Original Research Paper

A time-released osmotic pump fabricated by compression-coated method: Formulation screen, mechanism research and pharmacokinetic study

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ARTICLE INFO

Article history:
Received 26 February 2014
Received in revised form
17 May 2014
Accepted 19 May 2014
Available online 2 June 2014

Keywords:
Time-released
Osmotic pump
Compression-coated
Central composite design
Pharmacokinetic

ABSTRACT

In this investigation, time-released monolithic osmotic pump (TMOP) tablets containing diltiazem hydrochloride (DIL) were prepared on the basis of osmotic pumping mechanism. The developed dosage forms were coated by Kollidon®SR-Polyethylene Glycol (PEG) mixtures via compression-coated technology instead of spray-coating method to form the outer membrane. For more efficient formulation screening, a three-factor five-level central composite design (CCD) was introduced to explore the optimal TMOP formulation during the experiments. The in vitro tests showed that the optimized formulation of DIL-loaded TMOP had a lag time of 4 h and a following 20-h drug release at an approximate zero-order rate. Moreover, the release mechanism was proven based on osmotic pressure and its profile could be well simulated by a dynamic equation. After oral administration by beagle dogs, the comparison of parameters with the TMOP tablets and reference preparations show no significant differences for \( C_{\text{max}} \) (111.56 ± 20.42, 128.38 ± 29.46 ng/ml) and \( \text{AUC}_{0-48\ h} \) (1654.97 ± 283.77, 1625.10 ± 313.58 ng h/ml) but show significant differences for \( T_{\text{max}} \) (13.00 ± 1.16, 4.00 ± 0.82 h). These pharmacokinetic parameters were consistent with the dissolution tests that the TMOP tablets had turned out to prolong the lag time of DIL release.

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1. Introduction

Oral time-released preparations which are designed to release the drug within a proper period of time after a predetermined lag time are developing quickly as more and more extensive application of chronotherapeutics in clinical practice. Several diseases, including arthritis, asthma, allergies, peptic ulcer disease, dyslipidemia and cancer exhibited predictable circadian rhythms [1,2]. In particular, aggravation of cardiovascular diseases, including arthritis, asthma, allergies, peptic ulcer are developing quickly as more and more extensive application of chronotherapeutics in clinical practice. Several lag time are developing quickly as more and more extensive the drug within a proper period of time after a predetermined Oral time-released preparations which are designed to release in the early morning before patients wake up [3]. It was badly inconvenient to take the conventional drug dosage providing relief of symptoms and protection from those adverse events when necessary. Consequently, we need the administration of a drug formulated in time-released delivery system, i.e. taken at bed time with a programmed start of drug release based on circadian rhythms.

There were various approaches for the time-released drug delivery system, such as system based on osmosis, or capsule, system with change in membrane permeability and system with erodible, soluble or rupturable membrane. Now all of them were gaining popularity for prime advantage that drug is released solely when necessity comes. As a result, risks of development of drug resistance, usually seen in conventional and sustained-release formulations, could be reduced. Among the time-released products mentioned above, osmotic pump preparations have stood out, with superiority for not only matching with circadian rhythms, but also exhibiting reliable comparable in vitro/in vivo drug release [4,5]. The release rate from these types of system depended on the coating components and the osmotic pump across the membrane, without influences from the pH, peristalsis or other interference in gastrointestinal (GI) tract.

Osmotic pump tablets (OPTs) belonged to the class of rate-controlled systems which provided continuous delivery and different types such as monolithic, two-compartment, two-layer push—pull and three-layer osmotic tablets systems were developed [6]. Theeuwes introduced the monolithic osmotic pump (MOP) and brought forward its basic theory in the 1970s [7,8]. It consisted of an osmotic core coated by a semi-permeable membrane drilled with a delivery orifice. The MOP was very simple to prepare and could release water-soluble drugs at the rate of approximate zero-order [9]. Due to its simple production procedures, the MOP avoiding a sophisticated technique had been an emphasis of recent researches. However, the common osmotic pumps were still facing two technical problems, use of organic solvent for coating outer membrane and drilling process for delivering pharmaceutical ingredients, which extremely limit the industrialization of osmotic pumps in pharmaceutical industry. Although many attempts had been made to resolve these two problems, the current situation of industrialization was still difficult.

With the joint efforts of all explorers, a new face had been put on these matters via microporous membrane and non-solvent coating technology. Recently, osmotic pump tablets had been developed in which the delivery orifice was formed by the addition of water-soluble components in the coating material. Once the tablets came in contact with the GI fluid, the water-soluble component dissolved to forming an osmotic pumping system. Subsequently, water diffused through the microporous membrane to dissolve core components, forming an osmotic gap to control the drug releasing [10,11]. As a consequence, the manufacturing process was simplified with the elimination of drilling orifice. Moreover, compression-coated technology, referred as non-solvent coating method, was employed to the TMOP tablets. Compared with traditional coating method, this new coating technique could avoid disadvantages in the pharmaceutical industrialization, such as environmental pollution accompanying with use of organic solution. In general, the compression-coated tablet was composed of an inner core tablet and an outer coating shell. And its thicker outer shell show inherent advantages for chronotherapeutics because of time taken for penetrating of the membrane i.e. is known as lag time [12]. It was generally accepted that the property of compression-coated tablets was the influence of the inner core tablet and outer coating shell in the formulation. We had taken the central composite design (CCD) method to determine the interaction of inner core tablet and an outer coating shell for TMOP tablets with optimal formulations. The CCD method which could provide information on direct effects, pair-wise interaction effects, curvilinear variables effects, was suitable for formulation and process optimization in the field of pharmaceuticals involving with multiple factors and levels since it was an efficient method to reduce the number of experiments [13–16].

The objective of our investigation is to develop time-released monolithic osmotic pump (TMOP) tablets with microporosity by compression-coated technology, in which involve with neither organic solvent nor drilling process. Diliazem Hydrochloride (DIL), a calcium channel blocker which inhibits influx of calcium (Ca^{2+}) ions [16], was chosen as the model drug. The DIL is frequently administered orally for the treatment of angina and hypertension as sustained-release formulations to improve compliance, but the constant delivery of DIL into the body also leads to drug resistance or side effects. Moreover, the high water-solubility (>50%, w/v at 25 °C) of DIL are suitable to apply in TMOP preparations. For the compression-coated microporous TMOP tablet, it provides new ideas to both pharmaceutical manufacture and clinical chronotherapeutics.

2. Materials and methods

2.1. Materials

Polyvinylacetate–polyvinylpyrrolidone (Kollidon®SR) is kindly donated by Basf Auxiliary Chemicals Co., Ltd. Shanghai, China. Microcrystalline cellulose (MCC, Ph102) was supplied by AsahiKasei. Polyethylene glycol (PEG) was received from Anhui Sunhere Pharmaceutical excipients Co., Ltd. The model drug of DIL, obtained from Shanghain Jianhuan Chemical Co., Ltd, was passed through 100 mesh sieve prior to the experiment. The reference preparation (sustained-release capsule, Herbesser) was purchased from Tianjin Tanabe Seiyaku Co., Ltd.
2.2. Preparation of TMOP tablets

DIL-loaded MOP was prepared by compression-coated methods and the sizes of inner cores and coating tablets, the coating quantity (240 mg) have been determined by pre-experiment. The process went like this: Firstly, a mixture of 120 mg DIL and some MCC were directly compacted into a circular tablet (8 mm in diameter) as inner core. Half of coating material consisting of Kollidon®SR and PEG was poured into a die having a diameter of 11 mm and pressed to smooth, then the 8 mm inner core tablet was artificially placed in the center of the pressed coating material. Finally, the remaining coating material was filled into the die and compacted to get the final compression-coated products. Fig. 1 shows the sketch map of the TMOP tablets.

2.3. Study of significant variables

The compression-coated TMOP consists of a pharmaceutical core and an outer coating shell made of release modifiers. So, TMOP tablets may be modified to provide different release pattern by varying composition of polymer material used in the core and outer shell. In this section, we investigated several separate elements to opt for the most important ones influencing the physical properties of the produced DIL-loaded TMOP tablets. As given in Table 1, variables including the coating thickness, the amount of PEG in outer shell, and MCC distribution in core tablet were taken into experiments.

The dissolution experiments of compression-coated tablets were carried out using the paddle method with three preparations per study in a medium of 900 ml 37 °C purified water and a stir of 100 rpm. Samples of 5 ml medium were drawn out with equivalent media replacement on schedule. The concentration of DIL dissolved in the medium was determined spectrophotometrically at the wavelength of 240 nm. According to FDA regulation, the similarity factor (determined spectrophotometrically at the wavelength of

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition of core tablets (mg)</th>
<th>Composition of coating layer (mg)</th>
<th>Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIL MCC</td>
<td>Kollidon®SR PEG 4000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1 120 60</td>
<td>200 40</td>
<td>4.85 ± 0.01</td>
</tr>
<tr>
<td>B</td>
<td>1 120 60</td>
<td>200 40</td>
<td>4.85 ± 0.02</td>
</tr>
<tr>
<td>C</td>
<td>1 120 60</td>
<td>200 40</td>
<td>4.98 ± 0.01</td>
</tr>
</tbody>
</table>

Fig. 1 – The introduction of the TMOP tablets (A. inner core; B. half of coating material; C. inner core with half coating material; D. the final product of TMOP tablets).

Table 1 – The composition of coating and thickness of the compression-coated TMOP tablets.

Y3 and cumulative drug ratio of 24 h (Y3) were selected as dependent variables. All the experimental formulations of the CCD matrix were constructed by Design-Expert software (Trial Version 8.0.5.0, Stat-Ease Inc., MN).

During the course of predicting of the optimal formulation, fitness of the model among the linear, two-factor (2F) interaction and quadratic model was assessed on basis of the analysis of variance p-value and focus on the model maximizing multiple correlation coefficient R2 (predicted) as assessment criteria in the model summary statistic list. Optimization was performed by using a desirability function to obtain the optimal points involving the predetermined constraints where the cumulative drug ratio of 4 h (Y1) was located in a reasonable range of less than 5%, cumulative drug ratio of 14 h (Y2) in its minimum level and cumulative drug ratio of 24 h (Y3) in its maximum levels [14,18,19].
2.5. Pharmacokinetic study

The study was approved by the Ethics Review Committee for Animal Experimentation of Shenyang Pharmaceutical University (Shenyang, China). Six beagle dogs weighing 10 ± 2 kg were obtained from Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). All the beagle dogs were divided randomly into two groups and fasted overnight but allowed to free access to water before experiment. Reference preparations (sustained-released capsules) and tested TMOP tablets were orally administrated to two groups at a dose of 120 mg/body. Blood samples (2 ml) of each animal were sampled via foreleg remaining needle at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36 and 48 h after administration. All the blood samples were immediately centrifuged at 4000 rpm for 10 min to separate the plasma. Thereafter, a 1000 µl of plasma was mixed with 500 µl of K2HPO3 (0.5 mol/l) and 100 µl internal standard (Verapamil HCl, 2 µg/ml) and shaken for 3 min using a vortex mixer. Then 5000 µl of mixed diethyl ether and n-hexane (1:1, v/v) was added and the mixture was vortexed at room temperature for 5 min. After centrifugation at 4000 rpm for 10 min, the organic layer was transferred into another clean tube and receiving 100 µl of HCl (0.01 mol/l). The mixture was vortexed at for 5 min and centrifuged at 4000 rpm for 5 min. The upper organic layer was abandoned and 60 µl of lower liquor was injected into the HPLC system (Pgeneral P6eN6, Beijing Purkinje General Instrument Co., Ltd) for analysis.

The main pharmacokinetic (PK) parameters were acquired with the help of a PK program DAS 2.0. The various PK parameters that were analyzed included maximum peak concentration of the drug in plasma ($C_{\text{max}}$), the time to reach maximum concentration ($T_{\text{max}}$), and the area under the plasma concentration–time curve ($\text{AUC}_{0-48\text{ h}}$). All results were presented as mean ± SD values.

3. Results and discussion

3.1. Study of significant variables

During the prior investigation of TMOP tablets processing, different variables (PEG 4000 amount in outer coat, MCC amount in core tablets and coating thickness) were tested to opt for the independent variables. Plots in Fig. 2 show the corresponding dissolution curves of TMOP prepared according

![Fig. 2](image-url)
to formulations in Section 2.4. Obvious differences were observed in each group of formulations and these were also reflected by the $f_2$ value (data not shown) that all the $f_2$ values were less than 50%. Finally, the three factors (PEG 4000 amount, MCC amount and coating thickness) were recognized as independent variables for TMOP releasing, and prepared for the CCD study.

The time when 5% or more DIL was dissolving into the dissolution medium was regarded as the termination of lag time in this experiment. In general, 4-h lag time was appropriate for time-released preparations aiming at cardiovascular disease. As shown in Fig. 2A, the produced TMOP tablets, with either 40 mg or 60 mg PEG in outer layers, could generate the qualified lag time while 80 mg PEG led to a much shortened lag time (less than 2 h). The larger quantity of PEG had made coating layer more porous, accelerating water molecule going inside pharmaceutical core and enhancing permeation ability for DIL solution rushing outside the membrane. Thus, the PEG amount was negatively related to lag time. For coating layer, it had been studied [20–22] that an increase in hardness or compressive pressure could lead to the decrease in porosity, slowing down the water inflow. Due to equivalent coating quantity of TMOP in Fig. 2B, an increased pressure produced a thinner coating layer where there's less porosity than thicker one. The changes in outer layer had resulted in different lag time of the compression-coated tablet. As shown in Fig. 2B, a more than 6-h lag time was observed in the thinnest TMOP (4.75–4.76 mm), while a just 2-h lag time in the thickest one (4.98–5.00 mm). Significant difference was also seen in cumulative release (CR). So the coating thickness had important influence on TMOP profiles, too. Moreover, one of the core materials, MCC, had turned out to be a delayed component for DIL release. As was reflected in Fig. 2C, the MCC quantity was negatively related to 4-h CR. The 4-h CR of DIL increased obviously with MCC amount decreasing from 80 mg to 40 mg. It was the water-insolubility of MCC that restrained inner DIL from further hydration, so as to reducing the solution exuding out. The existence of MCC prolonged core DIL release and leaded to the extended lag time. Accompanying with the coating layer, the MCC in pharmaceutical core surely facilitated forming the lag time for chronotherapeutics while the PEG in coating layer retarded such process.

### 3.2. Statistical analysis of experimental data from CCD study

The three-factor, five-level CCD for TMOP tablets was established to explore the optimum levels of variables and the coded and actual values of the variables are given in Table 2. For three variables ($n = 3$), the central composite design consisted of 20 trials, including $2^n$ ($2^3 = 8$) factor points, $2n$ ($2 \times 3 = 6$) axial points and 6 center points (six replications). After dissolution tests to the 20 formulations generated by CCD, the results of the experimental design indicated that this system was significantly influenced by PEG, MCC, and the thickness of coating layers which resulted in different lag time and drug release for the evaluation of TMOP tablets. The data were analyzed using Design-Expert software and Table 3 summarized that, the best fit for each of the responses $Y_1$ ($CR_{4h}$), $Y_2$ ($CR_{14h}$), and $Y_3$ ($CR_{24h}$) were found for either the quadratic models or the linear models and the selected predicted $r^2$ was underlined. Subsequently, the suggested mathematical models were chosen to describe the relevant response variables.

The three-dimensional (3D) response surface plots (Fig. 3) were used to illustrate the relationship between two independent variables and response properties at center level of other variable. Response surface plot in those figures described the effects of the combination of every two variables, and their interaction on $Y_1$, $Y_2$ or $Y_3$. For example, Fig. 3A respectively shows the effect of PEG amount ($X_1$) and coating thickness ($X_2$) on $CR_{4h}$ ($Y_1$) at center level of MCC loading ($X_3$), the effect of PEG amount ($X_1$) and MCC loading ($X_3$) on $CR_{4h}$ ($Y_1$) while keeping coating thickness ($X_2$) at center level, and the effect of coating thickness ($X_2$) and MCC loading ($X_3$) on $CR_{4h}$ ($Y_1$) at center level of PEG amount ($X_1$) [23].

As shown in Table 3, the best fit for the responses $Y_1$ ($CR_{4h}$) was found for the quadratic models; compared to the linear model and the two-factor model the quadratic model had the largest predicted $r^2$ values for $Y_1$. Therefore the quadratic model incorporating intersectional and quadratic terms was chosen to describe the effects of the variables. The regression Eq. (2) of the fitted model constructed for $CR_{4h}$ was presented below:

$$
Y_1 = 26.04046 - 0.0656623X_1 - 11.74775X_2 + 0.090588X_3
+ 0.011233X_1X_2 - 0.0182323X_2X_3 + 0.000115305X_1^2 + 1.32135X_2^2
$$

(2)

The results obtained in this design indicated that independent factors affecting $CR_{4h}$ were $X_1$, $X_2$, $X_3$, $X_1X_2$, $X_1X_3$, $X_2X_3$, $X_1^2$ and $X_2^2$, based on individual $p$ values that were below 0.05 (data not shown). The values of coefficients $X_1$ to $X_2$ were associated with the effect of these variables on the responses. The interaction term (e.g., $X_1X_2$) showed how the response changed when two factors simultaneously changed, while the quadratic terms ($X_1^2$ and $X_2^2$) suggest that there was a nonlinear relationship in the response. As a consequence, quantitative estimation of the significant models showed that coating thickness ($X_2$) had the prime influence on the $CR_{4h}$, because of its largest coefficient (−11.75) than $X_1$ (−0.065663) and $X_3$ (0.090588), suggesting that the tiny variations in the thickness of TMOP tablets would change the $CR_{4h}$ quit a lot. Moreover, response surface plot in Fig. 3A described the effects of $X_1$, $X_2$ and $X_3$ on $Y_1$. It could be clearly seen that $Y_1$ was strongly affected by $X_3$, since $Y_1$ increased sharply with the increase of $X_3$, i.e. the thicker coating layer led to a shorten lag time.

| Table 2 – Independent variables and their levels for TMOP releasing. |
|-------------------------------|----------------|------------------------------|
| **Independent variables**     | **Levels**     |
| $X_1$: PEG amount (mg)        | 0 16.22 40.00 63.78 80.00 |
| $X_2$: Thickness (mm)         | 4.60 4.76 5.00 5.24 5.40  |
| $X_3$: MCC amount (mg)       | 40.00 48.11 60 71.89 80.00 |
| **Dependent variables**       | **Constraints** |
| $Y_1$: CR of 4 h              | Minimize       |
| $Y_2$: CR of 14 h             | Minimize       |
| $Y_3$: CR of 24 h             | Maximize       |
On the whole, $X_2$ was the key factor affecting $Y_1$. This illustration was also confirmed by former researches concerning compression-coated technology [24].

With regard to CR$_{14h}$, the best fitted model was linear for a predicted $r^2 = 0.8201$. It was observed in Fig. 3B that CR$_{14h}$ could be improved significantly with PEG amount and coating thickness increasing while the variation of MCC amount made an adverse effect. This was also indicated by Eq. (3) where the positive coefficients (0.00882017, 0.71064) were respectively attached to $X_1$ (PEG amount), $X_2$ (coating thickness) but a negative one ($-0.00649618$) for $X_3$ (MCC amount); compared to the $X_1$ (PEG amount) and $X_3$ (MCC amount), the $X_2$ (coating thickness) was significantly more influential.

### Table 3 – Results of model summary statistics analysis for responses (The selected predicted $r^2$ was underlined.)

<table>
<thead>
<tr>
<th>Model</th>
<th>$Y_1$ (CR$_{4h}$)</th>
<th>$Y_2$ (CR$_{14h}$)</th>
<th>$Y_3$ (CR$_{24h}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>Adjusted $r^2$</td>
<td>Predicted $r^2$</td>
</tr>
<tr>
<td>Linear</td>
<td>0.7663</td>
<td>0.7225</td>
<td>0.6063</td>
</tr>
<tr>
<td>2F</td>
<td>0.8262</td>
<td>0.746</td>
<td>0.5474</td>
</tr>
<tr>
<td>Quadratic</td>
<td>0.965</td>
<td>0.9335</td>
<td>0.7232</td>
</tr>
</tbody>
</table>

Fig. 3 – Response surfaces for cumulative release in 4 h (A: $Y_1$, CR$_{4h}$), 14 h (B: $Y_2$, CR$_{14h}$) and 24 h (C: $Y_3$, CR$_{24h}$) as functions of every two factors which were significantly influential.
thickness) still exerted the main influence on \( Y_2 \) values for its largest coefficients. A moderate CR24 h, here was set for balancing either fast release or slow release, maintaining relatively permanent drug releasing during 24 h.

\[
Y_2 = -2.88616 + 0.00882017X_1 + 0.71064X_2 - 0.00649618X_3 \quad (3)
\]

When CR24 h (Y3) was indicated as the response, the mathematical relationship of the response Y3 on the three significant independent variables X1, X2 and X3 can be approximated by a quadratic model including 3 squared terms, 3 two-factor interaction terms, 3 linear terms and 1 intercept term as shown below (Eq.(4)):

\[
Y_3 = 2.16395 + 0.096332X_1 - 1.26703X_2 - 0.040999X_3
\]

\[ -0.018159X_1X_2 + 0.000120221X_3X_3 - 0.0000734659X_1^2 \quad (4)
\]

As shown in response surface plots (Fig. 3C) and Eq. (4), CR24 h (Y3) was significantly influenced by the effects of X1, X2, and X3, and their interaction. It indicated that X1 and X2 had positive effects on CR24 h (Y3), i.e. the CR24 h (Y3) was increasing with the increase of X1, X2. At the low level of X2, Y3 increased from 33% to 85% with the increase of X1 from 16.22 mg to 63.78 mg. At the high level of X2, Y3 increased from 80% to 98% as X1 increased from 16.22 mg to 63.78 mg. At the low level of X1, Y3 increased from 45% to 88% as X2 increased from 4.76 mm to 5.24 mm. At the high level of X1, Y3 increased from 95% to 98% as X2 increased from 4.76 mm to 5.24 mm. So it could be clearly seen that Y3 was strongly affected by X2, since Y3 increased sharply with the increase of X1. On the other hand, it was suggested that X2 had an adverse effect on CR24 h (Y3). At low level of X1, Y3 decreased rapidly from 80 to 40% as X3 increased from 20 to 80 mg. At high level of X1, Y3 decreased rapidly from 100 to 91% as X3 increased from 20 to 80 mg. At to X3, the trend of Y1 was similar to that at levels of X1.

3.3. Optimization and validation

After analyzing the corresponding equations and the responses in response surface, a further optimum ranges for each factor were found to generate TMOP tablets which depended on the prescriptive criteria with minimum CR4h, minimum CR14h, and maximum CR24h, by means of the Design-Expert software. The suggested optimum formulation was as follow: PEG amount (X1) 60.28 mg, coating thickness (X2) 4.80 mm and MCC amount (X3) 65.36 mg. At these levels, the predicted values of Y1 (CR4h), Y2 (CR14h), and Y3 (CR24h) were 4.94%, 60.01%, and 90.20%, respectively. As indicated in Fig. 4, the final TMOP tablets prepared with the suggested formulation were observed as CR4h of (4.28 ± 1.19%), CR14h of (61.07 ± 1.28%) and CR24h of (90.12 ± 1.03%) in medium of purified water, which were in good agreement with the predicted values. The results confirm that the CCD method is effective for predicting the impact of formulation composition on the release profile of the DIL-TMOP tablets and providing researchers more efficient approach for formulation optimization.

3.4. Kinetics and release mechanism

The averaged dose release profiles of the compression-coated tablets are shown in Fig. 4. When the osmotic pressure of the release medium was equal to zero, i.e. purified water, an s-shaped release profile was obtained and an obvious lag time (drug releasing below 5%) was observed as the first 4 h; the later 8-h profile was similar to zero-order release, followed by a slightly sloping phase to the end. In order to exploring the release mechanism of compression-coated tablets further, complementary experiments were conducted in medium of different osmotic pressures that was realized by adding various quantity of NaCl. For an overview of the in vitro process in Fig. 4, the release profile show high dependence on the osmotic pressure of dissolution medium, and both average release rate and cumulative release amount decrease as the NaCl concentration of the dissolution medium increase. This phenomenon indicates that self-made TMOP tablets are authentic osmotic pressure-controlled delivery system. Because this result is in accordance with the finding of a study where the film was proven semi-permeable and the release mechanism of pharmaceutical ingredient from a coated formulation against the osmotic pressure of the release medium should be known as osmotic pumping [21]. The higher osmotic pressure in medium could reduce the transmembrane osmotic gap of osmotic device, which drove drug to release, so the weaker driving force lead to a slower release profiles in the medium of NaCl solution.

The internal-external osmotic pressure gap of osmotic pump is the driving force for drug release. Thus, the release behavior of the DIL osmotic pump tablet, so long as its saturated solution still exists inside for a period of time, can be called zero-order release. With the experimental data of the saturated concentration of DIL (Ysat) core tablet volume (Vcore) and others, the ending time of zero-order release can be obtained. Due to excellent water-solubility of DIL, the time when the rest of DIL in core just right dissolved is the ending point. The remaining quantity of DIL in coating pump could be calculated by the Ysat and Vcore, so the DIL concentration in bulk medium (Cbulk) is obtained, too. According to the obtained Cbulk, we can figure out the ending time of zero-order release in a certain time period based on the in vitro α-type profile. As stated above, the Cbulk is calculated at 77.39 ug/ml, so the cumulative release of DIL is gotten as 58.04%
which can be located within the period of 12 h–14 h in Fig. 4. For more visual information, a segmented dissolution figure for every 2 h is constructed in Fig. 5, and then an obvious decline of released DIL is observed during 12 h–14 h. It’s the decreasing internal-external osmotic pressure that leaded to a release decline of DIL from osmotic pump system. Analysis shows that the results complied well with the investigated findings of real dissolution profile that there’s an ending time of zero-order release within 12 h and 14 h.

Savastano had proposed that the release mechanism for a coated drug delivery system was the final outcome of three rate-limiting steps which occurred during dissolution, i.e. (1) water permeating across the outer film, (2) the drug core dissolving, and (3) the solution exuding out. Since the drug molecule was embodied by water molecule throughout the above mentioned steps, the transport and transformation of water was tracked to develop a set of model equations. The kinetic behavior of coated dosage in dissolution process is confirmed to follow first-order regulation. Using Levenspiel’s method, the rate of water transforming from (1) to (3) is:

\[ F = 1 - \frac{k_2 k_3 e^{-k_3 t} + k_1 k_3 e^{-k_3 t} - k_1 k_3}{(k_1 - k_2)(k_2 - k_3)} \]  

(5)

\[ F \] represents the release rate of drug and the kinetic constants \( k_i \) here represent first-order rate constants for each of the three processes.

In the following analysis, \( F_{mp} \) represents the rate of drug released from an osmotic pump coated with a microporous membrane, and the relation between different kinetic constants for each step on rate of appearance of drug in bulk dissolution medium is simplified as follow [Eq. (6)]:

\[ F_{mp} = 1 + \frac{k_2 e^{-k_2 t} - k_3}{k_3 - k_2} \]

(6)

Among the equation above, \( k_2 = \frac{k Y_{sat} A_o}{m_o} \) and \( k_3 = \frac{D_s}{m_0 g_s} \), where \( k_2, \) \( m_0 \) and \( A_0 \) is dissolution rate constant, mass and surface area of the core tablet, respectively. \( Y_{sat} \) is the saturated concentration of solute. \( D_s \) is diffusion coefficient of solute, \( \rho_s \) the density of coating layer, \( A_s \) the surface of layer and \( g_s \) the mass of coating layer [25].

The value of the water inflow depends on the initial drug concentration in the dissolved phase inside the core tablet. As this concentration is assumed to be very close to zero, the water inflow has a value close to zero at the initial time of the simulation. So the initial time is deemed to lag time for TMOP tablets. With the PEG in coating layer dissolving in medium, the coating is changing into microporous. The core comes to contact with dissolution medium and pharmaceutical ingredients started to dissolve. The water inflow then increases due to the increased drug concentration inside the core as the drug dissolves and the resulting high difference in osmotic pressure across the coating. Now, it is a real osmotic pressure-driven behavior following former models, and we began to analyze the in vitro release at the termination of lag time, i.e. the 5th hour. At the beginning, value of \( k_2 \) of the DIL core tablet is calculated as 14.3/h [26]. However, value of \( \rho_s \) is diminishing throughout the dissolution test due to soluble substance in coating layer, so the \( k_2 \) could not be calculated directly. Given the situation that \( k_3 \) represents the constant of water diffusion from coating tablet to bulk medium, and the water molecule is embodied by drug molecule in permanent proportion throughout the diffusion process, it could be derived from the releasing profile as \( k_3 = 0.1035/h \). Next, the value of \( k_2 \) and \( k_3 \) is introduced into Eq. (6) to simulate the profile. With the comparison of simulated and observed data in Fig. 6, the correlation between them is found significant. Thus, the Eq. (6) could explain the in vitro behaviors of self-made TMOP tablets well and it provides extra evidence for formulation design and improvement.

### 3.5. Pharmacokinetic study

A comparison of plasma concentration–time profiles for the TMOP tablets (test) and commercial preparations (reference) are shown in Fig. 7. As expected, the oral absorption of the

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**Fig. 5** – Column diagrams for segmented DIL release (every 2 h) from the TMOP in purified water (from 2 h to 14 h).

**Fig. 6** – Comparison of drug released profile observed and simulated (the first 4 h’ profile of observed one was eliminated).
commercial tablet is found to be very rapid and there are no lag time exhibited before drug release. On the other hand, the tested TMOP tablets exhibit an obvious lag time for about 4 h, followed by a drug increase in the plasma.

The PK (pharmacokinetic) parameters for both formulations are listed in Table 4. According to statistical analysis done by an ANOVA test for repeated measurements, the comparison of parameters with the two preparations shows no significant differences for of C_{max} and AUC_{0-48 h}, but show significant differences for T_{max}. Consequently, the TMOP tablets have turned out to prolong the lag time of drug release. Bioequivalence of the two tablets is accepted with AUC_{0} and C_{max} by the two one-sided tests. The relative bioavailability of test TMOP tablets to reference tablets is 102% which show that the generated lag time hadn’t interfered with following drug release. Fig. 8 show that these in vivo data of TMOP tablets are consistent with the dissolution tests for a good in vitro–in vivo correlation of Y = 1.15X + 0.0634, R = 0.9586, indicating that the DIL absorption are primarily attributed to the dissolution behavior of self-made devices, and it could be predicted well by the in vitro tests. With the application of TMOP, the chronotherapeutic purposes of lag time and controlled release are achieved simultaneously.

4. Conclusion

In the present work, a novel time-released osmotic pump preparation for oral administration is developed by means of compression-coated method. The optimal formulation is successfully obtained using the central composite design method, avoiding a large number of trials for formulation selection. With the optimum formulation, we construct a time-released osmotic pump with CR_{4 h} of 4.28%, CR_{14 h} of 61.07% and CR_{24 h} of 90.12% in dissolution tests. Compare with conventional sustained-release preparations, the tested osmotic pump tablets administrated by beagle dog exhibits not only good oral bioavailability but also appropriate lag time (almost 4 h) which is necessary for the chronotherapeutics. The in vivo results demonstrate that the compression-coated TMOP tablets can delivery drug in the gastrointestinal tract in a manner similar to that in vitro and that it may be suitable for the clinical use which is expected to display therapeutic effects several hours after administration. Due to the limitation of research conditions, there is some insufficiency about the dissolving behavior of other model drug in the TMOP to be done.

Acknowledgment

This work was supported by the State Key Laboratory (Long-acting and Targeting Drug Delivery System) and by the Special Construction Project (Taishan Scholar-Pharmacy Specially Recruited Experts).

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