Post-formulation studies of a product mainly involve its in vitro dissolution analysis to assess its safety and effectiveness in living body (1). In contrast to complex and lengthy in vivo testing, the in vitro dissolution analysis is an important quality control test, which simulates the possible in vivo performance of dosage form. This test guides the formulator to improve the product’s quality through modification of various variables. These variables are related to the process and/or formulation strategies (2). Process related variables include formulation development technique, stirring speed, order and speed of mixing, and effect of temperature. On the other hand, amount of drug, polymer, and/or excipients constitute the formulation variables. These variables can be varied to produce safe and effective formulation. Since it is not possible to assess these frequent changes through in vivo tests, there is significant dependence on in vitro dissolution analysis to approximate the probable in vivo outcome (3).

As one step advance, dissolution profiles obtained from these in vitro dissolution tests can be mathematically treated to predict plasma drug concentrations. One of the well-known mathematical approaches involves the use of convolution method. It is a direct method to predict the blood drug amounts from the dissolution profiles (4). Then, the predicted plasma drug concentration versus time data can be employed to evaluate three general pharmacokinetic parameters including Cmax (maximum blood drug level), Tmax (time required to attain maximum blood drug level), and AUC (area under blood drug concentration curve) followed by study of bioavailability and/or bioequivalence (4).

Thus, the aim of this article is to propose the effectiveness of convolution approach to predict
pharmacokinetics of tramadol hydrochloride floating tablets.

EXPERIMENTAL

Materials
A gift sample of tramadol hydrochloride was got from Leo Pharmaceuticals, India. SD Fine Chemicals provided with carbopol and HPMC K100M. Hibiscus rosa Sinensis was supplied by Colorcon, India. All chemicals were analytical in quality and used without further purification.

Preparation and in vitro evaluation of tablets

The preparation and in vitro analysis of tramadol hydrochloride floating tablets is already reported (5). The sustained release tablets of tramadol hydrochloride were prepared using direct compression technique employing various ratios of carbopol, HPMC K100M, and Hibiscus rosa Sinensis as excipients and drug release controlling ingredients. Except magnesium stearate, all ingredients were weighed, sieved and mixed for 20 min to ensure uniform mixing. Before tabletting, magnesium stearate was added and mixed for 30 s to ensure lubrication of mixture. For compression of mixture into tablets, single punch tablet machine having 8 mm flat-surface punches was used. The hardness of the prepared tablets was 4-6 kg/cm². For buoyancy, gas generation was achieved by sodium bicarbonate. The prepared tablets were named as F1 to F6, each contained 100 mg of tramadol. These tablets were then analyzed for quality control purpose adopting various tests including tablet dimensions, weight variation, friability, swellability, buoyancy, and drug content tests. The in vitro dissolution test was conducted using paddle method in 900 mL of HCl buffer with pH 1.2 to simulate the gastric condition. The stirring speed of paddles was set at 70 rpm. Temperature of dissolution medium was adjusted at 37 ± 5OC. At predetermined time points (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 20 h), 5 mL of dissolved samples were taken with a method to ensure uniform sampling. Before analysis, each time point was divided by its Vd, adapted from previous publication (7); (iv) all (C B)t values for each time point were added to get final blood drug quantities; and (v) these quantities at each time point were divided by its Vd, adapted from previous publication (7), to CB. This outcome acts as predicted blood drug profile, from which different pharmacokinetic parameters can be calculated. From kinetic analysis, it was observed that first order equation gave the best fit to the dissolution data. From results, it is clearly evident that the prepared tablets showed the controlled release behavior through hydrodynamic balance, elaborating their gastro-retentive feature. The physicochemical properties for all tablets were within compendial limits (5, 6). The intactness of tramadol in formulation was confirmed by FTIR test (5). Each experiment was run in triplicate.

Performance of convolution based calculations

Convolution approach is useful to derive blood drug levels from in vitro dissolution data. This approach involves unit impulse response (Cδ) and drug input rate in vitro (Xv, in) as represented in following equation:

\[ c(t) = \int_0^t c(\tau - u) X_{v, in}(u)du \]  

(Equation 1)

where, \( c_\delta \) is typically assessed from intravenous bolus dose data or standard oral solution data. It represents drug concentration time data resulting from the instantaneous absorption of a particular drug amount. Moreover, the function \( c(t) \) corresponds to the plasma drug level versus time of the prepared formulations. In addition, \( X_{v, in} \) and \( u \) represent the drug input rate of the oral solid formulation and variable of integration, respectively (4).

For determining blood drug levels (C B) from the in vitro dissolution profiles, the listed steps were followed: (i) the percentage values of in vitro dissolution data were changed into the respective discrete amounts of drug released from formulation during each sampling interval; (ii) these discrete amounts of drug released were changed into the bioavailable amounts of drug using drug’s bioavailability data taken from a published article (7). This previously published article reported the values for half life, elimination rate constant (Ks), bioavailability factor, volume of distribution (Vd), body weight, and dose as 6.4 h, 0.111 l/h, 0.7, 5.15 L/kg, 63.8 kg, and 100 mg, respectively; (iii) the declining C B during each interval [(C B)] were determined using Ks value, adapted from previous publication (7); (iv) all (C B) values for each time point were added to get final blood drug quantities; and (v) these quantities at each time point were divided by its Vd, adapted from previous publication (7), to C B. This outcome acts as predicted blood drug profile, from which different pharmacokinetic parameters can be calculated.

Data analysis

Microsoft Excel 2007 was used to analyze data. The results are presented as the mean ± standard deviation.
RESULTS AND DISCUSSION

The in vitro dissolution profiles and predicted blood drug levels of F1-F6 tablets are presented in Figures 1 and 2, respectively. At last, predicted D_b data were utilized to determine pharmacokinetic parameters including AUC, C_max and T_max using one compartment model approach (Table 1). For comparing the in vitro and in vivo profiles, C_b are not compared due to the tremendous inter- and intra-subject variability. To get rid of this problem, the observed and the predicted pharmacokinetic parameters including C_max and AUC are compared. The predicted values of C_max (ng/mL) for F1, F2, F3, F4, F5, and F6 were 119.6 ± 4.7, 114.2 ± 7.1, 113.4 ± 5.9, 101.1 ± 5.8, 80.8 ± 3.2 and 84.1 ± 4.9, respectively. The predicted values of T_max (h) were 12.1 ± 0.3, 12.2 ± 0.2, 12.2 ± 0.2, 11.4 ± 0.2, 11.7 ± 0.3 and
11.6 ± 0.3, respectively. The predicted values of AUC (ng·h/mL) were 1970.6 ± 287.4, 1921.7 ± 260.1, 1883.3 ± 301.7, 1589.1 ± 293.0, 1449.2 ± 240.1, and 1430.5 ± 209.5, respectively. These predicted values for AUC and Cmax are comparable to those previously reported observed values. The reported observed values for AUC and Cmax are 1227.3 ± 537.4 ng·h/mL and 217.8 ± 61.9 ng/mL, respectively (8). This similarity between published and our predicted results validates the application of convolution approach. The difference in dissolution features for F1-F6 products are noticeably responsible for differences in their respective predicted CB, which further leads to differences in their AUC and Cmax. It again validates the convolution approach.

The convolution approach (equation 1) has directly been applied to predict blood drug levels from in vitro dissolution data (4). After formulating dosage forms (F1-F6) with particular release characteristics, the dosage forms were assessed for their in vitro release feature aiming at the prediction of in vivo drug release in normal gastric physiology. The in vitro dissolution profiles and predicted blood drug levels of F1-F6 are presented in Figures 1 and 2, respectively. At last, predicted DB data were utilized to determine pharmacokinetic parameters including AUC, Cmax, and Tmax (Table 1).

On the basis of Cmax and AUC, there are various approaches available in the literature that deal with the prediction of CB from in vitro dissolution study. These approaches, however, need complicated approximating procedures, sometime with help of special software. In addition to these methods, convolution-based approach appears to provide a good information about drug product’s quality by using basic knowledge of pharmacokinetics and a simple spreadsheet software. This method has been discussed in detail in this article starting from in vitro dissolution data to gaining of pharmacokinetic parameters. In addition, convolution method of predicting CB is not product-specific, i.e., it does not require any in vivo data of that specific formulation. Rather it is a guiding marker used to get needed in vitro profile using only available in vitro findings. This method of comparing the observed and predicted blood drug levels assumes similarity between in vitro and in vivo conditions. It includes variation in vessel sizes, dissolution medium volumes as well as the mixing rate. In vivo drug dissolution and absorption is affected by numerous physiological factors, consequently pharmacokinetics is tremendously erratic also. On the contrary, such inconsistency is not present in in vitro conditions. The in vitro dissolution profile is reproducible and the predicted blood drug levels assumes similarity to the observed values. The difference in dissolution conditions as well as the mixing rate affects in vivo drug dissolution. The in vivo drug dissolution is affected by numerous physiological factors, consequently pharmacokinetics is tremendously erratic also. On the contrary, such inconsistency is not present in in vitro conditions. The in vitro dissolution profile is reproducible and the predicted blood drug levels assumes similarity to the observed values.

Table 1. Pharmacokinetic parameters predicted from in vitro dissolution data using convolution approach.

<table>
<thead>
<tr>
<th>No.</th>
<th>Predicted pharmacokinetic parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cmax (ng/mL)</td>
<td>119.6 ± 4.7</td>
<td>114.2 ± 7.1</td>
<td>113.4 ± 5.9</td>
<td>101.1 ± 5.8</td>
<td>80.8 ± 3.2</td>
<td>84.1 ± 4.9</td>
</tr>
<tr>
<td>2</td>
<td>T1/2 (h)</td>
<td>12.1 ± 0.3</td>
<td>12.2 ± 0.2</td>
<td>12.2 ± 0.2</td>
<td>11.4 ± 0.2</td>
<td>11.7 ± 0.3</td>
<td>11.6 ± 0.3</td>
</tr>
<tr>
<td>3</td>
<td>AUC (ng·h/mL)</td>
<td>1970.6 ± 287.4</td>
<td>1921.7 ± 260.1</td>
<td>1883.3 ± 301.7</td>
<td>1589.1 ± 293.0</td>
<td>1449.2 ± 240.1</td>
<td>1430.5 ± 209.5</td>
</tr>
</tbody>
</table>
imagined for *in vitro* data, because the *in vitro* dissolution testing is characteristically conducted under virtually controlled homogenous circumstances (4). This approach is equally effective for assessing the bioavailability/bioequivalence. After adopting some change in manufacturing, dissolution analysis of new formulation can be used to approximate its C<sub>θ</sub>, followed by their evaluation in accordance with criteria for bioavailability/bioequivalence. If the profiles congregate the bioequivalence criteria then it should be believed that the manufacturing modifications had no adverse influence on the product quality. Otherwise, formulation development would need alteration consequently (9).

**CONCLUSION**

To compute blood drug levels from *in vitro* dissolution data, the convolution approach is a useful mathematical procedure which is free from complicated and lengthy *in vivo* study procedures. However, freedom from physiological variabilities that affect observed blood drug levels is a limitation of this modality. However, this limitation can be minimized by using biosimilar dissolution test for improved prediction of blood drug concentration.

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**REFERENCES**


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