Powder Technology 294 (2016) 66–70

Contents lists available at ScienceDirect

Powder Technology

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

Research paper

Formulation and development of ternary hybrid matrix tablets of diltiazem hydrochloride

Jianwen Li [a,b], Chunli Luo [a], Dong Zhang [a], Mo Li [c], Qiang Fu [a,*], Zhonggui He [a]

[a] Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China
[b] GE Healthcare, No. 1, HuaTuo Road, Zhangjiang Hi-Tech Park, Shanghai 210203, China
[c] Liaoning Institute for Drug Control, No. 7, Chongshan Road, Shenyang 110036, China

ARTICLE INFO

Article history:
Received 7 September 2015
Received in revised form 23 January 2016
Accepted 9 February 2016
Available online 12 February 2016

Keywords:
Diltiazem hydrochloride
Extended-release
Ternary matrix
Polyethylene oxide
Chitosan
Sodium alginate

ABSTRACT

Polyethylene oxide (PEO) has been extensively used as an extended-release excipient in matrix tablets due to its extraordinarily safe, stable, soluble, swellable and erodible properties. The present study aimed to develop once-daily sustained-release tablets using PEO for a highly water-soluble drug, diltiazem hydrochloride (DH), the clinical application of which is limited because of its short half-life in vivo. However, the prophase study demonstrated that the use of PEO alone could only retard the drug release to 8 h. Thus, we proposed its combined use with chitosan/sodium alginate and formulated ternary matrix tablets by direct compression, in the hope of further extending the release of DH. The in vitro release study demonstrated that the ternary matrix synergistically prolonged DH release to 24 h while the kinetic mechanism study showed that its release was correlated with Korsmeyer–Peppas models and a non-Fickian drug release mechanism. Its release was primarily governed by diffusion and secondarily by erosion. The results of the present study demonstrated for the first time the feasibility of using a ternary hybrid matrix to prolong the release of highly water-soluble drugs, at least in the case of DH, which has a solubility as high as 625 mg/mL.

1. Introduction

Diltiazem hydrochloride (DH) is a nondihydropyridine calcium channel blocker mainly used for the treatment of hypertension, angina pectoris, and some types of arrhythmia. However, its critical drawback is the frequent dosing required due to its short half-life in vivo [1]. Consequently, an extended release formulation would be more convenient for patients and thereby potentially improve compliance, and the commercial product Dilacor XR® has already been approved by the FDA and its generic formulations are marketed in China. However, because it is a highly water-soluble drug (as high as 625 mg/mL), several research studies have focused on developing extended-release formulations for DH using different strategies, such as ion exchange resins [2–4], coating [5,6], and matrix systems [7,8]. Among them, the matrix formulations are the most popular preparations for wide application because of their easy production using traditional processes and equipment. However, the extended-release effect can last for only 12 h using a traditional matrix [7,8].

Polyethylene oxides (PEOs) are hydrophilic, linear and uncrosslinked polymers [9]. Upon exposure to gastrointestinal fluid, PEOs hydrate rapidly and then swell, and a hydrogel layer is formed on the surface of the tablet. This is followed by erosion of the PEOs. The swelling and erosion properties of PEOs modulate and control the drug release [10]. Consequently, PEOs have been widely used in matrix tablets, involving direct compression [11], granulation [10], or hot-melt extrusion [12]. Importantly, the PEOs are available in a wide range of molecular weights (1×10^5 to 6×10^6), rendering them good candidates for extended release, because PEOs with a low molecular weight provide complete release, while high molecular weight PEOs offer better extended release [9]. In addition, in order to better modulate the drug release, the PEOs have been used in combination with other excipients, including stearic acid [13], PEG [14], poly (e-caprolactone) [15], ethylcellulose [16], hypromelose [17], and sodium carboxymethylcellulose [18]. Generally, the incorporation of hydrophilic excipients promotes drug release, while the use of hydrophobic ones may retard this release. Interestingly, several PEO-based products, such as OxyContin®, Opana®, and Nucynta®ER, have been already approved and are commercially available [19]. Thus, the PEOs are attractive alternatives to HPMC for extended release [20].

Recently, physical mixtures of cationic and anionic polymers have been used in matrix tablets. For example, chitosan (CS) is a natural cationic polysaccharide and it has been reported that the association of CS with anionic polymers, such as sodium alginate (SAL) [21,22], xanthan

* Corresponding author at: Mailbox 59#, Department of Biopharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China.
E-mail address: graham_pharm@aliyun.com (Q. Fu).

http://dx.doi.org/10.1016/j.powtec.2016.02.017
0032-5910/

Table 1
Ternary matrix formulations of DH extended-release tablets.

Formulation	DH	PEO WSR303	SAL	CS	MCC	MS
1	90	0	120	–	90	3
2	90	0	–	120	90	3
3	90	0	60	60	90	3
4	90	120	90	–	–	3
5	90	120	–	90	–	3
6	90	120	45	45	–	3
7	90	60	75	75	–	3
8	90	120	45	45	–	3
9	90	150	30	30	–	3
10	90	180	15	15	–	3

gum [23,24] or carrageenan [25], can retard drug release by a synergistic effect. Thus, the study of physical mixtures of cationic and anionic polymers could allow development of extended drug-release matrices.

The aim of the present work is to explore the feasibility of developing extended-release tablets of diltiazem hydrochloride (DH) for once daily use, using PEOs as matrices. However, a preliminary study demonstrated that the release was only retarded to 8 h when PEO was used as a unique drug carrier. Thus, we proposed and formulated DH extended-release tablets using ternary matrices (PEOs, CS and SAL). Their release behavior was investigated and the release mechanism was also studied by fitting the profiles to mathematical release models. Importantly, to our knowledge, attempts to formulate extended-release tablets using a combination of PEOs with mixtures of cationic and anionic polymers have never been reported until now.

2. Materials & methods

2.1. Materials

DH was purchased from Shijiazhuang Pharmaceutical Co., Ltd. (Shijiazhuang, China). PEOs (POLYOX™ 1105, $M_w = 9 \times 10^5$; POLYOX™ N60K, $M_w = 2 \times 10^6$; POLYOX™ WSR301, $M_w = 4 \times 10^6$; POLYOX™ WSR303, $M_w = 6 \times 10^6$) were produced by Dow Chemical Company and distributed by Colorcon Co., Ltd. China (Shanghai, China). CS with a molecular weight of about 400 kDa and a degree of deacetylation of 95% was purchased from Jinan Haidebei Marine Bioengineering Co., Ltd. (Jinan, China). SAL (PROTANAL LF200M) was kindly provided as a gift by FMC Biopolymer (Philadelphia, Pennsylvania, USA). Microcrystalline cellulose (MCC, Avicel PH-101) was kindly provided as a gift by AsahiKASEI (Tokyo, Japan). Magnesium stearate was purchased from Zhengzhou Friend Bioengineering Co., Ltd. (Zhengzhou, China). DH sustained release tablets (QiaErXin) were purchased from Sine Wanxiang Pharm. (Shanghai, China). Deionized-distilled water was used throughout this study.

2.2. Preparation of DH ternary matrix tablets

Tablets containing 90 mg DH were prepared by direct compression and MCC and magnesium stearate (1%, *w/w*) were used as diluent and lubricant, respectively. DH and the excipients were blended for uniform mixing, and then the powder was compressed into tablets at a compression force of 2 tons using 8 mm round, flat and plain punches using a TDP single punch tablet-compressing machine (Shanghai First Pharmaceutical Machinery Factory, Shanghai, China). The types and amounts of PEOs used were evaluated, and then the ternary matrix formulations were investigated and optimized as shown in Table 1. The total mass of each tablet was 303.0 mg.

2.3. In vitro release of DH matrix tablets

The in vitro release studies were carried out to optimize the formulation and to evaluate the homogeneity of one batch and the repeatability of different batches. The USP XXII paddle method was applied for the in vitro release studies. The rotation speed was set at 75 rpm using a ZRS-8G dissolution tester (Tianda Tianfa Technology Co., Ltd., Tianjin, China). The medium was 1000 mL degassed distilled water and the temperature was maintained at 37 °C. Ten milliliters of filtered samples were withdrawn at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h and each time replaced with 10 mL fresh medium. Then, the subsequent filtrates were determined at 240 nm using a UV-1801 instrument (Beijing Rayleigh Analytical Instrument Co., Ltd., Beijing, China).

The release profiles were obtained based on the percentage of free drug released at each time point, and the time for 50% and 90% total drug release were defined as t_{50} and t_{90}, respectively. In addition, a similarity factor, f_2, suggested by the FDA, was introduced to evaluate the similarity in the release profiles of the optimized matrix tablets and QiaErXin [26]. The parameter, f_2, is defined by the following equation, in which *Rt* and *Tt* are the average cumulative percentage dissolved at each of the selected n time points of the reference and test product, respectively. The release profiles of the test samples would be considered similar when f_2 is larger than 50.

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

2.4. Kinetic mechanism

The tablets were formulated as ternary matrices and, thus, the release from matrix tablets is complicated. Therefore, it is necessary to clarify the kinetic mechanism. Several mathematical models (zero-order, first-order, Higuchi, and Korsmeyer–Peppas) have been used to describe the kinetics

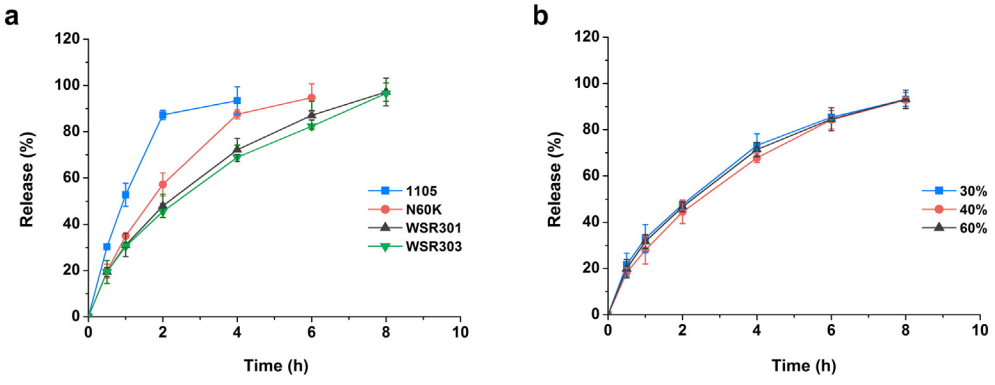

Fig. 1. Effects of molecular weights and amounts of PEOs on the in vitro release behaviors of DH.