Site-Specific Drug Delivery to the Middle-to-Lower Region of the Small Intestine Reduces Food–Drug Interactions that Are Responsible for Low Drug Absorption in the Fed State

FUMIÉ K. TANNO,[1] SHINJI SAKUMA,[2] YOSHIE MASAOKA,[2] MAKOTO KATAOKA,[2] TOSHIO KOZAKI,[3] RYOSEI KAMAGUCHI,[3] YUTAKA IKEDA,[1] HIROYASU KOKUBO,[1] SHINJI YAMASHITA[2]

[1]Specialty Chemicals Research Center, Shin-Etsu Chemical Co., Ltd, 28-1, Nishifukushima, Kubiki-ku, Joetsu, Niigata 942-8601, Japan

[2]Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaokatoge-cho, Hirakata, Osaka 573-0101, Japan

[3]Encapsulation Technology Development Division, Morishita Jintan Co., Ltd, 1-30, Tamatsukuri 1-chome, Chuo-ku, Osaka 540-8566, Japan

Received 24 December 2007; revised 7 February 2008; accepted 9 February 2008

Published online 3 April 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21382

ABSTRACT: Food–drug interactions may reduce the bioavailability of drugs taken after meals (negative food effects). We designed enteric-coated tablets that start to disintegrate when they reach the middle-to-lower region of the small intestine, and examined whether they could reduce negative food effects in dogs. Tablets containing trientine as a model drug were coated with hypromellose acetate succinate (HPMCAS) with various values of succinoyl group content. The time lag of drug dissolution from these enteric-coated tablets in simulated intestinal fluid of pH 6.8 increased as the succinoyl group content was decreased. The AUC of trientine after oral administration of its aqueous solution to fed dogs was one-eighth of that in fasted dogs. The low drug absorption in fed dogs was improved when trientine was administered as enteric-coated tablets. The average ratio of AUC in the fed state to that in the fasted state increased with decreasing succinoyl group content of HPMCAS. Negative food effects completely disappeared after oral administration of tablets coated with HPMCAS having a succinoyl group content of 6.2% or less, which probably disintegrated in the middle-to-lower small intestine. Our results indicated that food–drug interactions were avoided by separating the main absorption site of drugs from that of food components. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:5341–5353, 2008

Keywords: site-specific drug delivery; enteric coating; hypromellose acetate succinate; pH-dependent dissolution; food–drug interaction

INTRODUCTION

Drug absorption via the gastrointestinal (GI) tract is affected by the timing of drug administration in relation to meals.[1–3] Often, drug absorption is increased when patients take a drug after a meal (positive food effect), but in other cases, drugs show poor absorption when they are administered after a meal (negative food effect).[4–16] The most important concern regarding food–drug interactions is the high risk of treatment failure in patients who take a drug with a negative food effect after a meal.[1]

Our goal is to develop pharmaceutical technologies that reduce negative food effects. Negative food effects are mostly due to physicochemical

Correspondence to: Shinji Sakuma (Telephone: +81-72-866-3124; Fax: +81-72-866-3126; E-mail: sakuma@pharm.setsunan.ac.jp)

Journal of Pharmaceutical Sciences, Vol. 97, 5341–5353 (2008)

interactions between drugs and food components, such as proteins, carbohydrates, lipids, metal ions, etc., as well as GI secretions and digested food components.[1,4,17,18] Drugs with negative food effects are usually taken before a meal in order to maximize bioavailability through the avoidance of food–drug interactions. For example, risedronate sodium hydrate and alendronate sodium hydrate, which are bisphosphonates used for the treatment of osteoporosis, must be taken once a day at least 0.5 and 1.5 h, respectively, before the first food or beverage (http://www.merck.com/product/usa/pi_circulars/f/fosamax/fosamax_pi.pdf).[12] Patients with Wilson's disease who are intolerant of penicillamine should be directed to take trientine hydrochloride 2–4 times daily on an empty stomach, at least 1 h before meals or 2 h after meals and at least 1 h apart from any other drug, food or milk (http://www.merck.com/product/usa/pi_circulars/s/syprine/syprine_pi.pdf). Dosing instructions for these drugs are so complicated that poor compliance, resulting in treatment failure, is quite likely.

Since food components are removed by digestion and absorption during transport through the GI tract, we considered that the negative food effect might be reduced if the drug is delivered to the middle-to-lower region of the small intestine, which is distant from the pylorus. We have successfully developed enteric-coated dosage forms that deliver drugs to specific regions of the small intestine by using hypromellose acetate succinate (HPMCAS), a cellulose derivative bearing succinoyl groups.[19] The succinoyl group content of HPMCAS determines the pH-solubility profile, and a reduction of the content results in an increase in the pH at which the polymer starts to dissolve.[20] A gradual increase in pH is observed on passing through the small intestine: pH 5–6 at the duodenum, 6–6.6 at the jejunum, and 6.5–8 at the ileum.[21,22] The correlation between succinoyl group content of HPMCAS and disintegration site of HPMCAS-coated granules in rat small intestine was examined, and it was found that the enteric-coated granules disintegrated and the bulk of the drug was immediately released when the granules reached a specific site of the small intestine where the pH corresponded to the pH at which the HPMCAS started to dissolve.

We separately examined the effect of administration site within the GI tract on the bioavailability of several model drugs with negative food effects, including risedronate sodium and trientine hydrochloride, in rats.[4] Bioavailability after oral administration of an aqueous solution of these drugs in fed rats was one-fifth to one-tenth of that in fasted rats because of interactions between the drugs and large amounts of food components remaining in the stomach. This strong negative food effect was reduced when drug solutions were administered directly into any site of the small intestine of rats under anesthesia. Intracolonic administration, however, did not result in the reduction of negative food effects, presumably because of the presence of feces in the upper large intestine.

A consistent reduction of the negative food effect was observed, irrespective of the administration site within the small intestine. This was considered to be due to the absence of solids throughout the small intestine of fed rats, at least as observed with the naked eye.[4] However, it is probable that significant amounts of digested food components are continually emptied into the upper small intestine in larger species, such as humans and dogs in the fed state. We should also consider the possible effects of the operation and anesthesia on drug absorption in the rat study. Therefore, in this article, we prepared enteric-coated tablets containing a drug with a negative food effect and evaluated the practical potential of HPMCAS-coated dosage forms to reduce the negative food effect, using nonanesthetized dogs.

MATERIALS AND METHODS

Materials

Trientine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO). Theophylline and microcrystalline cellulose (Ceollus PH-301) were obtained from Shiratori Pharmaceutical Co., Ltd (Chiba, Japan) and Asahi Kasei Co., Ltd (Tokyo Japan), respectively. In-house hypromellose (HPMC, Pharmacoat 603) and low-substituted hydroxypropyl cellulose (L-HPC, LH-22) were used. Four types of HPMCAS with different succinoyl group contents were selected from our in-house products.[23] All other chemicals were commercial products of reagent grade. All materials were used without further purification.

Centrifugal filter devices with a nominal molecular weight limit of 10000 (Microcon YM-10) were purchased from Millipore Co. (Billerica, MA). Laboratory animal diet TC-1 (per 100 g of diet, proteins: 21 g; lipids: 11 g, minerals: 7 g, fiber: 3 g) was obtained from Aixia Co. (Tokyo, Japan).