International Journal of Pharmaceutics 462 (2014) 66–73

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Personalised Medicine

A novel pulsatile drug delivery system based on the physiochemical reaction between acrylic copolymer and organic acid: *In vitro* and *in vivo* evaluation

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ARTICLE INFO

Article history:
Received 27 September 2013
Received in revised form
18 November 2013
Accepted 15 December 2013
Available online 22 December 2013

Keywords:
Pulsatile pellets
Organic acid
Acrylic copolymer
Enalapril Maleate
Film coating

ABSTRACT

Multilayer-coating technology is the traditional method to achieve pulsatile drug release with the drawbacks of time consuming, more materials demanding and lack of efficiency. The purpose of this study was to design a novel pulsatile drug delivery system based on the physiochemical interaction between acrylic copolymer and organic acid with relatively simpler formulation and manufacturing process. The Enalapril Maleate (EM) pulsatile release pellets were prepared using extruding granulation, spheronization and fluid-bed coating technology. The ion-exchange experiment, hydration study and determination of glass transition temperature were conducted to explore the related drug release mechanism. Bioavailability experiment was carried out by administering the pulsatile release pellets to rats compared with marketed rapid release tablets Yisu®. An obvious 4 h lag time period and rapid drug release was observed from *in vitro* dissolution profiles. The release mechanism was a combination of both disassociated and undisassociated forms of succinic acid physiochemically interacting with Eudragit® RS. The AUC0-τ of the EM pulsatile pellets and the market tablets was 702.384 ± 96.891 h ng/mL and 810.817 ± 67.712 h ng/mL, while the relative bioavailability was 86.62%. These studies demonstrate this novel pulsatile release concept may be a promising strategy for oral pulsatile delivery system.

1. Introduction

A variety of diseases including hypertension, angina pectoris, epilepsy, asthma, diabetes, hyperchlorhydria and arthritis exhibit circadian variation (Hermida et al., 2007b; Lemmer, 1999; Miyamoto et al., 2004; Roy and Shahiwala, 2009a). With the development of chronotherapy, which refers to a clinical practice of drug delivery consistent with the body's circadian rhythm (Hermida et al., 2007a; Innominato et al., 2010; Ohdo, 2010; Portaluppi and Lemmer, 2007; Roy and Shahiwala, 2009b) to produce maximum health benefit and minimum harmful effects (Roy and Shahiwala, 2009a), time-controlled release systems for comparative drug efficacy have gained intensive attention worldwide since first introduced. And pulsatile drug delivery system is an important and desirable part among time-controlled release systems. Pulsatile drug delivery system is characterized by a predetermined lag time period in the starting stage followed by a drug release phase in the drug release profiles (Karavas et al., 2006; Kashyap et al., 2007; Lin et al., 2008; Sungthongjeen et al., 2004; Yadav et al., 2011). Pulsatile release has the advantages of avoiding drug tolerance, matching the release of specific peptides or hormones, and control of tissue (Iskakov et al., 2002) and drug release may be controlled by time, by site or a combination of the two parameters (Yadav et al., 2011). Devices which show pulsatile release upon applying an external trigger such as pH (Déjugnat et al., 2005; Lynn et al., 2001), electric field (Kiser et al., 1998, 2000), IR-light (Angelatos et al., 2005; Radt et al., 2004; Skirtach et al., 2005), *etc.* have been described. But generally all manufacturing approaches work on the same basic principles of swelling and rupturing (Bussemer and Bodmeier, 2003; Bussemer et al., 2003; Sungthongjeen et al., 2004), erosion (Gazzaniga et al., 1994; McConville et al., 2005) or dissolution, and systems based on changes in membrane permeability (Roy and Shahiwala, 2009a). As to the coating technology, multilayer-coating is the most popular method to achieve pulsatile drug release. However, this method has drawbacks of incomplete drug release and more materials demanding. Moreover, multilayer-coating is time consuming, tedious operating and lack

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http://dx.doi.org/10.1016/j.ijpharm.2013.12.026

of efficiency, leading to technical hurdles in commercial scale process.

Eudragit® RS is a kind of acrylic copolymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups in the form of chloride. The coating film formed by Eudragit® RS is insoluble in water and has a low permeability but swells in water by incorporating H_2O molecules into its hydrophilic groups. Researchers found that some organic acid solutions can induce the structural change of Eudragit® RS by physiochemical interaction, leading to the changing membrane permeability (Narisawa et al., 1994; Wagner and McGinity, 2002). In order to overcome the drawbacks of conventional multi-layer coating technology for pulsatile pellets, we proposed a novel pulsatile drug delivery system by incorporating organic acid in the core pellets and coating with Eudragit® RS copolymer based on the above principle. Various kinds and amount of organic acid were screened, respectively. Ideally, when water slowly penetrates across Eudragit® RS, organic acid in core pellets interacting with the low amount of quaternary ammonium groups of Eudragit RS copolymer is responsible for changes of the film surface properties, which contributes to drug release after a predetermined lag time period due to its low water permeability.

Enalapril Maleate (EM) is an angiotensin-converting enzyme inhibitor and used as an antihypertensive agent. Nowadays, marketed dosage forms of EM are mainly oral rapid release tablets. However, blood pressure in human body presents circadian rhythms – a dramatic morning rise and obvious bedtime decline, both of which act as a push for the chronotherapy of hypertension (Hermida et al., 2007b; Portaluppi and Lemmer, 2007). Therefore, EM was chosen as the model drug. Then patients can take the designated EM dosage form at a proper time in the evening and drug therapeutic concentrations will be achieved the next day in the occurrence of blood pressure morning peak.

A novel single-layer coated pulsatile release system, which is meant to contain organic acid in the core and coated with acrylic copolymer, was designed with a relatively simpler formulation and manufacturing process compared to the traditional multi-layer coated explosive pulsatile drug release system. *In vitro* and *in vivo* evaluation was conducted in contrast with marketed rapid release tablets of Yisu®. The drug release mechanism was demonstrated and investigated through a string of experiment, such as ion-exchange study, hydration research and determination of glass transition temperature.

2. Materials and methods

2.1. Materials

Enalapril Maleate (EM) was obtained from Yangtze Pharmaceutical Co., Ltd. (Taizhou, China). Eudragit® RS 30D using as the coating material was supplied by Röhm Pharma (Darmstadt, Germany). Lactose (GranuLac® 200) was obtained from Meggle (Wasserburg, Germany). Five organic acids including succinic acid, DL-tartaric acid, citric acid, malic acid and acetic acid, plus with all other chemicals were used as received and were of standard pharmaceutical grade: HPMC (E5, Colorcon, Orpington, UK), Microcrystalline Cellulose (MCC; Avicel® PH 101, Asahi Kasei. Co., Ltd., Tokyo, Japan) and triethyl citrate (TEC; Aladdin Chemistry Co., Ltd., Shanghai, China). The marketed rapid release tablets Yisu® (Yangtze Pharmaceutical Co., Ltd., Taizhou, China) were used as the reference.

2.2. Methods

2.2.1. Demonstration of feasibility of the mechanism

The components of EM, MCC and lactose (10:80:10) were passed through a 200 μm sieve to obtain a well-dispersed mixture and wet massed with 3% HPMC aqueous solution as a binder. The soft material was made into strip granules with 1 mm screen by means of an extruding granulator (JBZ-300, New Drug Research Institute of Liaoning Yilian, China), which were then broken into smaller cylindrical rods and rounded into spherical pellets using a high-speed rotating friction machine (JBZ-300, New Drug Research Institute of Liaoning Yilian, China). The extruding and rotating speed were both 385 × *g*. Then the pellets were dried for 3 h at 40 °C in the oven (DHG-9245A, Shanghai Huiyi Technology Co., Ltd, China). After drying, the core pellets were passed through two sieves of 800 μm and 1000 μm to remove fine, large and agglomerate particles. The pellets were then coated by spraying with a mixture of Eudragit® RS 30D, talc, TEC, water (20:2:2:76) in a fluid-bed coater (Werner Glatt, Germany). The coating conditions were as follows: spray air pressure, 0.14 MPa; spray solution speed, 1.0 mL/min; inlet temperature, 35 °C; outlet temperature, 30 °C. The coating level was 50%, which can be determined from the following equation (Lemmer, 1999)

$$L(\%) = \frac{M_{after} - M_{before}}{M_{before}} \times 100$$

where L represents the gaining weight of coating in terms of percentage, M_{before} and M_{after} are the weight of pellets before and after coating, respectively.

Release study of the acid unloaded pellets was performed using USP 32 apparatus 1 (basket) with 900 mL of 0.5 mol/L various testing fluid at 37 °C with the basket speed of 100 rpm using a dissolution tester (ZRS-8G, Tianda Tianfa Techenology Co., Ltd., Tianjin, China). Five organic acids including succinic acid, DL-tartaric acid, citric acid, malic acid and acetic acid solution (each 0.5 M) were selected as dissolution medium to demonstrate the feasibility of the principle and find suitable additives using release rate as the evaluation index. Samples through a 45 μm filter were taken at preparatory time interval and measured by HPLC (Shimadzu, Kyoto, Japan) with a reverse-phase column (Inertsil ODS-3, 4.6 × 250 mm, i.d. 5 μm, GL Sciences, Japan), and UV detection at 207 nm. An acidified (pH 2.2, adjusting with phosphoric acid) aqueous solution of potassium dihydrogen phosphate was used as the mobile phase at a flow rate of 1.0 mL/min. Methodological studies, such as linearity, specificity, precision of with-in and between days were also demonstrated to satisfy the requirements of the methodology. A linear detector response (r = 0.9999) was observed over the concentration range of 1–20 μg/mL and blank solvent did not interfere with the determination of EM.

Table 1
The core and coating layer composition of the Erudragit® RS coated pulsatile release pellets of EM.

Core		Coating layer	
Continents	Added amount	Continents	Added amount
EM	10%	Eudragit® RS 30D	20%
MCC	42%	TEC	2%
Succinic acid	38%	Talc	2%
Lactose	10%	Water	76%

2.2.2. Preparation of pulsatile release pellets

The formula of the core pellets and coating solution are shown in Table 1.

The experimental conditions and preparing method were referred to organic acid unloaded pellets in Section 2.2.1.

For one thing, to optimize extrusion – spheronization process and get the desired particle size range with adequate friability and flow properties, blank (without drug) pellets were prepared with MCC alone initially. Then the optimized process was applied to the