THE RELEVANCE OF DISSOLUTION TESTING FOR TRIMETAZIDINE

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Abstract. The paper describes the applicability of in-vitro in-vivo correlations previously developed for modified-release formulations of trimetazidine dihydrochloride (35 mg) to the immediate release products (20 mg). The dissolution profiles obtained in three different media were used for prediction of the in-vivo pharmacokinetic profiles, after oral administration as single dose. The accuracy of prediction were analyzed by comparison of estimated versus experimental values of peak and global exposure. Although water is far from being a biorelevant media, the integration of the corresponding in-vitro drug release profiles resulted in the most adequate prediction of peak exposure for this particular, high solubility, high permeability drug.

Keywords: in-vitro in-vivo correlations (IVIVC), trimetazidine dihydrochloride, dissolution test

Introduction

The in-vitro in-vivo relations or correlations (IVIVR / IVIVR) remain the main goal of drug dissolution applications [1]. The prediction of the exposure pattern after oral administration has gain a significant role in accurate development of solid dosage forms [2]. According to the current guidelines, the IVIVC are mainly developed and accepted from regulatory point of view for pharmaceutical formulations with a modified release profile of the active ingredient. Extrapolation to the lower strengths can be considered within the biowaiver procedures, considering that other quality control (QC) limits and formulation factors are fulfilled. To what extent the same pathway can be followed in order to accurately predict the in-vivo performance for a given, immediate release (IR) formulation, is still controversial. The current available developments of the biopharmaceutical classification system for the class II drugs (with a high permeability and low solubility characteristics) [3], include a further dichotomy in solubility-limited and dissolution-rate limited drugs [4]. Frequently, the main limitation in developing IVIVC for IR drug products is based on the short duration of dissolution methodology, using the compendial basket or paddle apparatus (identified by United States Pharmacopoeia as apparatus 1 or 2). Nevertheless, the common approach is to use the QC procedures as biorelevant evaluations, despite the lack of any physiological correspondent of every single parameter that is implemented during the experiments [5]. This further leads to the rapid release rates during the test (for example, up to 100% of the label-claimed content, for high solubility drugs), difficult to correlate with a more prolonged time interval in which absorption occurs.

The current paper analyze the applicability of IVIVC developed for modified-release formulations of trimetazidine dihydrochloride (35 mg) to the immediate release products (20 mg). The predictions on peak (maximum concentration, Cmax) and global exposure (area under curve, AUC) for single oral dose, based on in-vitro dissolution tests conducted...
on three different media, were compared with the parameters generated after in-vivo administration. The potential sources of errors and methodological limitations are further discussed.

**Materials and methods**

Four IR oral solid dosage forms registered in Romania were previously evaluated using in-house developed dissolution methodologies [6] (including the reference product, Preductal, containing 20 mg trimetazidine dihydrochloride, Les Laboratoires Servier, and three generic drug products; these products are further identified as R and T1, T2 and T3). The in-vitro release media consisted of 900 ml of either water, hydrochloric acid 0.1N, pH=1.2, and phosphate buffer 50 mM, pH=6.8. The paddle apparatus was used at 75 rotation per minute. The duration of tests was set at 1 hour. The in-vivo evaluations were available for R and T1 conducted as bioequivalence studies using single oral dose doses with pharmacokinetic analysis performed on plasma samples during 24 hours after administration. The clinical study protocol was approved prior to implementation by the Romanian National Ethics Committee and National Drug Agency. Various IVIVC previously developed on three different media, were compared with the parameters generated after in-vivo administration. Due to the prospected lack of correlations between the fraction absorbed in-vivo and the dissolution profile generated in-vitro, the relationships available for MR were applied to the IR drug products, based on convolution procedures.

The accuracy of prediction were analyzed by comparison of estimated versus experimental plasma profiles for R and T1 and the best correlation were further extended to the remaining T2 and T3 formulations. The pharmacokinetic analysis and the deconvolution or convolution procedures were performed using GastroPlus software, version 7.0.0010, developed by Simulation Plus Inc., USA.

**Results and discussions**

The non-compartmental pharmacokinetic analysis for R and T1 formulations confirmed the immediate release profile, with a rapid absorption. The maximum concentration for R product (154 ng/ml) was reached at 1.5 hours after administration. Minimal differences were reported for the peak exposure when the corresponding mean plasma profile was analyzed for T1 (145 ng/ml). The optimum pharmacokinetic model was the mono-compartmental one (figure 1).

The in-vitro profiles indicated a very rapid dissolution, with more than 85% of the claimed content of active pharmaceutical ingredient dissolved in less than 15 minutes, independent on the composition of the release media. Consequently, the direct IVIVC could not be developed, apparently the main release processes occurring at the gastric level. Therefore, it can be assumed that the pharmaceutical system can be compared to a solution, at the main level of absorption, the intestinal barrier. Furthermore, the

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*Figure 1. The mean plasma concentration profiles for a) R and b) T1 drug products (dotted). The exposure patterns estimated based on mono-compartment model are presented as a line.*
pharmacokinetic profile will be dependent only on the permeability profile of trimetazidine (estimated to be $1.779 \text{ cm/sec x } 10^4$).

For MR formulations, the linear correlation were reported between the fraction absorbed and the in-vitro drug release profiles, the preliminary results being presented in figure 2.

Even if developed for a modified release formulations, the available IVIVC proved to provide accurate predictions mainly on maximum concentrations (table I). The prediction errors were 2.78 and, respectively, -1.28%. It was surprisingly concluded that, although water is far from being considered biorelevant (without presence of buffer systems or tensioactive substances), the integration of the corresponding in-vitro drug release profiles resulted in most adequate prediction of peak exposure for this particular, high solubility, high permeability drug, conditioned as immediate release formulation. Nevertheless, this fact could

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC (ng/mL*h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug product</td>
<td>Experimental</td>
<td>Estimated</td>
</tr>
<tr>
<td>R</td>
<td>154.6</td>
<td>150.3</td>
</tr>
<tr>
<td>T1</td>
<td>145.9</td>
<td>147.8</td>
</tr>
</tbody>
</table>

Table I. Experimental and estimated values of peak and total exposure for R and T1, based on dissolution profiles in water

![Graph](image1.png)

Figure 2. IVIVC developed for MR formulations of trimetazidine dihydrochloride using water as dissolution media

![Graph](image2.png)

Figure 3. The estimated pharmacokinetic profiles for a) R and b) T1 formulations
suggest the lack of impact for other physiological factors, usually mentioned as having a considerable impact in intestinal dissolution and absorption processes (bile salts, pH, transit time and fluid volume etc). In concerns the AUC, the prediction errors are somewhat higher, possibly due to the errors in estimating the elimination part of the pharmacokinetic profile. It is to be pointed out that, based on the in-vitro dissolution tests results, the release patterns were considered as similar, when the compendial procedures for comparison were applied. In this context, the methodology led to accurate estimation of existing differences it concerns the in-vivo pharmacokinetics (figure 3).

One of the main goals of the development of IVIVC is to guide the selection of optimal, bio-equivalent generic formulations. The solubility profile of this particular class I drug (according to the biopharmaceutical classification system, BCS [7]) makes very difficult the selection of in-vivo relevant, discriminatory in-vitro methodology, especially for IR dosage forms. The current approach could be implemented in the cases where both, IR and MR are available for the same active pharmaceutical ingredient.

The impact of the rapid release rate observed during the in-vitro dissolution evaluations on the values of maximum concentration and area under curve are presented in table II. Considering the above mentioned accuracy of predictions for \( C_{\text{max}} \), it is to be underlined the prospected differences between the generic T2 and T3, on one hand, and the reference formulation is lower than 10%, independent on the in-vitro media.

Nevertheless, if the low impact of the qualitative and quantitative composition on in-vivo exposure, either estimated or experimentally observed (figure 4), is considered, together with the previously mentioned biopharmaceutical properties, trimetazidine dihydrochloride could be a good candidate for abbreviated drug registration procedures, mainly based on accurately developed and discriminatory dissolution tests.

**Conclusions**

In-vitro in-vivo correlation developed for modified release dosage forms were implemented for prediction of the pharmacokinetic profile of a high solubility, high permeability drug, from immediate release tablets. The predictions of maximum concentrations were more accurate, with percentage errors lower than 3%. The methodology can

<table>
<thead>
<tr>
<th>Media for in-vitro dissolution test</th>
<th>Formulation</th>
<th>( C_{\text{max}} ) (ng/mL)</th>
<th>AUC (ng/mL*h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>T2</td>
<td>141.3</td>
<td>1134</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>146.9</td>
<td>1270</td>
</tr>
<tr>
<td>HCl 0.1N pH=1.2</td>
<td>T2</td>
<td>160.4</td>
<td>1153</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>153.0</td>
<td>1251</td>
</tr>
<tr>
<td>Phosphate buffer 50 mM pH=6.8</td>
<td>T2</td>
<td>163.1</td>
<td>1368</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>156.6</td>
<td>1138</td>
</tr>
</tbody>
</table>

Table I. The dependence of estimated values for the main pharmacokinetic parameters on the in-vitro drug release data

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**Figure 4.** In vitro drug release and estimated in-vivo pharmacokinetic profiles for T2 and T3 formulations
be used for the selection of optimal formulations in generic drug development, based on simple in-vitro dissolution methodology. Based on the main biopharmaceutic characteristics, trimetazidine dihydrochloride could be considered a good candidate for biowaiver procedures.

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