Preparation and Drug Release Mechanism of Time Controlled Explosive Pulsatile Tablets with Ethylcellulose Coating

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Sha Li conceived the idea, designed and supervised the research. Jiabi Ouyang and Xingli Wang performed the research, conducted the analysis and wrote the paper. Mohui Yang, Yani Tan and Zhen Zhang contributed to data collection and analysis. All authors contributed to the writing and revisions.

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Core tip:
The development of pharmacology in the decade revealed the biological rhythm of the occurrence and development of certain diseases, usually the circadian rhythm. Therefore, chronopharmacological drug delivery is of great significance in the prevention and treatment of diseases having onset rhythm inconvenient to take drug. An easy-to-prepared, time-controlled explosive metoprolol tartrate pulsatile tablet was developed in order to provide patients with timed therapy of effective blood drug concentration at the optimal time. The formulation and process were optimized using single factor experiments and orthogonal experiments. In addition, the swelling and water absorption rate of tablet and the mechanical properties of the coating film were measured to further reveal its release mechanism. The results showed that the strong tensile strength of coating film and the weak flexibility of EC film resulted in a shell-type exploding rupture of the coating film followed by the pulsatile fast release of drug when the swelling force of core tablet caused by water uptake was high enough. Both the swelling capacity of core tablets and the thickness of coating film together controlled the lag time of drug release. The prepared time-controlled explosive pulsatile tablets with ethylcellulose coating thereafter are expected to be used for the delivery of therapeutic agents for chronotherapy by adjusting the lag time of drug release to match the different high attack rhythm of the exact diseases.

Abstract:

Background The time rhythm of human body is associated with the occurrence and development of many diseases, and it also affects the efficacy and pharmacokinetic characteristics of the corresponding therapeutic drugs. Therefore, the chronopharmacological drug delivery system has potential applications.
**Aim** In this work, it is proposed to develop a kind of pulsatile release tablet of simple structure and preparing process, thus to provide an alternative drug delivery system for therapeutically agents used in treatment of diseases of typical onset biorhythm at period inconvenient to take drug.

**Methods** Metoprolol tartrate (MT), a drug widely used clinically to treat cardiovascular diseases was selected as a model drug for developing pulsatile tablets of time-controlled explosive system (TES). The MT pulsatile tablets were ethyl cellulose (EC) coating tablets produced by pan coating process, and the core tablets were prepared by direct compression. The formulation and process was optimized by single factor test and orthogonal design. Also, the pulsatile release mechanism of the tablets was discussed through investigating the water absorption and swelling capacity of tablets as well as the mechanical properties of EC free film.

**Results** A kind of pulsatile tablets of MT were developed with a drug release lag time around 7 h and a fast release of drug after lag time. When the swelling force of core tablet caused by water uptake was high enough over the tensile strength of EC coating film, the MT pulsatile tablets demonstrated a shell-type exploding rupture due to the great rigidity and weak flexibility of EC film, and then a fast pulsatile release of drug was observed. Both the swelling capacity of core tablet and the thickness of coating film together controlled the lag time of drug release. The lag time showed a good linear relationship with the thickness of coating film ($r = 0.9984$, $P < 0.01$). The sort and amount of fillers and disintegrants dominated the release behaviour after lag time.

**Conclusion** The developed MT pulsatile tablets can exert a timely release of drug before peak onset period of hypertension and angina pectoris early in the morning after drug taking around 22:00 P.M the night before. The good linear relationship between lag time and coating thickness enabled the pulsatile tablets to be used for delivery of other therapeutic agents of similar chronotherapy demand by adjusting the coating thickness to achieve the appropriate lag time of drug release to match the different high attack rhythm of the exact diseases.

**Key words** Chronotherapy; Pulsatile release tablets; Metoprolol tartrate; Ethyl cellulose; Drug release mechanism.

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**INTRODUCTION**

Studies have shown that many diseases occur and develop in a circadian rhythm-dependent manner. Common chronic diseases, such as bronchial asthma, allergic rhinitis, osteoarthritis, and cardiovascular diseases like hypertension, angina pectoris and myocardial infarction, show the characteristics of circadian rhythm. For life-threatening diseases prone to sudden onset late at night or early in the morning, the timely administration of therapeutic agents is not conveniently accessible, thus risky situation may occur. The timely prevention and treatment of these kind of diseases causes it attractive to develop chronopharmacological drug delivery systems which may achieve synchronized drug release with the rhythm of disease onset. The chronopharmacological drug delivery systems, also termed as pulsatile drug delivery systems, enable achievements of both effective chronotherapy and good adherence of patients, which can release the required amount of drug after a designed lag time.

So far, pulsatile drug delivery systems have generally designed as plug-type time controlled capsules, pellets and tablets of coating or osmotic pump system using insoluble, soluble, erodible, swellable and biodegradable materials. Time-controlled explosive system (TES) is a chronopharmacological drug delivery system feasible for large-scale industrial production, which is generally designed as pellets and tablets. Typical TES, from center to outside, generally consists of a drug reservoir, a swelling layer and a water-insoluble rupturable coating film, which is somewhat complicated in structure and preparing process.

Cardiovascular disease is one of the life-threatening health killers of peak onset rhythm around 4:00-6:00 A.M. early in the morning. It is inconvenient for patients to wake up from deep sleep to take medicine to prevent cardiovascular events in time. Metoprolol tartrate (MT) is a widely used drug for controlling cardiovascular diseases including hypertension and angina pectoris. In this work, we intended to use MT as model drug to develop a new TES of simpler structure and preparing process than typical one. The designed TES of MT were ethyl cellulose (EC) coating pulsatile tablets, which were prepared by direct compression of core tablets followed by pan coating of EC film. The formulation and process was optimized through single-factor test and orthogonal design to achieve a lag time of 6-8 h and a fast complete pulse release of MT thereafter. Therefore, the MT pulsatile tablets, taken at night around 20:00-22:00 P.M., can
achieve drug release at 4:00-6:00 A.M. next morning to match up the high attack of hypertension and/or angina pectoris in the early morning. In addition, the release mechanism of MT pulsatile tablets was discussed by investigating the expansion and water uptake of tablets as well as the mechanical properties of coating film.

MATERIALS AND METHODS

CHEMICALS

Metoprolol tartrate was provided by Shandong Qihe Jinzun Chemical Co. Ltd. (Lot: 1001900, Shandong Province, China). Cross-linked sodium carboxymethyl cellulose (CC-Na), low substituted hydroxypropylcellulose (L-HPC), cross-linked polyvinylpyrrolidone (PVPP), sodium carboxymethyl starch (CMS-Na), pregelatinized starch (PS), microcrystalline cellulose (MCC), hydroxypropyl cellulose (HPC), aerosil and magnesium stearate were obtained from Shanghai Houcheng Fine Chemical Co. Ltd. (Shanghai, China). Ethyl cellulose (EC) T7, Eudragit RS and RL was supplied by Guangdong Shantai Cellulose Co. Ltd. (Guangdong Province, China) and Evonik Industries AG (Darmstadt, Germany), respectively. Diethyl phthalate (DEP) and triethyl citrate (TEC) was obtained from Tianjin Damao Chemical Reagent Factory (Tianjin, China) and Shanghai Aladdin Co. Ltd. (Shanghai, China), respectively. All other chemicals were analytical grade.

PREPARATION OF METOPROLOL TARTRATE PULSATILE TABLETS

SELECTION OF COATING MATERIALS

The properties of free films and coating tablets made of different sort of coating materials was investigated to select an appropriate coating material for MT pulsatile tablets. Free films of EC T7 and Eudragit RS/RL mixture were prepared with diethyl phthalate (DEP) and triethyl citrate (TEC) as plasticizer, respectively. The mechanical properties, Tg and water permeability was investigated using Electronic Universal Material Testing Machine (Jiangdu Tianyuan Experimental Machinery Co.), Differential Scanning Calorimeter (DSC-204, Netzsch Co., Germany; scanning range from -70 °C to 150 °C at a rate of 20 °C/min) and self-modified device based on horizontal diffusion cell, respectively. The drug release behavior and appearance of coating tablets were observed to figure out the influence of different sorts of coating materials.

OPTIMIZATION OF FORMULATION AND PROCESS

The preparation of pulsatile tablets was simply divided into two steps, preparation of core tablets and then film coating. Briefly, after sieving (80 mesh), the powder of metoprolol tartrate and excipients was mixed well, and then compressed directly into core tablets with a concave punch of 8 mm, and 25 mg MT in each tablet. Based on the above results of coating material screening, EC T7 was selected with DEP as plasticizer. The coating liquid was prepared by dissolving materials in ethanol and the pan coating method was adopted.

The influence of both formulation and process factors on features and preparation of MT pulsatile tablets was investigated by single-factor experiments first. Orthogonal test was then used for further optimization by studying 3 factors, the hardness of core tablets (A), the composition of fillers (B) and the percentage of weight increase by coating (WI%, C). Exactly, factor B was the ratio of microcrystalline cellulose to pregelatinized starch (MCC:PS) in filler mixture. The experiments were designed according to orthogonal array table L9(3⁴), each experiment for 3 replication. The lag time of drug release and the accumulative drug release percentage at 10 min after lag time (Q₁₀%) were used for evaluation. The drug release behavior of the MT pulsatile tablets prepared by optimized formulation and process was validated for 3 batches.

DRUG RELEASE MECHANISM OF METOPROLOL TARTRATE PULSATILE TABLETS

INFLUENCE OF THICKNESS OF COATING LAYER ON DRUG RELEASE BEHAVIOUR

Five batches of pulsatile tablets of different WI% (about 5%, 10%, 15%, 20% and 25%) were prepared to study the influence of thickness of coating layer on metoprolol tartrate release behaviour from the pulsatile tablets. The correlationship between WI% and lag time of drug
release was analyzed and a batch of MT pulsatile tablets with a WI% about 14% were prepared to validate the obtained relationship between lag time and WI%.

WATER UPTAKE OF METOPROLOL TARTRATE PULSATILE TABLETS
Pulsatile tablets of different thickness of coating layer were prepared and examined for water uptake under the same condition of drug release test, in 0.1 mol/L HCl solution for the first 2 hours followed by in phosphate buffer solution (PBS) of pH 6.8 to the end at 37 ± 0.5 °C and a rotation speed of 100 rpm. After weighed before test (W₀), the pulsatile tablets were taken out at preset time points, sucked up water on the tablet surface and then measured the weight (Wₜ) until the coating film burst. The water uptake was calculated as a percentage by the following formula.

\[ \text{Water uptake} (\%) = \left( \frac{Wₜ - W₀}{W₀} \right) \times 100\% \]

EXPANSION OF CORE TABLETS
The core tablets containing different fillers and disintegrants were prepared to observe the expansion behaviour after water uptake. The thickness of core tablets before the expansion test was measured as h₀. Distilled water of appropriate amount, which was determined according to the above water uptake test, was added gradually to core tablets, and the final thickness of core tablets at the maximal expansion (h₁) was measured. The expansion ratio was calculated as follows.

\[ \text{Expansion ratio} = \frac{h₁}{h₀} \]

STATISTICAL ANALYSIS
The data were expressed as mean ± standard deviation (SD). Data was statistically processed with SPSS 13.0 software using one-way ANOVA. P value less than 0.05 was considered to be significant.

RESULTS AND DISCUSSION
PREPARATION OF METOPROLOL TARTRATE PULSATILE TABLETS
SELECTION OF COATING MATERIALS
The Tₐ of powders and free films of EC, Eudragit RS and RL was summarized in Table 1. The addition of plasticizer markedly lowered down the Tₐ value of both EC and Eudragit. No matter for powders or free films, EC showed higher Tₐ than Eudragit of any ratio tested.

<table>
<thead>
<tr>
<th>Tₐ (°C)</th>
<th>EC Tₐ</th>
<th>Eudragit RS: Eudragit RL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10:0</td>
<td>7:3</td>
</tr>
<tr>
<td>Powder</td>
<td>73.8</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>5:5</td>
<td>68.2</td>
</tr>
<tr>
<td></td>
<td>3:7</td>
<td>68.6</td>
</tr>
<tr>
<td></td>
<td>0:10</td>
<td>73.1</td>
</tr>
<tr>
<td>Free film</td>
<td>52.8</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.7</td>
</tr>
</tbody>
</table>

The mechanical properties of free films made of EC, Eudragit RS and RL was illustrated in Fig. 1. The tensile strength of EC was much higher than that of Eudragit RS, Eudragit RL and their mixture of different ratios, indicating high rigidity of EC film. On the opposite, the Eudragit films showed much better elasticity than EC films with the elongation of breakage tens-fold as much as that of EC's.

EC films broke quickly around 3 min after the beginning of water permeability test, thus, the data for water permeation amount was not available. The water permeation amount through
the Eudragit films enhanced with time, and the films bulged gradually but not broke after 2 hours of test due to their high elasticity. The films of Eudragit in different ratios of RS/RL showed different water permeability (Fig. 2), augmenting with the increase of proportion of RL.

Figure 1 The mechanical properties of free films made of EC, Eudragit RS and Eudragit RL (A, tensile strength; B, elongation of breakage; C, Young’s modulus).

Figure 2 Water permeation amount of free films made of Eudragit RS/RL mixture of different ratios (n = 6).

The pulsatile tablets were prepared respectively by coating with EC T7 as well as Eudragit RL due to its highest water permeability but not of the highest elastic deformation capacity in Eudragit RL/RS mixture free films. Similar phenomenon was observed in drug release test as in water permeability test. For EC coating pulsatile tablets (WI% of 20%), the coating layer ruptured at a time lag of 7 hours followed by a fast release of metoprolol tartrate over 90% at 10 min after rupture (Q₁₀%). However, the Eudragit RL (WI% of 5%) coating layer did not break over 8 h although water permeated quickly inside after beginning to cause a swelling up, and no drug was detected as well. With regarding to these results, in order to prepare a TES type of metoprolol tartrate pulsatile tablets, EC was selected as coating material for the following optimization.

OPTIMIZATION OF FORMULATION AND PROCESS
Various formulation and process factors of core tablets and coating was investigated in single factor test, including sort and amount of fillers, disintegrants, binding agents and lubricants, the hardness of core tablets, the sort and concentration of EC, the amount of DEP, the coating temperature, the speed of spraying, the rotating speed of coating pan and the percentage of weight increase by coating. Base on the results of single-factor experiment, in the following orthogonal optimization, MCC, PS, PVPP, CC-Na, HPC, aerosil and magnesium stearate was used to prepare core tablets by direct compression and the coating liquid was an ethanol solution of EC with DEP as plasticizer.
To analyze the influence of different formulation and process factors, it followed that the sort and composition of disintegrants affected the disintegration time of core tablets apparently. An appropriate sort and composition of fillers was able to further speed up the disintegration time significantly, which let a quick drug release after lag time. Also the sort and composition of filler influenced the lag time. The hardness of core tablets demonstrated an obvious influence on lag
time. In coating procedure, the sort of EC and the WI% impacted the lag time to the most. The DEP amount changed the average value of lag time less but resulted in a poor repeatability of it. The purpose of this work was to obtain metoprolol tartrate pulsatile tablets of a lag time about 6-8 h with a fast complete release of drug thereafter. Thus, the further orthogonal optimization was studied on the following three factors, the hardness of core tablets (A), the MCC:PS ratio (B) and the percentage of weight increase by coating (WI%, C). Evaluation Index (EI) value was calculated from lag time and Q_{10} by the formula:

\[ EI = \left| \text{lag time} - 7 \right| \times 60\% + \left[ 10 \times \left( 100\% - Q_{10} \% \right) \right] \times 40\% \]

The levels of factors and the results of orthogonal test and the variance analysis were listed in Tables 2 and 3 respectively.

### Table 2

<table>
<thead>
<tr>
<th>No.</th>
<th>A (kg)</th>
<th>B</th>
<th>C (%)</th>
<th>D</th>
<th>Total EI</th>
<th>Lag time (h)</th>
<th>Q_{10} (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>5-6</td>
<td>3:7</td>
<td>12.27</td>
<td>1</td>
<td>15.42</td>
<td>1.91±0.30</td>
<td>47.82±2.47</td>
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<td>2</td>
<td>5-6</td>
<td>5:5</td>
<td>16.23</td>
<td>2</td>
<td>10.72</td>
<td>2.56±0.21</td>
<td>77.24±2.51</td>
</tr>
<tr>
<td>3</td>
<td>5-6</td>
<td>10:0</td>
<td>20.19</td>
<td>3</td>
<td>1.13</td>
<td>7.11±0.27</td>
<td>92.22±0.76</td>
</tr>
<tr>
<td>4</td>
<td>8-9</td>
<td>3:7</td>
<td>16.07</td>
<td>3</td>
<td>14.55</td>
<td>2.38±0.40</td>
<td>48.09±2.47</td>
</tr>
<tr>
<td>5</td>
<td>8-9</td>
<td>5:5</td>
<td>20.12</td>
<td>3</td>
<td>9.31</td>
<td>3.31±0.20</td>
<td>77.96±2.84</td>
</tr>
<tr>
<td>6</td>
<td>8-9</td>
<td>10:0</td>
<td>12.41</td>
<td>2</td>
<td>6.41</td>
<td>3.95±0.32</td>
<td>92.31±2.08</td>
</tr>
<tr>
<td>7</td>
<td>11-12</td>
<td>3:7</td>
<td>20.08</td>
<td>2</td>
<td>13.16</td>
<td>3.02±0.37</td>
<td>50.01±2.46</td>
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<tr>
<td>8</td>
<td>11-12</td>
<td>5:5</td>
<td>11.98</td>
<td>3</td>
<td>10.25</td>
<td>2.69±0.39</td>
<td>79.22±2.78</td>
</tr>
<tr>
<td>9</td>
<td>11-12</td>
<td>10:0</td>
<td>16.22</td>
<td>1</td>
<td>3.84</td>
<td>5.34±0.25</td>
<td>92.87±1.26</td>
</tr>
<tr>
<td>K1</td>
<td>27.27</td>
<td>43.13</td>
<td>32.08</td>
<td>28.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2</td>
<td>30.27</td>
<td>30.28</td>
<td>29.11</td>
<td>30.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K3</td>
<td>27.25</td>
<td>11.38</td>
<td>23.60</td>
<td>25.93</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>R</td>
<td>1.01</td>
<td>10.58</td>
<td>2.83</td>
<td>4.36</td>
<td></td>
<td></td>
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<tr>
<td>SS</td>
<td>0.67</td>
<td>56.68</td>
<td>4.11</td>
<td>1.07</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D: Blank column. Total EI was the sum of EI values of 3 parallel replicates of each experiment.

### Table 3

<table>
<thead>
<tr>
<th>Factor</th>
<th>SS</th>
<th>v</th>
<th>MS</th>
<th>F</th>
<th>P</th>
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<tbody>
<tr>
<td>A</td>
<td>0.67</td>
<td>2</td>
<td>0.34</td>
<td>1.85</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>B</td>
<td>56.68</td>
<td>2</td>
<td>28.34</td>
<td>156.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C</td>
<td>4.11</td>
<td>2</td>
<td>2.06</td>
<td>11.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>D</td>
<td>1.07</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e₁²*</td>
<td>2.56</td>
<td>18</td>
<td></td>
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<tr>
<td>Error</td>
<td>3.63</td>
<td>20</td>
<td>0.18</td>
<td></td>
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</tr>
</tbody>
</table>

*e₁ is the error of replicate experiments. F_{0.05(2,20)} = 3.49, F_{0.01(2,20)} = 5.85.

According to the 6-8 h of lag time designed, the median of 7 h was chosen as the target lag time for evaluation. From the formula to calculate EI value, it indicated that the less the EI value was, the more closely the pulsatile tablets prepared achieved our aim. To directly analyze the results in Table 2 by range analysis, the influence extent of the three factors was sequenced as B > C > A, and the optimal formulation and process condition might be A₃B₃C₃. The variance analysis also showed a highly significant difference for both factor B and C (P < 0.01), but no significant
difference was observed for factor A. The sum of total EI value of level 1 and 3 of factor A was almost the same. Moreover, experiment No. 3 \(A_1B_3C_3\) showed a minimal EI value, and matched the design aim well with a lag time of 7.11 h and a \(Q_{10}\)% of 92.22%. Therefore, \(A_1B_3C_3\) was determined as the optimal formulation and process. The results of validation experiment showed a perfect repeatability in 3 batches of metoprolol tartrate pulsatile tablets, with an average lag time and \(Q_{10}\)% around 7.10 h and 92% respectively (Fig. 3).

![Figure 3 Drug release curves of three batches of MT pulsatile tablets prepared by optimal formulation and process (n = 6).](image)

**DRUG RELEASE MECHANISM OF METOPROLOL TARTRATE PULSATILE TABLETS**

**INFLUENCE OF THICKNESS OF COATING LAYER ON DRUG RELEASE BEHAVIOUR**

The thickness of coating layer of MT pulsatile tablets showed a good linearity with the lag time. The linear regression equation between lag time \(t_{lag}\) and WI\% was \(t_{lag} = 0.4234\text{WI}\% - 1.3338\) (\(r = 0.9984, P < 0.01\)). The increase of WI\% brought a prolongation of lag time \((P < 0.01)\), but no effect on drug release rate and extent after lag time \((P > 0.05)\) (Fig. 4). In validation experiment, the lag time was measured as 4.79 ± 0.35 h when the WI\% of metoprolol tartrate pulsatile tablets was 14.25%, which was much close to the lag time of 4.70 h calculated from the linear equation. The results well validated the linear relationship between lag time and WI\% and indicated the good predictability of the equation.

![Figure 4 The influence of thickness of coating layer on drug release behaviour of metoprolol tartrate pulsatile tablets (n = 6). A-relationship between lag time and WI\%, B-drug release behaviour of metoprolol tartrate pulsatile tablets of different WI\%.](image)

**WATER UPTAKE OF METOPROLOL TARTRATE PULSATILE TABLETS**

The water uptake of metoprolol tartrate pulsatile tablets of different WI\% was measured and the results were illustrated in Fig. 5. With the coating layer of EC getting thicker, the water uptake of pulsatile tablets turned faster at the initial period followed by slowing down in the latter part of test. However, the water uptake rate was not of too much difference. The pulsatile
tablets of higher WI% took longer time and absorbed more water to enable the rupture of coating film to release drug.

Figure 5 Water uptake of metoprolol tartrate pulsatile tablets of different WI%.

EXPANSION OF CORE TABLETS
The expansion ratio of core tablets prepared by different disintegrants and fillers was summarized in Table 4. The core tablets prepared by different sort and composition of disintegrants showed similar expansion ratio ranging from 2.27-2.51 ($P > 0.05$). On the other hand, the composition of fillers (MCC:PS) affected the expansion ratio markedly ($P < 0.05$), which escalated with the proportion increase of MCC to reach a maximum of 4.90 in the core tablets prepared only by MCC.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Fillers</th>
<th>Disintegrants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCC:PS</td>
<td>L-HPC</td>
</tr>
<tr>
<td>10:0</td>
<td>4.90 ± 0.17</td>
<td>2.36 ± 0.06</td>
</tr>
<tr>
<td>8:2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5:5</td>
<td>2.72 ± 0.06</td>
<td>-</td>
</tr>
<tr>
<td>3:7</td>
<td>2.57 ± 0.09</td>
<td>-</td>
</tr>
<tr>
<td>2:8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0:10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

All the above results and mechanical properties of EC free film well explained the time-controlled explosive pulsatile release mechanism of the developed MT pulsatile tablets. The lag time of pulsatile release of MT was determined by the contest between the swelling force produced by water uptake of core tablet and the tensile strength of EC coating film. The strong tensile strength indicated the great rigidity of EC film, which made the developed MT pulsatile tablets maintaining the initial appearance without obvious deformation before the swelling force of core tablet exceeded the tensile strength of coating film. When the swelling force was higher than the tensile strength, it triggered a shell-type exploding rupture of the coating film of MT pulsatile tablets due to the great rigidity and poor elasticity of EC film. The fast expansion of core tablet after coating film rupture led a fast release of drug then.

CONCLUSIONS
In this work, a new kind of metoprolol tartrate pulsatile tablets was designed and developed with a drug release lag time around 7 h to meet the demand of timely prevention and treatment of onset of cardiovascular diseases early in the morning. The metoprolol tartrate pulsatile tablets were a time-controlled explosive system of simple structure and preparing process. The lag time of drug release was well controlled by the thickness of coating film, and there was a good linearity between them which could predict the percentage of weight increase by coating exactly according to the preset lag time needed for chronotherapy of diseases. The results suggested that the developed pulsatile tablets were of potential application in delivery of therapeutic agents for chronotherapy of diseases of different high attack rhythm.

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