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Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet

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Abstract

In this paper, a bilayer-core osmotic pump tablet (OPT) which does not require laser drilling to form the drug delivery orifice is described. The bilayer-core consisted of two layers: (a) push layer and (b) drug layer, and was made with a modified upper tablet punch, which produced an indentation at the center of the drug layer surface. The indented tablets were coated by using a conventional pan-coating process. Although the bottom of the indentation could be coated, the side face of the indentation was scarcely sprayed by the coating solution and this part of the tablet remained at least partly uncoated leaving an aperture from which drug release could occur. Nifedipine was selected as the model drug. Sodium chloride was used as osmotic agent, polyvinylpyrrolidone as suspending agent and croscarmellose sodium as expanding agent. The indented core tablet was coated by ethyl cellulose as semipermeable membrane containing polyethylene glycol 400 for controlling the membrane permeability. The formulation of core tablet was optimized by orthogonal design and the release profiles of various formulations were evaluated by similarity factor (f_2). It was found that the optimal OPT was able to deliver nifedipine at an approximate zero-order up to 24 h, independent on both release media and agitation rates. The preparation of bilayer-core OPT was simplified by coating the indented core tablet, by which sophisticated technology of the drug layer identification and laser drilling could be eliminated. It might be promising in the field of preparation of bilayer-core OPT.

Keywords: Bilayer-core osmotic pump tablet; Indented core tablet; Orthogonal design; Similarity factor; Nifedipine

1. Introduction

Nifedipine (1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine-dicarboxylic acid dimethyl ester) is a calcium channel blocking agent which blocks the transport of calcium into the smooth muscle cells of heart and blood vessels. After oral administration of nifedipine, blood vessels can be relaxed and the supply of blood and oxygen to the heart can be increased. Therefore, nifedipine is commonly used in the treatment of angina pectoris and hypertension (O'Rourke, 1985).

The conventional nifedipine tablet is usually administered three times per day, which will lead to the fluctuation of drug plasma concentration that may cause an inefficient treatment and side effects (Langer, 1998). The osmotic pump tablet (OPT) is one of the most important preparations in controlled release systems, OPT has many advantages, such as (1) releasing drug at an approximately constant rate up to 24 h; (2) releasing drug independent on environment media; (3) exhibiting comparable *in vitro*/*in vivo* drug release (Swanson et al., 1987; Abrahamsson et al., 1998; Liu et al., 2000a; Verma et al., 2002).

The first osmotic device was the Rose–Nelson pump invented in 1950s (Rose and Nelson, 1955). The first OPT was elementary osmotic pump (EOP) developed in 1970s (Theeuwes, 1975). EOP was a core tablet coated by semipermeable membrane with an orifice drilled on the surface. EOP could deliver water-soluble drugs only. To overcome the limitation, research had been carried out for the purpose of delivering water-insoluble drugs (Herbig et al., 1995; Okimoto et al., 1998; Liu et al., 2000b; Prabakaran et al., 2004; Thombre et al., 2004). One of these resulted in the development of bilayer-core OPT (Prabakaran et al., 2004; Thombre et al., 2004).

The bilayer-core OPT appeared in 1980s. Procardia XL® (Alza) was a commercialized one (Santus and Baker, 1995). The bilayer-core OPT whose core tablet consisted of two layers: (a) drug layer and (b) push layer, could deliver water-insoluble drugs. Compared with the monolithic OPT, by employing an

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expanding layer, the bilayer-core OPT had several advantages, including (1) it was more suitable for delivering water-insoluble drugs; (2) its release rate was much more closer to zero-order; (3) a higher cumulative released percentage at 24 h could be achieved. The bilayer-core OPT was generally used in delivering water-insoluble drugs, however it had a disadvantage in preparation that the expensive laser drilling technology was needed and a complicated drug layer identification technology must be employed to ensure the orifice drilled on the surface of drug layer after coating.

Recently, the monolithic OPT was successfully prepared by coating the indented core by us, which eliminated the laser drilling after coating and simplified the preparation of monolithic OPT (Liu and Che, 2006; Liu et al., 2007). There was sufficient space of the indentation to remain at least partly uncoated after coating, and then the uncovered apertures served as the drug release orifice. Although the similar method for preparing bilayer-core OPT have been described in a patent application (Shaw, 2002), it has not been reported in journal paper. So far the knowledge of the preparation of bilayer-core OPT with indented core tablet still remained superficial.

In this paper, the indented core strategy was employed to prepare bilayer-core OPT. The core tablet was made with a modified upper tablet punch, which produced an indentation at the center of the drug layer surface, and then the OPT was achieved by coating the indented core tablet. Although the bottom of the indentation could be coated, the side face of the indentation was scarcely sprayed by the coating solution and this part of the tablet remained at least partly uncoated leaving an aperture from which drug release could occur. As a result, the processes of drug layer identification and laser drilling in traditional preparation of bilayer-core OPT were not needed anymore. It would cut down the cost in preparation markedly. The influences of NaCl amount and polyvinylpyrrolidone (PVPk90) amount of drug layer and croscarmellose sodium (CCMC-Na) amount and NaCl amount of push layer on drug release profile were evaluated to determine significant associations of factors in the bilayer-core OPT based on the L9(3^4) orthogonal design. Also, the influences of membrane thickness, plasticizer level, release media and agitation rate on *in vitro* drug release profile were investigated.

2. Materials and methods

2.1. Materials

Nifedipine powder (Zhejiang Hisun Pharmaceutical Co., Ltd, China) was chosen as the model drug. PVPk90 (Shandong Ruitai Chemicals Co., Ltd, China) was used as suspending agent, CCMC-Na (J. Rettenmaier & Soehne GmbH & Co. KG, Germany) as expanding agent and NaCl (Jiangsu Qinfen Pharmaceutical Co., Ltd, China) as osmotic agent. Microcrystalline cellulose (MCC, Shandong Ruitai Chemicals Co., Ltd, China) was used as filler. Ethyl cellulose (EC60, Luzhou North Chemical Industry Co., Ltd, China) was employed as semipermeable membrane containing polyethylene glycol (PEG400, Pudong Gaonan Chemical Co., Ltd, China) to control membrane permeability. Other chemicals used were of analytical grade.

All experiments were carried out under strict protection from light to prevent undesirable photodegradation of nifedipine.

2.2. Tabletting

The granules of drug layer and push layer were prepared separately by wet granulation method with glycerin as the solvent. The resultant granules were compressed into core tablet using a TDP-1.5T single-punch tabletting machine (Shanghai Guanlian Pharmaceutical Device Co., Ltd., China) whose upper concave faced punch was modified with a needle by us (Liu and Che, 2006). The push layer granules were laid into the die cavity firstly, and then the drug layer granules were loaded on. Finally the bilayer-core tablet was compressed and an indentation at diameter of 1.00 mm and depth of 1.50 mm was produced at the center of drug layer surface. The weight of each tablet was maintained within the range of (300 ± 3) mg and the drug loading was 30 mg.

2.3. Coating

The indented core tablets were coated by using a conventional pan-coating process in a pan coater (Shanghai Huanghai Drug Inspection Instrument Co., Ltd, China). Ethyl cellulose in 95% ethanol containing PEG400 was prepared as coating solution. The temperature of inlet air was 50 °C; spray rate was 3 ml/min; pan-rotating rate was 30 rpm. The coated tablets were dried at 50 °C for 24 h to remove the residual solvent and then the bilayer-core OPT was achieved. Although the bottom of the indentation could be coated, the side face of the indentation was scarcely sprayed by the coating solution and this part of the tablet remained at least partly uncoated leaving an aperture from which drug release could occur. The photos of core tablets before and after coating process were showed in Fig. 1.

2.4. In vitro release test

In vitro release test was carried out according to USP XXIX paddle method in a dissolution apparatus (RCZ-8A, Precise

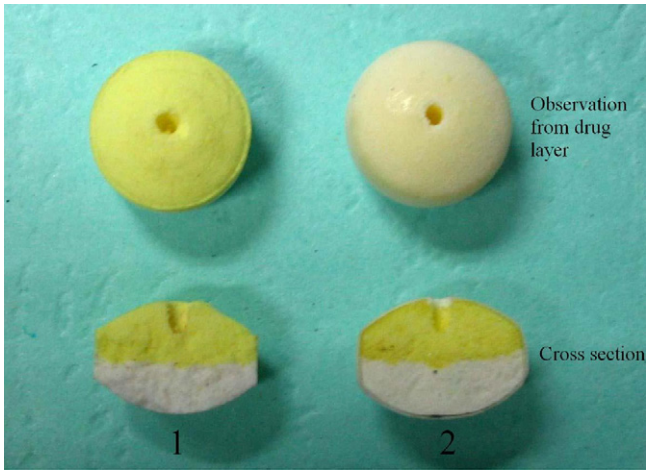

Fig. 1. The photos of the bilayer-core tablet (1) before and (2) after coating.

Apparatus of Tianjin University Co., Ltd, China). The OPT was entrapped into a sink basket and added to 900 ml release media. The release media contained 0.5% (w/v) sodium dodecylsulfate (SDS) to meet the sink condition according to USP XXIX (US Pharmacopeia XXIX, 2006). Five milliliter sample was withdrawn and the same volume of fresh media was added at 1, 2, 4, 8, 16, 24 h, respectively. The samples were immediately filtered through a 0.45 μm membrane filter, and 20 μl of them was chromatographed.

2.5. HPLC analysis

The HPLC system consisted of a Dionex® P680 LPG-4 pump, a Dionex® UVD170U UV detector, a Dionex® ASI-100 automated sample injector and a computer installed with Chromeleon® software for HPLC control and data process (Dionex corporation, USA). The UV detector wavelength was set at 235 nm (US Pharmacopeia XXIX, 2006). Separation was achieved using a Sepax® HP-C18 column (5 μm, 120 Å, 4.6 mm × 150 mm, Sepax Technologies, Inc., USA). The mobile phase consisted of HPLC grade methanol and water (70:30, v/v). The flow rate of the mobile phase was 1.0 ml/min.

3. Results and discussion

3.1. Optimization of formulation of core tablet

It was important to evaluate the drug release profiles through a scientific way in the kinetics study of drug release. In this work the similarity factor (f_2) was employed to evaluate the release profiles of various formulations compared with the ideal release profiles.

The f_2 is a logarithmic transformation of the sum-squared error of differences between the test and reference over all time points (Shah et al., 1998; Costa, 2001; Li et al., 2005).

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

where R_t and T_t represented the drug release percentage of reference and test at time t, n was the numbers of time points. The f_2 value fitted the result between 0 and 100. It approached to 0 as the dissimilarity of the test and the reference increased and attained to 100 when the test and reference were identical. The two dissolution profiles were believed to be similar when the f_2 value was larger than 50 for which the mean deviation over all time points was less than 10%.

For a commercialized nifedipine OPT, the cumulative released percentage was 0% at 0 h and the ideal cumulative released percentage was supposed to be 90% at 24 h (Swanson et al., 1987; Grundy et al., 1997). Therefore, the equation of ideal release profiles was $F = 3.75t$, where F was the ideal cumulative released percentage at time t.

Based on preliminary study, the main factors were set as follows: (A) NaCl amount in drug layer; (B) PVPk90 amount in drug layer; (C) CCMC-Na amount in push layer; (D) NaCl amount in push layer. To study the influence of core tablet formulation on drug release profile, osmotic core tablets with various formulations were prepared according to $L_9(3^4)$ orthogonal design (Table 1). Then, the core tablets were coated with coating solutions of 30% PEG level (EC, v/w) to the thickness of 122 μm.

Table 1
Factors and levels of orthogonal design

Factor	*A* (mg)	*B* (mg)	*C* (mg)	*D* (mg)
Level 1	40.0	60.0	50.0	50.0
Level 2	50.0	70.0	60.0	60.0
Level 3	60.0	80.0	70.0	70.0

A—NaCl amount in drug layer; *B*—PVPk90 amount in drug layer; *C*—CCMC-Na amount in push layer; *D*—NaCl amount in push layer.

The results of orthogonal design were showed in Table 2. k1, k2 and k3 were the average sum scores of Level 1, Level 2 and Level 3 for each factors. Apparently, the larger the average sum score was, the closer to ideal release the drug release profile was. The level which got the largest score was chosen as the optimal level of each factor. Therefore, the optimal formulation was found to be $A_3B_3C_1D_1$. The OPT with the optimal formulation was prepared and *in vitro* release test was performed. The f_2 value was calculated to be 62.4 by comparing with the ideal drug release profile. It was larger than f_2 value of the formulation no. 8 ($A_3B_2C_1D_3$) which was the maximum in Table 2. Therefore, $A_3B_3C_1D_1$ was decided to be the optimal formulation and it was obtained as follows: nifedipine, 30.0 mg; NaCl in drug layer, 60.0 mg; PVPk90 in drug layer, 80.0 mg; CCMC-Na in push layer, 50.0 mg; NaCl in push layer, 50.0 mg; MCC in push layer 30 mg. The formulation was adopted in the following studies.

Table 2
Results of orthogonal design

	Factor				f_2
	A	*B*	*C*	*D*	
1	1	1	1	1	58.0
2	1	2	2	2	49.3
3	1	3	3	3	55.5
4	2	1	2	3	55.5
5	2	2	3	1	53.8
6	2	3	1	2	54.3
7	3	1	3	2	51.3
8	3	2	1	3	58.2
9	3	3	2	1	57.6
K1	162.8	164.8	170.0	169.4	
K2	163.8	161.3	162.4	154.9	
K3	167.1	167.4	160.6	169.2	
k1	54.3	54.9	56.7	56.5	
k2	54.8	53.8	54.1	51.6	
k3	55.7	55.8	53.5	56.4	
Δ*k*	1.4	2.0	3.2	4.9	

K1, K2 and K3 are the sum scores of Level 1, Level 2 and Level 3 for each factor; k1, k2 and k3 are the average sum scores of Level 1, Level 2 and Level 3 for each factor; Δ*k* is the range among the average sum scores of Level 1, Level 2 and Level 3 for each factor.

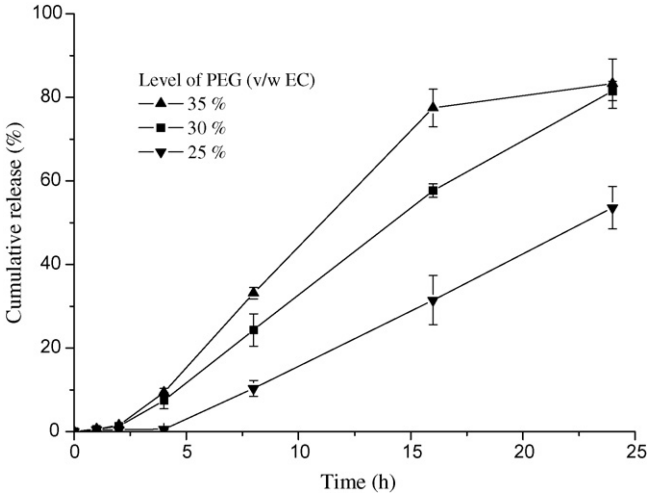

Fig. 2. Influence of PEG level on drug release profiles.

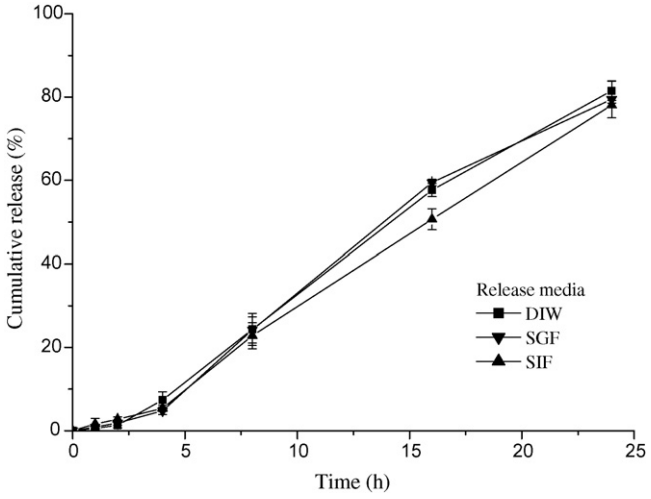

Fig. 4. Influence of release media on drug release profiles.

3.2. Influences of PEG level and membrane thickness on drug release profile

To study the influence of PEG level on drug release profile, the core tablets with optimal formulation were coated by coating solutions with various PEG levels of 25, 30 and 35% (EC, v/w), respectively. Fig. 2 showed that the increase of PEG level led to an increase of drug release rate. As PEG was a hydrophilic plasticizer, it could be leached easily and left behind porous structure, which enhanced the membrane permeability and drug release rate.

The f_2 was employed to evaluate the influence of PEG level on drug release profiles. Compared with the ideal release profile, the f_2 values of drug release curve of PEG level of 25, 30 and 35% were 34.9, 62.4 and 54.9, respectively. Therefore, the best PEG level of 30% was found and adopted in the following studies.

To study the influence of membrane thickness on drug release profile, the core tablets with optimal formulation were coated to thickness of 84, 122 and 166 μm, respectively, using a coating solution with PEG level of 30%. Fig. 3 showed that the drug release rate decreased as the membrane thickness increased. The thickness increase led to an increase of the membrane resistance to water penetration, resulting in the drug release rate decrease. The f_2 values of drug release curve of thickness of 84, 122 and 166 μm were 62.0, 62.4 and 41.8, respectively. The best membrane thickness of 122 μm was found and adopted in the following studies.

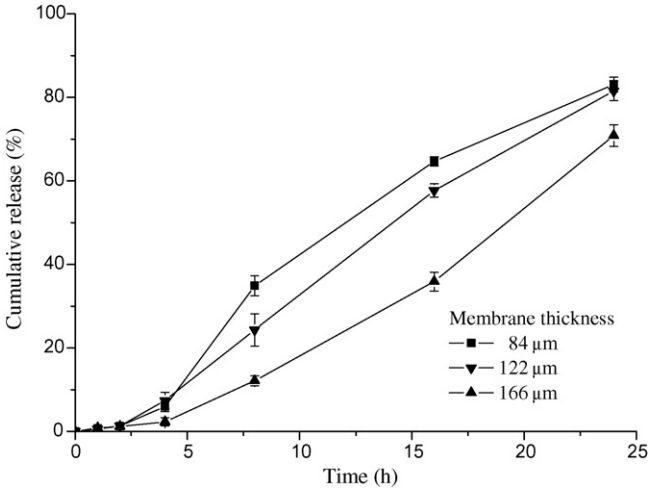

Fig. 3. Influence of membrane thickness on drug release profiles.

3.3. Influences of environmental media and agitation rate on drug release profile

To study the influence of environmental media on drug release profile, the drug *in vitro* release tests were carried out in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and deionized water (DIW), respectively. Fig. 4 showed the drug release profiles in these environmental media. Comparing the data of DIW with those of SGF and SIF by paired *t*-test, the *p* values were obtained to be 0.62 and 0.19, respectively, both larger than 0.05, indicated that no significant differences existed in drug release in different release media.

Drug release tests under different agitation rates were also conducted in order to investigate the influence of agitation rate on drug release profiles. Fig. 5 showed the drug release profiles at agitation rates of 50, 100 and 150 rpm, respectively. Comparing the data of 100 rpm with those of 50 rpm and 150 rpm by paired *t*-test, the *p* values were obtained to be 0.19 and 0.77, respectively, both larger than 0.05. It indicated that no significant differences existed in drug release under various agitation rates.

Based on these tests, it may be predicated that the environments of gastrointestinal tract hardly affect the drug release from the prepared OPT.

3.4. Comparison with the reported nifedipine monolithic OPT

The core tablet of reported nifedipine monolithic OPT consisted of the drug, an osmotic agent and a suspending agent.

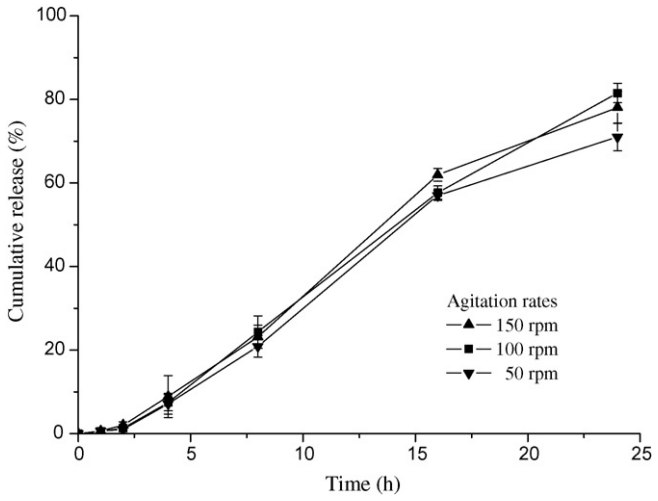

Fig. 5. Influence of agitation rates on drug release profiles.

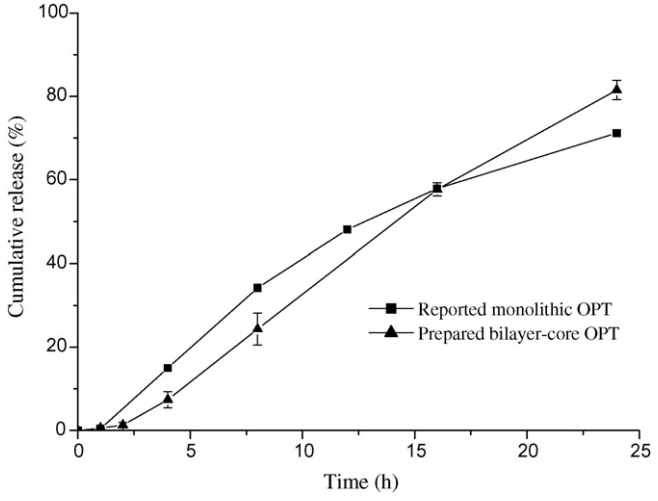

Fig. 6. Comparison of release profiles of prepared bilayer-core OPT with the reported monolithic OPT.

The drug was released by an osmotic-suspending co-controlled delivery mechanism (Liu et al., 2000b). The release profiles of the reported monolithic OPT and the prepared bilayer-core OPT were plotted in Fig. 6. The linear correlation coefficients of the release profiles of the reported monolithic OPT and the prepared bilayer-core OPT were calculated to be 0.978 and 0.996 and the cumulative released percentage at 24 h were 71.2 and 81.5%, respectively. It was clear that compared with the monolithic OPT, the release profile of prepared bilayer-core OPT was much closer to a straight line and the cumulative released percentage was elevated. It indicated that our bilayer-core OPT had a better performance compared with the reported monolithic OPT.

4. Conclusion

The bilayer-core OPT was successfully prepared by coating the indented core tablet. The prepared bilayer-core OPT was able to deliver nifedipine at an approximately constant rate up to 24 h, independent on both release media and agitation rate. Since the drug layer identification and laser drilling could be eliminated by employing this strategy, the preparation of bilayer-core OPT could be simplified and the cost could be cut down. The strategy may be promising in preparation of bilayer-core OPT.

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