International Journal of Pharmaceutics 489 (2015) 210–217

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Floating tablets for controlled release of ofloxacin via compression coating of hydroxypropyl cellulose combined with effervescent agent

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ARTICLE INFO

Article history:
Received 27 January 2015
Received in revised form 13 April 2015
Accepted 4 May 2015
Available online 5 May 2015

Keywords:
Ofloxacin
Floating tablets
Compression coating
Zero-release
Hydroxypropyl cellulose
Sodium alginate

ABSTRACT

To prolong the residence time of dosage forms within gastrointestinal trace until all drug released at desired rate was one of the real challenges for oral controlled-release drug delivery system. Herein, we developed a fine floating tablet via compression coating of hydrophilic polymer (hydroxypropyl cellulose) combined with effervescent agent (sodium bicarbonate) to achieve simultaneous control of release rate and location of ofloxacin. Sodium alginate was also added in the coating layer to regulate the drug release rate. The effects of the weight ratio of drug and the viscosity of HPC on the release profile were investigated. The optimized formulations were found to immediately float within 30 s and remain lastingly buoyant over a period of 12 h in simulated gastric fluid (SGF, pH 1.2) without pepsin, indicating a satisfactory floating and zero-order drug release profile. In addition, the oral bioavailability experiment in New Zealand rabbits showed that, the relative bioavailability of the ofloxacin after administrated of floating tablets was 172.19%, compared to marketed common release tablets TaiLiBiTuo®. These results demonstrated that those controlled-released floating tables would be a promising gastro-retentive delivery system for drugs acting in stomach.

1. Introduction

Oral route was one of the most convenient and preferable ways for drug administration (Kagan and Hoffman, 2008), when the bioavailability of peroral drug delivery systems was determined by various factors, including the retention time of those dosage forms within the gastrointestinal tract (GIT). It has been reported that the extent of drug absorption from the GIT was related to their contact time with the small intestinal mucosa (Deshpande et al., 1996; Hirtz, 1985), while most of the conventional oral delivery systems have shown some limited bioavailability due to fast gastric-emptying time (Acharya et al., 2014). Thus, the real challenge of developing a controlled drug delivery system was not just to sustain the drug release but also to prolong the residence time of the dosage form in the stomach or the upper small intestine until all drug released at the desired rate (Zhu et al., 2014). Hence, an optimum gastro retentive dosage forms (GRDF) system could be defined as a system which would retain in the stomach for a sufficient time interval against physiological barriers with drug releasing in a controlled manner, and finally be easily metabolized in the body (Pawar et al., 2011). Currently, GRDF may be broadly classified into: high-density (sinking) systems, low-density (floating) systems, expandable systems, superporous hydrogel systems, mucoadhesive systems and magnetic systems (Bardonnet et al., 2006).

Among them, floating drug delivery system (FDDS) could basically float in the gastric fluid and prolong GRT to obtain sufficient drug bioavailability (Baumgartner et al., 2000; Sauzet et al., 2009; Singh and Kim, 2000), because of their lower bulk density compared to that of the aqueous medium. Typically, FDDS could be divided into two types: effervescent drug delivery systems which depended on the generation of carbon dioxide gas upon contact with gastric fluids and non-effervescent drug delivery systems. According to previous report, FDDS was desirable for those drugs: (i) act locally in stomach; (ii) have a narrow absorption window in the small intestinal region; (iii) are unstable in the intestinal environment and (iv) have poor solubility in a high pH environment (Bardonnet et al., 2006; El Gamal et al., 2011; Nagarwal et al., 2010; Talukder and Fassihi, 2004).

Ofloxacin is a fluoroquinolone antibacterial agent, which has a broad antimicrobial spectrum against both gram-positive and

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http://dx.doi.org/10.1016/j.ijpharm.2015.05.007
0378-5173/

gram-negative bacteria, which has been approved for use in the treatment of gastrointestinal infections, respiratory tract infections and urinary tract infections (Zivanovic et al., 2006). Ofloxacin was readily soluble in stomach of acidic environment, but prone to precipitate in the intestine of neutral or slightly alkaline pH values, which affected their absorption in the lower section of the intestine. Apart from solubility, the absorption site is the upper part of the gastrointestinal tract (Chavanpatil et al., 2005). Therefore, various floating systems for ofloxacin have already been investigated. Chavanpatil et al. (2005) have developed ofloxacin sustained release tablet using psyllium husk, HPMC K100 M, crospovidone and sodium bicarbonate. However, when the tablets were immersed in simulated gastric fluid, the floating tablets showed burst drug release in the first 2 h. Zhang et al. (2012) reported a floating multi particulate system for ofloxacin based on a multilayer structure by coating with a release retarding film (EC), an effervescent layer ($NaHCO_3$) and a gas-entrapped polymeric membrane (Eudragit® RL 30D), respectively. The analysis of the release mechanism showed a zero-order release for the first 8 h. However, the film coating technique is complicated and expensive (Zhang et al., 2012).

In order to overcome those drawbacks mentioned above, we combined floating drug delivery systems with controlled release systems to realize simultaneous control of drug release rate and location. Moreover, researchers found that compression-coated tablet was promising candidate to control drug release rate. A novel compression coating tablet is design to achieve zero-order release by similar release manner with the osmotic systems (Guo and Shi, 2009). Drawing on the concept, we design a novel floating drug delivery system based on the compression coating technology combined with effervescent agent.

The aim of this study were to prepare fine floating tablets via compression coating and investigate the possibility of those tablets as a delivery system for controlled release of ofloxacin. The hydrophilic polymer (hydroxypropyl cellulose) combined with effervescent agent (sodium bicarbonate) was used as the functional materials, while the sodium alginate was also utilized in the coating layer to control the drug release rate. The effects of formulation factors on the *in vitro* drug release behavior of those zero-order released floating tablets were studied, as well as the swelling and floating ability. Moreover, the oral bioavailability evaluation was executed in rabbits compared with market tablets TaiLiBiTuo®.

2. Materials and methods

2.1. Materials

Ofloxacin (OFLX) was obtained from Yangtze Pharmaceutical Co., Ltd. (Taizhou, China). Three viscosity grades of hydroxypropyl cellulose (HPC) (HPC-SL: 4.0 mPa s; HPC-L: 8.0 mPa s; HPC-M: 350 mPa s) were gifted from Nippon Soda Co., Ltd. (Yokyo, Japan), and were used as a binder and hydrophilic materials to control the release rate of the compression-coated tablet. Sodium bicarbonate was obtained from Lingfeng Chemical Reagent Co., Ltd. (Shanghai, China). Magnesium stearate was obtained from Sunhere Pharmaceutical Excipients Co., Ltd. (Anhui, China). Sodium alginate was obtained from Huanghai Pharmaceutical Co., Ltd. (Qingdao, China). All other materials were of reagent grade and used as received. The marketed immediate release tablets TaiLiBiTuo® were used as the reference.

2.2. Method

2.2.1. Preparation of compression-coated floating tablet

2.2.1.1. Preparation of core tablets. The core tablets were prepared by a conventional wet granulation method. The powder mixture of ofloxacin and HPC were passed through a 80-mesh sieve to obtain a well-dispersed mixture and wet massed with ethanolic solution as the binder. The soft material was forced through a 40-mesh sieve. The granules were dried for 2 h at 60 °C in the oven (DHG-9245A, Shanghai Huiyi Technology Co., Ltd., China) and resized by passing through a 24-mush sieve. Magnesium stearate was added into the granules as a lubricant and mixed for 10 min. Tablets were prepared by 7 mm flat-face punch with single press tableting machine (Shanghai Pharmaceutical Machinery Factory, China). The hardness of the tablets was adjusted as 40–50 N using a Monsanto hardness tester (Shanghai Huanghai drug test instrument Co., Ltd., China). As shown in Table 1, optimized batch containing ofloxacin 80 mg, HPC 10 mg and magnesium stearate 0.5 mg in 90.5 mg tablet.

2.2.1.2. Preparation of compression-coating layer. A wet granulation method was applied to prepare the partial granules of the compression-coated layer (Huang et al., 2013). The compression-coating layer was prepared according to the design depicted in Table 1. The respective powder, namely ofloxacin, release-retarding polymer (sodium alginate), and a gas-forming agent ($NaHCO_3$) were mixed homogeneously and kneaded with binder solution. 5% HPC-SL was added to the mixture of ethanolic and water (9:1) to prepare the binder solution. The formed dough was passed through 40-mush sieve, dried and received through 40-mush sieve. The mixture of HPC-L and HPC-M was passed through 80-mush sieve, and then mixed with the granules and magnesium stearte as the coating layer.

2.2.1.3. Compression coating of core tablet. Half mount of prepared granules used for shell formation in each tablet, and 7 mm diameter tablet cores were compression-coated into 11 mm diameter tablets. The compression-coated tablets were prepared by first filling one-half of the coating layer powders into the die to form a powder bed. In the center, the tablet core was positioned on the powder bed followed by filling the remaining half of the compression-coated layer on top and then tablet under force of 70 N.

Table 1
The core tablet and coating layer Formulation of the floating controlled-release tablets of ofloxacin.

Formula code	Core tablet		Coating layer							
	f1	f2	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	80	80	120	120	120	120	120	120	120	120
HPC-L (mg)	10	–	50	90	120	90	90	90	90	90
HPC-M (mg)	–	10	120	80	50	80	80	80	80	80
Na alginate (mg)	–	–	30	30	30	10	45	30	30	-
$NaHCO_3$ (mg)	–	–	70	70	70	70	70	50	90	70
Mg stearate (mg)	0.5	0.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total (mg)	90.5	90.5	391.5	391.5	391.5	371.5	406.5	371.5	416.5	361.5