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Evaluation of carboxymethyl-β-cyclodextrin with acid function: Improvement of chemical stability, oral bioavailability and bitter taste of famotidine

Fatma M. Mady[a,b], Ahmed E. Abou-Taleb[c], Khaled A. Khaled[a], Keishi Yamasaki[d], Daisuke Iohara[d], Kazuaki Taguchi[b], Makoto Anraku[e], Fumitoshi Hirayama[d], Kaneto Uekama[d], Masaki Otagiri[b,d,*]

[a] Department of Pharmaceutics, Faculty of Pharmacy, El-Minia University, El-Minia Governate 61732, Egypt
[b] Department of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan
[c] Department of Industrial Pharmacy, Faculty of Pharmacy, Assuit University, Assuit City 71515, Egypt
[d] Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto 860-0082, Japan
[e] Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, 1 Sanzo, Gakuen-cho, Fukuyama 729-0292, Japan

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ABSTRACT

The objective of the present study was to evaluate the potential influence of carboxymethyl-β-cyclodextrin (CM-β-CyD) on the aqueous solubility, chemical stability and oral bioavailability of famotidine (FMT) as well as on its bitter taste. We examined the effect of the CM-β-CyD on the acidic degradation of FMT compared with that for sulfobutyl-ether-β-cyclodextrin (SBE-β-CyD). The potential use of CM-β-CyD for orally disintegrating tablets (ODTs) was evaluated in vitro and in vivo. A taste perception study was also carried out. A strong stabilizing influence of CM-β-CyD was observed against the acidic degradation, in sharp contrast to SBE-β-CyD which induced a weird destabilizing effect on FMT. ^{13}C NMR was used to investigate the interaction mode between FMT and the 2 CyDs. In vivo study of ODTs indicated a significant increase in C_{max}, AUC and oral bioavailability in the case of FMT-CM-β-CyD tablets, compared with plain drug tablets. However, no significant difference in T_{max} and $t_{1/2}$ was observed. CM-β-CyD complexation appears to be an acceptable strategy for enhancing the oral bioavailability of FMT owing to its dramatic effect on the aqueous solubility and chemical stability of the drug. In addition, it has a pronounced effect on masking the bitter taste of FMT.

1. Introduction

Cyclodextrins (CyDs) possess a unique ability to complex with drugs enabling them to increase solubility, reduce bitterness, enhance stability, and decrease tissue irritation upon dosing (Mosher and Thompson, 2002). One of the most common applications of CyDs cited in the pharmaceutical literature is its ability to enhance drug bioavailability (Carrier et al., 2007). The ability of water-soluble polymers to enhance the solubilizing effect of CyDs and thus possibly reduce the amount of CyD necessary in a given dosage form has been demonstrated (Loftsson et al., 1994; Loftsson et al., 1996; Savolainen et al., 1998; Valero et al., 2003). Formulations containing a water-soluble polymer (e.g., hydroxypropylmethylcellulose, HPMC or polyvinylpyrrolidone, povidone) have been able to achieve bioavailability enhancement equivalent to formulations containing up to 80% less CyD (Savolainen et al., 1998). Such results are generally attributed to a synergistic solubilizing effect of polymer and CyD, which is believed to be due to formation of ternary complexes or co-complexes between the drug, CyD, and polymer (Valero et al., 2003). Solubility can be a key factor in the kinetics of dissolution and can also influence permeation through the intestinal membrane by influencing the concentration of a drug in solution in the intestinal lumen. As many of these studies involve low-solubility compounds, it is difficult to determine if the enhancement of bioavailability is due to the effect of CyDs on dissolution, degradation, or both.

CyDs and their derivatives thereof may enhance drug degradation, depending on the reaction mechanisms and the steric arrangement of the drug in the complex. Drug–CyD complexation can reduce the rate of decomposition of a drug by protecting labile regions from potential reactants in an aqueous environment (Loftsson and Brewster, 1996). Under specific conditions, CyD complexation may accelerate drug degradation depending on the type of the used CyD. For exam-

* Corresponding author at: Department of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan. Tel.: +81 96 371 4150; fax: +81 96 362 7690.
E-mail addresses: otagirim@gpo.kumamoto-u.ac.jp, otagirim@ph.sojo-u.ac.jp (M. Otagiri).

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ple, CyD has been shown to catalyze the deacetylation and degradation of spiranolactone, the effect was qualitatively correlated with the ionization state of hydroxyl groups on CyDs, which were lower in sulfobutyl-ether-β-cyclodextrin (SBE-β-CyD) (Jarho et al., 2000). In addition, prostaglandin E_1 in neutral and alkaline solution is destabilized by β-CyD, but stabilized by carboxymethylethyl-β-CyD (CME-β-CyD) (Adachi et al., 1992).

Farmotidine (FMT) is a histamine H_2-receptor antagonist used to treat peptic ulcers; gastroesophageal reflux; and conditions where the stomach produces an excess of acid, such as Zollinger–Ellison syndrome (Dollery, 1999). It has been reported that FMT is relatively susceptible to acid-catalyzed hydrolysis. The degradation of FMT in HCl solutions followed pseudo-first-order kinetics (Islam and Narurkar, 1991). The drug has been shown to undergo hydrolysis to a sulfamoyl amide in the presence of excess hydrochloric acid and to a carboxylic acid at elevated temperatures. The degradation products were found to have only weak antagonistic potency (Yanagisawa et al., 1987). A number of possible degradation mechanisms of FMT have been previously proposed (Junnarkar and Stavchansky, 1995). Moreover, Guvener and Ates (1988) investigated the stability of FMT in simulated gastric medium. The drug was found to lose about 34% of the original concentration in 1 h and about 88% in 3 h. To assess the significance of the acid-catalyzed hydrolysis of FMT on the stability of the drug in the stomach after oral administration, important factors such as gastric acidity and gastric emptying time must be considered. The impact of the acid-catalyzed degradation of FMT in the stomach would be expected to be more significant in elderly patients who have a prolonged gastric emptying half-time (123 min). In these patients about 12.0–57.8% of the drug would undergo decomposition in the stomach, thus lowering the amount of intact drug available for absorption (Suleiman et al., 1989). It was reported that poor lipophilicity, poor aqueous solubility and susceptibility to gastric degradation may contribute to the low and variable oral bioavailability of FMT (Islam and Narurkar, 1991). Clinically, the use of FMT is beneficial for elderly patients. Therefore a new FMT preparation that is useful for swallow function deficient patients would be advantageous. The complete bitter-taste-masking of drugs is an extremely important factor in the formulation of oral disintegrating tablets (ODTs) and the palatability of ODTs is a critical factor in ensuring patient compliance (Fu et al., 2004; Khan et al., 2007). In addition, developing a formulation for ODTs in which taste is masked, and drug release is improved, is a major challenge.

Okimoto et al. (1996) reported that the binding constants of drugs (either in neutral or cationic form) were consistently greater with the anionic SBE-β-CyD than with the neutral HP-β-CyD. As we completed this study, our goal was to determine the solubility and stability of FMT as a function of two anionic CyDs (SBE-β-CyD and CM-β-CyD) and to elucidate the potential causes of any differences observed between the two compounds. We carried out the kinetic studies of the degradation of FMT in acidic solution (0.1 N HCl) and the effect of pH and temperature on the rate of degradation FMT was examined using the two CyD derivatives, SBE-β-CyD and CM-β-CyD. In this work, the formation of inclusion complexes between FMT and the CyD derivatives was assessed using phase-solubility techniques. The influence of povidone K30 (a water-soluble polymer) on the solubility of CyD complexes also investigated. The complexation of FMT with the CyD derivatives and the mechanism of the impact of CyD on the degradation of FMT were examined using ^{13}C nuclear magnetic resonance spectroscopy (^{13}C NMR). In vitro and in vivo evaluations of ODTs of CM-β-CyD complexes were also performed. Moreover, the masking effects of CM-β-CyD on the bitter taste of FMT was examined.

2. Materials and methods

2.1. Materials

Famotidine (FMT) was supplied by El Mehan pharmaceutical company (MUP), Al-Ismailia, Egypt; Polyvinyl pyrrolidone (povidone K30) was obtained from Tokyo Chemical Industry Co. LTD., Japan; SBE β-CyD (Captisol®) was purchased from Cydex Co., USA; CM-β–CyD was purchased from Sigma Co., USA; Sodium heptane sulfonic acid (SHS) was purchased from Sigma–Aldrich, UK; Acetonitrile for HPLC was obtained from Nacalai Tesque Co., Japan. All other chemicals and solvents used were of pharmaceutical and analytical grade. Double distilled water was used throughout the study.

2.2. Phase-solubility studies

Phase-solubility equilibrium diagrams (in water at 25 °C) were obtained for both binary and ternary systems as per Higuchi and Connors (1965) method. Studies for binary systems were carried out by adding an excess amount of drug to 25 ml aliquots of aqueous solutions containing increasing concentrations of CM-β-CyD and SBE-β-CyD (from 0 to 15 mM) or povidone K30 (from 0 to 3% w/v).

Experiments regarding ternary systems were performed analogously to those for the binary systems, but in the presence of 1% w/v povidone K30 (value obtained from phase-solubility data for the drug: polymer binary system), reported in our previous study (Mady et al., 2010). These series of suspensions were equilibrated for 48 h on a mechanical shaker followed by filtration and analysis. The samples were filtered through a 0.45 μm membrane filter (Millex-HV filter units, Millipore, Bedford, USA) and suitably diluted for analysis. The drug content was determined by UV spectrophotometry (Hitachi, U-2900 Spectrophotometer, Tokyo, Japan) at 265 nm. The presence of CyDs and povidone did not interfere with the spectrophotometric assay of the drug. Each experiment was performed in triplicate.

2.3. Preparation of FMT–CyDs ternary systems

Ternary systems comprised of 1% w/v polymer (povidone K30), drug and CyD derivative were prepared by the solution method. The required amounts of CyD and povidone K30 were first dissolved in double distilled water to give a clear solution. The drug was then dispersed in this aqueous solution of CyD in a molar ratio of (1:1) followed by continuous stirring for 24 h at room temperature. The resulting solution was then subjected to freeze drying using Freeze Dryer FD-1, EYELA, Tokyo Rikakikai, Co., LTD, Japan.

2.4. ^{13}C NMR spectroscopy

^{13}C NMR measurements were conducted on a JEOL JNM-ECA 500 model spectrometer (Tokyo, Japan), with a 5 mm inverse broadband probe, operating at 500 MHz. FMT and its CyDs complexes were dissolved in D_2O with the addition of 5 μL of CD_3COOD (The concentration of the drug was about 5 mg/ml and the pH was 4.2.). The samples were transferred to a capillary and spectra obtained. Chemical shifts are cited as parts per million (ppm) and were calibrated indirectly using tetramethylsilane as an external standard. The chemical shifts of FMT were assigned according to the report of (Barańska et al., 2001).

2.5. Kinetic studies

Studies were initiated by adding 0.1 ml of a 0.01 M stock solution of FMT in *N, N*-dimethylformamide to 9.9 ml of a 0.1 N HCl solution (pH 1.2) in screw-capped vials. The vials were kept in a