Future Journal of Pharmaceutical Sciences xxx (2017) 1–9

HOSTED BY

Contents lists available at ScienceDirect

Future Journal of Pharmaceutical Sciences

journal homepage: http://www.journals.elsevier.com/future-journal-of-pharmaceutical-sciences/

Floating tablets of minocycline hydrochloride: Formulation, in-vitro evaluation and optimization

Ali Raza*, Nadeem Irfan Bukhari, Sabiha Karim †, Muhammad Ahsan Hafiz, Uzma Hayat

Punjab University College of Pharmacy, University of the Punjab, Allama Iqbal Campus, Lahore, 54000, Pakistan

ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form
24 March 2017
Accepted 3 May 2017
Available online xxx

Keywords:
GRDDS
Floating tablets
Minocycline
Optimization

ABSTRACT

Current study was aimed to formulate gastroretentive floating tablets of minocycline hydrochloride with desired floating properties, desired drug release rate, its local action in stomach for treatment of *H. pylori* infection and prevention of a side effect, pseudomembranous colitis. Simplex lattice mixture design was used to get experimental layout. Methocel K100LV (X_1), Methocel K15M (X_2) and Carbopol 934 (X_3) were selected as independent variables. Ten formulations (F1 to F10) were developed by direct compression and were evaluated for physical parameters, swelling index, floating lag time, floating time and in-vitro drug release rate. Furthermore, FTIR spectroscopic studies were performed to determine drug polymer interaction. Floating lag time (Y_1), floating time (Y_2), cumulative drug release at 3 h (Y_3), 6 h (Y_4) and 12 h (Y_5) were selected as dependent variables. Results showed that floating lag time and floating time were decreased by presence of Carbopol 934 in formulation while increased by Methocel K100LV and Methocel K15M. Presence of Carbopol 934 also caused an increase in drug release rate while Methocel K100LV and Methocel K15M contributed in decreasing release rate. Except F1, all the other formulations showed floating time >12 h. On the basis of optimization criteria, composition of optimized formulation F_0 (Methocel K100LV = 77.98 mg and Carbopol 934 = 82.02 mg) was determined by statistical analysis. FTIR spectroscopic studies showed that no interaction found between polymers and drug. Concisely, concluded that Carbopol 934 and Methocel 100LV can be used to fabricate gastroretentive floating tablets of minocycline hydrochloride with good buoyancy properties and sustained release action.

1. Introduction

Different routes of drug administration including enteral and parenteral are used in practice, however; oral route of drug administration is preferred one because of patient compliance [1]. On the other hand, oral route has many disadvantages which include variable gastrointestinal transit that disturbs the uniform absorption of the drug, incomplete release of drug from dosage form and shorter gastric residence time. These disadvantages result into poor bioavailability of certain drugs particularly which have absorption window in the upper gastrointestinal tract [2]. Therefore, efforts are being directed to overcome these problems by increasing the gastric retention resulting in development of gastroretentive drug delivery system (GRDDS). GRDDS is controlled drug delivery system which enables prolongation in gastric retention time [3]. GRDDS also provides better therapeutic response in cases where local action of drugs in the stomach is required, for instance, eradication of *H. pylori* infection [4]. GRDDS can be classified into floating drug delivery system (FDDS), bioadhesive systems, expanding systems, high density systems and magnetic systems [5]. Meka, L. et al. [6] formulated gastroretentive floating tablets of captopril in order to improve bioavailability as it is primarily absorbed in upper gastrointestinal tract while unstable in intestine. Further, Patil, S. et al. [7] formulated gastroretentive mucoadhesive tablets of lafutidine (an H_2 receptor antagonist) to improve its bioavailability as it has selective absorption only in upper gastrointestinal tract. Dios, P. et al. [8] formulated optimized

* Corresponding author. Room No. 113, Wenxuan Building of Medicine, Shanghai Jiao Tong University, 800 Dongchuan Road, Minhang District, Shanghai, 20030, China.
E-mail addresses: aliraza7444@gmail.com, aliraza86@sjtu.edu.cn (A. Raza).
Peer review under responsibility of Future University.
† Deceased.

http://dx.doi.org/10.1016/j.fjps.2017.05.001

List of abbreviations

FDDS	Floating drug delivery system
FTIR	Fourier Transform Infrared
GRDDS	Gastroretentive drug delivery system
HCl	Hydrochloric acid
HPMC	Hydroxypropyl methylcellulose
IR	Infrared
MCC	Microcrystalline cellulose
PVP	Polyvinylpyrrolidone
USP	United States pharmacopoeia
UV	Ultraviolet

floating tablets of metronidazole, composed of sodium alginate, low substituted hydroxypropyl cellulose and sodium bicarbonate, to increase local action of metromidazole against *H. pylori*. Suitable candidates for formulating GRDDS are those which have narrow absorption window limited to upper gastrointestinal tract, which are intended for local action in stomach, which are unstable or less soluble at high pH of intestinal fluid and which can cause serious side effects after passing in lower gastrointestinal tract [9]. However, GRDDS is not suitable for such drugs that are unstable at low pH of gastric fluid, that are meant for selective release in lower gastrointestinal tract and those which have significant first pass effect [10].

Among different types of GRDDS, floating drug delivery system (FDDS) was found effective to increase gastric transit time since drug is release at slow rate during prolonged retention of dosage form in gastric environment [11]. In FDDS, dosage form is usually fabricated in such a way that its density becomes low enabling it to float over gastric fluid. Depending upon mechanism of floating, effervescent drug delivery systems and non-effervescent drug delivery systems are two types of FDDS [12]. In effervescent drug delivery system, carbon dioxide (CO_2) is librated when dosage form comes in contact with gastric fluid. Sodium bicarbonate, citric acid or tartaric acid is used for gas generation in this approach. In effervescent floating drug delivery system, CO_2 is usually entrapped by gel forming or swellable material such as hydroxypropyl methylcellulose (HPMC), polymethacrylates, polyacrylate and polystyrene [13]. Viscosity of agents used in such formulations influences drug release and flow properties of dosage form. In current study, HPMC K100LV and HPMC K15M were selected since they have great difference in viscosities (100 mPa s and 15000 mPa s respectively of 2% solution in water at 20 °C), therefore; their blend can produce viscosities of broad range. Furthermore, a polyacrylate (Carbopol 934) was also selected for incorporation into formulation as polyacrylates have high swelling behavior and can form gel in aqueous solutions [14].

The present research work was aimed to formulate floating tablets of mincycline hydrochloride. Minocycline hydrochloride belongs to tetracycline group of antibiotics. It has half life of 11–18 h and dose is 50–100 mg twice daily and is soluble in water. It is best absorbed in upper gastrointestinal tract. It is used for treatment of *H. pylori* infection as a part of regimen of second line therapy [15]. Furthermore, It is used for treatment of acne vulgaris and duration of treatment is up to months leading to its side effect i.e. pseudomembranous colitis [16]. These factors contribute demand of fabrication of minocycline hydrochloride in GRDDS. Therefore, Minocycline hydrochloride was selected for formulation of floating tablets.

2. Materials and methods

2.1. Materials

Minocycline hydrochloride, used as active substance, was gifted by Mass Pharma (PVT) Ltd, Lahore, Pakistan. Carbopol 934 (polyacrylate), Methocel K100LV (HPMC K100LV) and Methocel K15M (HPMC K15M) were used as gel forming and swellable agents, Sodium bicarbonate was applied as gas generating agent, microcrystalline cellulose (MCC) was applied as diluent, talc was used as lubricant, magnesium stearate was used as glidant and PVP (polyvinyl pyrrolidone) K30 was used as tablet binder. All these materials were obtained as a gift from SIZA International (PVT) Ltd, Lahore, Pakistan. Other chemicals used were of analytical grade and were used without any further purification.

2.2. Experimental design

A simplex lattice mixture design was created to analyze the effects of polymers used in formulation on floating properties and drug release rate. The design matrix contained three factors or independent variables i.e. Methocel K100LV (X_1), Methocel K15M (X_2) and Carbopol 934 (X_3) having amount ranging from 0 mg to 160 mg. Layout of the experimental design is given in Table 1. Each tablet had 100 mg of minocycline hydrochloride and fixed amounts of Sodium bicarbonate (78 mg), PVP K30 (34 mg), MCC (16 mg), magnesium stearate (8 mg) and talc (4 mg) in order to analyze the effect of independent variables on tablet properties. Floating lag time (Y_1), floating time (Y_2), percentage cumulative drug release at 3 h (Y_3), 6 h (Y_4) and 12 h (Y_5) were investigated as dependent variables. Data obtained from evaluation of tablets was analyzed using Design Expert® Software (ver.9.0 Trial) and the same software was also used to generate response surface plots. Polynomials models, including quadratic and linear, were used for data fitting. Best fit model with significant p value was selected for statistical analysis.

2.3. Preparation of floating tablets of minocycline hydrochloride

All contents of formulation were weighed precisely on calibrated analytical balance (Shimadzu, ATX224, Japan) according to experimental design. All the weighed ingredients were mixed using pestle and mortar. Stirring was performed for 1 min after addition of each ingredient. Finally, mixture was mixed for 10 min in order to get uniformity. Then mixture was passed through 40-mesh sieve. Resultant mixture was compressed using single punch tablet compression machine (Erweka AR400, Germany) at weight 400 mg per tablet at 5-7 Kg hardness. All the batches were of 100 tablets in size and were prepared using same method to ensure the uniformity to evaluate the effect of independent variables.

2.4. Physical parameters

Tablets were evaluated for different physical parameters such as weight variation, friability, thickness, diameter and hardness.

2.4.1. Weight variation

Weights of 20 randomly selected tablets were accurately determined individually using calibrated analytical balance and results were reported as mean ± standard deviation (SD) [14].

2.4.2. Friability

In accordance to USP specification, a sample of tablets matching up 6.5 g was placed in drum of friability test apparatus (Galvano Scientific, Pakistan) and apparatus was operated at 100 rpm for

Please cite this article in press as: A. Raza, et al., Floating tablets of minocycline hydrochloride: Formulation, in-vitro evaluation and optimization, Future Journal of Pharmaceutical Sciences (2017), http://dx.doi.org/10.1016/j.fjps.2017.05.001