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Generic sustained release tablets of trimetazidine hydrochloride: Preparation and in vitro–in vivo correlation studies

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ABSTRACT

The aim of the current work was to develop generic sustained-release tablets containing 35 mg trimetazidine dihydrochloride and to establish an in vitro–in vivo correlation that could predict the bioavailability. The marketed sustained release tablet (Vastarel MR) used as reference, a sustained-release matrix tablet was prepared using hydroxypropyl methylcellulose (HPMC) as matrix by wet granulation and the in vitro dissolution profiles of the self-made tablets were determined in four different dissolution media (0.1 M HCl, pH 4.5 PBS, pH 6.8 PBS and water). A higher similarity between prepared tablets and Vastarel MR was established, with similarity factor ($f_2$) ranging from 60 to 75 in the four media. The in vivo pharmacokinetics was studied in six healthy beagles. Compared with Vastarel MR, the $C_{\text{max}}$ of self-made tablets was slightly decreased, while the $T_{\text{max}}$ and MRT$_{0-t}$ were slightly prolonged, but with no significant difference ($P > 0.05$). The average of relative bioavailability (F) was 102.52% based on AUC$_{0-t}$. For log-transformed AUC$_{0-t}$ and $C_{\text{max}}$, the upper confidence limit on the appropriate criterion is <0, indicating these two formulations were population bioequivalent. The in vivo–in vitro correlation coefficient obtained from point-to-point analysis of self-made tablets was 0.9720. In conclusion, the prepared tablets were bioequivalent to the marketed tablets, according to both the in vitro release rate and extent of absorption, and a good in vivo–in vitro correlation was established for the self-made tablets that indicated in vitro dissolution tests could be used as a surrogate for bioavailability studies. © 2016 Production and hosting by Elsevier B.V. on behalf of Shenyang Pharmaceutical University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The marketed sustained release tablet (Vastarel MR) used as reference, a generic sustained-release tablet of trimetazidine hydrochloride was prepared by wet granulation. The prepared tablets were bioequivalent to Vastarel MR, and a good in vivo–in vitro correlation was established for the self-made tablets.

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1. Introduction

Angina pectoris, commonly known as angina, is a clinical manifestation of ischemic heart disease, generally arising from obstruction or spasm of the coronary arteries [1, 2]. In patients with angina pectoris, myocardial ischemia induces lower exercise capacity, more frequent angina attacks and reduces quality of life [3]. Trimetazidine dihydrochloride, 1-[[2,3,4-trimethoxyphenyl] methyl] piperazine is a clinically effective antianginal agent that has been used in the prophylaxis and management of angina pectoris [4]. Unlike other classical antianginal drugs, such as beta-blockers, calcium-channel antagonists, and long-acting nitrates, trimetazidine dihydrochloride displays anti-ischemic effects without inducing hemodynamic changes and thus protects the heart from the deleterious consequences of ischemia. So it is generally well tolerated and accompanied by minor side effects. Besides, trimetazidine dihydrochloride is freely soluble in water and has a relatively short half-life of 6 ± 1.4 h. Therefore, it is considered as an ideal candidate for sustained drug delivery [5].

In the market, trimetazidine dihydrochloride is available as both immediate release oral formulations (Vastarel IR, 20 mg) and modified release tablets (Vastarel MR, 35 mg). The optimal dosage regimen of IR tablets is approved three times a day while MR tablets are twice a day [6]. However, repeated administration of the IR tablets leads to poor compliance for angina pectoris patients who need a long term therapy. MR tablets with sustained drug release behaviors could maintain their therapeutically effective concentrations in systemic circulation for prolonged periods of time, which decreases the number of daily administrations, minimizing local and systemic side effects. Thus it improves the patient compliance with prescribed dosage regimens [7].

Hydrophilic polymers are becoming very popular in formulating oral sustained release tablets, such as xanthan gum, cellulose derivatives, alginate sodium or carbopol [8]. Hydroxypropyl methylcellulose (HPMC) is the most commonly and successfully used hydrophilic material for sustained drug delivery [9]. It possesses some important characteristics including nontoxicity, pH independence and high water swellability, which contribute to obtain a desirable drug sustained release profile. In this investigation, HPMC was used as a release retardant carrier in the design of sustained release matrix tablets for trimetazidine dihydrochloride.

Besides, a point-to-point in vitro–in vivo correlation was developed for relating percentage of drug dissolved to percentage of drug absorbed. The Food and Drug Administration (FDA) defines in vitro–in vivo correlation as a predictive mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response [10]. A good correlation could predict the rate and extent of drug absorption in vivo [11]. Developing an in vitro–in vivo correlation for a sustained release tablet is an important object to facilitate product development and serves as a quality control procedure during product manufacture. This reduces the need for expensive bioavailability testing in animals and humans [12].

Hence the objective of the work was to prepare oral administration of sustained release HPMC matrix tablets containing 35 mg trimetazidine dihydrochloride and study its bioequivalence to marketed formulations (Vastarel MR). Similar studies of the dissolution in vitro of these two formulations (self-made and marketed sustained release tablets) have been performed in four different dissolution media (0.1 M HCl, pH 4.5 PBS, pH 6.8 PBS and water). Their bioavailability and pharmacokinetic studies were conducted in beagles. Besides, the in vitro–in vivo correlation of self-made tablets was developed and used as a tool for predicting in vivo bioavailability based on in vitro dissolution data.

2. Materials and methods

2.1. Materials

Trimetazidine dihydrochloride was kindly supplied by Wuhan Wu Pharmaceutical Company, China. Hydroxypropyl methylcellulose (HPMC) and ethyl cellulose were purchased from Shanghai Colorcon Pharmaceutical Co. (Shanghai, China). Stearic acid was provided by Hunan Er-kang Pharmaceutical Co., Ltd. (China). Polyvinylpyrrolidone K30 (PVP K30) was purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Docosanoic acid glycerol ester was purchased from Guangzhou Tianrui Pharmaceutical Co., Ltd. (China). Calcium hydrogen phosphate dehydrate and potassium dihydrogen phosphate were purchased from Huzhou Zhanwang Pharmaceutical Co., Ltd. (China). Microcrystalline cellulose, starch and magnesium stearate were provided by Shandong Ahua Pharmaceutical Co., Ltd. (China). Sodium heptane-1-sulfonate was purchased from Tianjin Kernel Company. Trichloroacetic acid and Potassium dihydrogen phosphate was purchased from Tianjin Damao Chemical Reagent Co., Ltd. Ethanol was provided by Tianjin fuyu Chemical Reagent Co., Ltd. Acetonitrile (HPLC grade) and methanol (HPLC grade) were high-performance liquid chromatography (HPLC) grade. Double distilled water was used throughout the study.

Animal: Beagles (female or male were provided by Drug Safety Assessment Center of Shandong Institute of Materia Medica) were used for the in vivo pharmacokinetic studies.

2.2. Preparation and optimization of trimetazidine dihydrochloride sustained release tablets

The sustained release tablets of trimetazidine dihydrochloride were prepared using wet granulation method. After being grinded and sifted, required quantities of drug, HPMC and excipients were mixed thoroughly, subsequently passed through an 80-mesh screen (stainless steel) to blend the ingredients uniformly. The powder blend was moistened with the required amount of wetting agent (2% HPMC E50LV in 80% ethanol solution or 8% PVP K30 in 80% ethanol solution or 80% ethanol) and then pressed through a 30-mesh screen to prepare wet granules. The granules were dried at 45–55 °C for 2 h and the moisture content was controlled within 3% to 5%. The dried granules were then retained on 30-mesh screen (stainless steel), mixed with a prescribed amount of magnesium stearate as lubricant. Finally, the tablets were compressed using a flat-faced 8-mm punch in single-punch press tablet machine. Each
tablet contained 35 mg of trimetazidine dihydrochloride, keeping hardness between 5.0 and 7.0 kgf.

To study the influences of the tablet formulation, trimetazidine dihydrochloride sustained release matrix tablets were prepared according to the orthogonal design (Table 1). The three major factors were set as follows: A, the amount of HPMC; B, the amount of blocking agents; C, the amount of loading agents. The similarity factor ($f_2$) was employed to evaluate the release profiles of various formulations compared with the release profile of marketed tablets. In the orthogonal experimental design, $f_2$ was chosen as the evaluation index.

### Table 1 – Factors and levels of orthogonal experiment for trimetazidine dihydrochloride sustained release tablets

<table>
<thead>
<tr>
<th>Levels</th>
<th>A (mg/tablet)</th>
<th>B (mg/tablet)</th>
<th>C (mg/tablet)</th>
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<td>2</td>
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<td>75</td>
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<td>3</td>
<td>87.5</td>
<td>15</td>
<td>100</td>
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</table>

2.3. **Tablet weight variation**

Weight variation tests of marketed tablets and three batches of self-made tablets were done respectively. Twenty tablets were weighed to obtain the average tablet weight and the individual tablet weight was compared to the average. And then weight variation was evaluated for utilizing criteria based on the Chinese Pharmacopoeia (ChP).

2.4. **In vitro dissolution studies**

The release studies of trimetazidine dihydrochloride from the self-made and marketed sustained release tablets were performed according to the ChP paddle method. Studies were carried out at (37 ± 0.5) °C and 50 rpm rotation speed in 900 mL of 0.1 M HCl, pH 4.5 PBS, pH 6.8 PBS and water, respectively. The amount of drug used was equivalent to 35 mg. Five milliliters of the dissolution samples were withdrawn at different time intervals (0.5, 1, 2, 4 and 8 h) and were replaced with equal volume of fresh release medium to maintain a constant total volume [13]. Samples were filtered through 0.45 μm millipore filter and assayed for drug content by a UV spectrophotometer at λmax of 231 nm after appropriate dilution. Moreover, the selectivity of the UV method was studied by comparing UV spectrum of blank excipients with those of corresponding trimetazidine dihydrochloride standard solution. As a result, no interference from excipients was observed at λmax of 231 nm (Fig. 1).

Cumulative amount of trimetazidine dihydrochloride dissolved in the preparations was calculated using calibration curves. Dissolution tests were carried out in six vessels per

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![Fig. 1 – UV spectrums for trimetazidine dihydrochloride (a) and blank excipients (b) in 0.1 M HCl (Fig. 1A), pH 4.5 PBS (Fig. 1B), pH 6.8 PBS (Fig. 1C) and water (Fig. 1D).](image-url)
formulation \((n = 6)\). The similarity factor \((f_{2})\) was used as a basis to compare the difference between self-made tablets and marketed tablets in dissolution profiles, which was calculated using the following equation [14].

\[
f_{2} = 50 \log \left( \frac{1 + \frac{1}{n} \sum_{t=1}^{n} (R_{t} - T_{t})^2}{0.5} \right) \times 100
\]

where \(n\) is the number of time points for tested samples, \(R_{t}\) is the dissolution value of the reference batch at time \(t\), and \(T_{t}\) is the dissolution value of the test batch at time \(t\). The similarity factor \((f_{2})\) is a measurement of the similarity in the percent dissolution between the two curves. And \(f_{2}\) values greater than 50 \((50-100)\) ensure sameness or equivalence of the two curves.

2.5. Drug release mechanism

The description of in vitro dissolution profiles was analyzed using the following mathematical models with different equations [15].

Zero order model: \(M_{t}/M_{\infty} = k_{0}t\)

First order model: \(\ln(1 - M_{t}/M_{\infty}) = -k_{1}t\)

Higuchi model: \(M_{t}/M_{\infty} = k_{v}t^{1/2}\)

Ritger–Peppas model: \(M_{t}/M_{\infty} = k_{r}t^{n}\)

where \(M_{t}\) is the amount of drug released at time \(t\), \(M_{\infty}\) is the total amount of drug, \(k_{0}\) is zero order release rate constant, \(k_{1}\) is first order release rate constant, and \(k_{v}\) is the Higuchi rate constant. Besides, \(n\) is the release exponent (e.g. first order release when \(n = 1\)), describing the kinetic and the drug release operating mechanism for cylindrical shaped matrices.

In the Ritger–Peppas model, the value of \(n\), representing the diffusion pattern, \(n \leq 0.45\), corresponds to a Fickian diffusion mechanism, \(0.45 < n < 0.89\) to anomalous non-Fickian transport, \(n = 0.89\) to Case II transport, and \(n > 0.89\) to super case II transport [16]. The correlation coefficient \((r)\) was used as an indicator of the best fitting, for each of the models considered.

2.6. In vivo pharmacokinetics study in beagles

2.6.1. Study design

The study was conducted to compare the pharmacokinetics of trimetazidine from the self-made tablets to commercially available tablets (Vastarel MR, 35 mg), following the administration of single doses equivalent to 70 mg (two tablets per dose), each using a non-blind, two-treatment, two-period, randomized, crossover design. Six healthy beagle dogs of either sex were selected for experiment and divided into two groups (3 animals in each) randomly. The dogs were fasted for about 12 h before the study, while water was provided freely as much they required.

The study was performed on two phases. In Phase I, half the number of beagle dogs received the self-made tablet and the remainder received the commercially available tablet which is considered as a standard. Both treatments were ingested with 250 ml of water, while no food was allowed for 4 h after dosing. A washout period of 1 week separated the phases. In Phase II, the reverse of randomization took place. Venous blood samples (3 ml) were withdrawn and taken into heparinized tubes at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24 and 30 h after administration of each treatment. The blood samples were immediately centrifuged at 3000 rpm for 10 min, plasma obtained by and stored at \(-20 ^\circ\text{C}\) until analysis by HPLC.

2.6.2. Chromatographic conditions

The quantitative determination of trimetazidine dihydrochloride in plasma was performed using a modified HPLC method of Min Kyo Jeoung et al. [17]. Chromatographic separation was performed at 30 °C on reversed-phase C18 column (4.6 mm × 150 mm). The mobile phase consisted of potassium dihydrogen phosphate (0.05 mol/l, pH was adjusted to 4.0 with 10% phosphoric acid) and methanol (76:24, v/v) and was delivered to the system at the flow rate of 1.0 ml/min with UV detection at 210 nm.

2.6.3. Standard solutions

A 500 µl aliquot of blank plasma was accurately measured into a 5-ml centrifuge tube, spiked with appropriate standard solutions to produce concentrations of 25, 50, 100, 200, 500, 1000, 2000 ng/ml of trimetazidine dihydrochloride. 100 µl of 10% (w/v) trichloroacetic acid was added to the above plasma samples, which was vortexed for 3 min and centrifuged for 12 min at 12,000 rpm [18]. The resulting supernatant liquid contained 20.83, 41.67, 83.33, 166.67, 416.67, 833.33, 1666.67 ng/ml trimetazidine dihydrochloride in plasma, respectively. And then 20 µl of each sample was injected into the column for analysis. Under the described conditions, the retention time of trimetazidine dihydrochloride was about 12.8 min. A standard curve was established by plotting the peak area of trimetazidine dihydrochloride against its concentration in plasma. The lower limit of quantification was 20.83 ng/ml. The method showed good linearity \((R^2 = 0.9987)\) in the range of 20.83–1666.67 ng/ml in beagles plasma. The mean extraction recoveries of trimetazidine dihydrochloride were 85–115%, RSD < 7%. The inter-day and intra-day relative standard deviations (RSDs) for trimetazidine were less than 12% at the above concentrations.

2.6.4. Pharmacokinetic analysis

Pharmacokinetic analysis of the two treatments was performed for each dog by using DAS2.0 (drug and statistics for windows) program. Maximum drug concentration \((C_{max})\) and the corresponding time to \(C_{max}\) \((t_{max})\) were obtained from the plasma concentration-time curves directly. The area under the curves, \(AUC_{0\rightarrow t}\) \((ng h/ml)\), was calculated by the trapezoidal rule from 0 to 30 h. On the other hand, \(AUC_{0\rightarrow \infty}\) \((ng h/ml)\), the area under the curve from zero to infinity, was calculated as \(AUC_{0\rightarrow \infty} = AUC_{0\rightarrow t} + C/t_{k}\), where, \(C_{i}\) is the drug plasma concentration observed at time \(t\) and \(K_{e}\) is the apparent elimination rate constant. Half-life \((t_{1/2})\) was obtained by dividing 0.693 with \(K_{e}\). Mean residence time (MRT) was calculated from AUMC/AUC. The relative bioavailability \((F)\) of the self-made tablet was calculated by dividing its \(AUC_{0\rightarrow \infty}\) with that of marketed sustained release dosage form [19].
2.6.5. Statistical analysis
The results were expressed as mean ± standard deviation (SD).
The comparison between two groups was performed using unpaired Student’s t-test, a significant level of difference for the tests was considered at a level of P < 0.05. The pharmacokinetic parameters of the two groups were analyzed using the DAS 2.0 software package (Chinese Pharmacological Society).

2.7. In vitro–in vivo correlation

A point-to-point in vitro–in vivo correlation of self-made tablets was developed for relating percentage of drug in vitro dissolution to percentage of drug in vivo absorbed. Based on a good correlation, measuring the in vitro dissolution rate alone is sufficient to determine the pharmacokinetic profile in vivo. It allows the in vivo bioavailability test with the fewest possible trials in animals and man for the prepared formulation.

The fraction of the drug absorbed ($F_r$) was calculated by the Wagner–Nelson Eq. (1) or by the Loo–Riegelman Eq. (2) for both a one-compartment model and the two-compartment model [20].

$$F_r = \frac{C_t}{k_{int} \times \text{AUC}_{0\rightarrow\infty}} \times 100\%$$  \hspace{1cm} (1)

$$F_r = \frac{C_t + k_{int} \times \text{AUC}_{0\rightarrow\infty} + X_{t}/V_i \times 100\%}{k_0 \times \text{AUC}_{0\rightarrow\infty}}$$ \hspace{1cm} (2)

where $F_r$ is the fraction of the drug absorbed, $C_t$ is the concentration of drug in the plasma at time point $t$, $k_{int}$ is the elimination rate constant, AUC<sub>0→∞</sub> is the calculated area under the plasma concentration curve from zero to time $t$, and AUC<sub>0→∞</sub> is the calculated area under the plasma concentration curve from time zero to infinity. $X_{t}/V_i$ is the apparent tissue compartment concentration at the time $t$. The percent of drug absorbed ($F_r$) at the specified time points was plotted against the percent of drug dissolved in vitro at the same time points. The linear regression coefficient ($R^2$) was used to evaluate the correlation between in vitro release and in vivo absorption.

3. Results and discussions

3.1. Optimization of formulation of trimetazidine dihydrochloride sustained release matrix tablets

3.1.1. Results of the test of orthogonal design

Based on preliminary study, three factors were chosen as research objects, including A, B and C. Furthermore, the factors affecting $f_2$ were studied in orthogonal experimental design. Table 2 showed the results of drug release and orthogonal design. The range (R) among the score averages is the difference between the highest and the lowest score average. According to Table 2, the effect of B (the amount of blocking agents) was extremely significant; the effect of other factors was not significant. The effects of each factor on the $f_2$ were as follows: B (the amount of blocking agents) > A (the amount of HPMC) > C (the amount of loading agents). $K_{1a}, K_{2a}$ and $K_{3a}$ were the average sum scores of Level 1, Level 2 and Level 3 for each factor, respectively. Apparently, the larger the average sum score was the closer to the release profile of marketed tablets. Analytical results of three factors were A: 3 > 2 > 1; B: 3 > 2 > 1; C: 3 > 2 > 1, so the optimal formulation was found to be A<sub>3</sub>B<sub>2</sub>C<sub>1</sub> and it was obtained as follows: HPMC, 87.5 mg; blocking agents, 15 mg; loading agents, 100 mg.

3.1.2. Lot reproducibility

Three batches of the trimetazidine dihydrochloride sustained release tablet were prepared by the optimal formulation and the in vitro release tests were performed. Batches I, II and III showed similarity factor $f_2$ values of 71.41, 69.16 and 67.60, respectively. Hence, the drug release from the three batches tablets was similar to that of the marketed product (Vastarel MR, 35 mg). Moreover, ANOVA test shows that batches I, II and III are not significantly different in their drug release profile (P > 0.05 at each time point) and the values of $f_2$ (P > 0.05). The batch reproducibility study indicated that the formulation methodology employed was found to be suitable for trimetazidine dihydrochloride sustained release tablets.

<table>
<thead>
<tr>
<th>Run</th>
<th>Factors</th>
<th>Release rate (%)</th>
<th>Similarity factor</th>
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</thead>
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<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
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</table>

Table 2 – Results of orthogonal experiment design.
3.2. Tablet weight variation

The results of weight variation are shown in Table 3. Average weights of marketed tablets and three batches of self-made tablets were calculated as 0.2105, 0.2033, 0.2043, 0.2067, respectively \((n = 20)\). As shown in Table 3, no tablet deviated from the average weight by more than 7.5% and indicated that the self-made tablets were obtained of uniform weight.

3.3. In vitro dissolution studies

In the present study, the in vitro dissolution studies were carried out for the self-made sustained release tablets in four different dissolution media (0.1 M HCl, pH 4.5 PBS, pH 6.8 PBS and water) and the release profiles are shown in Fig. 2. It is clear that the self-made sustained release tablets released about 20% of its trimetazidine dihydrochloride content in the four media after 0.5 h and the amount of the drug released in 8 h was not less than 80% of the labeled amount in the four media. Moreover, the in vitro release behavior of the self-made formulation was not affected by pH of dissolution medium. These results suggested that the self-made tablet exhibited a slow release in vitro which is independent of the pH of dissolution media.

Besides, the results of the in vitro release of trimetazidine dihydrochloride from the self-made sustained release tablets in comparison with that of market product (Vastarel MR) in four media are graphically shown in Table 4 and Fig. 3. As shown in Table 4, the similarity factor \(f_2\) was used to compare the two dissolution profiles, and the results showed the \(f_2\) values ranged from 60 to 75, indicating that the self-made sustained release tablets shared a similar drug in vitro release behaviors with the marketed tablets. Dissolution studies revealed it is expected to provide a new excellent candidate for trimetazidine dihydrochloride sustained release tablets in the market.

3.4. Drug release mechanism studies

The in vitro release studies were carried out for the marketed and self-made sustained release tablets in 0.1 M HCl, water, and phosphate buffers with pH 4.5 and 6.8 media. In order to determine the suitable drug release kinetic model, the in vitro release data were analyzed according to zero-order model, first-order model, Higuchi model and Ritger–Peppas model. Correlation is higher as absolute value of the correlation coefficient \((r)\) is closer to 1.

Firstly, analysis was performed by the zero order model, first order model and Higuchi model equations. In case of the marketed tablets, the correlation coefficient \((r)\) values for Higuchi model were found to be higher in 0.1M HCl (0.9988) and water.

Table 3 – Results of tablet weight variation.

<table>
<thead>
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<th>No</th>
<th>Marketed (g)</th>
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<td>0.2106</td>
<td>0.2045</td>
<td>0.2032</td>
<td>0.2059</td>
</tr>
<tr>
<td>20</td>
<td>0.2110</td>
<td>0.2074</td>
<td>0.2018</td>
<td>0.2093</td>
</tr>
<tr>
<td>Average weight (g)</td>
<td>0.2105</td>
<td>0.2033</td>
<td>0.2043</td>
<td>0.2067</td>
</tr>
<tr>
<td>The limit of weight variation %</td>
<td>±7.5%</td>
<td>±7.5%</td>
<td>±7.5%</td>
<td>±7.5%</td>
</tr>
<tr>
<td>Upper and lower limits of weight (g)</td>
<td>0.1947-0.223</td>
<td>0.1880-0.215</td>
<td>0.1890-0.216</td>
<td>0.1912-0.222</td>
</tr>
<tr>
<td>Result</td>
<td>Qualified</td>
<td>Qualified</td>
<td>Qualified</td>
<td>Qualified</td>
</tr>
</tbody>
</table>

Fig. 2 – Dissolution profiles of trimetazidine dihydrochloride from self-made sustained release tablets in 0.1 M HCl, pH 4.5 PBS, pH 6.8 PBS and water.
media (0.9974), when compared to that of first order kinetics and zero order kinetics. However, the ‘r’ values for the first order release kinetics were found to be higher in phosphate buffers with pH 4.5 (0.9991) and 6.8 media (0.9987), when compared to that of zero order kinetics and Higuchi model. It indicates that the release of trimetazidine dihydrochloride from marketed sustained release tablets was fitted to Higuchi model in 0.1 M HCl and water media, while the drug release followed first order kinetics in phosphate buffers with pH 4.5 and 6.8 media (Table 5). From Table 5, for the self-made formulation, first-order kinetics had the higher regression value compared to the zero and Higuchi kinetics in four media, which indicates that the release of trimetazidine dihydrochloride from the prepared sustained release tablets was fitted well with the first-order in the four media. In addition, the dissolution data of self-made and marketed tablets were fitted to the Ritger–Peppas model; the diffusion exponent values ranged between 0.45 and 0.89, but were close to 0.45, which appears to indicate trimetazidine hydrochloride was released from the two sustained-release formulations by the synergistic effect of diffusion and erosion skeleton, but with diffusion serving as the main release way. This may be attributed to the high water-solubility of the trimetazidine dihydrochloride in the sustained release matrix tablets.

3.5. In vivo pharmacokinetics study in beagle dogs

Pharmacokinetic studies of self-made sustained release tablets (test tablets) of trimetazidine dihydrochloride compared with commercially available sustained-release tablets (reference tablets) were investigated. The plasma drug concentrations of the two sustained-release tablets at different time intervals were determined respectively. And the mean concentration-time profiles for test and reference tablets are shown in Fig. 4. Similar to the commercially available products, a steady plasma concentration of trimetazidine dihydrochloride was obtained for the self-made sustained release tablets. Most importantly, the

**Table 4 – The cumulative amount of drug release ($F_t$) from the self-made and marketed tablets and the calculated similarity factor ($f_2$) for trimetazidine dihydrochloride dissolution profiles obtained from self-made tablets compared to the marketed tablets.**

<table>
<thead>
<tr>
<th>Medium</th>
<th>Sample</th>
<th>$F_t$ (%)</th>
<th>$f_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
<td>1 h</td>
</tr>
<tr>
<td>0.1 M HCl</td>
<td>Marketed</td>
<td>25.83</td>
<td>35.51</td>
</tr>
<tr>
<td></td>
<td>Self-made</td>
<td>23.55</td>
<td>33.86</td>
</tr>
<tr>
<td>pH 4.5 PBS</td>
<td>Marketed</td>
<td>24.53</td>
<td>35.94</td>
</tr>
<tr>
<td></td>
<td>Self-made</td>
<td>22.13</td>
<td>33.07</td>
</tr>
<tr>
<td>pH 6.8 PBS</td>
<td>Marketed</td>
<td>27.12</td>
<td>37.63</td>
</tr>
<tr>
<td></td>
<td>Self-made</td>
<td>21.47</td>
<td>31.00</td>
</tr>
<tr>
<td>Water</td>
<td>Marketed</td>
<td>24.55</td>
<td>35.76</td>
</tr>
<tr>
<td></td>
<td>Self-made</td>
<td>21.49</td>
<td>31.91</td>
</tr>
</tbody>
</table>

Fig. 3 – Comparison of in vitro dissolution profiles of self-made sustained release tablet and the marketed tablet in 0.1 M HCl (a), pH 4.5 PBS (b), pH 6.8 PBS (c) and water (d), respectively.
in vivo Care related to the rate and values for self-made sustained release tablets and marketed tablets. Then it could be seen that the drug release behavior from self-made tablets was similar to the commercially available sustained-release tablets. The values of the pharmacokinetic parameters; moreover, the two formulations were population bioequivalent. DAS 2.0 software was used to perform the population bioequivalent (PBE) statistical analyses. For log transformed observations AUC_{0–∞} and C_{max} the upper confidence limit on the appropriate was >0, indicating these two formulations were population bioequivalent. Moreover, test for the analyzed T_{max} showed no significant differences (P = 0.26 > 0.05). Then it could be established that the self-made tablets were bioequivalent to the marketed sustain release tablets and that both formulations could be considered equally effective and safe in therapeutics in angina pectoris patients.

Thus, the drug release behavior from self-made sustained release tablets in vivo was similar to the commercially available products, evidenced by the similarity in their pharmacokinetic parameters; moreover, the two formulations were population bioequivalent based on AUC_{0–∞} and C_{max}. Therefore, the self-made tablets were bioequivalent to commercially available sustained-release tablets, and the two formulations are interchangeable.

3.6 In vivo–in vitro correlation

The IVIVC for trimetazidine dihydrochloride was examined. The optimization one compartment models was determined for the drug dosage forms after validation by DAS 2.0 (drug and statistics for windows) program. Therefore, in vivo–in vitro correlation was investigated using the percentage of drug release in a water medium of self-made sustained release tablets and the drug absorption fraction in beagle dogs at fasted condition. The accumulative absorption fraction of trimetazidine dihydrochloride was calculated according to the Loo–Riegelman method. As shown in Fig. 5, the correlation coefficient (R²) between the drug release from the tablets and absorption of drug was 0.9720, indicating that the drug release correlated well with the fraction absorption. Therefore, the in vivo absorption behavior could be predicted by the test of in vitro drug release.

4. Conclusions

The present study was carried out for the prepared sustained release tablets of trimetazidine dihydrochloride compared with...
the commercially available modified release tablets (Vastarel MR, 35 mg). For the dissolution studies in vitro, the $f_t$ factor confirmed that the release of trimetazidine dihydrochloride from the prepared tablets was similar to that of the marketed tablets. Results from in vivo pharmacokinetics study in beagle dogs also clearly indicated that the variability in the prepared trimetazidine dihydrochloride absorption profiles was equivalent to the marketed products. The in vivo comparative study results confirmed that the pharmacokinetic parameters AUC and the $C_{max}$ of trimetazidine dihydrochloride were similar after oral administration with the self-made and the marketed sustained released tablets. Besides, compared with the marketed tablets, the relative bioavailability judged from the AUC$_{0-\infty}$ was found to be 102.52%. Moreover, the two formulations were population bioequivalent based on AUC$_{0-\infty}$ and $C_{max}$. Thus, it could be concluded the self-made sustained release tablets were bioequivalent to the branded products in the market (Vastarel MR, 35 mg), which proved that the prepared tablets can be used interchangeably with Vastarel MR. The in vitro–in vivo correlation coefficient (R²) was 0.9720, suggesting that the prepared tablets followed a strong correlation between in vitro release and pharmacokinetic effect; moreover, it seemed to be reasonable to predict the drug absorption in vivo through the in vitro release study. Therefore, the high correlation between in vitro dissolution and in vivo absorption could be used to forecast the in vivo bioavailability with allowing dosage form optimization with the fewest possible trials in animals and man.

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**REFERENCES**


