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

Longxiao Liu *, Xiangning Xu

College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, PR China

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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

* Corresponding author. Tel.: +86 571 8820 6791; fax: +86 571 8796 4475.
E-mail address: liulx@zju.edu.cn (L. Liu).

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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

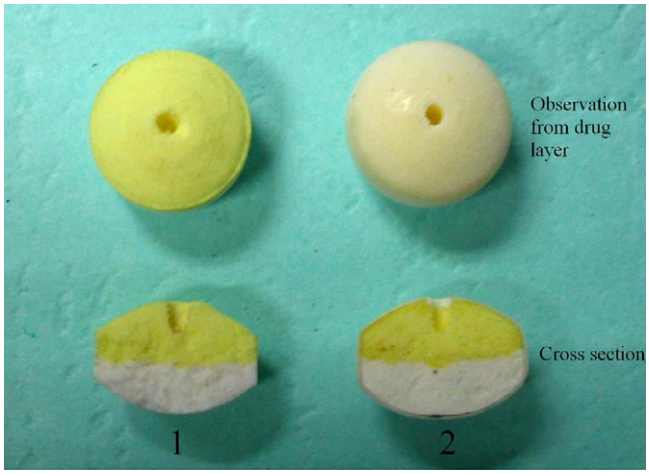

Fig. 1. The photos of the bilayer-core tablet (1) before and (2) after coating.