Preparation and evaluation of sustained-release diltiazem hydrochloride pellets

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1. Introduction

Diltiazem hydrochloride (DTZ), one member of calcium channel blockers, is widely used in the treatment of angina pectoris and hypertension [1]. DTZ is extensively metabolized by the liver and excreted by the kidney. And it is absorbed fraction up to about 80%. However, due to an extensive first-effect, DTZ is subject to an absolute bioavailability of about 40%. The plasma elimination half life following single or multiple administration is approximately 3–5 h. Frequent administration of immediate release preparations is often recommended to maintain effective blood plasma levels of DTZ. A slow and sustained release of the active ingredient is beneficial to patients to maintain sustainable levels of DTZ in the blood plasma [2,3].

We aimed to develop sustained release capsules of DTZ in multiple-unit pellet system (MUS) by extrusion–spheronization method and coating technique. In comparison to the

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conventional or immediate-release dosage forms, MUS has some unique advantages. In MUS, pellets are often filled into hard gelatin capsules or compressed into tablets [4]. In one single dose of MUS, pellets are rapidly and homogeneously distributed in the gastrointestinal tract (GIT) in spite of feeding or fasting condition, thus reduce the risk of high local concentration and side effects, increase the contract region between drug and the GIT, furthermore, enhance drug absorption and lower the fluctuations of peak plasma. Therefore, MUS could decrease dose frequency and increase patient compliance, improve the safety and efficacy of drug [5–7].

Though there are many approaches to prepare pellets, such as extrusion and spheronization, fluid bed granulation [8], centrifugal granulation [9]. Extrusion—spheronization is one of common strategies to prepare pellets for acquiring modified release systems in pharmaceutical industry since 1970 [10], and the method consists of two basic processes of extrusion and spheronization. Pellets prepared by the method of extrusion—spheronization have some advantages, such as high sphericity, compact structure, low hygroscopicity, narrow particle size distribution and smooth surface [11,12].

In this study, we attempt to apply extrusion—spheronization, simply and easily industrialized preparation method to prepare uncoated pellets, followed by coating process using methacrylic or ethylcellulose copolymers to achieve the sustained release, which have the similar pharmacokinetic characteristic to Herbesser®. Herbesser® was a commercially available DTZ sustained release capsules. Many factors have been studied to adjust the drug release rate by different coating formulations. The dissolution tests are performed in different media, the profiles of dissolution from the commercial one and self-made are compared by similar factors method, and the performances in vivo from commercial one and self-made formulation are carried out in beagle dogs.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride was purchased from Nanchong Science and Technology Development Co., Ltd (Hubei, China), Herbesser® was purchased from Tianjin Tanabe Seiyaku Co., Ltd (Tianjin, China). Huling® PH 101 (microcrystalline cellulose) was purchased from Zhanwang Pharmaceutical Co., Ltd (Zhejiang, China). Eudragit® NE30D, Eudragit® RS30D and Surelease® were kindly provided by Colorcon (Shanghai, China). HPLC-grade methanol and acetonitrile were purchased from Fisher Scientific (Pittsburgh, PA, USA). All other materials were of analytical grade and used as received.

2.2. Preparation of diltiazem hydrochloride (DTZ) sustained release pellets

Drug-loaded pellets were prepared by the extrusion—spheronization method. The formulation of the cores was as follows: DTZ 125 g; MCC 125 g; HPMC (K4M, 2%) 110 ml, which was used as a binder. The powders were mixed for 30 min before the adhesive was added, then appropriate quantity of binder was added slowly during constant mixing, and the process continued for a further 20 min. The wet mass was extruded at room temperature, through a die of 0.8 mm diameter and 4 mm in length by 20 rpm equipped with an axial screen extruder (WL350, Wenzhou, China), the extrudate was collected in a container before it was spheronized. About 50 g of extrudate was spheronized at a time, on a spheronizer 40 cm in diameter equipped with a grooved plate, for 2 and 10 min at 2000 and 8000 rpm, respectively. The pellets were dried under conditions at 40 ± 2 °C for 24 h. The 18–24 mesh pellets were chosen for coating.

Eudragit® NE30D, Eudragit® RS30D and Surelease® three types of aqueous polymeric dispersions, were used for the preparation of sustained release pellets. The formulations were followed as:

Formulation 1 (F1): coated with Eudragit® NE30D, resulting in 6–13% coat loading. Coating suspension includes talc, HPMC (E5) and SDS.

Formulation 2 (F2): coated with Eudragit® RS30D, resulting in 10–25% coat loading. Coating suspension includes t alc, TEC and SDS.

Formulation 3 (F3): Surelease®, resulting in 10–30% coat loading.

A fluid-bed bottom spray processor was adopted for the coating of the pellets by using Eudragit® NE30D or Eudragit® RS30D as the coating solution. The coating suspensions were prepared as follows steps: (1) Eudragit® NE30D or Eudragit® RS30D was dripped into the desired volumes of water and agitated by magnetic stirrer at room temperature for at least 30 min; (2) micronized talc was dispersed in water and stirred until no lumps formed; (3) materials (1) and (2) were mixed and stirred, then the HPMC/TEC, SDS were also added into the suspensions. After stirred for at least 1 h, the coating suspensions were spraying onto the pellets. After Surelease® dispersed in water 1 h, the solutions were spraying onto the pellets.

Coating conditions: inlet temperature: 30 °C, outlet temperature: 25–30 °C, spray rate: 2 ml/min, atomization pressure is 0.2 MPa, blast pressure is 0.3 MPa. The final pellets were dried in oven at 40 °C for 12 h.

2.3. Assay of the drug content

Drug content was determined by the HPLC method. The HPLC system included a LC-AT pump and SPD-10A UV—Vis detector (SHIMADZU Japan). A Kromasil C18 column (5 μm, 200 × 4.6 mm) was used. The mobile phase consisted of sodium acetate—camphor sulfonic acid buffer (dissolve 9.0 g of sodium acetate and 1.2 g of camphor sulfuric acid in 500 ml of water)—acetonitrile—methanol (50:26:24, V/V/V), adjust the pH value to 6.5 with acetic acid, the flow rate was 1.0 ml/min, and the UV detector was set at 240 nm.

From each batch of the coated pellets, a certain amount was taken and milled to fine powders. Then fine powders containing 100 mg drug were weighed and added to a 100 ml volumetric flask containing 70 ml of methanol. After, a 30-min ultrasonic extraction, the solution was diluted with methanol to 100 ml and then filtered through a 0.45 μm membrane. Precisely 5 ml of this solution was transferred to 25 ml volumetric flask and methanol was added to give a volume of
Table 1 – Formulation of uncoated pellets containing different amounts of MCC.

<table>
<thead>
<tr>
<th>Uncoated pellets</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTZ (%)</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>MCC (%)</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Binder</td>
<td>HPMC (2%)</td>
<td>HPMC (2%)</td>
<td>HPMC (2%)</td>
<td>HPMC (2%)</td>
<td>HPMC (2%)</td>
</tr>
<tr>
<td>Angles of repose (θ)</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
<td>17 ± 2</td>
<td>25 ± 3</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>1 h dissolution (%)</td>
<td>100.12 ± 5.36</td>
<td>101.02 ± 1.46</td>
<td>99.21 ± 4.94</td>
<td>99.93 ± 4.12</td>
<td>101.23 ± 1.68</td>
</tr>
</tbody>
</table>

100 ml. 20 μl of the solution was injected for analysis. All samples were analyzed in triplicate.

2.4  In vitro dissolution tests

The release of diltiazem hydrochloride (DTZ) from pellets was investigated based on ChP 2010 Type 2 dissolution apparatus (paddle method) and all the release tests were conducted in triplicate. In this case, the 900 ml medium was kept at 37 ± 0.5 °C and the rotating speed was 100 rpm. 0.1 M HCl solution, pH 4.5 sodium acetate buffer, pH 6.8 and pH 7.2 phosphate buffers, and purified water were used as dissolution media. The capsules containing the drug pellets equivalent to 90 mg DTZ were used in all dissolution tests. At each predetermined time point, a 5 ml aliquot of dissolution medium was withdrawn and replaced by the same volume of fresh medium. The total volume of medium was kept at 900 ml. The sample solution was filtered through 0.45 μm filtration membrane and analyzed using a UV spectrophotometer (Beijing Rayleigh Analytical Instrument Co.) at 240 nm.

2.5  Bioavailability studies

2.5.1  In vivo studies

The sustained pellets of DTZ were filled into hard gelatin capsules for the pharmacokinetic parameters studies. Meanwhile, Herbesser® was served as the control. The experimental protocol was admitted by the university ethics committee for the use of experimental animals and conformed to the guideline for care and use of laboratory animals. The study was based on single-dose, open-label, randomized two-way crossover design with wash out period of one week. The six male beagle dogs were divided into 2 groups. After 12 h of fasting, 90 mg of DTZ test and reference preparations were orally administered to test and reference group dogs under fasted conditions, respectively. Venous blood samples (5 ml) were collected 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24 and 36 h after dosing and immediately centrifuged. Plasma samples were kept frozen at −20 °C until assay. Diltiazem hydrochloride in plasma was determined using liquid chromatography–tandem mass spectrometry (LC–MS/MS).

100 μl of plasma was mixed with 50 μl of internal standard (verapamil solution) and 50 μl of mobile phase solution. The solution vortexed for 1 min, 100 μl of acetonitrile added to precipitate the proteins in the plasma. After centrifugation (10,000 rpm) for 10 min, 5 μl aliquot of supernatant was directly injected into the high performance liquid chromatography system.

Chromatographic conditions [13]: ACQUITY UPLCTM BEH C18 column (1.7 μm, 50 mm x 2.1 mm, Waters Corp, Milford, MA, USA); mobile phase consisted of acetonitrile: 8 mM ammonium acetate (70:30, v/v); flow rate 0.2 ml/min; UV detector wave length 240 nm.

2.5.2  Data analysis

The concentrations of DTZ in plasma were calculated, and all the data were processed by DAS 2.0 statistical software. The area under the mean plasma concentration–time curves from zero to time (AUC0–36 h) and (AUC0–∞) was calculated.

3. Results and discussion

In this study, DTZ sustained release pellets were prepared by the extrusion/spheronization method, and then were subjected to coating with methacrylic acid copolymers (Eudragit NE30 or Eudragit RS30) or derivative of ethylcellulose (Surelease). The in vivo release studies showed that the dissolution profiles of the pellets coated with Eudragit NE30D were similar to the commercially available DTZ sustained release capsules. In vivo study, the principal pharmaceutical parameters showed that the profiles of DTZ from self-made and the marketed one were comparable.

3.1  Formulation and process parameters optimization

3.1.1  Effect of amount of MCC

Formulations of the uncoated pellets are described in Table 1 and the release profile of DTZ in water in 1 h is shown in Fig. 1. The drug release behavior was similar from different formulations. At 5 min, the accumulative release of the uncoated pellets was about 80% and reached 100% at 20 min. That is to say, DTZ could be completely released from the uncoated pellets in water at 1 h (each point represents the mean ± SD, n ≥ 3).

**Fig. 1 –** In vitro release profiles of DTZ from the uncoated pellets in water at 1 h (each point represents the mean ± SD, n ≥ 3).
Table 2 – The effect of disc speed on pellet physical characteristics.

<table>
<thead>
<tr>
<th>Disc speed (rpm)</th>
<th>1000</th>
<th>2000</th>
<th>5000</th>
<th>8000</th>
<th>10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–24 mesh cut yield (%)</td>
<td>74 ± 2.3</td>
<td>84 ± 4.3</td>
<td>87 ± 4.1</td>
<td>87 ± 3.3</td>
<td>76 ± 1.3</td>
</tr>
<tr>
<td>Roundness</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Sphericity (d)</td>
<td>40.2 ± 1.3</td>
<td>22.3 ± 2.5</td>
<td>24.5 ± 3.6</td>
<td>23.3 ± 4.3</td>
<td>24 ± 2.7</td>
</tr>
<tr>
<td>Bulk density (g/ml)</td>
<td>0.77 ± 0.1</td>
<td>0.79 ± 0.3</td>
<td>0.81 ± 0.2</td>
<td>0.82 ± 0.1</td>
<td>0.81 ± 0.2</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.43 ± 0.11</td>
<td>0.45 ± 0.12</td>
<td>0.46 ± 0.12</td>
<td>0.43 ± 0.1</td>
<td>0.45 ± 0.1</td>
</tr>
</tbody>
</table>

Table 3 – Analog analysis of the home-made sustained release capsules and reference capsules in different media (n = 3).

<table>
<thead>
<tr>
<th>Medium</th>
<th>f2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>pH 1.0</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>pH 4.5</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>pH 6.8</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>pH 7.2</td>
<td>68 ± 3</td>
</tr>
</tbody>
</table>
In order to avoid the burst release at the initial stage of the dissolution, we chose Eudragit® NE30D as the coating polymer, coat weight gain of 8.5%, and the final coating formulation included sodium dodecylsulfate (1% of Eudragit® RS30D, w/w) as antistatic agents and talc (20% of Eudragit® RS30D, w/w) as antiadherent.

3.2. Drug release comparison

Dissolution profiles of home-made preparations and marketed sustained-release capsules were compared in various media, including 0.1 M HCl, pH 4.5 NaAc–HAc buffers, water, pH 6.8 and pH 7.2 phosphate buffer solutions. The dissolution profiles of self-made pellets and Herbesser® are shown in Fig. 3. From the dissolution results, the self-made pellets shown slower release rates than that of the marketed ones in 0.1 M HCl and pH 4.5 NaAc–HAc buffer solution, while in the higher pH such as pH 6.8 and pH 7.2 phosphate buffer solutions, the different release rates were present. In general, there were nearly no various profiles of dissolution from the self-made pellets in various media, resulting from the non-sensitive to pH of Eudragit® NE30D.
The similarity factors which are calculated between the market formulation and self-made preparing are presented in Table 3. Similar index was calculated by the similarity factor \( f_2 \) [18]:

\[
f_2 = \frac{50 \times \log \left\{ 1 + \frac{1}{n} \sum \left( \frac{R_t - T_t}{100} \right)^2 \right\}^{0.5} \times 100
\]

where \( n \) is the number of dissolution sample, and \( R_t \) and \( T_t \) are the percentages of the Herbesser\(^\text{®}\) and self-made pellets drug release, respectively. The valve of \( f_2 \) value is between 0 and 100. If \( f_2 \) of control and test preparation is between 50 and 100, then these two preparations drug release are similar. From the data of Table 3, the results of \( f_2 \) in different medium were all more than 50, indicating that self-made sustained release pellets and Herbesser\(^\text{®}\) have similar drug release profiles.

### 3.3 Drug release mechanism

The drug-release data was fitted according to different models in attempt to elucidate the release mechanism. The kinetic models consist of zero order [19], first-order [20], Higuchi model [21] and Ritger–Peppas model [22]. The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods. As shown in Table 4, the first-order model was best fitted for the home-made sustained release pellets.

Many modes of drug release from the extend-control pellets were first-order model, which releases the drug from the dosage form at the constant rate, reducing the fluctuation of drug level in the blood, maintain blood concentration of drug at

![Diagram A](image)

![Diagram B](image)

**Fig. 3** – The effect of pH values on the release profile of marketed and self-made sustained-release capsules. A: Herbesser\(^\text{®}\), B: home-made (each point represents the mean ± SD, \( n \geq 3 \)).

**Table 4** – Models for drug release fitting and correlation coefficients.

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
<th>( r )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero-order model</td>
<td>( Q_t = 8.1736 + 8.8219t )</td>
<td>0.9620</td>
</tr>
<tr>
<td>First-order model</td>
<td>( \ln(100 - Q_t) = -0.1855t + 4.6067 )</td>
<td>0.9970</td>
</tr>
<tr>
<td>Higuchi</td>
<td>( Q_t = 33.571t^{1/2} - 16.847 )</td>
<td>0.9910</td>
</tr>
<tr>
<td>Ritger–Peppas</td>
<td>( \log Q_t = 0.7228 \log t + 1.2703 )</td>
<td>0.9827</td>
</tr>
</tbody>
</table>

**Fig. 4** – Average diltiazem plasma concentration–time curves of the reference and test capsules (each point represents the mean ± SD of 6 dogs).
Table 5 – Pharmacokinetic parameters of test and reference preparations.

<table>
<thead>
<tr>
<th></th>
<th>T½ (h)</th>
<th>Cmax (ng/ml)</th>
<th>Tmax (h)</th>
<th>AUC0–t (ng h/ml)</th>
<th>AUC0–∞ (ng h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>4.2 ± 1.9</td>
<td>85.0 ± 55.1</td>
<td>4.5 ± 1.9</td>
<td>761.1 ± 528.4</td>
<td>767.3 ± 535.5</td>
</tr>
<tr>
<td>Test</td>
<td>4.9 ± 1.9</td>
<td>100.0 ± 66.4</td>
<td>3.5 ± 0.8</td>
<td>824.9 ± 523.6</td>
<td>838.4 ± 601.2</td>
</tr>
</tbody>
</table>

desirable level for an extended period. In order to obtain first order drug release profiles, different technologies can be used, such as, hydrophilic or matrix systems with channel forming agents and barrier membrane coated multiparticulate systems. Eudragit® NE30D was one of low permeability, pH independent swelling coating polymers. It was assumed that some drives, as follows, to obtain the first order drug release profiles for Eudragit® NE30D: (1) Concentration gradient. Once the film was in contact with water, the film swelled, and water slowly permeated into the core of pellets, and the drug was dissolved, thus, the saturable solution of drugs within the coating. Drug molecules diffused down the concentration gradient, and finally released into the outer medium. (2) Channel effect. The influx water induced swelling of membrane and expanded the copolymer network; the compact membrane was converting to un-continuous one, leading to the pore for the water molecule and drug molecule freely influx and efflux the pellet film. In addition, a number of aqueous channels were formed across the film once the pellets are in contact with water, and acted as the release gate for the drug.

3.4. Bioavailability

The in vivo pharmacokinetic behavior of self-made sustained and commercial available capsules (Herbesser®) were investigated following oral administration of 90 mg of DTZ to six healthy beagle dogs. Mean plasma concentration–time curves after administration of test and control preparation were shown in Fig. 4. There main bioavailability parameters are listed in Table 5. The mean relative bioavailability of DTZ self-made sustained pellets to Herbesser®, which was calculated from the AUC0–∞ of DTZ, was 98.5 ± 36.4%. The average peak concentration (Cmax) of the reference (85.0 ± 55.1 ng/ml) was slightly lower than that of the test (100.0 ± 66.4 ng/ml), AUC0–∞ of test and reference were 767.3 ± 535.5 h ng/ml, and 383.4 ± 601.2 ng h/ml, respectively. From the data of main bioavailability parameters, it could conclude that the pharmacokinetic profiles of self-made pellets and marketed ones in vivo were comparable.

4. Conclusion

The DTZ sustained release pellets were successful prepared. The formulation of the uncoated pellets included MCC, binders and DTZ. The uncoated pellets achieved good sphericity, low friability, narrow particle size distribution and smooth surface. It was found that the rotational speed has a significant effect on the physic characteristics of pellets prepared by extrusion and spherization method. The coating polymer Eudragit® RS30D and coating weight gain 8.5% could prepare the desired DTZ sustained-release pellets, which had similar release profiles to the marketed Herbesser® with f2 more than 60. From the bioavailability studies, it was obvious that the home-made sustained pellets could prolong the release of DTZ and has comparable in vivo pharmacokinetic performance to the marketed Herbesser®.

References


