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Research paper

Solubility-modulated monolithic osmotic pump tablet for atenolol delivery

Longxiao Liu *, Xiaocui Wang

Zhejiang University, College of Pharmaceutical Sciences, Hangzhou, PR China

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Abstract

A method for the preparation of monolithic osmotic pump tablet was obtained by modulating atenolol solubility with acid. Tartaric acid was used as solubility promoter, sodium chloride as osmotic agent and polyvinyl pyrrolidone as retardant agent. Ethyl cellulose was employed as semipermeable membrane containing polyethylene glycol 400 as plasticizer. The formulation of atenolol monolithic osmotic pump tablet was optimized by orthogonal design and evaluated by similarity factor (f_2). The optimal monolithic osmotic pump tablet was found to be able to deliver atenolol at the rate of approximate zero-order up to 24 h, independent of release media and agitation rate. The approach of solubility-modulated by acid-alkali reaction might be used for the preparation of osmotic pump tablet of other poorly water-soluble drugs with alkaline or acid groups.

Keywords: Atenolol; Monolithic osmotic pump tablet; Solubility-modulated; Orthogonal design

1. Introduction

Atenolol, also known as 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzeneacetamide (Fig. 1), is a β-blocking agent, could effectively reduce systolic and diastolic blood pressures, and it is widely used alone or in combination to treat hypertension [1]. Atenolol is commercially available as conventional tablet. The tablet is usually administered two or three times a day, which would lead to large fluctuation in drug plasma concentration and side effect on human body. Controlled release systems are desirable to solve these problems. Among these, osmotic pump tablet offers several advantages, such as reducing risk of adverse reactions, improving compliance of patients and exhibiting comparable *in vitro*/*in vivo* drug release.

Rose and Nelson invented the first osmotic pump device which used osmotic pressure as energy to deliver active ingredients in the 1950s [2]. Theeuwes introduced oral osmotic pump tablet known as elementary osmotic pump (EOP) in the 1970s. It consisted of an osmotic core coated by a semipermeable membrane drilled with a delivery orifice. The EOP was very simple to prepare and could release water-soluble drugs at the rate of approximate zero-order [3,4]. However, it was not suitable for delivering the drugs with low solubility. To overcome this limitation, two-layer-core [5,6] osmotic pump tablet was developed. This tablet appeared in the 1980s. Its core tablet consisted of two layers, one containing drug, the other an osmotic agent and an expanding agent. Sastry et al. [7,8] reported atenolol two-layer-core osmotic pump tablet. While two-layer-core osmotic pump tablet could deliver water-insoluble or poorly water-soluble drugs, it had a disadvantage that a complicated side identification technology should be employed to ensure the orifice drilled on the surface of the drug layer. Therefore, three-layer-core [9,10] osmotic pump tablet was proposed. Liu et al. [10] studied three-layer-core osmotic pump tablet with the elimination of side identification. Its core tablet consisted of a middle push layer and two attached drug layers. Two orifices were

* Corresponding author. Zhejiang University, College of Pharmaceutical Sciences, Hangzhou 310058, PR China. Tel.: +86 571 8820 6791; fax: +86 571 8796 4475.
E-mail address: liulx@zju.edu.cn (L. Liu).

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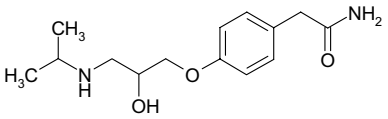

Fig. 1. The chemical structure of atenolol.

drilled on both sides of the surface after coating with avoiding side identification. However, either two-layer-core or three-layer-core osmotic pump tablet had a common disadvantage: a complicated tableting technology was needed. Therefore, some researchers made efforts to develop monolithic osmotic pump tablet [11]. This tablet could be prepared by a much easier technology.

Atenolol is a sparingly soluble drug (27 mg/ml at 37 °C). Some methods had been attempted to improve its solubility. Ficarra et al. [12] prepared β-cyclodextrin inclusion complex. However, it was proved that atenolol solubility could not be significantly enhanced by this way. Moneghini et al. [13] prepared atenolol solid dispersion to improve solubility. Although this method improved the solubility of atenolol somewhat, large amounts of carrier were consumed. In addition, solid dispersion had some problems, such as the difficulty of scale-up, the physical stability of dispersion, and the reproducibility of physicochemical properties, etc. [14], which limited its commercial application. For some alkaline drugs, it was feasible to convert them into salt by reacting with acid. Ayer et al. [15] used citric acid, maleic acid, malic acid and succinic acid as solubility promoter to increase the solubility of haloperidol substantially.

Atenolol is an alkaline drug with imide group. Appropriate solubility of tartaric acid made it a suitable candidate for modulating solubility of alkaline drugs. Therefore, tartaric acid was used as the solubility promoter to prepare atenolol monolithic osmotic pump tablet in this study. The influences of tartaric acid, polyvinyl pyrrolidone (PVP), sodium chloride and membrane thickness on drug release profile were investigated to determine significant associations of factors based on the L_9 orthogonal design. The influences of release media and agitation rate on *in vitro* release profile were evaluated.

2. Materials and methods

2.1. Materials

Atenolol powder and conventional tablets with strength of 50 mg were obtained from Shanghai Sunve Pharmaceutical Co., Ltd. (Shanghai, China). NaCl was purchased from Jiangsu Qinfen Pharmaceutical Co., Ltd. (Jiangsu, China). Tartaric acid was supplied by Shanghai Qinghong Chemical Co., Ltd. (Shanghai, China). PVPk30 was obtained from Huzhou Zhanwang Pharmaceutical Co., Ltd. (Zhejiang, China), ethyl cellulose (EC) from Luzhou North Chemical Industry Co., Ltd. (Sichuan, China), polyethylene glycol 400 (PEG 400) from Pudong Gaonan Chemical Co., Ltd. (Shanghai, China). Methanol (HPLC grade) was supplied by Tianjin Shield Company (Tianjin, China). HPLC grade water was used for the HPLC analysis. All the other reagents used were of analytical grade.

2.2. Preparation of core tablets

Atenolol powder was mixed with tartaric acid, NaCl and PVP manually, and then the mixture was granulated through a 1000 μm sieve using wet method and dried at 50 °C for 4 h. After that the granules were screened by a 1250 μm sieve. The resultant granules were compressed into core tablets with an indentation using TDP-1.5T single-punch tableting machine (Shanghai Guanlian Pharmaceutical Device Co., Ltd., China) whose upper concave faced punch was modified by us with a needle [16]. The diameter and the deepness of the indentation were 1.00 mm and 1.50 mm, respectively. The weight of each tablet was maintained within the range of (250 ± 5) mg and the drug loading was 25 mg.

2.3. Coating and drying

The prepared core tablets with an indentation were coated. EC (3%, w/v) in 95% ethanol containing PEG400 (33%, PEG400/EC, v/w) was used as coating solution. The coating was performed in a pan coater (Shanghai Huanghai Drug Inspection Instrument Co., Ltd., China). Pan-rotating rate was 33 rpm; spray rate was 3 ml/min. The coated tablets were dried overnight at 50 °C to remove the residual solvent. After coating, the indentation remained of sufficient size at least partly uncoated as the orifice for drug release [16,17]. The prepared osmotic pump tablets were kept in a desiccator for future experiments.

2.4. In vitro release test

In vitro release test was performed in a dissolution apparatus (RCZ-8A, Precise Apparatus of Tianjin University Co., Ltd., China) using the paddle method according to USP 29 [18]. The temperature was maintained at (37 ± 0.5) °C. At the predetermined intervals (2, 4, 8, 12, 14, 24 h), 5 ml samples were withdrawn from each vessel, filtered with a 0.45 μm membrane, and analyzed with HPLC method for atenolol. The same volume of fresh medium was replaced after sampling.

2.5. Measurement of atenolol concentration in tartaric acid aqueous solution

Excess amounts of atenolol were added to 10 ml of different concentrations of tartaric acid (0–200 mg/ml). Then the suspensions were shaken at 37 °C. After equilibrium attainment, the supernatant liquid was withdrawn, filtered through 0.45 μm membrane filter, appropriately diluted and analyzed for atenolol by HPLC.

2.6. HPLC analysis

Concentration of atenolol was determined using a HPLC system (Dionex Corporation, USA). The system consisted of a Dionex® P680A LPG-4 pump, a Dionex® UVD-170U UV detector, a Dionex® AST-100 automated sample injector and a computer installed with a Chromeleon® version 6.60 software. The wavelength of detection was set at 228 nm. Separation was achieved by using a KR-100 Kromasil column (C18, 5 μm, 100 Å, 4.6 × 250 mm). The mobile phase consisted of methanol and 10 mmol/l potassium dihydrogen phosphate aqueous solution at a ratio of 70:30 (v/v). The flow rate was 0.8 ml/min, and the injection volume was 30 μl. All chromatographic separations were performed at 25 °C.

3. Results and discussion

3.1. Concentration of atenolol in tartaric acid aqueous solutions

The concentration of atenolol in various concentrations of tartaric acid aqueous solution is shown in Fig. 2. The solubility of atenolol (37 °C) in deionized water was 27 mg/ml. It was clear that the concentration of atenolol in tartaric acid aqueous solution increased with the increase of original tartaric acid concentration. A more than 20-fold increase in atenolol concentration was achieved at original tartaric acid concentration of 200 mg/ml. It could be explained by its molecular structure. Atenolol had an imide group exhibiting alkality. When atenolol contacted with tartaric acid aqueous solution, it reacted and changed to salt. As a consequence, atenolol became freely soluble, and the concentration was increased markedly. It could be concluded that this method should be much more suited for the solubilization of atenolol and the preparation of monolithic osmotic pump tablet compared with technologies of solid dispersion and cyclodextrin inclusion.

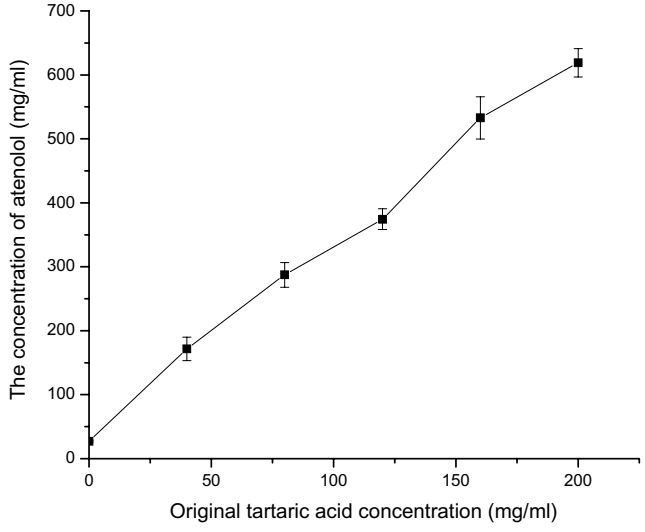

Fig. 2. The concentration of atenolol in tartaric acid aqueous solutions.

3.2. Optimization of formulation of osmotic pump tablet

PEG400 was found to be a suitable plasticizer for EC membrane. As it was hydrophilic, it could be leached easily and left behind a porous structure. Therefore it could be used to enhance the permeability of EC membrane. It was also found that the level of PEG400 of 33% (PEG400/EC, v/w) was suitable for achieving good linearity of release profile of osmotic pump tablet.

To study the influences of core tablet formulation and membrane thickness on drug release profile, osmotic pump tablets with various formulations were prepared according to the orthogonal design (Table 1). The four factors were set as follows: A, amount of tartaric acid; B, amount of PVP; C, amount of NaCl; D, membrane thickness.

For a commercialized osmotic pump tablet, the cumulative released percentage was 0% at 0 h and the ideal released percentage was supposed to be 90% at 24 h [19]. Other osmotic pump tablets might also follow this principle. Therefore, the equation of ideal zero-order release profile is $F = 3.75t$ [16], where F is the cumulative released percentage and t is the release time.

Similarity factor (f_2) has been adopted by U.S. Food and Drug Administration (FDA) [20] and European Medicines Agency (EMEA) [21] as a criterion for assessment of similarity between two *in vitro* release profiles. Therefore, in this study, f_2 was employed [16,22–24] to evaluate the release profiles of various formulations compared with the ideal release profile. The formula of f_2 was as follows:

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

The f_2 was a logarithmic transformation of the sum-squared error of differences between the testing drug release T_t and the ideal release R_t over all time points (n). The f_2 fitted the result between 0 and 100. When $f_2$was larger than 50, the mean deviation over all time points was less than 10%, and the testing profile was believed to be similar to the ideal profile.

According to Table 2, the optimal formulation was found to be $A_3B_1C_1D_3$. The osmotic pump tablet with the optimal formulation was prepared and its *in vitro* release profile was obtained. The f_2 was calculated to be 50.8. It was less than the f_2 of formulation No. 8 whose f_2 was the highest in Table 2. Therefore, formulation No. 8 was decided as the optimal formulation.

Table 1
Factors and levels of orthogonal design

Factors:	*A* (g)	*B* (g)	*C* (g)	*D* (mm)
Level 1	0	1	4	0.170
Level 2	0.5	2	5	0.235
Level 3	1	3	6	0.300

Table 2
Results of orthogonal design

	A	*B*	*C*	*D*	f_2
1	1	1	1	1	32.4
2	1	2	2	2	29.6
3	1	3	3	3	24.7
4	2	1	2	3	48.2
5	2	2	3	1	34.2
6	2	3	1	2	38.8
7	3	1	3	2	61.8
8	3	2	1	3	62.9
9	3	3	2	1	26.0
K1	86.7	142.4	134.1	92.6	
K2	121.2	126.7	103.8	130.2	
K3	150.7	89.5	120.7	135.8	
k1	28.9	47.5	44.7	30.9	
k2	40.4	42.2	34.6	43.4	
k3	50.2	29.8	40.2	45.3	
Δk	21.3	17.7	10.1	14.4	

3.3. Influences of release media 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 monolithic osmotic pump tablets in these release media. Paired *T*-test was carried out between the data of SGF and SIF, SGF and SCF, respectively. *p* values were both larger than 0.05 (0.590, 0.543). Thus, it might be expected that the gastrointestinal fluid scarcely affected atenolol release.

3.4. Influences of agitation rate on drug release profile

To study the effect of agitation rate on drug release profiles, release tests of optimal monolithic osmotic pump tablet were also carried out at agitation rates of 50, 75 and 100 rpm, respectively. The profiles at various agitation rates are presented in Fig. 4. Paired *T*-test was carried out between the data of 50 and 75 rpm, 75 and 100 rpm, respectively. *p* values were both larger than 0.05 (0.330, 0.341). It showed that a change in agitation rate did not significantly affect atenolol release. Therefore, the mobility of the gastrointestinal tract might scarcely affect the drug release.

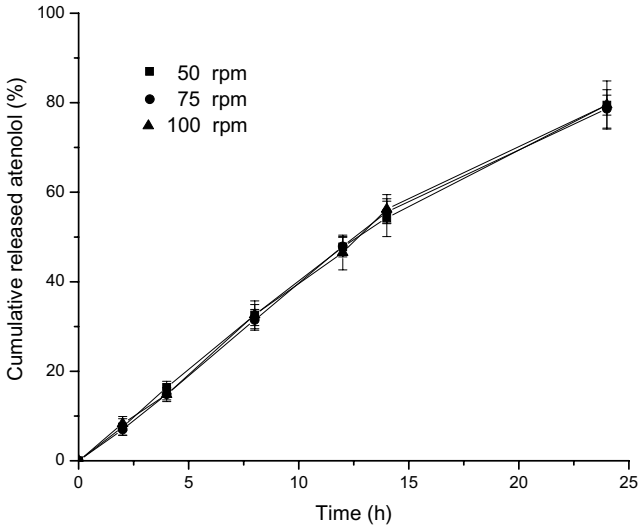

Fig. 4. Effect of agitation rate on drug release profile.

3.5. Comparison with commercialized conventional tablet and the reported osmotic pump tablet

The core tablet of a reported atenolol osmotic pump tablet consisted of drug, suspending agent and osmotic agent. The drug was released by both osmotic and suspending mechanisms [16]. The release profiles of commercialized conventional tablet twice daily, the reported osmotic pump tablet and the prepared monolithic osmotic pump table once daily at the same total dose are plotted in Fig. 5. It

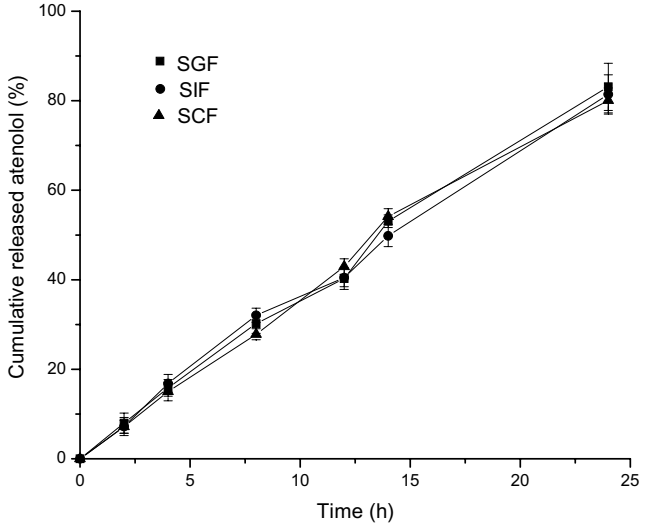

Fig. 3. Effect of release media on drug release profile.

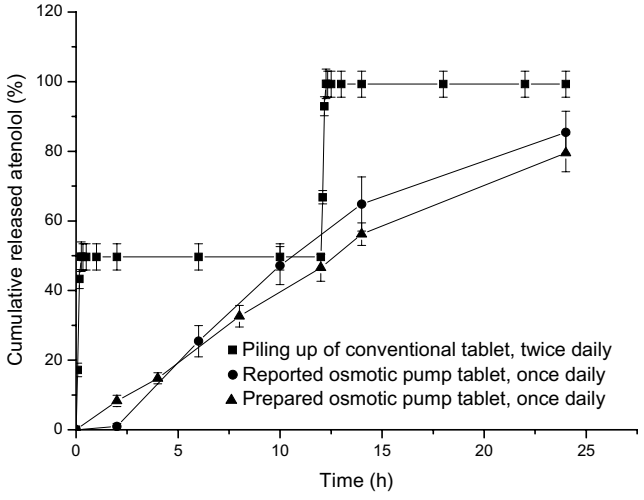

Fig. 5. Comparison with commercialized conventional tablet and the reported osmotic pump tablet.

was found that the drug release rate of conventional tablet was very high initially and the cumulative released percentage was up to 90% within 30 min. In the case of osmotic pump tablets, both of them could release drug at an approximately constant rate up to 24 h, but the lag time of the prepared osmotic pump tablet was shortened compared with the reported osmotic pump tablet. The linear correlation coefficients of the release profiles of the reported and the prepared osmotic pump tablets were calculated to be 0.953 and 0.983, and the similarity factors were 54.8 and 62.9, respectively. This indicated that the linearity of the release profile of the prepared osmotic pump tablet was improved compared with that of the reported osmotic pump tablet.

4. Conclusion

The monolithic osmotic pump tablet of atenolol had been successfully prepared using tartaric acid as solubility promoter. The optimal monolithic osmotic pump tablet was able to deliver atenolol at the rate of approximate zero-order up to 24 h, independent of release media and agitation rate. The approach of solubility modulated by acid-alkali reaction might be used for the preparation of osmotic pump tablet of other poorly water-soluble drugs with alkaline or acid groups.

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