Prediction of the Oral Pharmacokinetics and Food Effects of Gabapentin Enacarbil Extended-Release Tablets Using Biorelevant Dissolution Tests

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The purpose of this research was to establish an in vitro dissolution testing method to predict the oral pharmacokinetic (PK) profiles and food effects of gabapentin enacarbil formulated as wax matrix extended-release (ER) tablets in humans. We adopted various biorelevant dissolution methods using the United States Pharmacopeia (USP) apparatus 2, 3 and 4 under simulated fasted and fed states. Simulated PK profiles using the convolution approach were compared to published in vivo human PK data. USP apparatus 2 and 4 underestimated the in vivo performance due to slow in vitro dissolution behaviors. In contrast, biorelevant dissolution using USP apparatus 3 coupled with the convolution approach successfully predicted the oral PK profile of gabapentin enacarbil after oral administration of a Regnite® tablet under fasted state. This approach might be useful for predicting the oral PK profiles of other drugs formulated as wax matrix-type ER tablets under fasted state.

Key words biorelevant dissolution testing; extended-release; pharmacokinetics; oral administration; United States Pharmacopeia (USP) apparatus 3 (BioDis); USP apparatus 4 (flow-through cell)

Oral extended-release (ER) formulations of drugs are developed to reduce side effects and maximize drug efficacy by modifying their pharmacokinetic (PK) characteristics. The formulation of a drug is not always optimized in the early phase of clinical trials. Once it is decided that a drug will be developed as an ER formulation, however, extensive formulation work is needed to establish the manufacturability and stability of the drug product. Possible changes in the PK of dosage forms throughout the course of clinical development are taken into consideration during ER formulation development. If the PK changes significantly, reformulation and additional clinical trials are required because the PK profile of a drug can affect its pharmacological effect and/or safety profiles. Therefore, exploratory clinical studies are sometimes implemented to understand the relationship between the rate of drug release and the PK of the drug. Accordingly, prediction of the in vivo performance of ER formulations in advance can reduce the development period with minimization of clinical trials.

In recent years, a number of technologies have been developed to enable prediction of the in vivo performance of dosage forms. For oral immediate release (IR) dosage forms, many researchers have successfully used biorelevant dissolution testing coupled with physiologically-based pharmacokinetic modeling approaches, to predict in vivo drug performance. Okumu et al. established the in vitro/in vivo correlation (IVIVC) for etoricoxib solid oral drug products by comparing the dissolution behavior in different dissolution media and using computer simulations.

Methods developed to predict the oral performance of ER dosage forms have also been reported. Klein et al. established the Level A IVIVC for two ER formulations containing caffeine using the United States Pharmacopeia (USP) apparatus 3 (reciprocating cylinder, BioDis) and 4 (flow-through cell). Fotaki et al. reported the importance of in vitro hydrodynamics when using the dissolution apparatus 2 (paddle), 3 and 4 to determine the IVIVC of two monoolithic ER products, a hydrophilic matrix formulation containing carbomer and an osmotic pump formulation. Andreas et al. developed in vitro biorelevant test setups by using the USP dissolution apparatus 3 and 4 to predict the food effects of several ER formulations of 5-aminosalicylic acid which were pH-dependent coating formulations, a Multi-Matrix system, and ethylcellulose-coated microgranules. Further, Andreas et al. predicted the food effects of two nifedipine ER formulations (an osmotic pump and a matrix-type coat-core) and ER zolpidem (Ambien® CR). Garbacz et al. developed a dissolution stress test device to simulate the physiologically-based mechanical stress that a dosage form may experience when it moves through the gastrointestinal (GI) tract, and evaluated the performance of ER tablets with hydrophilic matrices containing 100 mg diclofenac sodium.

Gabapentin enacarbil is a prodrug of gabapentin that is effective in the treatment of restless legs syndrome and has been developed as a wax matrix, erosion-based ER tablet comprising glycercin fatty acid ester. While many attempts have been made to predict the in vivo performance of oral ER formulations, as mentioned above, we are unaware of any efforts to predict the in vivo performance of wax matrix-type oral ER formulations.

The purpose of this research was to establish an in vitro dissolution method to predict the oral PK profiles and food effects of gabapentin enacarbil ER tablets. By combining in vitro dissolution profiles of the ER tablet in simulated fasted and fed biorelevant media with a convolution approach using
post-absorptive PK parameters in humans, we compared the predicted \textit{in vivo} plasma concentration profiles of gabapentin with observed data under both prandial states.

**MATERIALS AND METHODS**

**Materials** Commercially available gabapentin enacarbil ER tablets 300 mg (Regnite® tablets 300 mg, Astellas Pharma Inc., Tokyo, Japan, lot L001) were purchased from the Japanese market. Gabapentin enacarbil ER tablets are a wax matrix-type formulation containing glycerin fatty acid ester, with a tablet size of 15.1×8.0 mm. Gabapentin enacarbil powder was produced by Astellas Pharma Inc. (lot 1001140G). FaSSIF/FeSSIF/FaSSGF powder (lot 01-1504-05NP) and FaSSIF-V2 powder (lot 02-1405-09) were purchased from Biorelevant.com Ltd. (London, U.K.). Acetic acid, acetonitrile, glycerol monooleate, hydrochloric acid solution (1 mol/L HCl), maleic anhydride, phosphoric acid, potassium dihydrogen phosphate, sodium acetate, sodium chloride, sodium hydroxide pellets and sodium hydroxide solution (1 mol/L NaOH) were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). β-D-glucose was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Tris-(hydroxymethyl)aminomethane was purchased from MP Biomedicals, LLC. (Santa Ana, CA, U.S.A.). Milk (Meiji Holdings Co., Ltd., Tokyo, Japan) containing 3.5% fat was purchased commercially. Nomethane was purchased from MP Biomedicals, LLC. (Santa Ana, CA, U.S.A.). Milk (Meiji Holdings Co., Ltd., Tokyo, Japan) containing 3.5% fat was purchased commercially. Pepsin (lot SLBB2141V), sodium cholate (lot SLBN0541V), sodium oleate (lot SLBD5492V) were purchased from Sigma-Aldrich Co., LLC. (St. Louis, MO, U.S.A.). Lecithin (Lipoid E PC S, lot SL0800-21440089-04/046) was purchased from Lipoid GmbH (Ludwigshafen, Germany).

**Dissolution Media** The following biorelevant dissolution media were used for solubility and dissolution testing: Fasted State Simulated Gastric Fluid (FaSSGF), Fed State Simulated Gastric Fluid (FeSSGF\textsubscript{middle}), Fasted State Simulated Intestinal Fluid version 2 (FaSSIF-V2), Fed State Simulated Intestinal Fluid version 2 (FeSSIF-V2), Fasted State Simulated Intestinal Fluid (FaSSIF/FeSSIF), Fasted State Simulated Colonic Fluid (FaSSCoF). The compositions and preparation of these biorelevant dissolution media have been described previously.\textsuperscript{14,15} Gabapentin enacarbil \textit{in vitro} dissolution media: a paddle apparatus (USP Apparatus 2), the BioDis apparatus (USP Apparatus 3), and a flow-through cell apparatus (USP Apparatus 4)

**Paddle Experiments** A NTR-6400 type paddle dissolution apparatus (Toyama Sangyo Co., Ltd., Osaka, Japan) was used in this study. The dissolution media were used were 300 mL of FeSSGF or 500 mL of FeSSGF\textsubscript{middle}, FaSSIF-V2 or FeSSIF-V2 per vessel. Two different paddle revolutions at 50 or 100 rpm were applied. The temperature of the dissolution media in the vessels was maintained at 37±0.5°C throughout each test run. Samples (approximately 5 mL) were taken at 30, 60, 90, 120, 180, 240, 360, 480 and 1440 min, using a stainless cannula and plastic syringe. Samples were immediately filtered through a syringe filter of 0.45-µm PVDF membrane (Whatman™ 13 mm GD/X) into test tubes after discarding the first 2 mL of filtrate. Filtered solutions and the same volume of acetonitrile comprised samples for HPLC analysis. FeSSGF\textsubscript{middle} samples were pretreated using the same procedure as in the solubility assay. All dissolution experiments were conducted in triplicate.

**BioDis Experiments** A BIO-DIS III type reciprocating cylinder dissolution apparatus (Agilent Technologies, Inc., Santa Clara, CA, U.S.A.) was used in this study. The dissolution test set-up and dip rate are shown in Table 1. The temperature and volume of the dissolution media were 37±0.5°C and 220 mL, respectively. The detailed experimental procedures were performed according to previously reported methods.\textsuperscript{8-10} However, FeSSCoF, instead of FaSSCoF (Fasted State Simulated Colonic Fluid), was used as a colonic biorelevant medium for dissolution testing under both the fasted and fed states because the FaSSCoF medium was designed from human colonic contents after using bowel cleansing agent.\textsuperscript{16} We therefore concluded that it was reasonable to use FeSSCoF under the standard fasting condition in clinical trials. Further, the effect of share stress during gastric emptying was added to the dissolution test by increasing the dip rate to 30 dips/min for two minutes, given that several studies have shown that solid oral dosage forms can be exposed to mechanical pressures as high as 300 mbar during gastric emptying,\textsuperscript{11,17} and many studies have confirmed that the stress peaks in the antropyloric region.\textsuperscript{18-21} The tops and bottoms of the reciprocating cylinders were fitted with polypropylene mesh screens with mesh size of 405-µm (40 mesh) as a tablet holder. For the fasted state, samples were taken at 58, 60, 75, 90, 120, 240, 360 and 480 min. For the fed state, the samples were taken at 60, 120, 180, 238, 240, 270, 300, 420, 480, 540, 600 and 1440 min. Approximately 5 mL of samples were withdrawn using a stainless cannula and plastic syringe. All other conditions, including sample treatment, were the same as in the paddle experiment. Dissolution experiments were conducted in triplicate.

**Flow-through Cell Experiments** A DZF 720 type flow-through cell dissolution apparatus (Erweka GmbH, Heusen- stamm, Germany) was used in this study. A 5-mm-diameter glass bead was placed at the bottom of the cell. A total of 1.7 g of 1-mm-diameter glass beads were added to the 5-mm bead. In each cell, the Regnite® tablet 300 mg was placed on top of the 1-mm beads. A glass filter (Whatman™ 25 mm GF/F filter) was placed on top of each cell. The durations of the dissolution test were 8...
and 9 h for simulating the fasted and fed states, respectively. The media were maintained at 37 ± 0.5°C. The dissolution test set-up and flow rate are shown in Table 1. The detailed experimental procedures were performed according to previously reported methods.8–10 The dissolution tests were performed using an open-loop configuration with manual sample collection. For the fasted state, samples were taken at 20, 40, 60, 75, 90, 120, 165, 210, 240, 285, 320, 370, 420 and 480 min. For the fed state, samples were taken at 20, 40, 60, 80, 100, 120, 140, 160, 180, 210, 240, 255, 285, 330, 375, 480 and 540 min. Approximately 5 mL of samples were withdrawn with a stainless cannula and plastic syringe at each time point. All other conditions were the same as those for the paddle experiment. Dissolution experiments were conducted in triplicate.

Analytical Methods Samples obtained from the dissolution tests and solubility assessments were quantitatively analyzed to determine the concentration of gabapentin enacarbil by HPLC using the Alliance Separations Module 2695 with a type 2487 detector (Waters Corporation, Milford, MA, U.S.A.) at 35°C with a TSKgel ODS-100Z 5 µm column (4.6 mm i.d. × 150 mm, Tosoh Corporation, Tokyo, Japan). The mobile phase was a mixture of acetonitrile, 0.02 M phosphate buffer (pH 2.5) and water (volume ratio 585:363:52). The flow rate was 1 mL/min and the injection volume was 10 µL. The detection wavelength was set at 210 nm. HPLC chromatograms were evaluated using Empower 3 (Waters Corporation).

Reference Pharmacokinetic Data Blood concentration–time profiles after oral administration of a gabapentin enacarbil IR capsule 350 mg in the fasted state were obtained from the literature.22 Similarly, plasma concentration-time profiles after oral dosing of a gabapentin enacarbil ER tablet 300 mg in the both fasted and fed states (U.S. Food and Drug Administration recommended high fat breakfast) were reported methods.8–10 The blood drug concentration–time profile of the IR capsule was described as a one-compartment model. The UIR function (A: 0.01433 L⁻¹, α: 0.205821 h⁻¹) was calculated from the PK profile of the IR capsule under the fasted state. To simulate the plasma concentration–time profiles of the gabapentin enacarbil ER tablet under both fasted and fed states, the dissolution profile at each prandial state was convoluted using the UIR function described above.

To conduct PK simulation of the ER tablet using paddle dissolution data, in vitro profiles in the intestinal media (FaSSIF-V2 or FeSSIF-V2) were superposed onto those in the stomach media (FaSSGF or FeSSGF middle) in consideration of the GI tract. The gastric emptying times in the superposed in vitro data were set to 1 h under the fasted state (FaSSGF to FaSSIF-V2) and 4 h under the fed state (FeSSGF middle to FeSSIF-V2), which matched the BioDis and flow-through cell settings.23,24 The paddle dissolution profiles in the stomach media were used up until set gastric emptying times of 1 h for the fasted state and 4 h for the fed state, respectively. The dissolution profiles in the intestinal media were corrected by multiplying the original values by undissolved ratio of the drug in the stomach media at the gastric emptying times. After the simulated gastric emptying time, the corrected dissolution profiles in the intestinal media from time 0 were superposed to the dissolved amount in FaSSGF or FeSSGF middle at the gastric emptying times. The superposed dissolution profiles were used to simulate the plasma profiles using convolution approach in the case of paddle apparatus, although the dissolution profiles from USP apparatus 3 and 4 were directly used for the simulation.

The PK parameters $T_{\text{max}}$, $C_{\text{max}}$ and area under the plasma–drug concentration curve ($AUC_{0-\text{inf}}$) were calculated for each simulated profile using non-compartmental analysis in Phoenix® WinNonlin® 6.3.22

Evaluation of Prediction Accuracy of PK Simulation To evaluate the prediction accuracy of each PK simulation, absolute percent prediction errors (%PE) for $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ were calculated using the following Eq. 1:

$$\% \text{PE} = 100 \times \frac{\text{Observed value} - \text{Predicted value}}{\text{Observed value}}$$

### Table 1. In Vitro Dissolution Set-Up of BioDis and Flow-through Cell Experiments

<table>
<thead>
<tr>
<th>Region</th>
<th>Medium</th>
<th>pH of medium</th>
<th>Duration (min)</th>
<th>Dip rate (dips/min)</th>
<th>Duration (min)</th>
<th>Flow rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>FaSSGF</td>
<td>1.6</td>
<td>58</td>
<td>12</td>
<td>60</td>
<td>8</td>
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<td></td>
<td></td>
<td>2</td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Proximal gut</td>
<td>FaSSIF-V2</td>
<td>6.5</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Distal gut</td>
<td>FaSSIF-V2</td>
<td>6.8</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Midgut</td>
<td>FaSSIF middle</td>
<td>6.8</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Distal ileum</td>
<td>SiF ileum</td>
<td>7.5</td>
<td>120</td>
<td>10</td>
<td>120</td>
<td>4</td>
</tr>
<tr>
<td>Colon</td>
<td>FeSSCoFa</td>
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<td>240</td>
<td>6</td>
<td>240</td>
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<tr>
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<td>15</td>
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<td>1020</td>
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</tbody>
</table>
RESULTS AND DISCUSSION

Solubility of Gabapentin Enacarbil in Various Biorelevant Media

The solubility of gabapentin enacarbil (Regnite® tablet) in biorelevant media using the shake flask method after 24 h of incubation at room temperature is shown in Fig. 1. Drug solubility in FaSSGF at pH 1.6 was approximately 0.7 mg/mL. This increased in SIF ileum at pH 7.5 by about...
Gabapentin enacarbil is a weakly acidic drug with a $pK_a$ of 5.0$^{25}$ and has the highest pH among the media tested (Fig. 1a). The solubility of gabapentin enacarbil in FeSSGF$_{middle}$ (pH 6.5) was approximately 1.4-fold higher than that in FaSSGF$_{middle}$ (pH 6.8). It is likely that the higher concentrations of bile salts and lipids in the fed state media (FeSSGF$_{middle}$, FeSSIF-V2 and FeSSIF$_{midgut}$) increased the solubility of the drug compared with the fasted state media.$^{26,27}$ The solubility of gabapentin enacarbil in FeSSIF-V2 (pH 5.8) was higher than that in FeSSGF$_{middle}$, probably because the higher pH of FeSSGF$_{middle}$ improved the dissolution rate of the drug up to a 1.7-fold dip rate and 2-fold flow rate (data not shown), while the paddle revolution rate strongly affected the dissolution profiles of the drug product. The dissolution did not reach 100% in 24 h in the simulated fed condition using BioDis. This suggests that the released but undissolved drug particles might pass through the mesh in the reciprocating cylinders, resulting in under-recovery of the drug, although according to the drug’s solubility (Fig. 1), the drug likely dissolves completely. In contrast, the dissolution was less than 40% at 8 h in both the fasted and fed conditions in the flow-through cell apparatus. This low fraction dissolved was probably due to the lower hydrodynamic forces in the flow-through cell system compared to the BioDis system, which prevented complete drug diffusion from the wax matrix.

**Simulations of Gabapentin Plasma Concentration Profiles**

Figure 3 shows the simulated in vivo dissolution profiles obtained using in vitro paddle data at both 50 and 100 rpm for convolution analysis to predict oral PK profiles in humans. The paddle dissolution profiles in stomach media (Figs. 2a and c) were used up until set gastric emptying times of 1 h for the fasted state and 4 h for the fed state. The observed dissolution profiles in the intestinal media (Figs. 2b and d) were corrected by multiplying them by the undissolved ratio of the drug in the stomach media at the gastric emptying times. After the simulated gastric emptying time, these corrected dissolution profiles in the intestinal media were superposed to the dissolved amount in FaSSGF or FeSSGF$_{middle}$ at the gastric emptying time. For example, the paddle dissolution profile under 50 rpm in FaSSGF (Fig. 2a) was used until 1 h in which 2.1%
of gabapentin dissolved. Then, the dissolution profile in the intestinal medium was corrected by multiplying the dissolution profile under 50 rpm in FaSSIF-V2 (Fig. 2b) from time 0 to 24 h by the undissolved ratio of 97.9%. Subsequently, the corrected dissolution profile under 50 rpm in FaSSIF-V2 was superposed on the drug dissolved in FaSSGF at 1 h (2.1%). Consequently, the simulated in vivo dissolution profile under the fasted state using paddle 50 rpm data (Fig. 3a) was obtained.

Figure 4a and Table 2 show the predicted and observed PK profiles and parameters, respectively, under the fasted state. Predicted $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ values with paddle revolutions of 50 rpm were underestimated by 67 and 27%, respectively. Similarly, these values with the flow-through cell were underestimated by 51 and 53%. In paddle revolutions of 100 rpm, there was little predictive error for $AUC_{0-\text{inf}}$ whereas the %PE for $C_{\text{max}}$ value was 57%. Moreover, the predicted $T_{\text{max}}$ value was substantially delayed compared to the observed value and the predicted plasma profile was far from the observed data in Fig. 4a. In contrast, the predicted $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ with BioDis were close to the observed values with their %PE values of within 15%, which is generally considered to be high prediction accuracy. The simulated $T_{\text{max}}$ was 0.83 h earlier than the observed mean value, suggesting that some subjects in clinical studies might exhibit slower gastric emptying of the gabapentin enacarbil ER tablet than the assumed 1 h in the in vitro dissolution test under the simulated fasted state. However, the simulated $T_{\text{max}}$ was within the standard deviation range of the observed $T_{\text{max}}$ value. These results suggest that the PK simulation using the BioDis data is the closest to the observed PK profile.

Figure 4b and Table 3 show the predicted and observed PK profiles and parameters, respectively, under the fed state. Predicted $C_{\text{max}}$ values with paddle revolutions of 50 and 100 rpm were underestimated by 67 and 58%, respectively. Similarly, the %PE of $AUC_{0-\text{inf}}$ values were 36 and 24%, respectively. The %PE values with flow-through cell were 60% for $C_{\text{max}}$.
and 72% for \( AUC_{\text{0-inf}} \). In contrast, the %PE of \( C_{\text{max}} \) value with BioDis was 17%, which was the closest to the observed data among the dissolution methods studied and the %PE of \( AUC_{\text{0-inf}} \) was 33%. The simulated value of \( T_{\text{max}} \) under the fed state was earlier than the observed mean value, similar to that for the fasted state. Our findings suggest that the predicted apparent absorption duration of gabapentin is shorter than the observed durations. The %PE values for both \( C_{\text{max}} \) and \( AUC_{\text{0-inf}} \) were higher than 15%, suggesting inaccurate prediction accuracy under the fed state. Although the simulated fed state dissolution media have been used in this study, many factors (e.g., hydrolysis of the prodrug, GI transit, hydrodynamics, shear forces and physical pressures, etc.) under the fed state need to be optimized for more precise prediction. Another possible reason for the inaccurate prediction under the fed state would be that the UIR function from the PK data under the fasted state was used in the simulation for both prandial state.

Based on the above results, the \textit{in vivo} performance of gabapentin enacarbil ER tablets was best predicted by BioDis among the \textit{in vitro} dissolution apparatuses under the current experimental conditions. In the paddle method, because a fixed volume of a single dissolution medium is often used, it was difficult to simulate the transit of an ER dosage form through the GI tract. In contrast, BioDis and flow-through-cell methods could simulate the GI tract environment by changing the test media smoothly. In terms of hydrodynamics, a previous study suggested that the current flow-through cell conditions might be too low for both the fasted and fed conditions. In contrast, the hydrodynamic force used in BioDis seemed to be closer to \textit{in vivo} values than that used in the flow-through-cell. Regnite® tablets 300 mg is a wax matrix-type ER formulation and drug release occurs following both erosion of the wax matrix component and diffusion of the drug. The mechanism of the erosion of the wax matrix component is presumed to be as follows: \textit{in vitro} dissolution media or \textit{in vivo} GI fluids penetrate into the wax matrix, leading to disintegration of the matrix from the surface of the tablet and subsequent dissolution and release of the drug from the resultant solid particles. In contrast, the mechanism of diffusion is presumed to be as follows: dissolution media or GI tract fluids penetrate into the wax matrix, dissolving the drug, leading to its diffusion through the wax matrix. Our findings suggest that the BioDis method may accurately simulate the erosion and diffusion of the ER formulation in the GI tract \textit{in vivo}.

While various \textit{in vitro} dissolution conditions can be employed by adjusting the dip and the flow rates using BioDis and flow-through-cell methods, respectively, there are limitations to mimicking the \textit{in vivo} dissolution of ER formulations. In addition to simulating the composition of GI fluids, drug release and dissolution in \textit{in vivo} can also be influenced by transit time, hydrodynamics, shear force and physical pressures in the GI tract. It is challenging to simulate shear forces and pressures using the compendial dissolution equipment like BioDis and flow-through-cell. In particular, additional investigation is needed for solid dosage forms that are sensitive to shear force and pressures. The \textit{in vivo} performance of dosage forms might be better predicted using more complicated dissolution systems, such as the dynamic gastric model and stress test device.

**CONCLUSION**

Biorelevant dissolution using BioDis coupled with a convolution approach successfully predicted the PK profile of gabapentin enacarbil after oral administration of an ER tablet under the fasted state. Among the dissolution methods studied, the predicted PK profile using the BioDis data was closest to the observed one under the fed state, however, that prediction was not adequate accuracy with large prediction errors. This approach might be useful for predicting oral PK profiles of other drugs formulated as wax matrix-type ER tablets under the fasted state.

**Conflict of Interest** Satomi Yamaguchi Ikeuchi, Atsushi Kambayashi and Hiroyuki Kojima are employees of Astellas Pharma Inc. The other authors declare no conflict of interest.

**REFERENCES**


12) Garbacz G, Weitschies W. Investigation of dissolution behavior of


