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A novel riboflavin gastro-mucoadhesive delivery system based on ion-exchange fiber

Huimin Yao, Lu Xu, Fei Han, Xin Che, Yang Dong, Min Wei, Jiao Guan, Xiaolei Shi, Sanming Li *

School of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang 110016, People's Republic of China

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ABSTRACT

A novel gastro-mucoadhesive delivery system based on ion-exchange fiber has been developed. Rriboflavin-5′-phosphate sodium salt (RF5P), which is site-specifically absorbed from the upper gastrointestinal tract, was used as model drug. A modified dissolution system, which can also be called 'flow through diffusion cell' (FTDC), was used to study the drug release from the drug fibers. Gastrointestinal transit studies of the RF5P fiber complexes in rats and gamma imaging study in volunteer was carried out to evaluate the gastro-retentive behavior of the fiber. The pharmacokinetic profile and parameters of riboflavin via analysis of urinary excretion of riboflavin on man were measured. Study on rat and man provide evidence for the validity of the hypothesis that the drug fiber provided good mucoadhesive properties *in vivo* and should therefore be of considerable interest for the development of future mucoadhesive oral drug delivery dosage forms.

1. 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 due to incomplete absorption and/or degradation in the gastrointestinal (GI) tract or due to a narrow absorption window (NAW) at the upper part of the gastrointestinal tract (Sanjay and Shringi, 2003). One strategy is to prolong the residence time of drug in the stomach. Various attempts 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 gastro-mucoadhesive system (Streubel et al., 2006).

The anionic exchange resin, cholestyramine, has the ability to coat the gastric mucosa evenly and provide extended gastric residence (Burton et al., 1995; Thairs et al., 1998) and exhibits these properties through its action as a mucoadhesive (Jackson et al., 2000). The experiment result implied that cholestyramine could forms 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 were studied extensively (Jackson, 1999; Jackson et al., 2000, 2001; CunÄa et al., 2001).

Ion-exchange materials have long been used for isolation of chemicals (Helfferich, 1995), masking taste of bitter drugs (Anand et al., 2001), improve drug stability (Kankkunen et al., 2002a,b), delivery of anticancer drugs and chemosensitizers to multidrug resistant cells and solid tumors (Liu et al., 2001), controlled drug release for ocular (Joshi, 1994; Jani et al., 1994), transdermal (Conaghey et al., 1998; Kankkunen et al., 2002a,b; Jaskari et al., 2000; Vuorio et al., 2004; Yu et al., 2006), nasal (Illum, 1999) and primarily oral applications (Irwin et al., 1990) in pharmacy and medicine. 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 et al., 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. So anion ion-exchange fiber is suggested to be gastro-mucoadhesive for the same drug loading mechanism with ion-exchange resin.

Ion-exchange fibers are promising drug reservoir materials for storage and controlled drug delivery (Jaskari et al., 2000, 2001; Kankkunen et al., 2002a,b; Vuorio et al., 2004; Yu et al., 2006). Drug can release from the drug fiber only in the presence of mobile counter ions, and also due to the existence of Donnan equilibrium, the experimental conditions, maintained in the release studies by

* Corresponding author.
E-mail address: li_sanming@126.com (S. Li).

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traditional method, do not match with the *in vivo* GI conditions. Therefore, in order to mimic stomach conditions in the release experiments, we developed a novel modified dissolution system which can be also called 'flow through diffusion cell' (FTDC), was used to study the release drug from the drug fibers. The modified release drug delivery system is essentially a modification of the Rossett–Rice test (Splvey and Goodhart, 1979) and the release system proposed by Mukesh et al. (2004) that was designed for the floating drug delivery system. Vuorio et al. (2003) also studied the kinetics and extent of drug release from different ion-exchange materials using an in-house-designed flow-cell similar to ours. In the dissolution system we proposed, drug can release from the drug fibers in freshly release medium continuously, which can successfully avoided saturation phenomenon that ion-exchange materials countered.

The model drug we used, riboflavin (vitamin B2), is a water-soluble vitamin. It has a recognized narrow absorption window in the upper part of the intestine and a saturable absorption mechanism (Jusko and Levy, 1967). In the present study the riboflavin-5′-phosphate sodium salt (RF5P) was used because of its better solubility. RF5P was demonstrated to have the same absorption and excretion characteristics as riboflavin (Jusko and Levy, 1967).

The main aim of the study was to identify the gastro-mucoadhesive characteristic of anion ion-exchange fiber in the rat stomach and human, using riboflavin with limited absorption window as model drug. To the best of our knowledge, the gastro-mucoadhesive property of ion-exchange fiber was studied for the first time. The pharmacokinetic profile of riboflavin via analysis of urinary excretion of riboflavin on man was used in evaluating the possible gastro-mucoadhesive behavior of anion ion-exchange fiber. If ion-exchange fiber is gastro-mucoadhesive, the drug fiber can reside the stomach or the upper small intestine closing to the adsorption window for longer periods compared with single drug solution. Thus, the bioavailability would be expected to improve.

2. Materials and methods

2.1. Materials

Strong anion ion-exchange fiber [poly(ethylene-g-styrene-trimethyl-ammonium-chloride)] were obtained from Guilin Zhenhan Co. Ltd. (Guangxi, China) with the maximum ion-exchange capacity about 3.5 mmol g^{-1}. The staple form fiber had a diameter of about 30 μm, and was cut into about 0.1 mm units before use. Riboflavin-5′-phosphate (RF5P) sodium salt was obtained from Zhengzhou Tuoyang Co. Ltd. (Henan, China). All the other chemicals were at least analytical grade and were used without further purification. Self-prepared double deionized water with a resistivity of more than 18 MΩ/cm was used to prepare all the solutions.

2.2. 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. The fiber was cut into about 0.1 mm units before use.

2.3. Loading of the fibers

The activated fibers (1 g dry weight) were suspended in 1 l 0.25 mmol l^{-1} RF5P solution. After stirring at room temperature for 15 min the RF5P fiber complex formed was separated from the supernatant by vacuum filtration, washed with a known amount of deionized water to remove unbounded drug, and squeezed dry at room temperature and subsequently at 313 K in an oven to constant weight. The amount of adsorbed drug in the fibers was determined by HPLC from the different concentration in the collected washing solutions and the initial solution.

2.4. Drug release

The RF5P fiber complexes (400 mg) were put in the modified beaker (100 ml capacity) containing 70 ml dissolution medium (0.1 mol l^{-1} NaCl acidified to pH 1.2 by hydrochloric acid) placed in a thermostatic magnetic water-bath (Gong Yi Machine Corporation) 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^{-1}. 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 Fig. 1. The released sample was collected using a 20-ml tube every 5 min and analyzed by high performance liquid chromatography (HPLC) (Shimadzu RF-540, Kyoto, Japan) with flurorimetric detection (λ_{ex} 450 nm and λ_{em} 530 nm) with the mobile phase of 60:40 orthophosphoric acid (0.5%)–methanol adjusted to pH 3.0 using triethylamine. The column was a reverse-phase micro-particulate C_{18} (5 μm, 4.6 mm × 200 mm). Measurements were performed in triplicate.

2.5. Gastrointestinal transit of the RF5P fiber complexes

Male Sprague–Dawley rats (250 ± 20 g) were fasted overnight but were allowed free access to water. The riboflavin 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 stomach were dissected free and spread out on a sheet. The fiber attached to the stomach can be investigated visually. Then each stomach was homogenised by cutting into small pieces with a pair of scissors and subsequently incubated in 500 ml of 0.5 mol l^{-1} NaCl, acidified to pH 1.2 by hydrochloric acid for determination of riboflavin, sonicated for 40 min, to release RF5P completely to dissolution medium. Then the released sample was filtered through a 0.45-μm membrane and determined by the HPLC method.

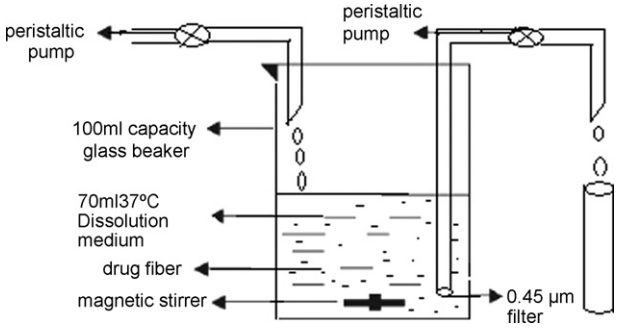

Fig. 1. Schematic diagram of the modified dissolution method.

2.6. In vivo evaluation of the gastro-retentive ability of fiber (gamma scintigraphy)

2.6.1. Radio-labeling of fiber

Technetium (99mTc) 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 radioactivity of 100 mci eluted from the technetium generator. After stirring at room temperature for 15 min the radio-labelled fiber complex formed was separated from the supernatant by vacuum filtration, washed with 100 ml of deionized water to remove unbounded pertechnetate, and squeezed dry at room temperature and subsequently dried to constant weight.

2.6.2. Stability of radio-labelled fibers

Stability tests of 99mTc-labelled 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 Atyabi et al. (1996) and Jain et al. (2006) described: three different 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-labelled 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, USA). The sum of radioactivity of fibers, the filtrate and the extreme fibers was expressed as the total radioactivity.

2.6.3. Gamma imaging in volunteer

One healthy male, the age, height, weight was 24 years old, 1.64, 51 kg, respectively, was selected as volunteer and he had given their informed consent to participate in the study. The volunteer was not taking any regular medication or had a history of gastro-intestinal disorders. The study was approved by Ethics Committee. The volunteer was fasted for 10 h before the dose and for a further 8 h afterwards, but allowed to drink water freely. He ingested the radio-labelled 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, USA) and static 10-s anterior images were acquired at suitable time intervals. Between the images, volunteer was not allowed to take any food, but allowed to drink water freely for the duration of the study.

2.7. Administration to volunteers of the RF5P fiber complexes

The study was performed on volunteers at fasting state to evaluate the adhesiveness of the fiber complexes. Six healthy male volunteers, 23–27 years old, gave informed written consent before participation. All subjects were judged to be healthy on the basis of medical history and were not taking any medication including multiple vitamins or riboflavin. Subjects were also asked to avoid eating certain foods known to contain appreciable amounts of riboflavin (such as liver, milk, eggs, and riboflavin-enriched food such as cereals, corn products and noodle products) for at least 48 h prior to and during the study. Participants fasted for 10 h before the dose and for a further 6 h afterwards, but allowed to drink water freely. Each of them ingested the RF5P fiber complexes (400 mg containing RF5P 50 mg) and the RF5P solution (50 mg) with 20 ml of water in a randomized crossover design with a washout period of at least 1 week.

2.8. Collection of urine sample

Subjects emptied their bladder and provided a zero time urine sample prior to dosing, then ingested a formulation. Subjects collected the contents of their urine in volumetric cylinder at 1, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dosing. Volume and time elapsed since vitamin ingestion was recorded directly after voiding for each urine sample. Aliquots were frozen at −20 °C until analyzed for riboflavin. Urine samples were protected against exposure to light because of light sensitivity of riboflavin. The amounts of riboflavin were determined by the HPLC method used for the *in vitro* dissolution test.

2.9. Analyses of samples

Approximately 10 ml of urine was centrifuged at 4000 rpm for 10 min. The supernatant was injected onto the HPLC column. Endogenous riboflavin was taken into account by subtracting the area obtained from analysis of zero time urine sample from standards and samples.

2.10. Pharmacokinetic analysis

The different treatments were compared in terms of urinary recovery of riboflavin during the first 24 h after administration, $\text{Recovery}_{0-24\,\text{h}}$, maximum urinary excretion rate ($R_{\max}$), and the time ($T_{\max}$) required to reach $R_{\max}$. All parameters were determined from the individual urinary excretion rate–time curves, a plot of urinary excretion rate against the midpoint of a urine collection interval. Urinary excretion rate for each time point of urine collection was calculated by multiplying the concentration of drug in urine for each time point (as determined from the standard curve) by the volume of urine collected to get the amount of unchanged drug excreted in urine during this time interval (D_u). This amount was then divided by the time interval for collection of urine sample to obtain the urinary excretion rate (D_u/t). Graphs were constructed by plotting (D_u/t) versus the midpoint of collection period (t^*). $\text{Recovery}_{0-24\,\text{h}}$ was determined from the individual cumulative urinary drug excretion time curves, a plot relating the cumulative unchanged drug excreted (D_u) to the collection time. Urinary excretion data can be used to estimate bioavailability because the cumulative amount of drug excreted in urine is directly related to the total amount of drug absorbed and then excreted through a first-order elimination process (Wagner, 1979; Shargel and Yu, 1985).

2.11. 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 0.05 was considered to be significant. Differences between pairs of means were performed on $\text{Recovery}_{0-24\,\text{h}}$, $R_{\max}$, and $T_{\max}$ for urinary recovery data were computed. All data are presented as mean ± S.D., if not stated otherwise.

3. Results and discussion

3.1. 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 $125.2 \pm 5.3\ \text{mg g}^{-1}$. It was found that the loading efficiency could achieve 97.3 ± 2.1%, i.e. almost all the ionized RF5P were adsorbed at the concentration of $0.2\ \text{mmol l}^{-1}$.

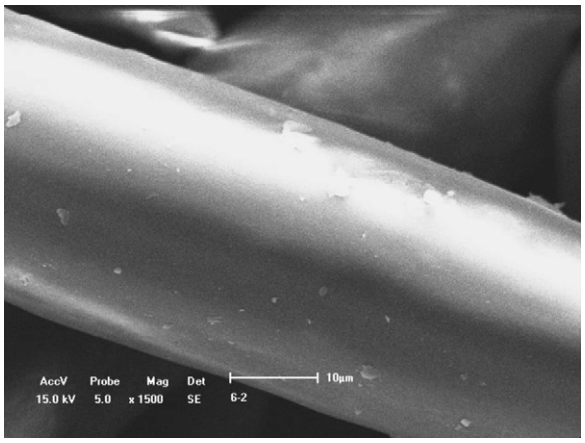

Fig. 2. The surface characteristic (morphology) and the dimension of the ion-exchange fiber are evaluated by scanning electron microscopy (SEM). The ion-exchange fiber were deposited on a round metal plate, sputtered for 20 s with platinum (Ion Sputter, E-1010, Hitachi, Japan) and then analyzed with SEM (S-3400N, Hitachi, Japan).

3.2. Drug release of the RF5P 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 with the adding of the fresh medium. The released drug was removed through another peristaltic pump and was collected every 5 min. The plot of accumulate drug release percentage versus average time gives the drug release profile. The drug release profile was shown in Fig. 3. From the figure, we can see that drug release 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 Vuorio et al. (2003) obtained was similar to ours.

Scanning electron microscope photograph of ion-exchange fiber reveals that the surface is compact, smooth and rodlike (Fig. 2). Drug release from the ion-exchange fiber is affected by two procedures, i.e. drug molecule ion-exchange reaction with the competing ions and the diffusion process in the fiber. Compared to the rate of diffusion (Helfferich, 1995), the exchange reaction is presumably very fast. Therefore, the Donnan equilibrium can be assumed to be valid only on the surface of the fiber. The kinetic problem is, therefore, reduced to a transport problem. A theoretically model based on the Nernst–Planck equation proposed by Vuorio et al. modelled the kinetics and extent of drug release from different ion-exchange materials using an in-house-designed flow-cell and provided satisfactory explanations for the experimental observations. The limiting release rate procedure is the diffusion of drug in the fiber due to the fibers' compact structure. In the dissolution system, *in vivo* conditions including the gastric acid secretion rate, gastric volume and gastric emptying are mimicked. And it is particularly suitable to the drug fiber for its special drug release mechanism (Fig. 3).

3.3. The amount of riboflavin remaining in the stomach of rats

It can be seen virtually that the drug fibers were distributed evenly throughout the gastric surface especially in the rat stomach. The amounts of the drug remaining in the rat stomach were shown in Fig. 4. The drug remained was found to be 60.7 ± 6.6% at 1 h after administration. At 2 h, most drugs were still remaining in the stomach, the drug remained was found to be 41.6 ± 3.7%. At 6 h, there are still some fibers remaining in the stomach, the drug remained was found to be 11.2 ± 2.4%. These result also indicated that the RF5P fiber released the drug slowly *in vivo*.

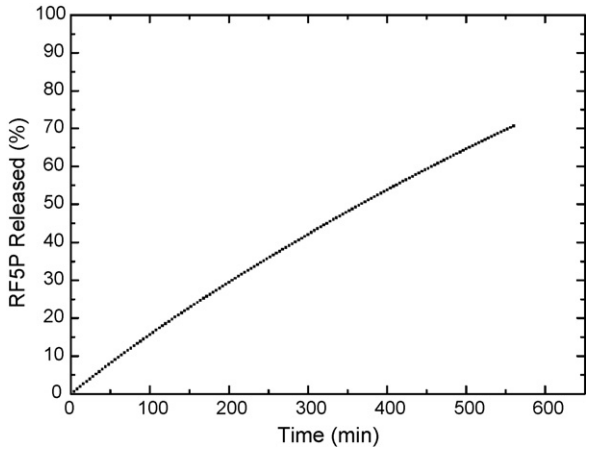

Fig. 3. Drug release profile of the RF5P fiber using modified dissolution system (data are mean values ($n = 3$)).

3.4. Gamma scintigraphy studies

The gamma scintigraphy was applied in order to assess gastro-retentive behavior of the ion-exchange fiber in healthy human volunteer. The stability of 99mTc-labelled 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 leached out from the fibers during transit through GI tract. The activity released from 99mTc-labelled 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 volunteer were shown in Fig. 5. From Fig. 5, we can see that almost all the fibers could retain in the stomach for 2 h, only slight fibers were excreted to intestine. Two hours after dosing, some fibers began to be removed due to the turnover of stomach. About 60% fibers were still remaining in the stomach at 5 h. About 20% fibers were even remaining in the stomach at 8 h. The result showed that a significant gastro-retentive characteristic of ion-exchange fibers. The interaction between the fiber and the mucus appears to be very strong,

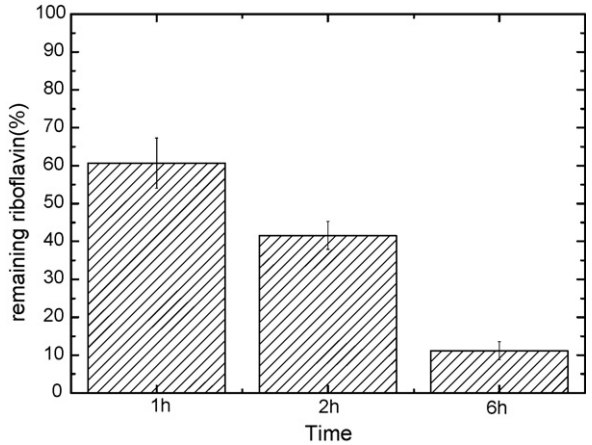

Fig. 4. The amount of riboflavin remaining in the stomach of fasted rats after administrating the riboflavin fibers (data are mean values ($n = 3$) ±S.E.).

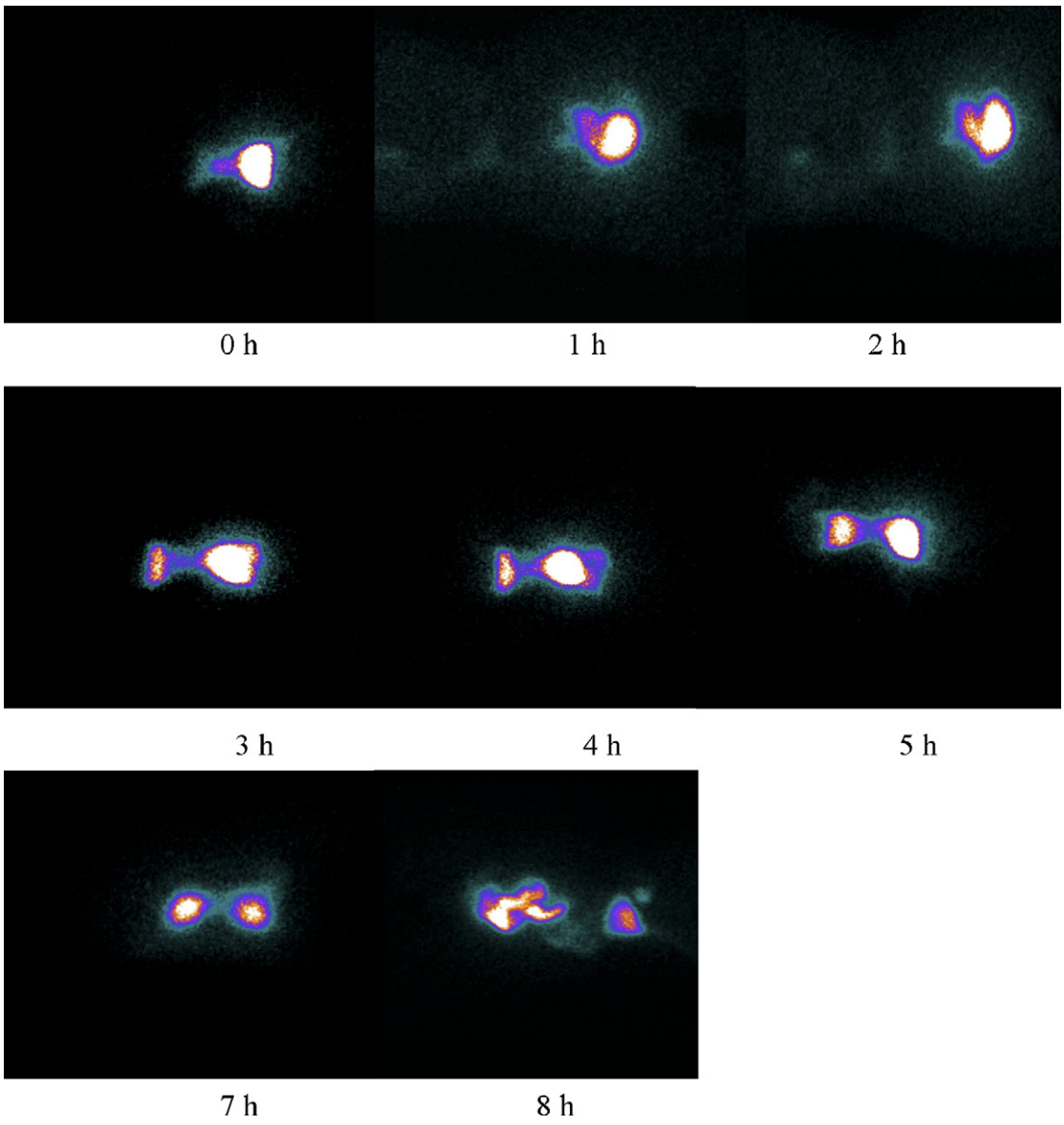

Fig. 5. Gamma scintigraphic images of ion-exchange fiber in fasted volunteer.

since about 20% fibers for the fasted volunteer were still remaining in the stomach at 8 h.

3.5. Bioavailability studies with man

The adsorption of riboflavin was evaluated from urinary excretion data (Fig. 6). The cumulative unchanged drug excreted (D_u) to the collection time was shown in Fig. 7. Statistical comparison of $Recovery_{0-24\,h}$ parameters indicated a significant difference ($P < 0.05$) between results obtained from the riboflavin fiber and the riboflavin solution, i.e. $Recovery_{0-24\,h}$ for the riboflavin fibers was 12.82 ± 2.21 mg, whereas that for the riboflavin solution was 6.48 ± 0.54 mg. Statistical comparison of T_{max} parameters also indicated a significant difference ($P < 0.05$) between results obtained from the riboflavin fiber and the riboflavin solution. There was no significant difference between R_{max} or MRT. The improved bioavailability of riboflavin from the drug fiber (urinary recovery was more than twice that measured after administration of the solution) obtained in this study, suggests that the fiber could retain in the stomach. The fiber stayed in the stomach for enough time to slowly

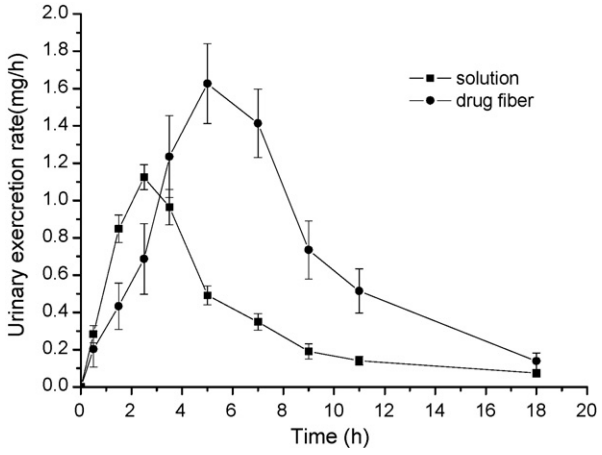

Fig. 6. Average urinary excretion rate of riboflavin for fasted volunteers after administration of the riboflavin solution or riboflavin fiber (data are mean values ($n = 6$) ±S.E.).

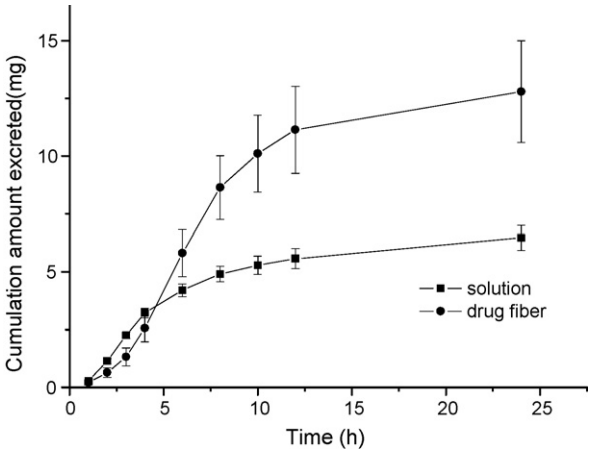

Fig. 7. Average cumulative amount of riboflavin excreted in urine for fasted volunteers after administration of the riboflavin solution or riboflavin fiber (data are mean values ($n = 6$) ±S.E.).

release its drug and consequently the released riboflavin passed gradually through the absorption window and was absorbed more efficiently.

4. Conclusions

In the present 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 on rat and man provide evidence for the validity of the hypothesis that the drug fiber provided better mucoadhesive properties *in vivo* and should therefore be of considerable interest for the development of future mucoadhesive oral drug delivery dosage forms. However, the results are preliminary and further studies under different conditions such as varying conditions of food intake and longer fasting times should be conducted to show that the drug fiber could be retained in the stomach under more challenging circumstances.

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