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Research paper

Preparation of monolithic osmotic pump system by coating the indented core tablet

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Abstract

A method for the preparation of monolithic osmotic pump tablet was obtained by coating the indented core tablet compressed by the punch with a needle. Atenolol was used as the model drug, sodium chloride as osmotic agent and polyethylene oxide as suspending agent. Ethyl cellulose was employed as semipermeable membrane containing polyethylene glycol 400 as plasticizer for controlling membrane permeability. The formulation of atenolol osmotic pump tablet was optimized by orthogonal design and evaluated by similarity factor (f_2). The optimal formulation was evaluated in various release media and agitation rates. Indentation size of core tablet hardly affected drug release in the range of (1.00–1.14) mm. The optimal osmotic tablet was found to be able to deliver atenolol at an approximately constant rate up to 24 h, independent of both release media and agitation rate. The method that is simplified by coating the indented core tablet with the elimination of laser drilling may be promising in the field of the preparation of osmotic pump tablet.

Keywords: Atenolol; Monolithic osmotic pump tablet; Orthogonal design; Similarity factor; Indented tablet

1. Introduction

Conventional preparation is usually administered two or three times a day, which will lead to large fluctuation in drug plasma concentration and side effect on human body. Constant plasma level can offer a therapeutic advantage for many drugs in terms of both efficacy and tolerance of the treatment [1]. Once-daily controlled release preparation is often desirable.

The osmotic pump tablet that holds a prominent place among controlled release systems has many advantages, such as reducing risk of adverse reactions, improving compliance of patients and exhibiting comparable *in vitro*/*in vivo* drug release.

The first osmotic pump for delivery of active ingredients was invented by Rose Nelson in the 1950s [2]. The first commercial osmotic device was introduced by Theeuwes known as elementary osmotic pump (EOP) in the 1970s [3]. The EOP was a core tablet coated by semipermeable membrane with a micro-orifice drilled on the surface. The EOP was very simple in preparation and could deliver water-soluble drugs at an approximately constant rate up to 24 h. However, it was not feasible for the delivery of drugs with low solubility, for the drugs dissolved insufficiently and settled in the bottom of the tablet. Therefore, researches were carried out to enhance the solubility of the drugs [4,5] and to modify the performance of the semipermeable membrane [6–8], but these methods were only practicable for a few kinds of drugs. To overcome this limitation, many attempts were made for the delivery of low-solubility drugs. One approach was the development of two-layer osmotic pump tablet whose core tablet consisted of two layers, one containing drug and the other an osmotic agent and an expanding agent [9,10]. The disadvantage of this system was that a complicated side identification technology should be employed to ensure the orifice drilled

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on the surface of the drug layer after coating. Sandwiched osmotic pump tablet was developed with the elimination of side identification [11]. Its core tablet consisted of a middle push layer and two attached drug layers. Two orifices were simply drilled on both sides of the surface after coating, which avoided side identification before drilling of that of two-layer osmotic pump tablet. However, either two-layer or sandwiched core tablet needed a complicated tableting technology. Monolithic osmotic pump tablet whose core tablet consisted of osmotic agent and suspending agent was prepared by a much easier tableting technology and it was proved to be able to deliver the drugs with low solubility [12]. Up to now, an expensive laser-drilling machine was necessary for the large-scale preparation of all kinds of osmotic pump tablets.

It was reported that the preparation of the osmotic pump tablets could be performed by coating the indented core tablets [13]. In this system, the orifice for drug release was formed automatically during the coating, which indentation is of sufficient size to remain at least partly uncoated by the membrane. Though the ability to prepare osmotic pump tablets that do not need special drilling has been recognized for years, the approach was limited in the large-scale industry for little research was made. In this paper, the preparation of osmotic pump tablet was simplified with the elimination of laser drilling. The core tablet with an indentation was compressed by the punch with a needle, and then the osmotic pump tablet was achieved by coating the indented tablet. Atenolol was selected as the model drug in the preparation of osmotic pump tablet. It was a β-blocking agent, which could effectively reduce systolic and diastolic blood pressures [14]. The influences of sodium chloride (NaCl) weight, polyethylene oxides (PEOs) weight (M_w, 2×10^5, 5×10^5) and membrane thickness on drug release profile were evaluated to determine significant associations of factors in the osmotic pump tablet based on the L9 orthogonal experimental design. Also, the influences of indentation size, plasticizer level, release media and agitation rate on *in vitro* drug release profile were investigated.

2. Materials and methods

2.1. Materials

Atenolol powder (Shanghai Sunve Pharmaceutical Co., Ltd., China) was the model drug. NaCl (Jiangsu Qinfen Pharmaceutical Co., Ltd., China) was used as osmotic agent and PEO (M_w, 2×10^5, M_w, 5×10^5, Shanghai Liansheng Chemical Co., Ltd., China) as suspending agent. Ethyl cellulose (EC, Shandong Ruitai Chemical Co., Ltd., China) was employed as semipermeable membrane containing polyethylene glycol 400 (PEG-400, Pudong Gaonan Chemical Co., Ltd., China) as plasticizer for controlling membrane permeability. The atenolol conventional tablet of 25 mg strength (Shanghai Sunve Pharmaceutical Co., Ltd., China) was used as the reference for comparison. Other chemicals used were of analytical grade.

2.2. Preparation of core tablet with an indentation

Atenolol powder was mixed with NaCl and PEO manually using 10% PEO (M_w, 2×10^5) solution as binder, and then the mixture was passed through a 1270 μm sieve to generate granules and dried at 50 °C for 4 h. Then the above-mentioned mixture was sifted by a 1375-μm sieve. The resultant granules were compressed into core tablet using the TDP-1.5T single-punch tableting machine (Shanghai Guanlian Pharmaceutical Device Co., Ltd., China) whose upper concave faced punch was modified with a needle by us. The indentation depth of the core tablets was 1.50 mm, while the diameter of the needle could be altered to produce indentation sizes in the range of (0.84–1.14) mm. The weight of each core tablet was maintained within the range of (250 ± 5) mg. The hardness of the core tablets was kept within (3–4) kg (hardness tester, Shanghai Huanghai Drug Inspection Instrument Co., Ltd., China).

2.3. Coating and drying

EC in 95% ethanol (2%, w/v) containing plasticizer (PEG-400) was used as coating solution. The coating was carried out in a pan coater (Shanghai Huanghai Drug Inspection Instrument Co., Ltd., China). The temperature of coating pan was 30 °C; pan-rotating rate was 30 rpm. The coated tablets were dried to remove the residual solvent at 50 °C for 24 h.

2.4. In vitro release test

In vitro drug release test was conducted in a dissolution apparatus (RCZ-8A, Precise Apparatus of Tianjin University Co., Ltd, China) using the paddle method according to USP XXVIII. The temperature was maintained at (37 ± 0.5) °C. Every osmotic pump tablet entrapped into a sink basket was added to 900 ml of release medium. Five milliliter of solution was withdrawn and the same volume of fresh medium was added in 2, 6, 10, 14 and 24 h, respectively. The solution was immediately filtered through a 0.45 μm membrane filter, suitably diluted and determined at 224 nm using the UV-S52 spectrophotometer (Shanghai Lengguang Technology Co., Ltd., China).

All the release data were analyzed by Origin version 6.0 Software. Paired T-test was used to calculate p value and evaluate the difference of release profiles.

3. Results and discussion

3.1. Optimization of formulation

To study the influences of core tablet formulation and thickness of semipermeable membrane on drug release profile, osmotic pump tablets with various formulations were prepared according to the orthogonal design (Table 1).

Table 1
Factors and levels of orthogonal design

Factors	A (g)	B (g)	C (g)	D (mm)
Level 1	6.00	2.00	3.00	0.105
Level 2	6.50	2.75	3.50	0.156
Level 3	7.00	3.50	4.00	0.198

The four factors were set as follows, A, NaCl weight; B, PEO (M_w, 5×10^5) weight; C, PEO (M_w, 2×10^5) weight; D, membrane thickness.

For commercialized nifedipine osmotic pump tablet, the cumulative drug release was 0% at 0 h and the ideal drug release was supposed to be 90% in 24 h [15]. Other osmotic pump tablets might also follow this principle. Therefore, the equation of zero-order release is $F(\%) = 3.75t$ where $F(\%)$ is the cumulative released drug and t is the release time. The similarity factor (f_2) was employed to evaluate the release profiles of various formulations compared with the ideal release profile [16–18].

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

The similarity factor f_2 was a logarithmic transformation of the sum-squared error of differences between the experimental drug release T_t and the ideal release R_t over all time points n. The similarity factor fit the result between 0 and 100. It approached 0 as the dissimilarity of the test and the reference profile increased, whereas, it attained 100 when the test and the reference profile were identical. The two profiles were believed to be similar when the f_2 value of them was larger than 50 for which the mean deviation over all time points n was less than 10% based on Eq. (1).

The optimal formulation was found to be $A_2B_3C_1D_3$ according to Table 2. The osmotic pump tablet with the optimal formulation was prepared and the *in vitro* release test was performed. The f_2 value was obtained to be 48.6 by comparing the drug release profile of optimal formulation with the ideal release profile. As it was less than that obtained by comparing the drug release profile of formulation No. 3 with the ideal release profile, formulation No. 3 was decided as the optimal formulation and it was achieved as follows, atenolol, 25.0 mg; NaCl, 100.0 mg; PEO (M_w, 5×10^5), 58.3 mg; PEO (M_w, 2×10^5), 66.7 mg. The optimal thickness of membrane was 0.198 mm. This formulation was adopted in the following studies.

Table 2
Results of orthogonal design

	A	B	C	D	f_2
1	1	1	1	1	31.7
2	1	2	2	2	43.9
3	1	3	3	3	54.8
4	2	1	2	3	54.6
5	2	2	3	1	28.4
6	2	3	1	2	52.8
7	3	1	3	2	38.6
8	3	2	1	3	54.2
9	3	3	2	1	34.5
K1	130.4	124.9	138.7	94.6	
K2	135.8	126.5	133.0	135.3	
K3	127.3	142.1	121.8	163.6	
k1	43.5	41.6	46.2	31.5	
k2	45.3	42.2	44.3	45.1	
k3	42.4	47.4	40.6	54.5	
Δk	2.8	5.7	5.6	23.0	

3.2. Influence of PEG-400 level on drug release profile

In order to study the influence of PEG-400 level on drug release profile, EC semipermeable membranes were plasticized with various PEG-400 levels (EC, v/w) of 25.0%, 33.0% and 40.0%, respectively. Fig. 1 shows that the increment in PEG-400 level led to an increase in drug release. Since PEG-400 was a hydrophilic plasticizer, it could be leached out easily and left behind porous structure. The more PEG-400 incorporated into EC semipermeable membrane, the higher membrane permeability and drug release rate obtained.

The similarity factor f_2 was used to evaluate the influence of PEG-400 level on drug release profile. The drug release curves of 25.0%, 33.0% and 40.0% were compared with the ideal drug release profile and the f_2 values were obtained to be 36.2, 54.8 and 34.8, respectively. Therefore, the best PEG-400 level should be 33.0%. This PEG level was adopted in the following studies.

3.3. Influence of indentation size on drug release profile

Once the tablet formulation and membrane variable were fixed, the indentation size would be the key factor affecting the drug release. The influence of indentation size on drug release profile is shown in Fig. 2. Taking the drug release profiles of 1.14 and 1.00 mm in indentation diameter for paired T-test, p value was obtained to be 0.46 (>0.05), indicating that no significant difference existed in the release profile between 1.00 and 1.14 mm in indentation diameter. The profile of 0.84 mm was also compared with that of 1.00 mm by paired T-test, and p value was obtained to be 0.04, smaller

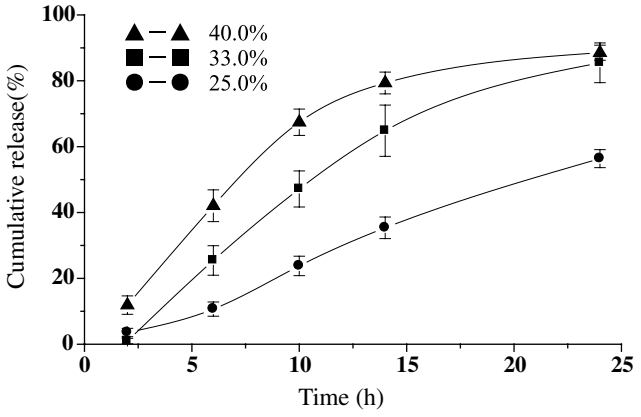

Fig. 1. Effect of PEG-400 level on drug release profile.

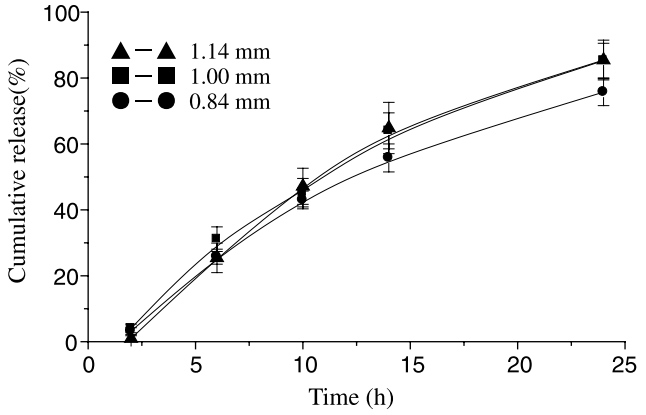

Fig. 2. Effect of indentation size of core tablet on drug release profile.

than 0.05, indicating that there was significant difference between them. In fact, the drug release was markedly slow in the indentation diameter of 0.84 mm. The small indentation led to the increment in hydrostatic pressure inside the system, which would depress drug release.

It was concluded that there was an appropriate range (1.00–1.15 mm) of indentation diameter for atenolol monolithic osmotic tablet. An indentation diameter of 1.00 mm was adopted in the following studies.

3.4. Influences of release media and agitation rate on drug release profile

To investigate the influence of release media on drug release, *in vitro* release tests were conducted in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid (SCF), respectively. Fig. 3 shows the release profiles of the osmotic pump tablets in these release media. Paired *T*-test was carried out between the data of SGF and SCF, *p* value was obtained to be 0.14; paired *T*-test was also carried out between the data of SIF and SCF, *p* value was obtained to be 0.42, both larger than 0.05, indicating no significant difference. In other word, the monolithic osmotic tablet exhibited a media-independent release. Thus, it might be expected that the fluid in different parts of the gastrointestinal tract scarcely affected the drug release of the atenolol osmotic tablet.

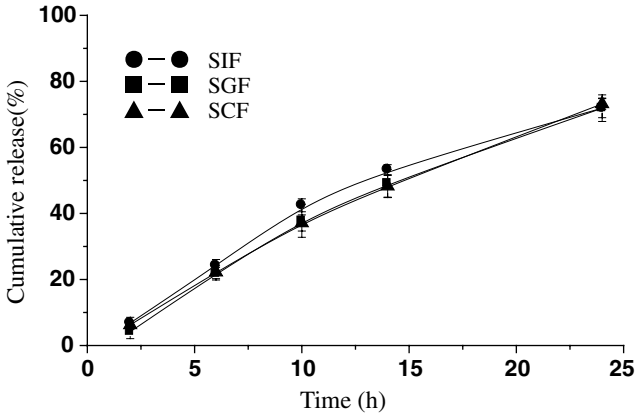

Fig. 3. Effect of release media on drug release profiles.

Release tests were also carried out at various agitation rates to investigate the effect of agitation rate on drug release profile. The profiles at agitation rates of 50, 100 and 150 rpm are presented in Fig. 4. The data of 100 rpm were compared with those of 50 rpm and 150 rpm by paired *T*-test, the *p* values were obtained to be 0.52 and 0.38, respectively, both larger than 0.05, indicating no significant difference existed in drug release profile under various agitation rates. Therefore, it might be predicted that the mobility of the gastrointestinal tract hardly affected the drug release of the atenolol osmotic tablet.

Since drug release was independent of both release media and agitation rate, the atenolol osmotic tablet might exhibit a comparable *in vitro*/*in vivo* release profile.

3.5. Comparison with conventional tablet

The release profiles of atenolol conventional tablet and the prepared osmotic tablet were plotted in Fig. 5 for comparison. It was found that in the case of conventional

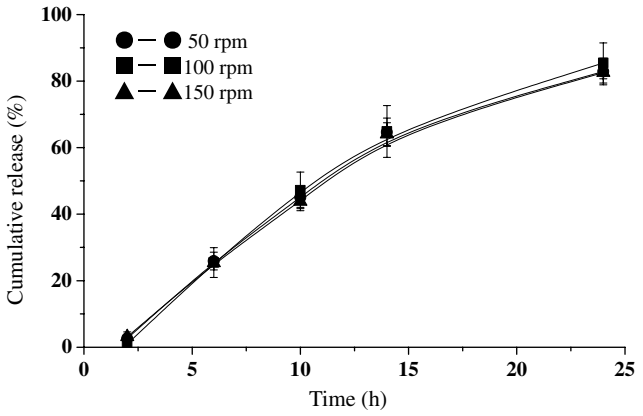

Fig. 4. Effect of agitation rate on drug release profile.

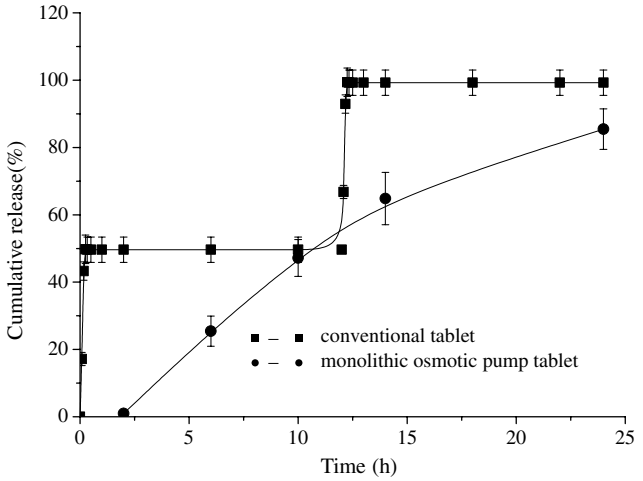

Fig. 5. Comparison of release profiles of atenolol osmotic pump tablet with conventional tablet.

tablet, the drug release rate was very high initially and the cumulative release was up to 90% within 30 min. However, in the case of osmotic pump tablet, an approximately constant rate was observed up to 24 h.

4. Conclusion

The osmotic pump tablet could deliver atenolol at an approximately constant rate up to 24 h, independent of both release media and agitation rate. Indentation size of core tablet in the range of (1.00–1.14) mm hardly affected drug release. The preparation of osmotic pump tablet is simplified by coating the core tablet with an indentation and the cost is reduced with the elimination of laser drilling. This method may be promising in the field of the preparation of osmotic pump tablet.

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