Journal of Drug Delivery Science and Technology 35 (2016) 172–183

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Research paper

Novel chewable colon targeted tablets of bumadizone calcium for treatment of ulcerative colitis: Formulation and optimization

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ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form
9 May 2016
Accepted 8 June 2016
Available online 23 June 2016

Keywords:
Colon targeting
Chewable tablets
Bumadizone
Optimization
Histopathology
Myeloperoxidase

ABSTRACT

The aim of the present study was the formulation of a novel chewable tablet containing the non-steroidal anti-inflammatory bumadizone calcium (BZ) to deliver the drug to the colon for the local treatment of ulcerative colitis. Colon targeted granules were prepared following 3^2 full factorial design. The effect of two independent variables, namely, polymer type (Eudragit ® S100, Eudragit ® L100, and a mixture of both in the ratio of 4:1) and drug to polymer ratio (1:1, 1:3& 1:5) on the % of BZ released for 12 h was studied. In order to produce chewability, candidate formulae were then mixed with different amount of maize starch and mannitol, and compressed into tablets. F11 tablets(composed of drug: Eudragit® S100 in the ratio of 1:3, 250 mg mannitol and 50 mg maize starch with a desirability of 0.925) achieved the required release profile i.e: lowest release before target area (pH 1.2 & 6.8) reaching only 11.00% at the end of the fourth hour, and 100.27% after 12 h (pH7.4). Histopathological studies results declared clearly the ability of the chewable colon targeted tablets F11 to locally treat acetic acid induced colitis. Furthermore, the measurements of myeloperoxidase enzyme activities in colon specimens showed that F11 achieved a significantly lower levels in comparison to both untreated group and group that received the marketed tablets ($p<0.05$).

1. Introduction

Inflammatory Bowel Diseases (IBD) are an immune mediated chronic or relapsing disorders of the gastrointestinal (GI) tract. IBD which is comprised of two main types, ulcerative colitis (UC) and Crohn's disease (CD), affects approximately 3.6 million people in the United States and Europe. An alarming rise in previous low-incidence areas, such as Asia, is currently being observed. They are gaining more and more attention. Although considerable progress has been made the last few years, a major gap in knowledge of the pathogenesis of UC remains [1]. UC is considered as an idiopathic inflammatory disorder involving the mucosa and submucosa of the colon [2,3]. It is characterized by chronic or relapsing immune activation and inflammation within the gastrointestinal (GI) tract that markedly alters GI function [4]. UC causes inflammation and ulcers in the top layer lining the large intestine [5,6] and is characterized by superficial mucosal inflammation, rectal bleeding, diarrhea and abdominal pain [7,8]. When the gut is inflamed, there is breakdown of intestinal barrier function, abnormal secretion, changes in the patterns of motility and visceral sensation, which contributes to symptom generation [9].

The general principle of drug treatment in UC is to induce and maintain remission of outbreaks and to achieve mucosal healing [10]. However, conventional administration of drugs used in treatment of UC are associated with a number of side effects [11,12], decreased efficacy and frequent drug dosing [11,13]. This necessitates the development of colon targeted dosage forms that selectively deliver the drug to the inflamed areas with minimum release of the drug in upper gastrointestinal tract [2,14]. This could help to reduce conventional dose and frequency [15] in addition to reduced incidence of adverse side effects [16]. Colon targeting could be achieved by a wide variety of mechanisms. This ranges from the use of prodrugs that are activated by enzymes in the colon [17,18], microbial triggered systems that depend on the presence of a high bacterial count up to 10^{11}–10^{12} C.F.U./ml [13,19,20], the use of pH-sensitive polymers. These polymers have ability to withstand an environment ranging from low pH (~1.2) to neutral pH (~7.5) for several hours [21].

Based on the aforementioned literature and to overcome side effects accompanied with conventional drug administration, the major scientific purpose of this study was to prepare chewable colon targeted tablets containing the NSAID bumadizone calcium (BZ)

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http://dx.doi.org/10.1016/j.jddst.2016.06.001
1773-2247/

using pH-dependent polymers. NSAIDs are widely used in the treatment of chronic inflammatory states. In addition, they showed a promising activity for prevention and treatment of colitis but with tendency to cause gastric bleeding and form ulceration in the gastric lining [22]. Formulation of BZ into colon-targeted dosage forms will avoid these undesirable effects. Some published researches have explored the potential of formulating pH-dependent colon targeted tablets [23–25], yet, none of researchers have tried formulating chewable tablets with the ability of colonic delivery. Chewable tablets offer several advantages over conventional tablets. This is due to the ease of use which leads to improved patient compliance in addition water is not required for swallowing [26]. Geriatric and bedridden patient show inconvenience in swallowing conventional tablets or capsules so chewable tablets offer a better alternative for drug application [27]. Upon searching the literature, no previous studies were carried out to formulate colon-targeted dosage forms containing BZ except our previous attempt where BZ microspheres were formulated using time-dependent polymers and compressed into tablets for colon targeting [28]. Time -dependent polymers are generally water-insoluble polymers that act as barrier hindering drug release so drug release takes place by time. These may include Eudragit® RS100, ethyl cellulose and cellulose acetate butyrate [29–31]. However, El-Gazayerly et al. [32] formulated chewable tablets containing verapamil aiming to sustain drug release. Sustainment of drug release was achieved via spray coating sugar beads with different binder solutions containing HPMC, polyox and ethylcellulose. Controlled release properties of the developed formulation didn't change by chewing or crushing the tablet.

The aim of the present study was the development and evaluation of BZ chewable tablets so to deliver the drug specifically to the colon to avoid its gastrointestinal side effects and to increase the patient compliance. We aimed to decrease the percentage of drug released before target area (pH 1.2 and 6.8) to less than 20% [33] and to maximize the BZ released in target area (pH 7.4) and total BZ released after 12 h. One of the most common side effects of NSAIDs is gastric discomfort, namely, ulcers and erosions. This is due to their ability to inhibit COX I enzyme leading to prostaglandin (PGs) deficiency. PGs have protective role in the stomach as they regulate bicarbonate and mucous production. So generally decreasing drug release before target area will lead to both decreasing side effects of the drug and shifting drug release to the target area. BZ marketed tablets Octomotol® are enteric coated tablets and show up to 30% release in the stomach. The selected colon targeted tablets were examined for its efficacy using acetic acid-induced rabbit colitis model in order to elucidate its usefulness as a specific drug delivery system for the treatment of ulcerative colitis in rabbits compared to marketed tablet.

2. Materials and methods

2.1. Materials

Bumadizone calcium (BZ) and Octomotol® tablets(110 mg) were kindly provided by October Pharma, Egypt. Eudragit® S 100 (EU S100), Eudragit® L100 (EU L100), were kindly provided by Degussa, Rhome and Co. KG, Pharma Polymer, Germany. Polyvinyl pyrrolidone(PVP) K30 was purchased from Fluka chemicals, Switzerland. Mannitol was obtained from Roquette, France. Maize starch was purchased from Sigma-Aldrich Corporation, USA. Isopropyl alcohol, El Nasr pharmaceutical chemical company, Egypt.

2.2. Compatibility studies

2.2.1. Differential scanning calorimetry (DSC)

The DSC studies were performed for bumadizone powder, Eudragit® S100 and Eudragit® L100 and for drug-Eudragit® S100 and drug-Eudragit® L100 physical mixtures (1:1) using Differential scanning calorimeter(DSC), Model -50; Shimadzu, Kyoto, Japan. Samples were heated in a pan at a rate of 5 °C/min in an atmosphere of nitrogen to 200 °C and the thermograms were recorded.

2.2.2. X-ray diffraction

X-ray diffraction patterns of bumadizone powder, pure polymers (Eudragit® S100 and Eudragit® L100) and physical mixtures of drug and each polymer in the ratio of 1:1 were recorded using a Phillips X-ray diffractometer (PW1792) Legroupe Interconnexion, Saint -Juire, Clubac, Canada with a copper target at a voltage of 40 kV and a current intensity of 30 mA at a scanning speed of 1 °C/min.

2.3. Formulation of BZ -granules

2.3.1. Experimental design

A 3^2 full factorial design was adopted to formulate colon targeted BZ granules using two independent variables; (i) polymer type (ii) Drug to polymer ratio. Two pH-dependent polymers were used, namely, Eudragit® S100, Eudragit® L100 and a mixture of both in the ratio of (4:1), respectively [34]. Three drug to polymer ratio namely 1:1, 1:3 and 1:5 were also used. Table 1 summarizes the independent variables along with their levels. The effect of selected factors was studied on release before target area, in target area and total percentage released after 12 h.

2.3.2. Preparation of the granules

Drug and polymers were thoroughly mixed using mortar and pestle for 20 min. Dough mass was then made by addition of few drops of 1% PVP K30 in isopropyl alcohol (binder solution). Granules were obtained by passing the dough mass through sieve number 10. The formed granules were left to dry at room temperature for 24 h [35]. The composition of the prepared granules are shown in Table 2.

2.4. Characterization of formed granules

2.4.1. Content uniformity, angle of repose and Hausner ratio determination

Exactly, one hundred mgs of the prepared granules were weighed, crushed and the drug was allowed to be extracted in phosphate buffer of pH 7.4 overnight using a magnetic stirrer (DAIHAN Scientific Co., USA.) The solution was filtered through a 0.45 μm millipore filter and the drug content was determined by UV spectroscopy at 234 nm after suitable dilution with reference to the calibration curve [36]. For determination of angle of repose, the fixed height cone method was adopted [37] and tan θ was calculated according to equation $\tan\theta = h/d$. Regarding Hausner ratio determination, five grams of each of prepared granules were placed in a graduated cylinder and the volume occupied was measured as Vi (initial bulk volume). The cylindrical graduate was then tapped till a constant volume was obtained when the powder was considered to reach the most stable, unchanging arrangement; the volume of the powder was then recorded as the final bulk volume

Table 1
The experimental plan of the 3^2 factorial design.

Variables	Polymer type	Drug: Polymer ratio
Levels	Eudragit® S100	1:1
	Eudragit® L100	1:3
	Mixture(S100:L100) 4:1	1:5