European Journal of Pharmaceutical Sciences 102 (2017) 172–179

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Colon-targeted delivery of solubilized bisacodyl by doubly enteric-coated multiple-unit tablet

Hee J. Park [a,1], Hyuck J. Jung [b,1], Myoung J. Ho [b], Dae R. Lee [b], Ha R. Cho [b], Yong S. Choi [b], Joonho Jun [a], Miwon Son [a], Myung J. Kang [b,*]

[a] Dong-A Pharmaceutical Co. Ltd., Giheung-gu, Yongin, Gyeonggi 446-905, Republic of Korea
[b] College of Pharmacy, Dankook University, 119 Dandae-ro, Dongnam-gu, Cheonan, Chungnam 330-714, Republic of Korea

ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form 7 February 2017
Accepted 5 March 2017
Available online 6 March 2017

Keywords:
Bisacodyl
Colon targeted delivery
Eudragit®
Multiple-unit tablet
Stimulant laxative
Solubilization
Constipation

ABSTRACT

A doubly enteric-coated multiple-unit tablet (DET) of bisacodyl (BD) was formulated to selectively deliver the stimulant laxative to the large intestine. Solubilized BD in surfactants was adsorbed into the porous carrier and primarily coated with different combinations of pH-sensitive polymers (Eudragit S and Eudragit L) and time-dependent release polymer (Eudragit RS). BD-loaded granules were compressed into tablets and coated again with pH-sensitive polymers (Eudragit S:Eudragit L = 1:1). The multiple-unit tablet was optimized with respect to the granular coating compositions (Eudragit S:Eudragit L:Eudragit RS = 5:1:4) and coating level (12.5%), and coating level on the tablet (25%), by evaluating *in vitro* release profile in continuous dissolution medium. Drug release from the optimized tablet was effectively retarded in the simulated gastric and small intestinal fluids (below 7%), but profound drug liberation was attained in the colonic fluid (over 50%). On the other hand, drug release from the marketed product (Dulcolax®, Boehringer Ingelheim Pharma), a reference drug, in the gastric and small intestinal fluids was reached to 30%, while that in the colonic fluid was only 7%. In an *in vivo* efficacy study in loperamide-induced constipated rabbits, a remarkable recovery in fecal secretion was observed in the DET-treated group 24 h post-dosing, compared to vehicle-treated ($p < 0.05$) and the marketed product-treated groups ($p < 0.05$). Moreover, pharmacokinetic evaluation in the constipated rabbits revealed that the DET system significantly lowered the systemic exposure compared with the marketed product ($p < 0.05$), by hindering drug release in the upper intestine, a preferential absorption site. Therefore, the novel colon-targeted delivery system may be an alternative for boosting pharmacological responses in the colon, while diminishing the intestinal irritation and/or systemic adverse effect of the stimulant laxative.

1. Introduction

Bisacodyl ((2-pyridinylmethylene)di-4,1-phenylene diacetate, BD), a stimulant laxative, has frequently prescribed to treat functional constipation and/or to evacuate the bowels before colonoscopy (Adams et al., 1994). After oral administration, the inactive prodrug is hydrolyzed into the active metabolite, bis(*p*-hydroxyphenyl)pyridyl-2-methane (BHPM), by intestinal brush border enzymes and/or bacteria present in the large intestine (Jauch et al., 1975; Reynolds, 1993). BHPM inhibits the reabsorption of water and electrolytes and increases their secretion into the intestinal lumen, by stimulating the epithelial cells in the large intestine (Reynolds, 1993). To minimize exposure in the upper intestine or intestinal absorption of the stimulant laxative, the originator of BD (Boehringer Ingelheim Pharma, Biberach an der Riss, Germany) developed an enteric-coated tablet (Dulcolax®) using methacylic acid/ethyl acrylate copolymer (Eudragit L100-55) as coating material (Dulcolax® Product Monograph, 2014). However, its oral therapy is still hampered by gastrointestinal side effects including stomach or abdominal irritation, pains, and vomiting. Actually, over 9.2% of the dose was preferentially absorbed in the upper intestine and excreted as glucuronide form in urine in healthy subjects, after oral administration of the marketed product (Roth and Beschke, 1988).

Several pharmaceutical approaches including pH-, time-, and enzyme-dependent release systems have been explored to selectively deliver locally active compounds in the colon (Sinha and Kumria, 2001; Krishnaiah et al., 2003; Sinha and Kumria, 2003; Chourasia and Jain, 2003; Friend, 2005). Of these, the enteric coating of a solid dosage form with a pH-sensitive release polymer is commonly used for colonic targeted drug delivery. This approach utilizes polymeric materials that are insoluble in the low pH environment of the stomach (pH < 2.5) and in the more neutral environment of the proximal small intestine

* Corresponding author at: College of Pharmacy, Dankook University, 119 Dandae-ro, Dongnam-gu, Cheonan 330-714, Republic of Korea.
E-mail address: kangmj@dankook.ac.kr (M.J. Kang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejps.2017.03.006
0928-0987/

(6.6 ± 0.5), but which dissolve at the higher pH of the distal gastrointestinal (GI) tract (7.5 ± 0.4 in the distal small intestine). The polymethacrylate polymers Eudragit S and Eudragit L, which are soluble at pH exceeding 7.0 and 6.0, respectively, have been routinely used in preparing colon-specific formulations that hindering drug release in the upper parts of the GI tract (Kotagale et al., 2010; Illangakoon et al., 2015). However, despite their simplicity in preparation and commercial success, tablets coated only with pH-sensitive enteric polymers often produce unreliable colonic release in patients, because of large inter- and intra-individual variability in intestinal acidity (Ashford et al., 1993). Alternatively, the combinatory use of pH-dependent polymers and time-dependent release polymers is a simple and effective approach to ensure invariable drug delivery throughout the colon, even with different individual physiological or pathological GI conditions (Akhgari et al., 2006). Naeem et al. (2015) reported that an enteric coating system of budesonide consisting of Eudragit-based pH-dependent and time-dependent controlled release polymers provided selective drug delivery in the colon and lowered systemic exposure compared to a single pH-triggered system. The findings suggest that the embedment of granules primary coated with both pH-sensitive and time-dependent release polymers into tablets coated with a pH-sensitive release polymer may further lessen undesired drug release in the upper intestine before reaching ileal and/or large intestinal segments.

While a doubly enteric coating system is effective to reduce systemic exposure of BD, harmonization of the system with solubilization technology is expected to yield more profound pharmacological effects of the poorly water-soluble laxative in the large intestine. The poor aqueous solubility of BD in physiological fluids (1.3 μg/ml in water) and the lack of free fluid present in the large intestine might hamper the pharmacological effect of BD in the large intestine (Kelm et al., 1997). The volumes of large intestinal fluid under fasted and fed state were only 1–44 ml and 2–97 ml, respectively, in healthy subjects (Schiller et al., 2005).

Therefore, the aim of this study was to design a novel doubly enteric-coated tablet (DET) of solubilized BD for colon targeted delivery. The premise was that the Eudragits-based double coating system would retard the liberation of the stimulant laxative in the upper intestine, thus reducing abdominal irritation and/or preferential absorption in small intestine. Subsequently, the solubilized BD embedded in the tablet would be rapidly released in the large intestine, providing therapeutically effective drug concentration and thus, facilitating stool secretion. To accomplish this, solubilized BD in surfactant was adsorbed onto a porous inorganic carrier and then enteric coated with pH-sensitive polymers (Eudragit S and Eudragit L) and a time-dependent release polymer (Eudragit RS). Primary coated granules were directly compressed with pharmaceutical excipients and subsequently layered again with the aforementioned pH-sensitive polymers. The effect of primary and secondary coating processes on the release profile of BD from the DETs was assessed in a continuous dissolution medium. Subsequently, pharmacokinetic and pharmacological aspects of the optimized DET system were comparatively evaluated with the marketed product (Dulcolax®) in loperamide-induced constipated rabbits.

2. Materials and Methods

2.1. Materials

Drug powder (purity over 99%) was purchased from Dishman (Ahmedabad, India). Polyoxyethylene, polyoxypropylene block polymer (poloxamer 188 and 407), polyvinyl pyrrolidone (PVP K30), hydroxypropyl cellulose (HPC EXF), Solutol HS15, and crospovidone (Kollidon CL) were supplied from BASF Chemicals Co. (Florham, NJ, USA). Labrasol and Capmul MCM were obtained from Gattefosse (Saint Priest, France) and Abitec (Columbus, OH, USA), respectively. Microcrystalline cellulose granules (MCC, Avicel PH102) were kindly provided by FMC Biopolymer (Philadelphia, PN, USA). Eudragit S, Eudragit L, Eudragit RS, and fumed silica with a specific surface area of 200 m^2/g (Aerosil 200) were purchased from Evonik Industries (Essen, Germany). Docusate sodium, mannitol, talc, and magnesium stearate were obtained from Hwawon Pharm. Co., Ltd (Seoul, Korea). BMPM β-D-glucuronide was obtained from TRC (Toronto Research Chemicals, Toronto, Canada). Aminobenzophenone (98%), the internal standard (IS) for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis, ammonium acetate, formic acid, triethyl citrate (TEC), hydroxypropyl-β-cyclodextrin (HP-β-CD) and loperamide were purchased from Sigma Aldrich Co. (St. Louis, MO, USA). Acetonitrile for high-performance liquid chromatography (HPLC) was purchased from Burdick & Jackson (Muskegon, MI, USA). Ultrapure water was produced using a Milli-Q system (Millipore, Bedford, MA, USA). All other chemicals were of reagent grade and were used without further purification.

2.2. Equilibrium Drug Solubility in Different Solubilizing Agents

An excess amount of drug (500 mg) was added to different kinds of vehicle (20 ml) in a scintillation vial. When the excipient was solid state at room temperature, the excipient was dissolved in distilled water (0.2% w/v) for solubility testing. Drug suspensions were sonicated for 30 min and then shaken at 37 °C for 3 days using a shaking incubator. The samples were centrifuged at 13,000 rpm for 10 min and the supernatant was appropriately diluted with an acetone and ethanol mixture (1:1 v/v). The concentration of BD in the sample was analyzed using a Dionex HPLC system (Model 3000RS pump, Model 3000RS auto sampler, Model 3000RS UV detector) equipped with a 3.9 mm × 300 mm ODS column. The mobile phase consisted of 0.005 mol/l tetrabutylammonium phosphate solution, acetonitrile, and methanol, at a volume ratio of 26:23:1. The flow rate was 1.0 ml/min, and the eluent was monitored at 214 nm.

2.3. Preparation of BD-loaded DETs

BD-loaded DETs were prepared by adsorption of solubilized drug in the porous material, enteric-coating of the BD-loaded granules, direct compression of granules with excipients, and enteric coating of the tablet dosage form. Tables 1 and 2 presents the compositions of enteric-

Table 1
Compositions (mg) of EGs of BD.

	EG1	EG2	EG3	EG4	EG5	EG6	EG7	EG8	EG9	EG10
Bare granules[a]	85.0	85.0	85.0	85.0	85.0	85.0	85.0	85.0	85.0	85.0
Eudragit S	22.0	–	–	17.5	13.2	11.0	2.32	4.9	6.3	7.8
Eudragit L	–	22.0	–	4.5	3.3	2.2	0.5	1.0	1.3	1.6
Eudragit RS	–	–	22.0	–	5.5	8.8	1.9	3.9	5.0	6.2
TEC	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Total	110.2	110.2	110.2	110.2	110.2	110.2	92.84	98.0	100.8	103.8

[a] Consisted of 5 mg of BD, 8 mg of docusate sodium, 15 mg of Labrasol, 5 mg of poloxamer 407, 18.5 mg of Aerosil 200, 6 mg of PVP K30, 22.5 mg of mannitol bead, and 5 mg of Kollidon CL.