Drug Development and Industrial Pharmacy, 35:548–554, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802459445

informa
healthcare

In Vivo Assessment of Novel Furosemide Gastro-Mucoadhesive Delivery System Based on a Kind of Anion Ion-Exchange Fiber

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A novel gastro-mucoadhesive delivery system based on a kind of anion ion-exchange fiber has been developed. Furosemide (FM), which is site-specifically absorbed from the upper gastrointestinal (GI) tract, was used as model drug. A novel-modified dissolution system, which can also be called "flow through diffusion cell," was used to study the drug release from the drug fibers. The GI transit studies of the FM fiber complexes in rats and gamma imaging studies in volunteers were carried out to evaluate the gastro-mucoadhesive behavior of the fiber. The pharmacokinetic profile and parameters of the FM suspension and FM fiber in fasted and fed rats were measured, respectively. Studies on rats and volunteers provided evidence for the validity of the hypothesis that the drug fiber provided better gastro-mucoadhesive properties in vivo.

Keywords gastro-mucoadhesive dosage form; furosemide; ion-exchange fiber; flow through diffusion cell; pharmacokinetic; gamma imaging

INTRODUCTION

Compared with other routes of administration, oral application is the most convenient route of drug delivery and is associated with superior patient compliance. However, from various pharmacological categories, oral administration is limited for many drugs which have poor oral bioavailability because of incomplete absorption and/or degradation in the gastrointestinal (GI) tract or because of a narrow absorption window at the upper part of the GI tract (Sanjay & Shringi, 2003). One strategy is to prolong the residence time of drug in the stomach. Various attempts, such as introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices, and co-administration of gastric-emptying delaying drugs, have been made to retain the dosage form in the stomach as a way of increasing the retention time. However, most of these approaches are influenced by a number of factors that affect their efficacy as a gastro-mucoadhesive system.

The anionic exchange resin, cholestyramine, has the ability to coat the gastric mucosa evenly and provides extended gastric residence (Burton, Washington, Steele, Musson, & Feely, 1995; Thairs et al., 1998), and exhibits these properties through its action as a mucoadhesive (Jackson, 1999). It implied that cholestyramine could form an intimate contact with the gastric mucosa via electrostatic forces. The topical delivery of antibiotics to sites of *Helicobacter pylori* colonization using ion-exchange resin was studied extensively (Cuña, Alonso, & Torres, 2001; Jackson, 1999; Jackson, Bush, & Perkins, 2001; Jackson, Bush, Washington, & Perkins, 2000).

Ion-exchange materials have long been used for isolation of chemicals (Helfferich, 1995), masking taste of bitter drugs (Anand, Kandarapu, & Garg, 2001), improving drug stability (Kankkunen, Sulkava, Vuorio, Kontturi, & Hirvonen, 2002), delivery of anticancer drugs and chemosensitizers to multidrug resistant cells and solid tumors (Liu et al., 2001), controlled drug release for ocular (Jani, Gan, Ali, Rodstrom, & Hancock, 1994; Joshi, 1994), transdermal (Conaghey, Corish, & Corrigan, 1998; Jaskari et al., 2000; Kankkunen et al., 2002; Vuorio, Murtomäki, Hirvonen, & Kontturi, 2004; Yu, Li, Yuan, Dai, & Liu, 2006), nasal (Illum, 1999), and oral applications (Irwin, MacHale, & Watts, 1990) in pharmacy. Compared with the resin, fibrous ion-exchange materials are suggested to have a larger surface area to unit volume ratio, which leads to a higher absorption rate and absorption capacity (Lin & Hsieh, 1996). Unlike ion-exchange resins, ion-exchange fibers consist of a non-cross-linked polymeric framework carrying a positive (anion exchanger) or a negative (cation exchanger) fixed electric charge (Kaisa, Marie, Lasse, & Jouni, 2007). The ionized groups are covalently attached to the framework, and they are compensated by mobile counter ions of opposite charge. Charged (ionized) drugs are bound to the ion-exchange groups of the fibers by electrostatic interactions until they are released by competing with mobile co-ions. Therefore, anion ion-exchange fiber is suggested to be gastro-mucoadhesive for the same drug loading mechanism with ion-exchange resin.

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Drug can be released from the drug fiber only in the presence of mobile counter ions, and also because of the existence of Donnan equilibrium, the experimental conditions, maintained in the release studies by traditional methods, do not match with the in vivo GI conditions. Therefore, in order to simulate stomach conditions in the release experiments, we developed a novel-modified dissolution system, which can also be called "flow through diffusion cell" (FTDC), was used to study the drug release from the drug fibers. An FTDC is essentially a modification of the Rossett–Rice test (Splvey & Goodhart, 1979) and the release system proposed by Gohel for designing the floating drug delivery system (Gohel, Mehta, Dave, & Bariya, 2004).

The main aim of the study was to determine whether anion ion-exchange fiber is gastro-mucoadhesive in the rat stomach and human using furosemide (FM) with limited absorption window as a model drug. The GI transit of the FM fiber complexes in rats was studied. Gamma scintigraphy was employed to investigate the in vivo transit behaviors of the fibers in volunteers. According to the study of Jackson (1999), Jackson et al. (2000), and Jackson et al. (2001) on ion-exchange resin, we carried out the experiment based on the hypothesis that ion-exchange fiber is gastro-mucoadhesive. If ion-exchange fiber is gastro-mucoadhesive, the drug fiber can reside in the stomach or in the upper small intestine close to the adsorption window for longer periods compared with single drug solution. Thus, the bioavailability would be expected to improve.

MATERIALS AND METHODS

Materials

Strong anion ion-exchange fiber [poly (ethylene-*g*-styrene-trimethyl-ammonium-chloride) was obtained from Guilin Zhenhan Co. Ltd. (Guangxi, China) with the maximum ion-exchange capacity of about 3.5 mmol/g. The staple form of fiber had a diameter of about 30 μm, and was cut into about 0.1 mm units before use. FM was obtained from Hainan Liangfang Co. Ltd. (Hainan, China). All the other chemicals were at least analytical grade and were used without further purification. Self-prepared double de-ionized water with a resistivity of more than 18 MΩ/cm was used to prepare all the solutions.

Pretreatment of the Fibers

The fiber in staple form was washed consecutively with methanol and double-distilled water to remove impurities. Then the fiber was activated by three treatments with alternate aliquots of 1 M NaOH and 1 M HCl and finally the fiber, in acid form, was washed with double-distilled water and dried.

Loading of the Fibers

The activated fibers (1 g dry weight) were suspended in 1 L of 0.3 mmol/L FM solution (containing 5 mL of 0.2% sodium hydroxide). After stirring at room temperature for 15 min, the FM fiber complex formed was separated from the supernatant by vacuum filtration, washed with 100 mL of de-ionized water to remove unbounded drug, and squeezed dry at room temperature and subsequently dried to constant weight. The amount of adsorbed drug in the fibers was determined using high-performance liquid chromatography (HPLC) (Shimadzu RF-540, Kyoto, Japan) from the different concentration in the collected washing solutions and the initial solution.

Drug Release in Vitro

The FM fiber complexes (400 mg) was put in the modified beaker (100-mL capacity) containing 70 mL dissolution medium (0.1 mol/L NaCl acidified to pH 1.2 using hydrochloric acid), placed in a thermostatic magnetic water bath (Gong Yi Machine Corporation, Henan, China), and stirred at a speed of 75 rpm. The temperature of the dissolution medium was maintained at 37 ± 0.5°C. The dissolution medium was pumped into the beaker using a peristaltic pump at a flow rate of 2 mL/min. At the same time, the dissolution medium along with the dissolved drug was pumped out from a burette attached with a 0.45-μm cellulose acetate filter mounted at the bottom of the beaker using another peristaltic pump. The schematic diagram was shown in Figure 1. The released sample was collected using a 20-mL tube every 5 min and analyzed by HPLC with flurorimetric detection (λ_{ex} 250 nm and λ_{em} 389 nm) with the mobile phase of orthophosphoric acid (0.5%)—methanol (40:60, vol/vol) adjusted to pH 3.0 by triethylamine using a reverse-phase micro-particulate C_{18} (5 μm, 4.6 × 200 mm). The measurements were performed in triplicate.

Gastrointestinal Transit of the Furosemide Fiber Complexes in Rats

Male Wistar rats (250 ± 20 g) purchased from the Experimental Animal Center of Shenyang Pharmaceutical University, were kept in an environmental-controlled breeding room for 3 days before starting the experiment. All procedures involving animals were in accordance with the Regulations of Experimental Animal Administration issued by the State Committee of Science and Technology of People's Republic of China.

Eighteen male Wistar rats (250 ± 20 g) were divided evenly into two groups. The first group was fasted overnight but allowed free access to water. The other group was allowed free access to food and water before the dose. The FM fiber complex (100 mg) was administered in 0.5 mL of water directly to the stomachs of conscious rats by means of a glass syringe fitted to a gastric cannula. After 1, 2, and 6 h of administration, three rats were sacrificed, the stomachs were dissected free and spread out on a sheet. Then each stomach was homogenized by cutting into small pieces with scissors and subsequently incubated in 500 mL of 0.5 mol/L NaCl, acidified to pH 1.2 using hydrochloric acid for the determination of FM, sonicated for 40 min to completely release FM to the release medium.

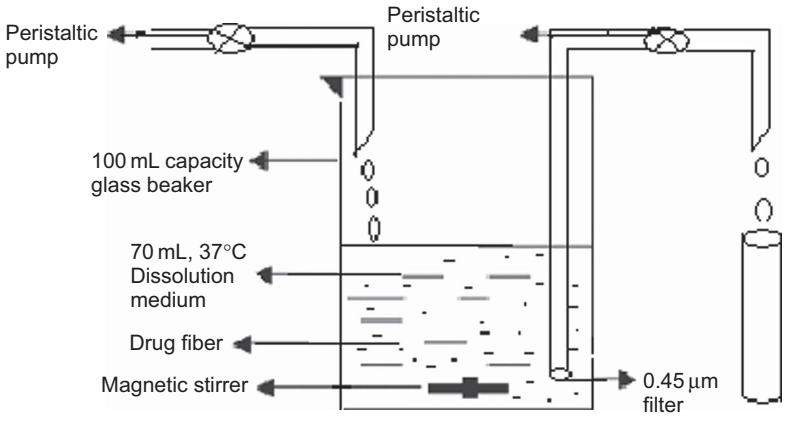

FIGURE 1. Schematic diagram of the modified dissolution method.

The recovery value was in the range of 97.3–99.5%. Then the released sample was filtered through a 0.45 μm membrane and determined using the HPLC method as described in the in vitro dissolution test.

In Vivo Evaluation of the Gastro-Mucoadhesive Ability of Fiber (Gamma Scintigraphy)

Radio-Labeling of Fiber

Technetium (99mTc, Shandong Dayin Co. Ltd., Shandong, China) was selected to radiolabel the fibers because of its short half-life of 6 h and very less amount of electron emission. The activated fibers (1 g dry weight) were suspended in 10 mL sodium pertechnetate solution equivalent to the radioactivity of 100 mCi eluted from the technetium generator. After stirring at room temperature for 15 min, the radio-labeled fiber complex formed was separated from the supernatant by vacuum filtration, washed with 100 mL of de-ionized water to remove unbounded pertechnetate, and squeezed dry at room temperature and subsequently dried to constant weight.

Stability of Radio-Labeled Fibers

Stability tests of 99mTc-labeled fibers were carried out to confirm that the pertechnetate was bounded to the fibers for the duration of the study. Tests were carried out according to the study of Atyabi, Sharma, Mohammad, and Fell (1996) and Jain, Agrawal, and Jain (2006) as follows: three standard buffers solutions (pH 1.2, 6.8, and 7.4) were added to three tubes, respectively, and kept in a water bath maintained at 37°C. Radio-labeled fibers (100 mg) were placed in three beakers, respectively, stirred in a thermostatic magnetic water bath. At predetermined time intervals, 0.2 mL of samples were taken using a burette attached with a 0.45-μm cellulose acetate filter and at the end of the experiment the fibers were recovered, washed, and dried. The radioactivities of the samples, fibers, and the filtrate were counted in an auto gamma counter (CRC-15R, Capintec Inc., Ramsey, USA). The sum of radioactivities of fibers, the filtrate, and the extreme fibers was expressed as the total radioactivity.

Gamma Imaging in Volunteers

Twelve healthy males (weight ranged from 51 to 68 kg) were selected as volunteers and divided evenly into two groups. They had given their informed consent to participate in the study. The first of the two groups was fasted overnight but allowed free access to water. The other group was allowed free access to food and water before the dose. No volunteer was taking any regular medication or had a history of GI disorders. The study was approved by Ethics Committee. Group 1 was fasted for 10 h before the dose and for a further 8 h afterwards, but allowed to drink water freely. Group 2 was allowed to consume a common breakfast consisting of egg, bread, and milk half an hour before the experiment. Each of them ingested the radio-labeled fiber complexes (400 mg) with 20 mL of water. The 140 keV gamma rays emitted by 99mTc were imaged. The gamma images were recorded using an online computer system (Millennium VG hawk-eye, Milwaukee, WI, USA) and static 10-s anterior images were acquired at suitable time intervals. During recording of the images, volunteers were not allowed to take any food, but allowed to drink water freely for the duration of the study.

In Vivo Assessment of Bioavailability Studies in Rats

Eighteen male Wistar rats (250 ± 20 g) were divided evenly into three groups. The first two groups were fasted overnight but allowed free access to water. The other group was allowed free access to food and water before the dose. The fasted groups were administered the FM methylcellulose suspension and FM fiber complex, whereas the other group was administered the FM fiber complex suspension, both with the dose of 10 mg/kg and the given volume of about 0.5 mL. Rats were fasted, but allowed free access to water for the duration of the study. Blood samples (0.4 mL) were drawn from the ocular vein into heparinized tube at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 h after dosing. Plasma was separated by centrifugation (1,000 × g for 10 min) within 1 h and frozen immediately at −20°C.

FM concentrations in plasma were determined by means of HPLC using the method described by Hisham, Chuah, Syarif, Nik Nasri, and Fairulnizam (1998). To a 10-mL stoppered glass tube, 0.15 mL of plasma specimen, 20 μL of internal standard (10 mg/mL warfarin), 50 μL of 3 M hydrochloric acid, and 2 mL of HPLC-grade diethyl ether were added. The tube was closed tightly and vortex-mixed for 60 s and centrifuged at a speed of 2,000 × *g* for 10 min. The ether layer was quantitatively transferred to another clean centrifuge tube. In a water bath adjusted at 45°C, the ether was allowed to evaporate under a stream of nitrogen gas. The residue was reconstituted in 100 μL of methanol, and a 20 μL aliquot was injected onto the column. The amounts of FM were determined using the HPLC method used for the in vitro dissolution test. The standard curve was found to be linear (r = .9914) with the concentration ranging from 0.03 to 10.00 mg/L. The accuracy and precision of the method have been investigated by Hisham et al. (1998).

Statistical Analysis

Statistical data were analyzed by one-way analysis of variance (ANOVA). A multiple comparison test (Dunnett's test) was used to compare different formulations, and a p value of .05 was considered to be significant. The plasma concentrations of FM at different time points were expressed as $M \pm SD$, and the mean concentration–time curves were plotted. All the pharmacokinetic data were calculated using the DAS 2.0 statistical software (Pharmacology Institute of China, Beijing, China).

RESULTS AND DISCUSSION

Drug Content

From the different concentration in the collected washing solutions and the initial solution, the mean drug content of the drug fiber was determined to be 95.7 ± 3.1 mg/g. And the loading efficiency could achieve 96.4 ± 2.6%, that is, most of the ionized FM were adsorbed at the concentration of 0.2 mmol/L.

Drug Release of the Furosemide Fiber Using Modified Release System

In our dissolution system similar to the flow cell proposed by Vuorio, the dissolution medium moved through the beaker continuously. New equilibrium was reached in the solution/fiber interface accompanied by the addition of the fresh medium. The released drug was removed through another peristaltic pump and was collected every 5 min. The plot of accumulated drug-release percentage versus average time gives the drug-release profile. The drug-release profile is shown in Figure 2. From the figure, we can see that the drug is released from the fiber in a sustained-release fashion. The riboflavin fiber complex released 70.7 ± 1.2% of their riboflavin content in 7 h. The release feature obtained by Vuorio et al. (2004) was similar to ours.

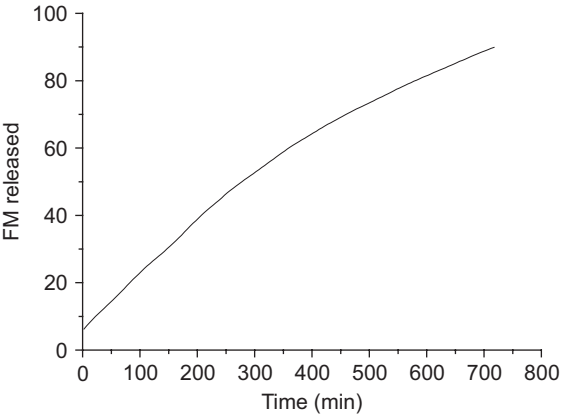

FIGURE 2. Drug-release profile of the FM fiber using modified dissolution system.

In the dissolution system, in vivo conditions including the gastric acid secretion rate, gastric volume, and gastric emptying are mimicked; hence, it was expected to show good in vivo and in vitro correlations. And it is particularly suitable to the drug fiber for its special drug-release mechanism.

The Amount of Furosemide Remaining in the Stomach of Rats

It can be seen that the light yellow drug fibers were distributed evenly throughout the gastric surface especially in the stomach of rats virtually. The amounts of the drug remaining in the stomach of fasted and fed rats are shown in Figures 3 and 4, respectively. For the fasted rats, the drug remained was found to be 66.2 ± 3.2% at 1 h after administration. At 2 h, many fibers are still remaining in the stomach, the drug remained was found to be 49.2 ± 3.9%. At 6 h, there are still some fibers remaining in the stomach, the drug remained was found to be 22.8 ± 2.5%. For the fed rats, the drug remained was found to

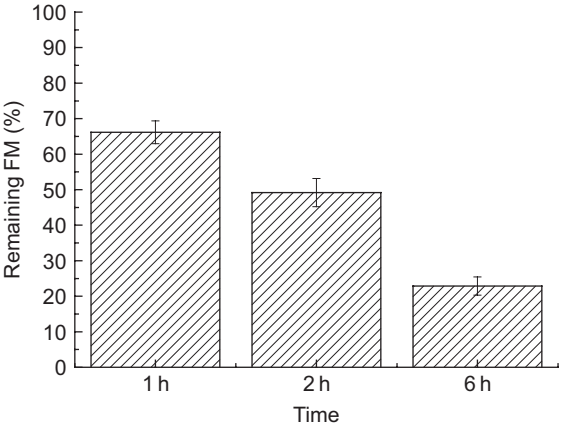

FIGURE 3. The amount of FM remaining in the stomach of fasted rats after administrating the FM fibers (data are $M \pm SE$ [n = 3]).

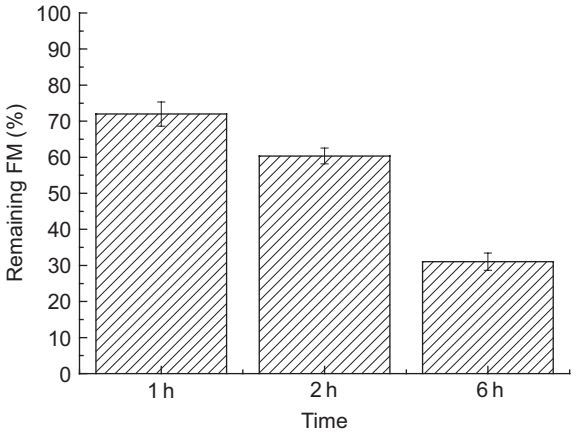

FIGURE 4. The amount of FM remaining in the stomach of fed rats after administrating the FM fibers (data are $M \pm SE$ [$n = 3$]).

be 71.9 ± 3.4% at 1 h after administration. At 2 h, most fibers are still remaining in the stomach, the drug remained was found to be 60.3 ± 2.2%. At 6 h, there are still some fibers remaining in the stomach, the drug remained was found to be 31.1 ± 2.4%. These results showed that the FM fiber could be retained in the stomach of rats for a long time.

Gamma Scintigraphy Studies

The gamma scintigraphy was applied to assess the gastro-mucoadhesive behavior of the ion-exchange fiber and also to evaluate the influence of food on the gastro-mucoadhesive behavior of the fiber in healthy human volunteers. The stability of 99mTc-labeled ion-exchange fiber was tested in standard buffer solutions of pH 1.2, 6.8, and 7.4 in order to confirm that the activity would not be leached out from the fibers during transit through the GI tract. The activity released from 99mTc-labeled fiber was only about 0.06% in pH 1.2, 0.03% in pH 6.8, 0.05% in pH 7.4, respectively, in the study period of 8 h. Sufficient stability allowed successive gamma imaging for the duration of the study.

Gamma scintigraphic images of the fasted and fed volunteers are shown in Figures 5 and 6, respectively. From Figure 5, we can see that almost all the fibers could be retained in the stomach for 2 h, only slight fibers were excreted to intestine. Two hours after dosing, some fibers began to be removed because of the turnover of the stomach. About 60% of fibers were still remaining in the stomach at 5 h. About 20% of fibers were even remaining in the stomach at 8 h. From Figure 6, we can see that almost all the fibers could be retained in the stomach for 4 h, only very little fibers were excreted. Four hours after dosing, some fibers began to be removed. There were about 85% still remaining in the stomach at 5 h, and 70% at 7 h. About 50% of fibers were even remaining in the stomach at 8 h. The results showed a significant gastro-mucoadhesive characteristic of ion-exchange

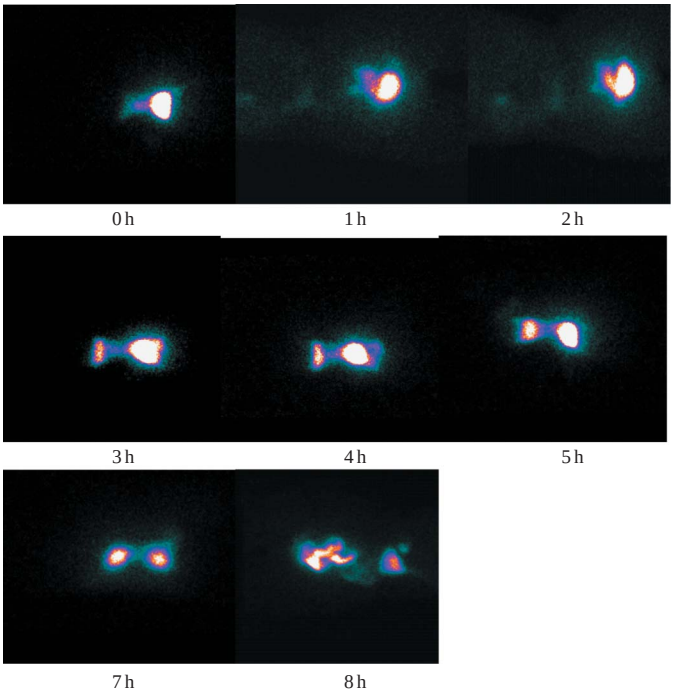

FIGURE 5. Gamma scintigraphic images of ion-exchange fiber in fasted volunteers.

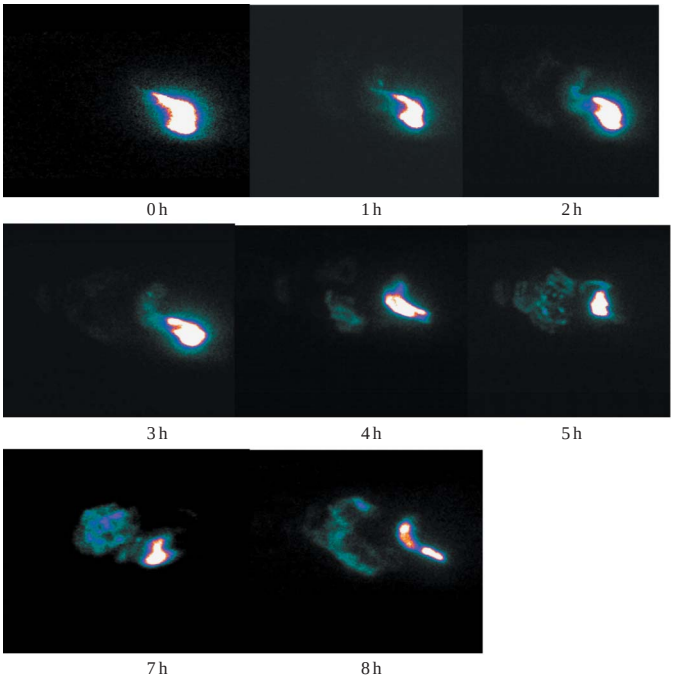

FIGURE 6. Gamma scintigraphic images of ion-exchange fiber in fed volunteers.

fibers. The interaction between the resin and the mucus appears to be very strong, since about 20% of fibers for the fasted volunteer and 50% of fibers for the fed volunteer were

still remaining in the stomach at 8 h. Feeding stimulates mucus production by mechanical abrasion and it may be expected that this would increase the emptying of the resin in the fed subject compared with the fasted subject, but it was observed that more fibers adhered to the stomachs in fed volunteers than in fasted volunteers. Perhaps in the fed condition the sufficient migration of the food and fibers could provide the fibers enough time to come in contact with the stomach mucus. Once the fibers adhered to the mucus, they would not be excreted along with the food. The other factor perhaps was that food could delay gastric emptying time.

Bioavailability Studies in Rats

The mean plasma concentration–time profiles are shown in Figure 7 and its pharmacokinetic data are listed in Table 1.

It was shown that the pharmacokinetic parameters of the rat after administering the FM suspension were different from administering the FM fiber complex at the same dosage (10 mg/kg). For the fasted rats, compared with the FM suspension, the maximum plasma concentration (C_{max}) of the FM fiber complex was smaller, the time taken to reach the maximum plasma concentration (T_{max}), and the mean retention time($t_{1/2}$) were all prolonged ($p < .05$). Compared with the fasted rats, the maximum plasma concentration (C_{max}) of the FM fiber complex for fed rats was similar ($p > .05$), but the time taken to reach the maximum plasma concentration (T_{max}) and the apparent elimination half-life ($t_{1/2}$) were all prolonged ($p < .05$). The area under the plasma concentration time curve (AUC_{0-t}) value of FM of the FM fiber complex was 11.08 ± 1.06 μg h/mL, which was about 2-fold variance compared with that (5.52 ± 1.19 μg h/mL) obtained for the FM suspension. The AUC_{0-t} value of FM of the FM fiber complex for fed rats was 14.09 ± 1.39 μg h/mL, which was about 1.27-fold variance compared with that obtained for the fasted rats (11.08 ± 1.06 μg h/mL).

The improved bioavailability of the FM fiber obtained in our experiment in fasted rats showed that the fiber can be retained in the stomach for a long time. The improved bioavailability of

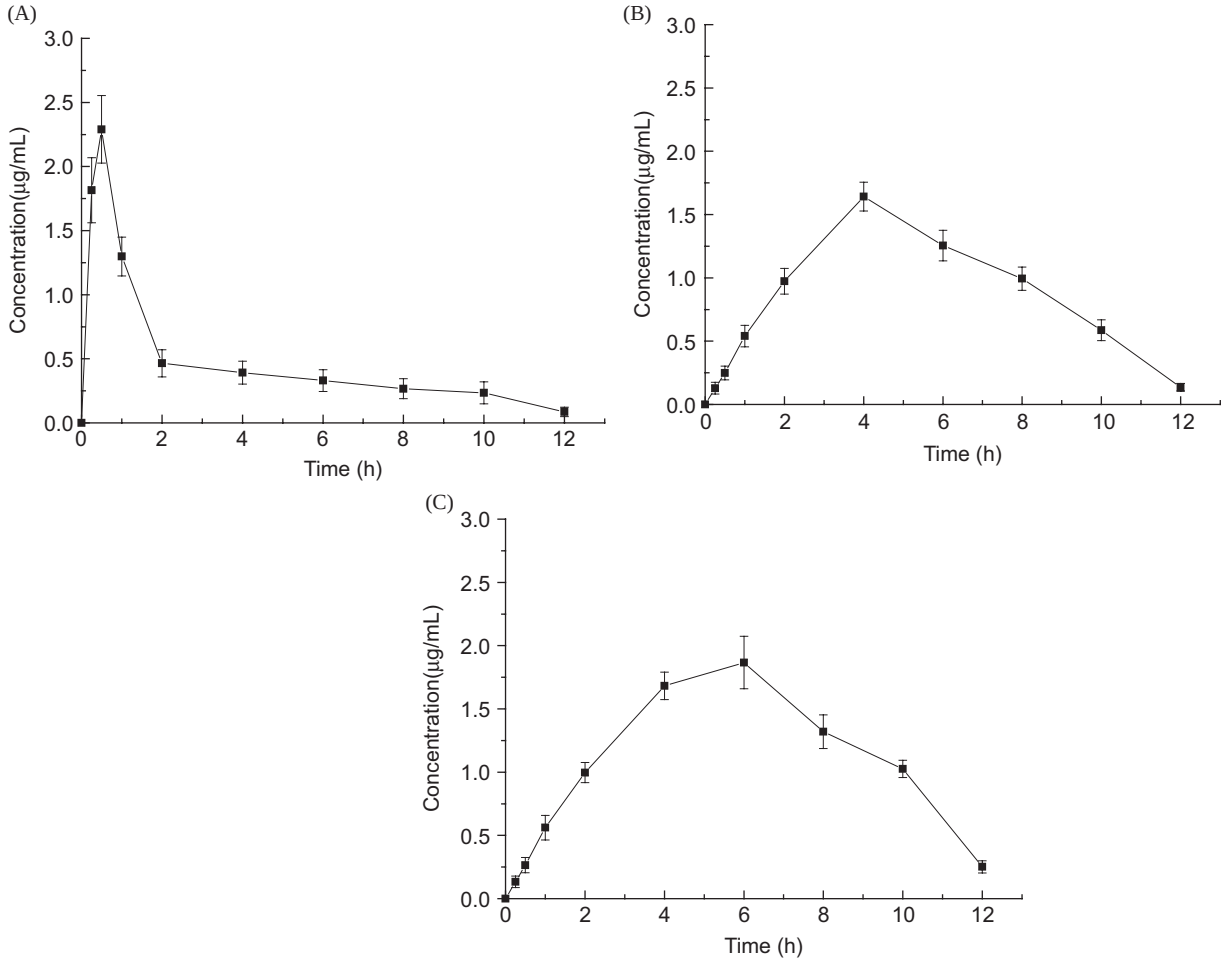

FIGURE 7. Mean plasma concentration–time curve for FM in rat plasma after administering the FM suspension (A), the FM fiber complex in fasted state (B), and the FM fiber complex in fed state (C); each point and bar represents the $M \pm SD$ ($n = 6$).

TABLE 1
Pharmacokinetic Data of FP in Rats (n = 6)

Parameter	Estimate ($M \pm SD$)		
	FM Suspension	FM Fiber in Fasted Rats	FM Fiber in Fed Rats
T_{max} (h)	0.57 ± 0.16	4.32 ± 0.53	5.66 ± 0.81
C_{max} (μg/mL)	2.29 ± 0.29	1.64 ± 0.13	1.87 ± 0.22
MRT (h)	3.16 ± 0.39	5.49 ± 0.21	6.18 ± 0.94
AUC_{0-t} (μg h/mL)	5.52 ± 1.19	11.08 ± 1.06	14.09 ± 1.39

the FM fiber obtained in the fed rats than in fasted rats showed that food can enhance the fibers to retain in the stomach for a longer time, which were certified by the gamma imaging study in volunteers and by the GI transit in rats. The fiber remained in the stomach for enough time to slowly release its drug, and consequently the released FM passed gradually through the absorption window and was absorbed more efficiently.

CONCLUSIONS

In this study, a novel in vitro dissolution system is proposed wherein the gastric acid secretion rate, gastric volume, and gastric emptying are mimicked. The results of this study in rats and volunteers provided evidence for the validity of the hypothesis that the drug fiber provided better gastric-mucoadhesive properties in vivo. Food can enhance the fibers to retain in the stomach for a longer time and improve the bioavailability of FM to some extent but not too significant. The fiber should be of considerable interest for the development of future gastric-mucoadhesive oral drug delivery dosage forms. The findings of this study also showed that ion-exchange fibers have possible therapeutic value as drug delivery vehicles in topical treatment of the stomach because of their extended gastric residence and uniform coating of the stomach. The gastromucoadhesive behavior of ion-exchange fiber is better than ion-exchange resin when compared with the study of Jackson (1999) and Jackson et al. (2000), and Jackson et al. (2001). However, the results are preliminary and further studies under different conditions, such as fiber dose, administration volume, and drug content of the fiber should be conducted to show that the drug fiber could be retained in the stomach.

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