Development of in vitro-in vivo correlation for encapsulated metoprolol tartrate

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Abstract: This study was aimed to develop level A, B and C in vitro-in vivo correlation (IVIVC) for encapsulated metoprolol tartrate (T1, T2 and T3 having metoprolol tartrate/polymer ratio of 1 : 1, 1 : 1.5 and 1 : 2, w/w). The in vitro data were correlated with in vivo data. For level A IVIVC, drug absorption data were calculated using Wagner-Nelson method. In addition, convolution approach was used to approximate plasma drug levels from in vitro dissolution data. The coefficient of determination (R²) for level A IVIVC was 0.720, 0.905, 0.928 and 0.878 for Mepressor®, T1, T2 and T3 formulations, respectively, with acceptable percent error (< 15%). The value of R² for level B and C IVIVC was 0.231 and 0.714, respectively. It is also concluded that level A IVIVC is a proficient mathematical model for biowaiver studies involving study parameters as those implemented for T1S (T1 formulation tested for dissolution in the presence of sodium lauryl sulfate) revealing that IVIVC level A is dosage form specific, rather than to be drug specific.

Key words: metoprolol tartrate; Eudragit® FS; convolution; IVIVC

Based on FDA guidelines, level A in vitro-in vivo correlation (IVIVC) is expected for modified release formulations of BCS class I drugs (like metoprolol tartrate), where dissolution is the rate limiting step. Level A IVIVC is the highest correlation for the submission of New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) (1). Level B and C IVIVC is also of remarkable importance in biowaiver studies. An increasing trend of IVIVC development has been observed in recent research. The main advantage of IVIVC is the prediction capability of in vivo performance of an alternative formulation of predefined nature from specific dissolution characteristics and IVIVC function (2). According to Food and Drug Administration (FDA) guidelines for the establishment of IVIVC, three formulations of the subject drug with different release rates are required followed by the internal or external validation of IVIVC (3). Previously, many studies have been conducted for the formulation of metoprolol tartrate sustained release solid oral dosage form (1-4). However, present polymer for enteral delivery of drug is not available in literature except our work (5-7).

This article is a part of our study that was designed to develop metoprolol tartrate-Eudragit® FS modified release pH-dependent formulations i.e., tabletted microparticles using various concentrations of polymer. Then, the in vitro and in vivo evaluation of the prepared and reference formulations (Mepressor® 200 mg, Novartis Pharmaceuticals, Karachi, Pakistan) was conducted followed by the development of IVIVC.

MATERIALS AND METHODS

Materials

Metoprolol tartrate (Novartis Pharmaceuticals, Karachi, Pakistan), Eudragit® FS (Rohm Pharma, Germany) as well as analytical grade liquid paraffin, methanol, and petroleum ether (Merck, Germany) were employed in this study. Mepressor® 200 mg SR tablets (Batch No. 457X, Novartis Pharma, Pakistan) was used as reference formulation.

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Encapsulated metoprolol tartrate

Encapsulated metoprolol tartrate (T1, T2 and T3 having metoprolol tartrate/polymer ratio of 1 : 1, 1 : 1.5 and 1 : 2; w/w) was synthesized by solvent evaporation method and then was compressed into adequately hard tablets so that each tablet contained 200 mg of metoprolol (5).

For drug-polymer compatibility analysis, Fourier transform infra-red spectroscopy, x-ray diffractometry and differential scanning calorimetry of un-compressed T2 formulation was conducted. Compatibility analysis showed that metoprolol tartrate maintained its chemical integrity in the form of encapsulated metoprolol tartrate (5). Other compendial tests like weight variation, tablet hardness, friability, disintegration and dissolution for the reference and test formulations were also carried out, which was in accordance with the compendial criteria (5). The dissolution test was performed by sequential pH change technique and high-performance liquid chromatography was employed for the analysis of metoprolol samples (5, 6). Drug release kinetics was calculated using various kinetic models like zero-order, first-order, Higuchi and Korsmeyer-Peppas models. The in vivo study as well as the calculation of pharmacokinetic parameters has been narrated previously (7). Zero order kinetic model best explained the in vitro dissolution data of developed formulations; zero order model illustrates the concentration independent release of drug (7).

Computation of absorption data and IVIVC development

In order to establish a level A IVIVC, in vivo absorption (%) data were calculated using Wagner-Nelson equation. Firstly, the area under the plasma concentration-time curve from zero to time “t” (AUC_0,t) was evaluated from plasma drug concentration (C_t) data using the trapezoidal rule, and then the area under the plasma concentration-time curve from zero to time infinity (AUC_0,) was calculated by adding AUC_0,t to the last log-linear concentration divided by the terminal disposition rate constant. Secondly, elimination rate constant (K_e) was multiplied with AUC_0,t (resulting in K_e × AUC_0,t) as well as with AUC_0,∞ (resulting in K_e × AUC_0,∞) and then the product of K_e × AUC_0,t was added to the respective C_t at each time point [resulting in C_t + (K_e × AUC_0,t)]. Finally, each C_t + (K_e × AUC_0,t) was divided by the product of K_e × AUC_0,∞ × 100 to calculate the percentage of drug absorbed (F) at each time point using following equation (1):

\[ F = \frac{[C_t + (K_e \times AUC_0,t)]}{[K_e \times AUC_0,\infty]} \times 100 \]  (Eq. 1)

Level A IVIVC was developed by drawing a plot between the percentage drug absorbed (along x-axis) of a formulation and its percentage drug dissolved (along y-axis) followed by the regression analysis of each curve to evaluate the strength of correlation determining whether the curve is linear or non-linear. The closer the value of determination coefficient to 1, the stronger is the correlation and linear is the curve. Level B IVIVC is developed by plotting the values of MDT (along x-axis) against MRT (along y-axis) of a formulation followed by the regression analysis of the curve. Level C IVIVC is a single point correlation which is developed by plotting t_50% (along x-axis) and pharmacokinetic parameter like AUC (along y-axis) followed by the regression analysis of the curve (8).

Convolution of in vitro data to approximate plasma drug levels

Convolution of in vitro dissolution data was done to get the c(t) (predicted plasma drug concentration) from the dissolution data utilizing (unit impulse response which is found from the intravenous bolus dose data or standard oral solution data) and (drug input rate in vitro from oral solid dosage form) as follows:

\[ C(t) = \int_0^\infty C_d(t - \delta)X_{vitro}(\delta)d\delta \]  (Eq. 2)

The function “u” indicates the variable of integration.

To predict plasma drug concentration from the in vitro dissolution profiles, the distinct drug concentrations, obtained from the percentage in vitro dissolution data during each sampling interval, were converted into the bioavailable drug concentrations utilizing the published bioavailability data of the drug. Then, the calculation of reducing levels of plasma drug concentrations during each interval utilizing the published elimination data of drug was carried out. All the determined drug concentrations for each time point were added, and finally the predicted plasma drug level at each time point was determined using the published values of volume of distribution of drug as well as the adult body weight (70 kg in average) (6).

Predictability of IVIVC

Predictability of IVIVC was determined using the following formula (4):

\[ \text{Prediction error } (%)_{\text{abs}} = \frac{C_{\text{abs}} - C_{\text{abspredicted}}}{C_{\text{abspredicted}}} \]  (Eq. 3)

Statistical analysis

The experimentally obtained results were stated as the average ± standard deviation (SD). The sta-
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Table 1. In vitro in vivo correlation data

<table>
<thead>
<tr>
<th>Level of in vitro in vivo correlation</th>
<th>Factor</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIVC level A</td>
<td>R² for Mepressor®</td>
<td>0.720</td>
</tr>
<tr>
<td></td>
<td>R² for T1</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>R² for T2</td>
<td>0.905</td>
</tr>
<tr>
<td></td>
<td>R² for T3</td>
<td>0.878</td>
</tr>
<tr>
<td></td>
<td>R² for T1S</td>
<td>0.973</td>
</tr>
<tr>
<td></td>
<td>Prediction error (%)</td>
<td>14</td>
</tr>
<tr>
<td>IVIVC level B</td>
<td>R²</td>
<td>0.231</td>
</tr>
<tr>
<td>IVIVC level C</td>
<td>R²</td>
<td>0.714</td>
</tr>
</tbody>
</table>

![Graphs showing drug dissolution vs. drug absorbed for different formulations](image)

Figure 1. Level A IVIVC for formulations Mepressor® (A), T1 (B), T2 (C), T3 (D) and T1S (E)

Statistical analysis was conducted by one way analysis of variance using software, SPSS version 13.0 (IBM, USA). The level of significance was set at 0.05.

RESULTS AND DISCUSSION

In this article, the evaluation and application methods of IVIVC in setting in vitro release specifi-
For biowaiver studies, comparative dissolution analysis is employed in addition to routine quality control tests, and subsequently the obtained dissolution data are evaluated. Biowaiver study is usually carried out for formulations with different strengths (thus different release rates) (4). To approximate in vivo activity of a formulation, the application of dissolution testing as a quality control tool has considerably increased after developing IVIVC. There are many applications of IVIVC such as the selection of the biorelevant in vitro dissolution medium in bioequivalence studies, use of validated IVIVC for providing details for a biowaiver in scale-up or post approval changes. Indeed, a biowaiver is only granted if the prediction of in vivo performance of the formulation with the modified in vitro release rate remains bioequivalent with that of the originally tested formulation (4).

Figure 1 and Table 1 exhibit an effort at a level A IVIVC for encapsulated metoprolol tartrate formulation. The IVIVC is considered as the most valuable tool for the approximation of in vivo activity from dissolution profiles. It is also remarkable to identify the subsistence of a superb relationship between drug absorbed (%) in vivo and drug dissolved (%) in vitro in this article, which also involves the prediction of plasma drug concentration and absorption kinetics from dissolution data as well as the drug release kinetics. This feature is evidently expressed in Figure 1 reflecting the release behaviors for in vivo as well as the relevant in vitro absorption processes. It is apparent from the data that the developed formulations have revealed insensitivity to the hydrodynamic conditions, which is a climatic feature of gastrointestinal tract; this characteristic helps in the prediction of in vivo plasma drug levels. The IVIVC for T2 revealed a good correlation coefficient ($R^2 = 0.928$) followed by the T1 ($R^2 = 0.905$) and T3 ($R^2 = 0.878$) (Table 1). It clearly indicates the enteric nature of formulated products which is further confirmed from a weaker IVIVC ($R^2 = 0.720$) for Mepressor® (Figure 1) as it a non-enteric formulation performing unlikely in sequential pH change dissolution test. In addition, the value of $R^2 = 0.973$ is significantly ($p < 0.05$) higher for T1S which involved the dissolution in the presence of 0.1% sodium dodecyl sulfate. This use of surfactant enhanced the rate of dissolution which resulted in the close resemblance of dissolution conditions to that of normal physiology. In addition, percentage prediction error was found to be 14% exhibiting convolution technique as a proficient procedure for predicting plasma drug levels.

There was a very weak correlation coefficient ($R^2 = 0.231$) for level B IVIVC, while 0.714 was the correlation coefficient in case of level C IVIVC (Figure 2 and 3).

In short, Wagner-Nelson equation for the development of IVIVC was revealed using a targeted release formulation as a model system. The technique possesses the benefit of tolerating the data characteristically obtainable from a formulation development program to be used for establishing IVIVC.

**CONCLUSION**

This study corroborates that there is an excellent in vitro-in vivo correlation for metoprolol tartrate formulations encapsulated into Eudragit® FS, principally for T1S. It is also concluded that level A IVIVC is a proficient mathematical model for biowaiver studies involving study parameters as those implemented for T1S revealing that IVIVC level A is dosage form specific, rather than to be drug specific.
REFERENCES


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