<td>10.79</td>
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<td></td>
<td>6.8</td>
<td>USP 4</td>
<td>0.50</td>
<td>82.51 (1.8)</td>
<td>23.93</td>
<td>485.1 (10.4)</td>
<td>5.96</td>
</tr>
</tbody>
</table>

Values are mean (%RSD), n = 6. HCl: Hydrochloric acid; PE: prediction error. AUC: area under the curve.

†: Reported data by Haeri et al. (19).
The predicted curves of the flow-through cell at pH 1.2 and 4.5 were similar to the reported in vivo profile (Table 3). The %PE between the pharmacokinetic data and those calculated by the convolution method, using apparatus 2 at pH 1.2 and apparatus 4 at pH 1.2 and pH 4.5, did not exceed 15% (Table 3). With the flow-through cell, the %PE values between the actual and predicted values for C\text{max} and AUC\text{0-∞} at pH 1.2 were 15.0% and –1.35%, respectively, and 8.92% and –11.41%, respectively, for the same pharmacokinetic parameters at pH 4.5. This indicates the validity of the convolution method (21). Overall, the flow-through cell was more appropriate for predicting the in vivo performance of verapamil-HCl tablets in humans than USP apparatus 2.

CONCLUSIONS
It is important to study the effect of hydrodynamics from conventional dissolution apparatus together with different media to document the mechanism by which the pharmaceutical dosage form releases particular drugs. The flow-through cell has been tested herein, and it generated satisfactory results for the evaluation of verapamil-HCI tablets, and prediction of in vivo performance was best with data obtained from using the flow-through cell. It is necessary, however, to carry out human bioavailability studies and relate the data to validate these results.

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