Powder Technology 301 (2016) 405–411

Contents lists available at ScienceDirect

Powder Technology

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

Once-daily amoxicillin immediate- and extended-release bilayer tablets

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ARTICLE INFO

Article history:
Received 12 March 2016
Received in revised form 20 May 2016
Accepted 15 June 2016
Available online 16 June 2016

Keywords:
Amoxicillin
Bilayer tablets
Release kinetics
Stress testing
Bioavailability

ABSTRACT

Multilayer/bilayer tablets have been applied for the formulation of incompatible components for compound preparations, but more often they are used to modify drug release. The objective of this study was to explore the feasibility of developing, using a bilayer tablet strategy, an immediate- and extended-release formulation of amoxicillin. The formulation of each layer was optimized separately and the bilayer tablets were compressed at an immediate/extended layer weight ratio of 3:7. The *in vitro* release of the bilayer tablets was evaluated and it was found to be very similar to Moxatag®, an immediate- and extended-release formulation approved by FDA. The kinetic mechanism study showed that the release of the bilayer tablets correlated better with the Ritger–Peppas model (correlation coefficient $R = 0.9963$) and a non-Fickian drug release mechanism, and its release was principally driven by diffusion and secondarily by polymer erosion. The stress testing demonstrated that high temperature and humidity are potential risk factors affecting the quality of the bilayer tablets. In addition, the bilayer tablets showed a similar bioavailability to Moxatag® in beagle dogs. In conclusion, the results of the present study demonstrated for the first time the feasibility of developing an immediate- and extended-release formulation of amoxicillin for once-daily use using a bilayer tablet strategy.

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1. Introduction

Amoxicillin is a semi-synthetic, broad-spectrum beta-lactam antibiotic [1,2]. It is widely used because of its strong inhibitory effects against a wide range of both Gram-positive and Gram-negative bacteria [3,4]. It exhibits its bactericidal effects by binding to penicillin binding proteins, which leads to inhibition of the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis, finally resulting in death due to lysis of bacteria [5–7].

Clinically, to ensure the plasma concentration remains above the minimum inhibitory concentration (MIC), patients are asked to take the amoxicillin tablets every 6 h due to its short plasma half-life (1 h) [8], which reduces patient compliance. Therefore, extended-release formulations had been developed [9]. However, this delays the treatment because the active drug cannot quickly reach the MIC due to the slow release. To accelerate the speed of onset and prolong the time the plasma concentration is above the MIC, Moxatag®, a dual-release tablet of amoxicillin, has been marketed. This commercial preparation is a pH-dependent pulse-release tablet. Each Moxatag® tablet consists of immediate release granules and delayed-release pellets targeted to pH 6.0 and pH 6.8, respectively. The different pellets were obtained by coating the granules with different polymers, and the three pellets were mixed and compressed at a specific ratio. Thus, the release of amoxicillin in the gastrointestinal tract was carefully controlled [10]. In this study, we would like to explore the feasibility of, using other preparation techniques, developing a dual-release tablet of amoxicillin.

Recently, multilayer tablets have been proposed to increase the compatibility of the components in compound preparations, thereby increasing the efficacy and improving patient compliance by reducing the dosing burden [11,12]. Moreover, release profiles can also be modified using the multilayer tablet strategy [13,14]. For example, one layer is for immediate-release and the other layers are for modified-release. On one hand, the immediate-release layer will disintegrate rapidly and transiently after oral administration, thus providing enough drug for immediate action while, on the other hand, the modified-release part will dissolve slowly in the gastrointestinal tract to maintain a steady blood level.

The aim of the present study was to explore the feasibility of developing, using a bilayer tablet strategy, an immediate- and extended-release formulation of amoxicillin. The formulation and preparation were studied, and the *in vitro* release of the optimized formulation

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http://dx.doi.org/10.1016/j.powtec.2016.06.030
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was evaluated and compared with Moxatag®. The release kinetics was studied and a stress testing was performed. Finally, pharmacokinetic studies were carried out in beagle dogs.

2. Materials and methods

2.1. Materials

Moxatag® was purchased from MiddleBrook Pharmaceuticals, Inc. Bulk amoxicillin trihydrate was purchased from United Laboratories (Zhuhai, China). Kollidon® SR was kindly provided by BASF China Co., Ltd. (Shanghai, China) and HPC-H was kindly provided by Dalian Diligence Trade Co., Ltd. (Dalian, China). Lactose was a gift from Meggle Pharma - Excipients & Technology (Shanghai, China). Microcrystalline cellulose (MCC, Avicel PH-101) was kindly donated by AsahiKASEI (Tokyo, Japan). Magnesium stearate was purchased from Anhui Sunhere Pharmaceutical Excipients Co., Ltd. (Huainan, China) and potassium dihydrogen phosphate was purchased from Xilong Chemical Co., Ltd. (Shantou, China). Deionized-distilled water was used throughout this study.

2.2. Preparation of bilayer tablets

A dry granule method was used to prepare the bilayer tablets of amoxicillin. The formulation of both layers was optimized, and some important data are summarized in Table 1. All bulk materials were passed through an 80 mesh sieve. Dry granules were obtained by crushing the bulk materials for each layer. Then, the granules were sized and the fraction between 30 and 60 mesh were collected and mixed with magnesium stearate. For the immediate-release layer, the granules were first filled into the cavities of the lower punches and pre-compressed using a ZDY-8G single punched tablet compressing machine (Shanghai First Pharmaceutical Machinery Factory, Shanghai, China). Then, the granules of the extended-release layer were introduced and compressed again. The final weight of each bilayer tablet was about 1500 mg.

2.3. In vitro drug release

All drug release experiments were carried out in a ZRS-8G (Type II in Chinese Pharmacopeia) apparatus (Tianjin Tianda Tianfa Technology Co., Ltd., Tianjin, China) at 50 rpm. Purified water (900 mL) maintained at 37 ± 0.5 °C was chosen as the release medium. Each tablet contained 890 mg amoxicillin trihydrate. At predefined times (0.5, 1, 2, 4, and 6 h), aliquots of samples (5 mL) were withdrawn and passed through a 0.45 μm filter, and replaced with an equivalent volume of fresh medium. The drug release at each time point was measured using a UV-1801 ultraviolet spectrophotometer (Beijing Rayleigh Analytical Instrument Co., Ltd., Beijing, China) at an absorption wavelength of 272 nm.

The release profiles were compared by calculating the similarity factors (f_2) using Eq. ((1), in which n is the number of samplings, and Rt and Tt are the release percentages of a reference and test sample at each time point, respectively. The two release profiles can be considered similar when the f_2 value is not <50.

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

2.4. Drug release kinetics and the mechanism involved

To understand the drug release mechanism from the bilayer tablets, the release profiles were fitted to several classic mathematic models, including First-order [15], Higuchi [16] and Ritger–Peppas models [17]. The most suitable model is the one giving the best fit.

2.5. Stress testing

To evaluate the quality, the bilayer tablets were subjected to a stress testing. The samples were placed in glass containers and stored in an HPX-16085H-III Temperature Humidity Incubator (Shanghai CIMO Medical Instrument Manufacturing Co., Ltd., Shanghai, China) under the following conditions: (1) 4500 lx, (2) 40 °C, (3) 60 °C, (4) 25 °C/relative humidity (RH) 75%, and (5) 25 °C/RH 92.5%, respectively. On the 5th and 10th day, samples were withdrawn and immediately subjected to an investigation of their appearance, content and related substances assay, and *in vitro* release evaluation. The content and related substances assay was carried out using an HPLC method as described in the section below. In addition, samples stored at RH 75% and RH 92.5% were also examined to see if there was any weight gain.

2.6. HPLC analysis

A Hitachi HPLC system (Hitachi High-Technologies Co., Ltd., Tokyo, Japan) was used for the quantification of the amoxicillin and its related substances in the bilayer tablets. The HPLC system consisted of an L-2400 UV detector, an L-2300 column oven, an L-2200 autosampler, and an L-2130 pump. An Ecosil-C18 column (250 × 4.6 mm, 5 μm) was used for the chromatographic separation at 30 °C. The mobile phase used was a mixture of potassium dihydrogen phosphate (pH 5.0, 2 M)-acetonitrile (97.5: 2.5, v/v), and the mobile phase was pumped at 1.0 mL/min. The injection volume was 20 μL and analytes were monitored at a wavelength of 254 nm. The retention time was 9.5 min during a run of 30 min.

2.7. Pharmacokinetic study

2.7.1. Animal handling

The protocols for the pharmacokinetic study were approved by the Animal Management and Ethics Committee of Shenyang Pharmaceutical University, and this study complied with the Guide for Care and Use of Laboratory Animals.

Table 1
Formulation compositions of the extended- and immediate-release layers of the amoxicillin bilayer tablets.

Formulation	Extended-release layer							Immediate-release layer			
	E1	E2	E3	E4	E5	E6	E7	I1	I2	I3	I4
amoxicillin trihydrate	890	890	890	890	890	890	890	890	890	890	890
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10
HPC-H	–	–	35	50	70	100	70	–	–	–	–
HPMC K100LV	50	–	–	–	–	–	–	–	–	–	–
Kollidon® SR	–	500	–	–	–	–	–	–	–	–	–
MCC	550	100	565	550	530	500	–	570	555	525	–
lactose	–	–	–	–	–	–	530	–	–	–	570
CMS-Na	–	–	–	–	–	–	–	–	15	45	–

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