Application of the Correlation of in vitro Dissolution Behavior and in Vivo Plasma Concentration Profile (IVIVC) for Soft-Gel Capsules—a Pointless Pursuit?

Hidekatsu NISHIMURA,¹,b Chiaki HAYASHI, c Tetsuya AIBA, c Ichiro OKAMOTO, b Yuji MIYAMOTO, b Susumu NAKADE, b Kazuhisa TAKEDA, b and Yuji KUROSAKI* c

¹ Graduate School of Natural Science and Technology, Okayama University; ² Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University; ³ 1–1–1 Tsushima-naka, Okayama 700–8530, Japan; and ⁴ Pharmaceutical Development Laboratories, Ono Pharmaceutical Co., Ltd.; 3–1–1 Sakurai, Shimamoto-cho, Mishima-gun, Osaka 618–8585, Japan

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Plasma concentration profiles of arundic acid ((R)-(−)-2-propyloctanoic acid), an oil-like medicine, administered as soft-gel capsules in human clinical tests were predicted from the dissolution test data of the soft-gel capsules with different storage terms (short- and long-term stored drugs) by applying the in vitro–in vivo correlation (IVIVC). We established two linear-regression IVIVCs, which were characterized by either the in vitro dissolution behaviors against the pH 8.0 dissolution medium or the pH 6.8 dissolution medium containing 2% sodium dodecyl sulfate (SDS), in this study. Also, the prediction accuracies for the in vivo plasma profiles in humans for these two IVIVCs were compared. Regarding dissolution from the long-term stored capsule in pH 8.0 dissolution medium without surfactant, the prediction accuracies of the in vivo plasma profiles in humans were not satisfactory for the obtained IVIVC. The use of pH 6.8 dissolution medium containing 2% SDS, according to the Japanese guideline, improved the dissolution of the long-term stored capsule. Furthermore, the prediction accuracies for the in vivo plasma profiles in humans for these two IVIVCs were compared. The IVIVC established by the in vitro dissolution data obtained with the dissolution medium containing surfactant more effectively predicted the plasma drug concentration profiles following oral administrations of the soft-gel capsules under both storage conditions.

Key words soft-gel capsule; in vitro–in vivo correlation; IVIVC; storage condition; prediction accuracy

Evaluation of the in vitro dissolution characteristics of oral dosage forms provides useful information on additives used in formulation development. The in vitro dissolution test is an important test guaranteeing the consistency of dissolution behavior, such as collapse of the dosage form followed by the release of drug molecules, dictating the effectiveness of orally administered drugs. In addition, the in vitro dissolution test is utilized as an effective criterion for the prediction of the biological equivalency of drugs. In cases whereby the kinetics of dissolution behavior of orally delivered drugs have been linked to the plasma concentration data of such drugs in human clinical tests, the establishment of appropriate standards for the in vitro dissolution testing of oral drugs in terms of the realization of the optimal concentration profile of medicine in blood will become possible. However, there is no report of an IVIVC study covering soft-gel capsules enclosing oil-like medicine.

In this study, we tried to predict plasma drug concentrations in human clinical tests from the dissolution test data of drugs with different storage terms (short- and long-term stored drugs), using a soft-gel capsule containing a high permeability and low solubility drug, arundic acid ((R)-(−)-2-propyloctanoic acid), which is a novel neurological agent for intractable diseases such as neurodegenerative diseases (Alzheimer’s/Parkinson’s diseases) and amyotrophic lateral sclerosis.

MATERIALS AND METHODS

Soft-Gel Capsule Drug Used in This Study Two differently stored preparations of a soft-gel capsule drug containing arundic acid (300 mg) prepared by Ono Pharmaceutical Co., Ltd. (Osaka, Japan) were used for both the dissolution test and the clinical study. The storage conditions for short- and long-term stored drugs were 15 °C for 3 months and 25 °C under 60% RH for 30 months, respectively. Arundic acid for injection used in the clinical study was also prepared by Ono Pharmaceutical Co., Ltd. All clinical studies were performed by Pharma Bio-Research Group B.V. (Utrecht, The Netherlands) in accordance with the principles of GMP and GCP. The plasma concentration profiles of arundic acid were investigated in six male healthy volunteers (20—35 year, 52.8—74.2 kg) in the intravenous drip study, while those were examined in twelve male healthy volunteers (18—24 year, 61.7—90.0 kg) in the oral administration study.

Determination of Arundic Acid Dissolution tests were conducted using a dissolution apparatus with USP paddle (apparatus II). Dissolution medium (a mixture of 50 mmol/l Na2HPO4 and 25 mmol/l citric acid pH 8.0 or pH 6.8 dissolution medium containing 2% SDS; 900 ml) was used at a temperature of 37 ± 0.5 °C. Before commencement of the dissolution test, we calibrated the dissolution test apparatus using 2 kinds of standard tablets (predonisone and salicylic acid tablets) approved by the USP standards.

The determination of dissolution profiles of arundic acid from the soft-gel capsules was carried out using HPLC connected to a UV detector in a mobile phase of the mixture of acetonitrile/20 mmol/l KH2PO4 (pH 3.0, adjusted by phosphoric acid) = 3/2; flow rate, 1 ml/min; wavelength, 210 nm; column, ODS C₁₈ (4.6 mm i.d. X 150 mm).

Dissolution Behavior of Arundic Acid Soft-Gel Capsules (a) Mean Dissolution Time (MDT): MDT of arundic acid was calculated using the following equation (Eq. 1):
Absorption Behavior of Arundic Acid in Humans in Intravenous Drip Study

Four pharmacokinetic parameters ($V_1$, $k_{21}$, $\alpha$, and $\beta$) were estimated by the non-linear least squares data fitting using WinNonlin (Pharsight Corp., U.S.A.).

$$C_i = \frac{k_0}{V_i} \left\{ \frac{\left(1-e^{-\alpha T} \left(k_{21} - \alpha \right) \right) \times e^{-\beta T} + \left(1-e^{-\alpha T} \left(k_{21} - \beta \right) \right) \times e^{-\beta T}}{\beta \left(k_{21} - \alpha \right)} \right\}$$

(b) Parameters Characterizing Dissolution Profile: Dissolution profiles of arundic acid from the soft-gel capsules were characterized by the in vitro fraction dissolved % (FRD). Each dissolution profile was approximated by the Hill formula (Eq. 2) using the non-linear least square regression program (WinNonlin, Pharsight Corp., Mountain View, CA, U.S.A.):

$$\% \text{dissolved} = \frac{D_{\text{max}} \cdot T^T}{D_0 + T^T}$$  

Prediction of Plasma Drug Concentration Profiles from IVIVC The plasma drug concentrations after the oral administration of soft-gel capsules were simulated by the convolution of the absorption behavior, predicted by the linear IVIVC and the pharmacokinetic parameters estimated in a rapid intravenous injection study as the input function and the weight function, respectively (Eq. 4). The % prediction errors (%PEs) defined in Eq. 6 were calculated for each measurement point and related parameters.

RESULTS

Plasma Concentration Profile of Arundic Acid in Human Intravenous Drip Study Figure 1 shows the changes in plasma arundic acid concentrations after intravenous drip (1 mg/kg/h for 1 h and 4 mg/kg/h for 1 h) observed in a clinical test. Simulation curves calculated by the pharmacokinetic parameters obtained through the standard two-stage method summarized in Table 1 are presented as the solid line in Fig. 1. The model, and thus the obtained pharmacokinetic parameters, expressed the plasma profiles well.

Plasma Concentration Profiles of Arundic Acid after Oral Administration of Short- and Long-Term Stored Soft-Gel Capsules Figure 2 summarizes the plasma-concentration profiles of arundic acid after the oral administration of short-term (Fig. 2A) and long-term (Fig. 2B) stored soft-gel capsules. The relevant model-independent pharmacokinetic parameters are shown in Table 2. There was no significant difference in these parameters ($C_{\text{max}}$, $T_{\text{max}}$, $AUC$, and $t_{1/2}$) in vivo and in vitro dissolution time on the abscissa and in vivo absorption time on the ordinate. A linear regression defined below (Eq. 5) was established as the relationship of in vitro dissolution and in vivo absorption behavior (IVIVC):
Absorption Rates of Orally Administered Arundic Acid Estimated by Deconvolution

Figure 3 shows the cumulative fraction absorbed (FRA) of arundic acid after the oral administration of soft-gel capsules, calculated by the deconvolution of the mean plasma profile of the oral short-term stored capsule shown in Fig. 2A by the plasma elimination profile calculated by the pharmacokinetic parameters (Table 1) and the relevant two-compartment model obtained by the intravenous drip study. The FRA reached a plateau 3 h after administration. This means that practical gastrointestinal absorption was completed within 3 h.

Dissolution Behavior of Soft-Gel Capsules

The in vitro dissolution behavior of the soft-gel capsules under these two different storage conditions was examined in two dissolution test mediums. Figure 4 shows the FRDs of the short- and long-term stored soft-gel capsules containing arundic acid in pH 8.0 buffered solution (Fig. 4A) or in 2% SDS added pH 6.8 solution (Fig. 4B). Both these test mediums are recommended for arundic acid soft-gel capsules by the Guidelines for the Bioavailability and Bioequivalence Studies for Orally Administered Drug Products either with or without...
out surfactant. The solubility of arudic acid in these test solutions were almost the same (\( \pm 1 \) mg/ml). Dissolution parameters, i.e., MDT, D50, and \( \gamma \), for each dissolution profile are summarized in Table 3.

Establishment of the Correlation between in Vitro FRD and in Vivo FRA (IVIVC) Although FRDs in the in vitro dissolution tests reached 100% (Fig. 4), the maximum FRAs calculated by the deconvolution in the short-term (Fig. 3) and long-term stored soft-gel capsules (data not shown) were both 84%. Then, we set the value of 0.84 as the bioavailability of the soft-gel capsules of arundic acid. The dissolution time up to reaching the FRD figures equivalent to FRA was calculated according to the Hill formula (Eq. 2). We plotted the in vitro dissolution time and in vivo absorption time on the abscissa and ordinate, respectively, to obtain linear-regression IVIVCs in two dissolution conditions (Fig. 5). As the dissolution profiles of short- and long-term stored soft-gel capsules were different in pH 8.0 (Fig. 4A), a linear-regression obtained by the short-term stored soft-gel capsule was presented and applied to the following simulation study.

Prediction of Plasma Profiles of Short- and Long-Term Stored Soft-Gel Capsules According to the two linear-regression IVIVCs (Fig. 5) and the dissolution behavior under the two different storage conditions (Fig. 4), plasma profiles of arundic acid in humans after the oral administration of short- and long-term stored soft-gel capsules were calculated. The dotted and solid lines shown in Fig. 2 are the predicted plasma-concentration profiles of arundic acid after the oral administration of the soft-gel capsules based on these IVIVCs. Table 4 summarizes the % prediction errors (%PEs) of the pharmacokinetic parameters to those observed in the clinical data (Table 2). According to the definition of FDA, a good prediction level is realized if, in the internal validation of IVIVC, the %PE of \( C_{\text{max}} \) and AUC of any drug is not more than 15%. As shown in Table 4, the %PEs of \( C_{\text{max}} \) and AUC for either storage condition were less than 15% in both predictions. However, the dotted line in Fig. 2 shows that the predicted profile is delayed, particularly in the long-term stored drugs (Fig. 2B). Accordingly, the %PE of \( T_{\text{max}} \) and MRT for the long-term stored drug predicted by the pH 8.0 buffered solution were considerably larger (Table 4). Thus, the IVIVC established by in vitro FRD in the conventional dissolution test medium without SDS did not fully succeed in predicting the plasma profiles in humans. However, more accurate simulation with smaller values of %PE would be realized in the IVIVC based on dissolution behavior data ob-

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Dissolution medium</th>
<th>MDT (min)</th>
<th>D50 (min)</th>
<th>( \gamma ) (—)</th>
<th>MDT (min)</th>
<th>D50 (min)</th>
<th>( \gamma ) (—)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term stored</td>
<td>pH 8.0 buffered solution</td>
<td>12.3</td>
<td>11.5</td>
<td>4.5</td>
<td>10.1</td>
<td>11.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Long-term stored</td>
<td>pH 8.0 buffered solution</td>
<td>19.9</td>
<td>21.7</td>
<td>2.3</td>
<td>13.0</td>
<td>11.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Short-term stored</td>
<td>2% SDS added pH 6.8 solution</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Long-term stored</td>
<td>2% SDS added pH 6.8 solution</td>
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Fig. 5. Linear-Regression IVIVCs for Arundic Acid Soft-Gel Capsules Obtained in pH 8.0 Buffered Solution (A) and 2% SDS Added pH 6.8 Solution (B) Key: ●, short-term stored (pH 8.0); ○, short-term stored (pH 6.8, 2% SDS); △, long-term stored (pH 6.8, 2% SDS).

Table 4. Comparison of the %PEs of Pharmacokinetic Parameters of Arundic Acid after Oral Administrations of Short- and Long-Term Stored Soft-Gel Capsules in Human Volunteers According to the Prediction Based on Two IVIVCs

<table>
<thead>
<tr>
<th>Formulation</th>
<th>( %PE_a^{(a)} )</th>
<th>( %PE_b^{(b)} )</th>
<th>( T_{\text{max}} )</th>
<th>( T_{\text{1/2}} )</th>
<th>( AUC^{(c)} )</th>
<th>MRT(^{(d)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term stored</td>
<td>+12.2/+0.8</td>
<td>+46.8/+32.1</td>
<td>-6.6/-7.2</td>
<td>+5.4/+0.1</td>
<td>+2.6/-1.2</td>
<td></td>
</tr>
<tr>
<td>Long-term stored</td>
<td>+3.2/-2.9</td>
<td>+60.9/+15.8</td>
<td>-8.4/-8.3</td>
<td>+10.9/-1.3</td>
<td>+10.8/-2.3</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) %PE calculated from simulation by IVIVC established from the dissolution behavior in pH 8.0 buffered solution (Fig. 5A). \( b \) %PE calculated from simulation by IVIVC established from the dissolution behavior in pH 6.8 buffered solution containing 2% SDS (Fig. 5B). \( c \) AUC calculated by the trapezoidal rule extrapolated infinity. \( d \) MRT calculated by the following equation:

\[
MRT = \int_0^\infty \frac{1}{AUC} C(t) \, dt
\]
tained by the dissolution tests using pH 6.8 dissolution medium containing 2% SDS (Fig. 4), especially for the long-term stored soft-gel capsules. The applicability of IVIVC to predict the plasma profiles of soft-gel capsules in humans by the dissolution test medium containing SDS recommended by the Japanese guideline was suggested, even in the formulations administered after long-term storage.

DISCUSSION

In formulation development, establishment of the final formulation for phase III clinical studies must be an urgent matter in pharmaceutical research divisions of all pharmaceutical companies. However, during the progression of clinical studies, modifications of the compositions of the formulation itself and/or associated production method of the initial formulation are often required to obtain more desirable plasma concentration profiles in patients. In such cases, implementation of the remaining clinical tests involving multiple candidates for a new drug using different formulations is often necessary, leading to huge costs.

The recent trend to facilitate formulation modification is the application of the criterion called BSC (Biopharmaceutics Classification System), which is categorized by the solubility and membrane permeability characteristics of drugs. Suitable conditions for dissolution tests based on the pharmacopeia to establish effective in vitro–in vivo correlations (IVIVCs) in solid peroral dosage forms have been reported for several drugs. BCS was well studied in Class I (theophylline, sodium valproate, metoprolol, diltiazem, levosimendan), Class II (loratadine), and Class III (metformin) medicines. However, there has been no report on the application of the IVIVC study regarding soft-gel capsules enclosing oil-like medicine.

Hakata et al. reported the effect of storage conditions on the disintegration time of soft gelatin capsules. In these capsules, collagen micelles in the networks of gelatin xerogels were suggested to be denatured by the long-term storage of the soft gelatin capsules. Once capsules have undergone such a structural change, swelled capsules in the dissolution medium become much less soluble, so that the disintegration time is markedly prolonged. For these prolonged dissolution cases, it is difficult to predict the human blood levels using long-term stored soft-gel capsules with IVIVC. In this study, we established two linear-regression IVIVCs (Fig. 5) which were characterized by either the in vitro dissolution behaviors against the pH 8.0 dissolution medium or the pH 6.8 dissolution medium containing 2% SDS (Fig. 4). Subsequently, the prediction accuracies of the in vivo plasma profiles in humans using these two IVIVCs were compared. The predicted $T_{\text{max}}$ and MRT for the long-term stored drug were considerably larger than those obtained in the clinical study. However, the prediction accuracies were improved much more markedly using the IVIVC based on the dissolution condition containing 2% SDS in both the short- and long-term stored drugs. We observed a marked delay in the in vitro dissolution test for the long-term stored drug in pH 8.0 dissolution medium without SDS, in comparison with the short-term drug (Fig. 4A). This delay was reduced when we used the pH 6.8 dissolution medium containing 2% SDS, according to the Japanese guideline. The guideline recommended the use of surfactant for the dissolution test to ensure that more than 85% of the drug would be dissolved within 60 min in cases of poorly soluble drugs. While the addition of polysorbate to the dissolution test medium did not accelerate the dissolution of arundic acid from the long-term stored drug, the minimal addition of 2% SDS to the test medium met the criterion of the guideline (data not shown). Although the precise mechanism for the delayed dissolution phenomenon using the long-term stored soft-gel capsules in simple buffered dissolution medium still needs clarification, it is more appropriate to adopt the in vitro dissolution data in dissolution medium containing 2% SDS to predict the in-plasma drug concentration after oral administration of the long-term stored arundic acid soft-gel capsule. These findings indicate that the establishment of a proper IVIVC will be useful in the formulation development of soft-gel capsules containing oil-like pharmaceutics if the retardation of in vitro dissolution characteristics is recognized in conventional dissolution medium after long-term storage.

REFERENCES