International Journal of Pharmaceutics 495 (2015) 1–8

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Formulation of a modified-release pregabalin tablet using hot-melt coating with glyceryl behenate

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ARTICLE INFO

Article history:
Received 22 May 2015
Received in revised form 13 August 2015
Accepted 20 August 2015
Available online 24 August 2015

Keywords:
Pregabalin
Glyceryl behenate
Hot-melt coating
Drug release
Pharmacokinetic
Stability

ABSTRACT

A modified-release (MR) tablet of the anti-anxiety drug pregabalin (PRE) was prepared by hot-melt coating PRE with glyceryl behenate (GB) as a release retardant and compressing to form a matrix with microcrystalline cellulose (MCC) as a hydrophilic diluent. GB-coated PRE had a size in the range of 177–290 μm with good to acceptable flowability. Tablet hardness decreased slightly as GB content increased. PRE release from the tablet matrices was successfully modified by altering the ratio of MCC and GB, and it was found that dissolution- or diffusion-controlled release depended on the amount of GB used. Drug release was pH-independent. An accelerated stability test on the most promising MR tablet at 40 °C and 75% relative humidity for 6 months showed no significant changes in PRE content, and the occurrence of total impurities—including PRE-lactam—was within acceptable limits. After oral administration of the selected MR tablet or a commercial IR capsule (Lyrica) to healthy human volunteers, pharmacokinetic parameters including T_{max}, C_{max}, AUC_{0-24}, and $T_{1/2}$ were compared. The confidence interval of AUC_{0-24} was within the adequate range, but that of C_{max} was inadequate. This study demonstrated the potential use of GB for PRE-containing MR formulations.

1. Introduction

Pregabalin (PRE; *S*-(3)-amino methyl hexanoic acid) is a structural analogue of γ-aminobutyric acid, which is used to treat refractory partial seizures, diabetic neuropathy, post-therapeutic neuralgia, and social anxiety disorders. Its main site of action appears to be the α_2-δ subunit of the voltage-dependent calcium channels that are widely distributed throughout the peripheral and central nervous system (Gee et al., 1996; Bryans and Wustrow, 1999; Bian et al., 2006). PRE is a highly soluble and highly permeable drug, categorized according to the biopharmaceutics classification system (BCS) as a class 1 compound. PRE has an oral bioavailability (BA) of more than 90% with an average elimination half life of 6.3 h, and it is excreted unchanged in the urine (French et al., 2003). The absorption of PRE is limited to the upper small intestine, where l-amino transporters that govern PRE absorption exclusively exist (Su et al., 2005; Cundy et al., 2004). In 2004, Pfizer introduced PRE to the market under the brand name Lyrica as a conventional, immediate release (IR)-type capsule with a recommended dosage regimen of 150–600 mg per day divided into 2 or 3 doses (NDA 21446, 2004; Dworkin and Kirkpatrick, 2005). Therefore, modified release (MR)-type dosage forms would be useful to reduce dosing frequency and improve patient compliance.

Orally administered, controlled-release tablets are an attractive new class of drug delivery system (Chien, 1992). Controlled-release systems are generally classified as either monolithic matrix or reservoir type. In monolithic matrix systems, the drug is distributed throughout a polymer matrix. Sustained or modified drug release is attained by the use of water-swellable or -erodible matrices consisting of various polymeric excipients such as hydrophilic polymers (hypromellose, hydroxypropylcellulose, sodium alginate, chitosan, polyethylene oxide, etc.) and hydrophobic polymers (ethylcellulose, hypromellose acetate succinate, methacrylic acid co-polymers, etc.). Alternatively, lipids can be used as a release rate-controlling agent for solid oral dosage forms. Lipidic excipients include long-chain, saturated fatty acids and/or their partial glycerides, hydrogenated vegetable oils, polyoxylglycerides, and

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http://dx.doi.org/10.1016/j.ijpharm.2015.08.057
0378-5173/

fatty alcohols (Rosiaux et al., 2014; Saraiya and Bolton, 1990; Barthelemy et al., 1999). The advantages of the lipid matrix system are that it avoids drug-excipient interactions, has pH-independent drug release properties, and has a high correlation between in vitro and in vivo properties (Schroeder et al., 1978). Various methods for preparing lipid matrices have been proposed, including direct compression, wet granulation, the hot-melt granulation/spray method, cold/hot extrusion, etc. (Obaidat, 2001; Mehta, 1986; Miyagawa, 1996). Sustained-release tablet formulations have been successfully prepared using the hot-melt granulation method (Zhang and Schwartz, 2003).

Glyceryl behenate (GB) is a widely used lipid excipient, which is synthesized by an esterification reaction between glycerol and behenic acid (C_{22} fatty acid). It has a melting point of 69–74 °C and an HLB value of 2. GB was initially used as a tablet lubricant and taste-masking agent, but has recently found use as a controlled-release agent. Many reports have demonstrated the use of GB to prolong or modify the release of numerous drugs, including theophylline, metoprolol succinate, and tramadol (Barthelemy et al., 1999; Roberts et al., 2012; Obaidat, 2001). Drug release from lipophilic matrix systems is dependent on several factors such as solubility, dosing contents, excipients, physical dimensions of the tablet, and the level of matrix-forming agent (Roberts et al., 2012). The release of the drug from the lipid matrix is generally slow and mainly due to diffusion (Obaidat, 2001). Drug release can be controlled by the addition of hydrophilic excipients such as lactose or microcrystalline cellulose derivatives, which generate pores in the matrix or accelerate disintegration of the matrix by causing swelling (Obaidat, 2001).

In this study, in order to develop a once-a-day PRE product, various MR tablets were formulated with different amounts of GB and microcrystalline cellulose (MCC)—as a release retardant and a hydrophilic diluent, respectively. The in vitro drug release characteristics of various MR tablets were investigated, and the stability of the most promising MR tablet was evaluated. The pharmacokinetic (PK) profiles of the selected MR tablet and a commercial IR product (Lyrica) were studied in healthy human volunteers.

2. Materials and methods

2.1. Materials

PRE and 4-isobuyl-pyrrolidin-2-one (PRE-lactam) were purchased from TEVA (Be'er sheva, Israel). GB (trade name of Compritol® 888 ATO) was purchased from Gateffossé (Nanterre, France). MCC was purchased from JRS Pharma (Weissenbern, Germany). The other excipients used to prepare the tablets were of standard pharmaceutical grade. All other reagents were of analytical grade. Commercially available IR-type PRE capsules (150 mg, Lyrica, Pfizer, Germany) were used as the reference for the in vivo study.

Table 1
Compositions of PRE-MR tablets.

Composition	F1	F2	F3	F4	F5	F6
PRE	300	300	300	300	300	300
Glyceryl behenate	0	30	60	100	200	300
Microcrystalline cellulose	250.2	220.2	190.2	150.2	50.2	50.2
Colloidal silicon dioxide	10.2	10.2	10.2	10.2	10.2	10.2
Talc	19.8	19.8	19.8	19.8	19.8	19.8
Magnesium stearate	19.8	19.8	19.8	19.8	19.8	19.8
Total weight (mg)	600.0	600.0	600.0	600.0	600.0	700.0

2.2. Methods

2.2.1. Preparation of MR tablets

The compositions of the various PRE-containing MR (PRE-MR) tablets are shown in Table 1. GB was selected as a lipid coating material to control the release of PRE, and MCC was used as a directly compressible diluent. A combination of colloidal silicon dioxide, talc, and magnesium stearate was used as lubricant. All constituents were weighed accurately, and a hot-melt coating technique was adopted for granulation. Briefly, GB was melted at 80–90 °C in a vertical granulator (FM-VG-5P; Powrex, Osaka, Japan), PRE was added while shearing with impeller at 300 rpm and chopper at 2000 rpm, and then the melted mass were cooled down to 20 °C and passed through no. 20 mesh. The coated granules were collected with over 97% yield. After homogeneous blending with MCC and lubricant, direct compression was performed on a rotary tablet machine (Pressima; IMA-KILAN, Cologne, Germany) at compression force of 1.5 kN using 11.2 mm oval type punches.

2.2.2. Physical property observation

2.2.2.1. Property of the hot-melt-coated granules. The shapes of the particles in the hot-melt-coated granules were observed using an optical microscope system (Eclipse TE2000-U; Nikon Co., Tokyo, Japan), and the particle size distribution was measured using a laser diffraction particle size analyzer (Malvern Mastersizer 2000; Malvern Instruments Ltd., Malvern, UK). To evaluate the flow properties of the prepared granules, apparent bulk and tapped bulk densities were measured by the cylinder method using a powder tester (ABD-100, Tsutsui Scientific Instruments Co., Ltd., Tokyo, Japan). Accurately weighed granule samples were poured into a cylinder and the volume was measured to obtain the apparent bulk density; separately, a sample was tapped 100 times to measure tapped bulk density.

2.2.2.2. Property of PRE-MR tablets. Physical testing of PRE-MR tablets was performed after a relaxation period of at least 24 h. Weight variation tests were performed with 20 individually weighed tablets using a balance (AB204-S/FACT Analytical Balance; Mettler-Toledo, Greifensee, Switzerland). The thickness and diameter of 10 tablets were measured individually using vernier calipers (MN84; Mitutoyo, Kawasaki, Japan). The crushing strength was determined using a hardness tester (C50; Holland, Nottingham, UK). Tablet friability was calculated as the percentage of weight loss (4 min, 25 rpm, 20 tablets) using a friabilator (FAT-10, FineScientific Instrument, Seoul, Korea).

2.2.3. Drug content determination by HPLC assay

Twenty tablets were weighed individually, crushed into a fine powder, and combined to give a sample containing 300 mg of PRE. The mobile phase was poured into the flask and the drug was extracted for 5 min at 60 Hz using a bath sonicator (8510-DTH; Branson, Danbury, CT, USA). The drug contents were determined by HPLC assay using a pump (W2690/5; Waters, Milford, MA, USA), UV detector (W2489; Waters), and a data station (Empower3; Waters). Chromatographic separation was performed using cyano silica column (Hypersil BDS cyano, 4.6 × 150 mm, 5 μm, Thermo Fisher Scientific, San Jose, CA, USA) at a flow rate of 1.0 mL/min. Sample was injected and peaks were monitored at 210 nm. The isocratic mobile phase was composed of acetonitrile and buffer solution at a ratio of 13:88 (v/v). Buffer solution consisted of sodium hexanesulfonate (9.41 g), triethylamine (2 mL), and water (880 mL), with pH adjusted to 3.1 using orthophosphoric acid.