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Development and *in vitro/in vivo* evaluation of famotidine hydrochloride bioadhesive sustained release suspension

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Abstract: To develop a new kind of famotidine-resin microcapsule for gastric adhesion sustained release by screening out suitable excipients and designing reasonable prescriptions to improve patient drug activities to achieve the expected therapeutic effect. The famotidine drug resin was prepared using the water bath method with carbomer 934 used as coating material. Microcapsules were prepared using the emulsified solvent coating method and appropriate excipients were used to prepare famotidine sustained release suspension. Pharmacokinetics of the developed microcapsules were studied in the gastrointestinal tract of rats. The self-made sustained-release suspension of famotidine hydrochloride effectively reduced the blood concentration and prolonged the action time. The relative bioavailability of the self-made suspension of the famotidine hydrochloride to the commercially available famotidine hydrochloride was 146.44%, with an average retention time of about 5h longer, which indicated that the new suspension had acceptable adhesion properties. The findings showed that the newly developed famotidine-resin microcapsule increased the bioavailability of the drug with a significant sustained-release property.

Keywords: Famotidine, carbopol, ion exchange resin, mucoadhesive, *in vivo*, microcapsule.

INTRODUCTION

Famotidine (FAM), a third-generation histamine H_2 receptor inhibitor, can effectively inhibit gastric acid secretion. The intensity of the drug's action is higher than that of most other Tidine drugs. The duration of action is the longest in this class of drugs. The drugs are often used to treat stomach diseases caused by physiological dysfunction. However, there are some problems, such as a short half-life (around 2-3 hours) and low bioavailability (approximately 30%-40%) which necessitate multiple doses and significant fluctuations in the concentration of the drug in the bloodstream. Though several dosage forms are accessible, poor lipophilicity, low water solubility, decreased membrane permeability and other factors may lead to low oral bioavailability, which is not helpful for the elderly and children over 13 years old to consume. Therefore, it is prudent to prepare suspension with bio adhesion and slow-release effect to establish the slow-release oral administration of famotidine in the body (Qian and Xie, 2011; Donini *et al.*, 2002; Weihong *et al.*, 2021; Adel Penhasi and Albert Reuveni, 2019).

Ion exchange resin is a type of cross-linked water-insoluble high molecular weight polyelectrolyte, which can reversibly and stably exchange mobile ions of equal charge with the surrounding medium. Drugs can be loaded onto the resin through an exchange reaction to form drug resin compounds. More recently, they have been used in drug delivery systems, primarily in liquid form controlled release systems and flavor masking. Sustained-release microcapsules prepared with ion-exchange resins as drug carriers have been proven to be excellent sustained-release liquid drug delivery systems. However, there are few studies on applying of ion-exchange resin in bioadhesive forms. In this study, ion-exchange resin was applied in adhesion administration to prolong the drug's release time.

The epidermal cells of a human cavity, such as the mouth, vagina, nose and digestive tract, can produce mucus, which mainly contains glycoproteins, lipids and other substances with gelatinous and adhesive characteristics. This situation creates favorable conditions for the application of adhesive preparations. Carbomer polymers are polyacrylic acid cross-linked with polyolethers or diethylene glycol, which can be used to form highly viscous gels (Dufresne *et al.*, 2004; Zhang *et al.*, 2021). Since the 1950s, carbomer polymers have been used in a wide range of pharmaceutical applications, such as thickeners, suspensions, gel-based, bioadhesive materials and substrate materials in slow controlled-release preparations.

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Therefore, the study aimed to develop a gastric adhesion famotidine sustained release resin microcapsule, using Famotidine hydrochloride as the model drug and ion exchange resin as the critical excipients. After PEG impregnation treatment, suitable capsules were selected for emulsifying the solvent coating, and bioadhesive coated microcapsules with apparent slow-release effects were obtained. The formulation extended the residence time of drugs in the stomach and enhanced the therapeutic effect of the drugs (Bumsang Kim Nieholas, 2003). At the same time, the microcapsules were also prepared into oral liquid preparations by adding other excipients and the drug content, particle size and *in vitro* release were investigated. Finally, the gastric adhesion sustained release FAM-loaded resin microcapsules were evaluated in rats (fig. 1) (Goutham *et al.*, 2017; Guo *et al.*, 2009; Walsh *et al.*, 2014; Tan *et al.*, 2018; Han *et al.*, 2019).

MATERIALS AND METHODS

Materials

FAM was obtained from Weideli Co, Hubei, China. Cation-exchange resins Amberlite® IRP69 (sodium polystyrene sulfonate) were obtained from Rohm and Haas Company (Philadelphia, USA). Carbomer 934 was purchased from Hubei Yuanzheng Xingyuan Fine Chemical Co., LTD (China). Polyethylene Glycol 400, polyethylene Glycol 4000, petroleum ether, and liquid paraffin were purchased from Sinopath Group (China). Avicel CL 611 (Medicinal grade) was made by Eminste, sucrose was purchased from Hunan Huana Pharmaceutical Factory, propylene glycol was a product of Hunan Erkang, xanthan gum came from Jiangsu Shenhua Pharmaceutical, HFCS was purchased from Shijiazhuang Huiyuan Starch Co., Ltd, gum arabic was purchased from Aladdin Platform, methylparaben and propylparaben were products of Xi'an Jinxiang Pharmaceutical Excipients and the orange flavour was from Shandong Zhenghong Biotechnology.

Preparation of drug resin using static loading

FAM drug (500 mg) was dissolved in 100 mL of 0.1mol/L HCl and Amberlite®IRP69 resin was slowly added. The sample (5 mL) was collected at each time point using a syringe and filtered through the filtration membrane. An appropriate amount of the filtrate was diluted for UV (UV-Vis Spectrophotometer N5000S from Zibo Senyuan Electric Co.) analysis and the absorbance was measured at 266nm. The concentration was calculated as described in other studies. The reaction stopped when the values became constant. The filter paper containing the remaining solids was placed in an appropriate glass dish. The sample was wrapped in a plastic wrapper with pinholes in it. The package was put in an oven at 55℃ and dried to obtain the required product. The drug loading (Q_t) of the samples at different time points was calculated using the formula below:

$$Q_t = \frac{V(C_0 - C_t)}{W_R} \quad (1)$$

Where, C_0 (mg/mL) represented the formulated drug concentration at the initial stage of the experiment; C_t (mg/mL) represented the concentration of the drug in the sample at time t; W_R (mg) represented the mass of resin; Q_t (mg/mg) represented the drug loading capacity of resin at t; V(mL) was the volume of dissolved FAM solution.

The control variable method for carry out the single-factor temperature, drug concentration and drug-resin ratio test. Q_t (mg/mg) was also used to map t and the FAM-drug resin loading (Q_{∞}, mg/mg) and drug utilization ratio (E) were calculated. The effect of a single factor on drug loading in the static drug loading experiment was further investigated (fig. 2) and plotted using Origin 2021 to visualise the results (all used below).

Resin binding mechanism of FAM drugs

XRD(BRUKER's D8 ADVANCE X-ray diffractometer) and FTIR (ThermoFisher's IS10 Fourier Transform Infrared Spectrometer) tests were performed to ascertain the binding mechanism of FAM and ion-exchange resin Amberlite®IRP69 cationic resin, FAM API, FAM: resin (1:1) physical mixture and Famotidine-drug resin capsule(FAM-DRC) powder tablet were prepared and tested using X-ray diffraction. The applied conditions included: LynxEye semiconductor array detector, room temperature, Cu target material, scanning speed of 10°/min and angle test range (2θ) of 5°~80° (fig. 5). Simultaneously, the four samples were also prepared using the KBr laminating method and the Fourier infrared spectrum analysis was carried out in the range of 4000~500 cm^{-1} (fig. 6).

In vitro release of famotidine drug resin

The samples were put into the dissolution cups and sampled at preset time points according to the pharmacopeia release method (RCZ-8 Drug Dissolution Meter produced by Shanghai Huanghai Company). The drug content of the samples was determined at different time points to investigate the effects of different rotation speeds (50rpm, 75rpm, 100rpm), media volumes(250 mL, 500 mL, 900 mL), temperatures(25.0ºC ± 0.5ºC, 37.0ºC ± 0.5ºC, 45.0ºC ± 0.5ºC), ion types(H^+, Na^+, K^+) and ion strengths(0.1mol /L, 0.15mol /L, 0.2mol /L, 0.5mol /L) on the *in vitro* release of FAM-DRC (fig. 7).

Resin coating of famotidine bioadhesive drug

Compared with the unmodified drug, the drug-carrying resin has a slow release effect, but the use of ion exchange resin alone cannot achieve the ideal drug release effect. Therefore, we decided to improve the stability and slow-release effect of the resin composite further by adding other suitable slow-release adhesive materials in the drug-loaded resin technology. In this study, we chose hydroxypropyl methyl cellulose as the primary coating material (Siddiqui *et al.*, 2013; Yuan *et al.*, 2014; Aman *et al.*, 2014; Chenchula *et al.*, 2021; Rajesh A M and Popat

K M, 2017). The carbomer was also used as the biological adhesive material to prepare the FAM sustained-release microcapsules by selecting the best preparation methods from the different prescriptions.

Impregnation of FAM resin

The drug-resin was impregnated to prevent the resin swelling in the aqueous solution, which is likely to cause the rupture of the coating film with the sudden release of the drug. PEG4000 was therefore selected as the impregnating agent based on previous data from our research group and other relevant papers. The impregnating agent was added to pure water in a ratio of 1:4 and then heated to 60℃ to dissolve completely. A loading resin that weighed half as much as the impregnating agent was added and impregnated for 45 minutes. The sample was allowed to stand at room temperature to settle down, filtered and dried to obtain the impregnated resin.

Optimization of drug resin coating

The effects of capsule material type (hydroxypropyl methylcellulose and carbomer), ratio of drug resin to capsule material (5:1, 10:1, 15:1) and amount of plasticiser(10%, 20%, 30%PEG 400) on *in vitro* release of coated resin were investigated. Carbomer was selected for the coating of the microcapsules because of its good adhesion properties, while the emulsified solvent coating method was adopted in the experiment. Ethanol was stirred and added to hydroxypropyl methyl cellulose and carbomer under agitation to form the slow-sustained release capsule medium. PEG400 was also added to the capsules. FAM-impregnated resin was added to the dispersion phase in the final step. Span 80 was added to the liquid paraffin and stirred continuously. Under stirring conditions, the dispersed phase was added to the continuous phase at a constant temperature of 55℃ for 4 to 5 hours. The paraffin wax on the surface of the microcapsule was rinsed with petroleum ether several times after the filtration (fig. 13).

Morphology of FAM- coated microcapsules and particle size distribution

The surface morphology of the FAM-coated resin was observed using SEM (Emission Scanning Electron Microscope Model JSM-7001F from Nihon Electronics JEOL, Inc.). The conductive adhesive was fixed on the table and an appropriate amount of dried sample powder was evenly spread on the sample table connected with an accelerated voltage of 5 kV. Gold was sprayed under vacuum conditions and the surface morphological changes were observed under SEM. Secondary electronic imaging was used to determine the final coating effect after impregnating the resin coating (fig. 4).

The coated microcapsules' particle size distribution (Mastersizer 3000 laser particle size analyser) and zeta potential (Malvern NANOZS90 Zeta Potential Analyser) were tested initially and after 1, 2, 3 and 6 months to confirm their stability.

Biological adhesion of famotidine-coated microcapsules

In vitro animal retention assessment

The stomachs of rats were first rinsed with hydrochloric acid at pH 1.2. The gastric mucosa tissue of appropriate size (about 2*3cm) was cut and fixed on a slide. FAM microcapsules (1000 mg) were sprinkled on the surface of the gastric mucosa and then put together in an airtight container saturated with sodium chloride for 30 min moisture. The microcapsules were fully hydrated to attach them to the mucosa's surface. The loading platform was set at a 45° angle with the horizontal surface and washed with a hydrochloric acid solution (pH of 1.2) for 5 min. The flow rate of the washing was controlled at 20 mL/min. The mass of the remaining FAM was weighed after leaching.

Determination of shear force

Two smooth glass pieces of the same size (about 10cm*10cm) were taken and one of them was fixed on the telescopic table while the other was connected to the tray through a small pulley. FAM-coated microcapsules (FAM-CM) (1g) evenly coated on the surface of the glass plate were wetted with 0.5 mL to 1 mL of hydrochloric acid solution (pH of 1.2). A fixed mass weight was put on the other glass plate to pressure the permeated microcapsules. The samples were maintained for a few minutes and other weights were added to the tray. Each time the weights were added, the maintenance time was appropriately increased for 3-5 min until the top piece of glass slides. Write down the weight of the weights at this point. The mass of the weight was counted as the shear force.

Determination of separation force

Two identical glass plates were taken and the stomach mucosa of appropriate size was fixed on the lower glass. Microcapsules were evenly coated with 10% uniform suspension prepared using an appropriate amount of water on the other glass plate and dried in an oven at 50℃. The FAM microcapsules were moistened onto the mucous membrane using hydrochloric acid (pH 1.2). The lower glass was connected to a plastic bag while the upper glass was covered and a proper weight was put on it and left for about 20 minutes before removing it. Then, water was injected into the plastic bag at a slow and constant speed until the two glass sheets were separated. At this point, the water quality in the plastic bag was recorded and the separation force was determined.

Preparation of sustained-release suspension of Famotidine hydrochloride

The coated microcapsules obtained using emulsifying solvent coating method met the sustained-release effect. However, since there were residual organic solvents on the surface of the coated microcapsules, they were not suitable for patients to ingest. The formulation was made into an oral suspension dosage with a better taste and is also suitable for elderly patients.

Table 1: FAM suspension prescription sheet

FAM drug-resin microcapsule	Equivalent to FAM drug of 200 mg (100 mL suspension medium)			
	A	B	C	D
Sucrose	0.4g	0.4g	1.0g	0.4g
Propylene glycol	0.5 mL	0.5mL	0.5mL	0.5mL
Tragacanth	0.4g	0.6g	1.0g	0.6g
HFCS	48mL	36mL	32mL	40mL
Arabic gum	0.010g	0.005g	0.010g	0.010g
Methyl p-hydroxybenzoate	0.025g	0.025g	0.025g	0.025g
Propyl p-hydroxybenzoate	0.025g	0.025g	0.025g	0.025g
Orange Flavor	0.03g	0.03g	0.03g	0.03g

Table 2: *In vitro* remaining ratio of FAM

No	Amount of microcapsules without carbopol	Amount of microcapsules with carbopol
1	111	825
2	96	792
3	123	801
4	108	789
5	102	816
Mean	108	804.6
SD	10.7	15.50

Table 3: *In vitro* shear stress analysis

No.	Shear stress of microcapsules without carbopol	Shear stress of microcapsules with carbopol
1	12	55
2	9	61
3	10	66
4	15	59
5	11	63
Mean	11.4	60.8
SD	2.3	4.2

Table 4: *In vitro* shear stress activity

No	Detachment force of microcapsules without Carbopol (g/cm^2)	Detachment force of microcapsules with Carbopol (g/cm^2)
1	2.6	31.2
2	3.2	28.8
3	4.4	30.3
4	5.0	26.1
5	3.8	27.6
Mean	3.8	28.8
SD	0.9	2.0

Table 5: The stability test of FAM sustained-release suspension (n=3)

T (month)	$D_v(90)$	C (%)	L (%)	*RI*	*F*	Character
0	108.3	99.1	0.22	good	0.99	Homogeneous yellow liquid
1	108.0	98.5	0.28	good	0.97	Homogeneous yellow liquid
2	108.3	98.2	0.34	good	0.98	Homogeneous yellow liquid
3	108.3	97.6	0.38	good	0.97	Homogeneous yellow liquid
6	108.0	97.5	0.51	good	0.96	Homogeneous yellow liquid

Table 6: Pharmacokinetic parameters of homemade FAM bioadhesion sustained-release suspension

Parameter	Ordinary tablet	Sustained-released suspension
$t_{1/2}$ (h)	2.84	4.11
T_{max} (h)	4.00	6.00
C_{max} (ng/mL)	14018.00	9754.00
MRT_{0-24}(h)	5.93	10.37
AUC_{0-24} (ng·h/mL)	95085.75	139245.00

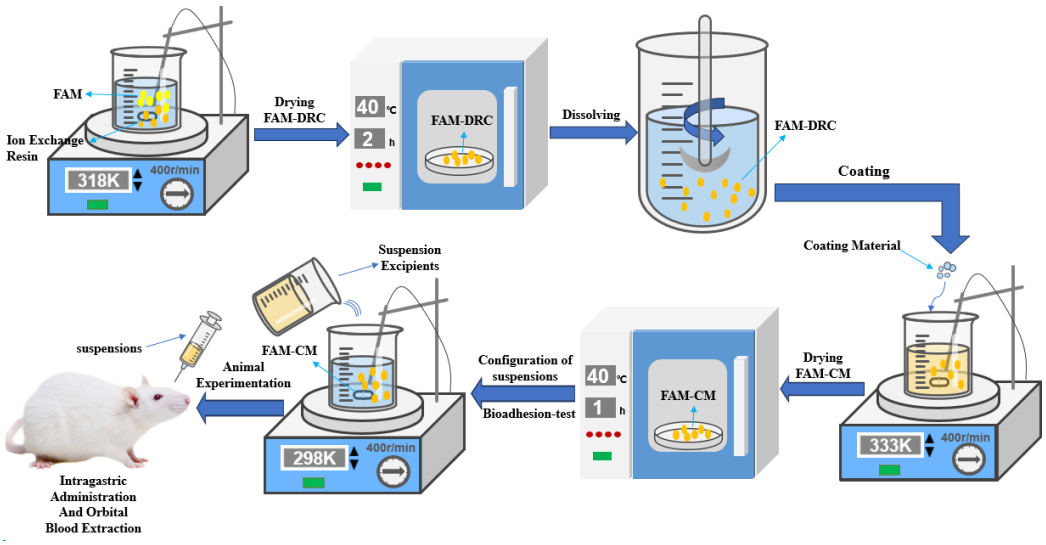

Fig. 1: Experimental process flow chart.

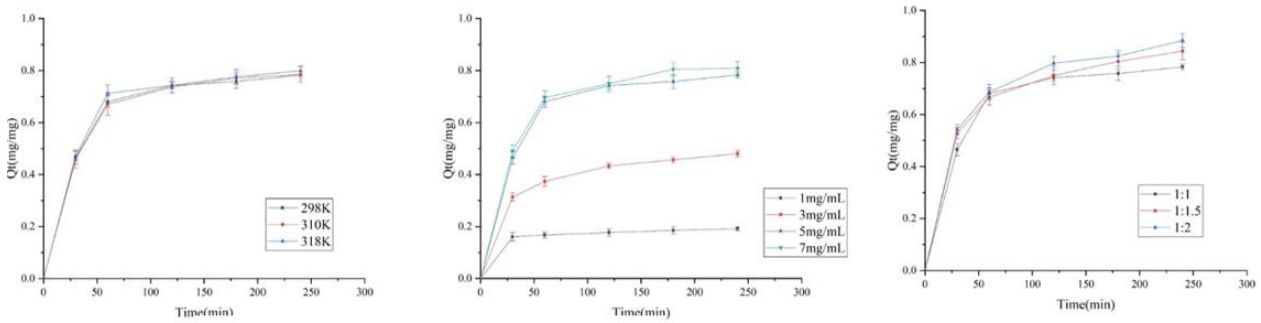

Fig. 2: Effect of single factor on drug loading in static loading experiment (n=3).

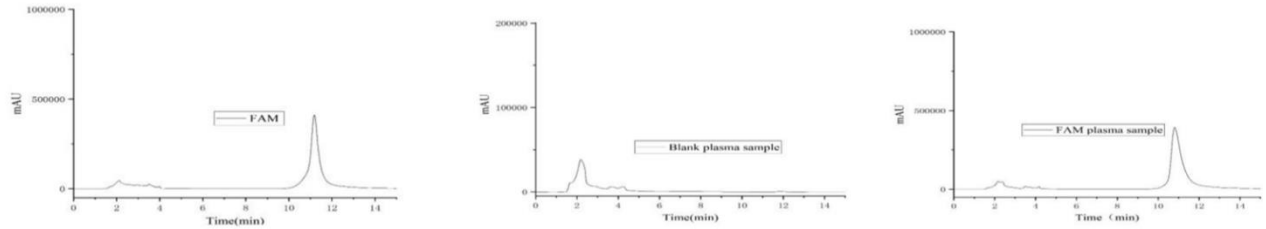

Fig. 3: Chromatograms of three different samples: s FAM solution, blank plasma and FAM plus plasma sample.

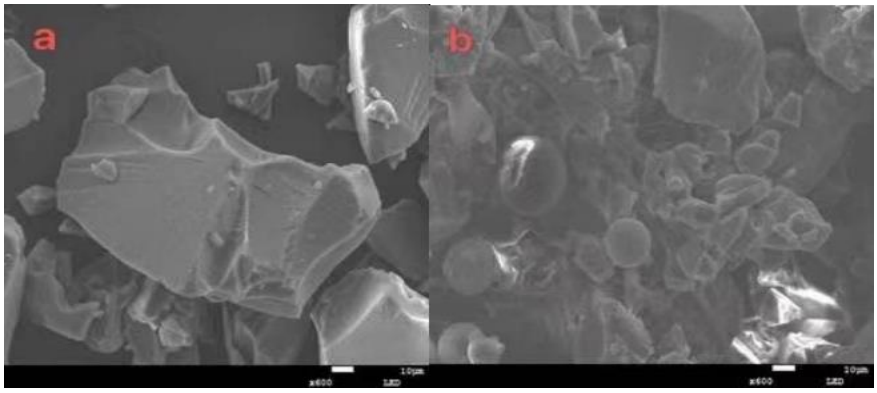

Fig. 4: The SEM images of FAM -drug loaded resin (a) and coating resin (b).

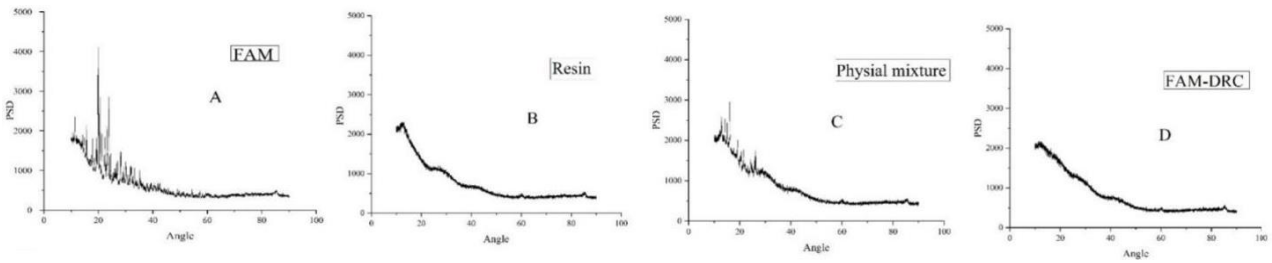

Fig. 5: The XRD patterns of FAM (A), Resin (B), physical mixture (C) and FAM -DRC (D)

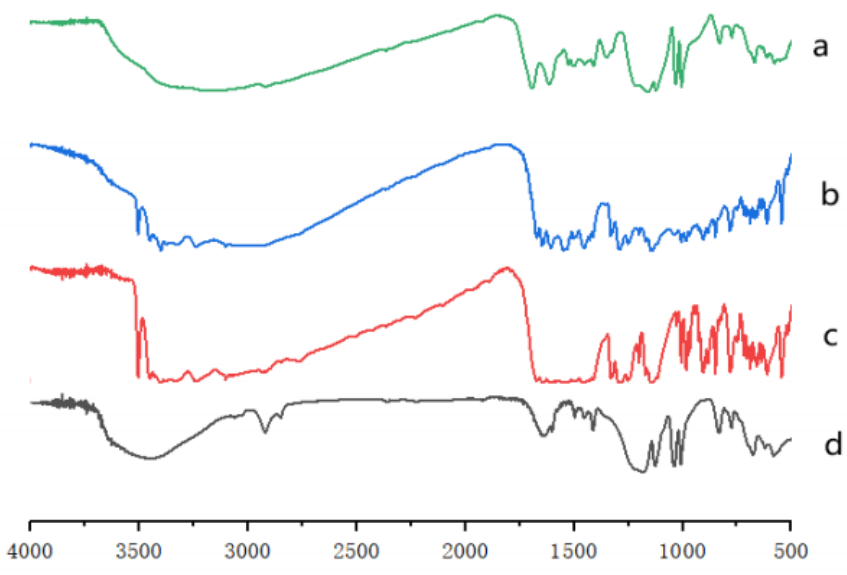

Fig. 6: The FTIR spectral of Resin(a), FAM (b), FAM-resin physical mixture (c) and FAM-DRC (d)

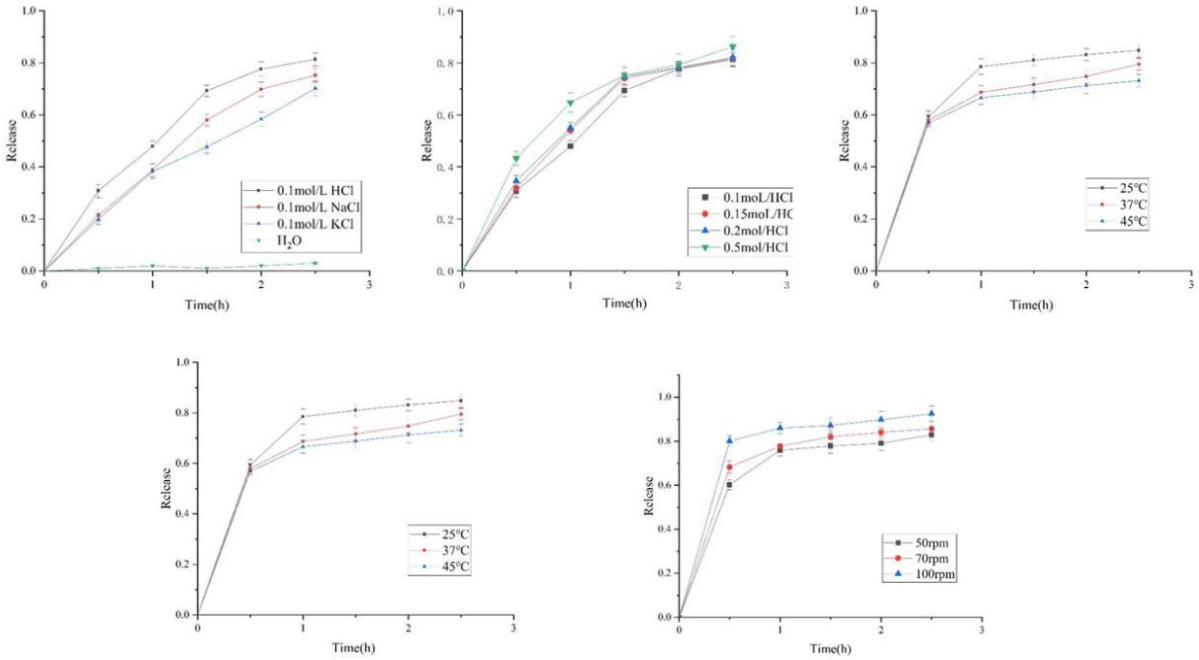

Fig. 7: Effect of different factors on release behavior of famotidine resin (n=3)

We weighed the coating resin equivalent to 20mg of the FAM drug to achieve this. We combined it with the requisite sweetener (sucrose and high fructose corn syrup(HFCS)), wetting agent (propylene glycol), suspension agent(tragacanth and acacia gum), flavor modifier(orange flavor) and preservative(Propyl phydroxybenzoate and Methyl phydroxybenzoate). Subsequently, an appropriate quantity of water was added and the mixture was thoroughly stirred to obtain the desired suspension.

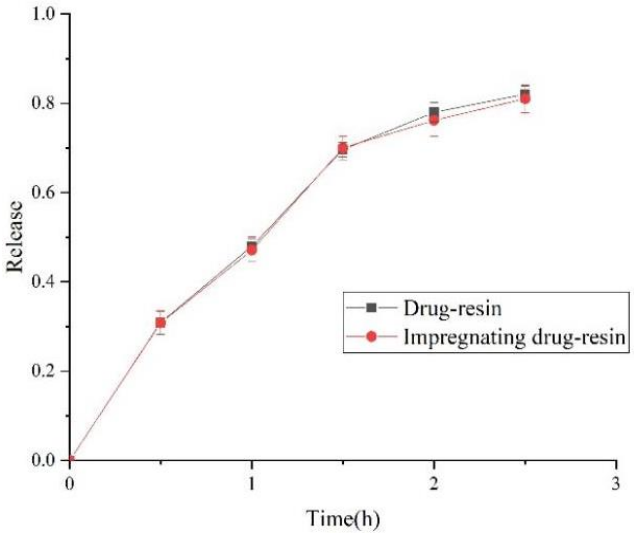

Fig. 8: Comparison of resin dissolution before and after impregnation (n=3).

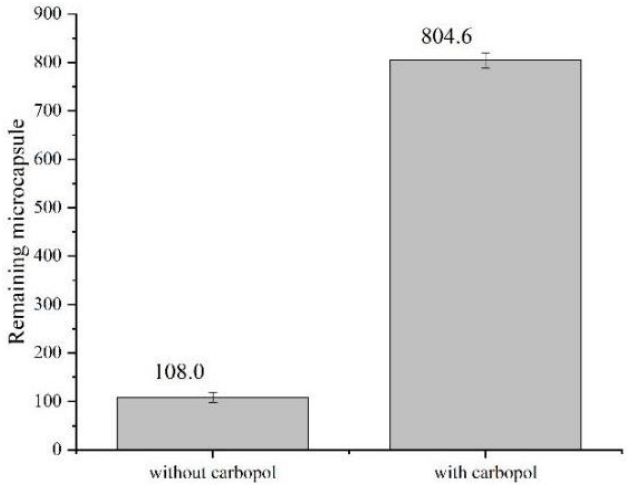

Fig. 9: *In vitro* remaining ratio of FAM (n=5).

Preparation process was also performed following ourprevious studies and described below. FAM-resin microcapsules was dispersed into propylene glycol by vigorous stirring and then added intosolution of HFCS, sucrose, tragacanth, acacia gum and orange flavor (volume less than 100 mL) drop-wise with continuous stirring. After adding Propyl phydroxybenzoate and Methyl phydroxybenzoate, the final suspension, named as FAM suspension, was diluted with deionized water to 100mL. We then designed four prescriptions for screening (table 1).

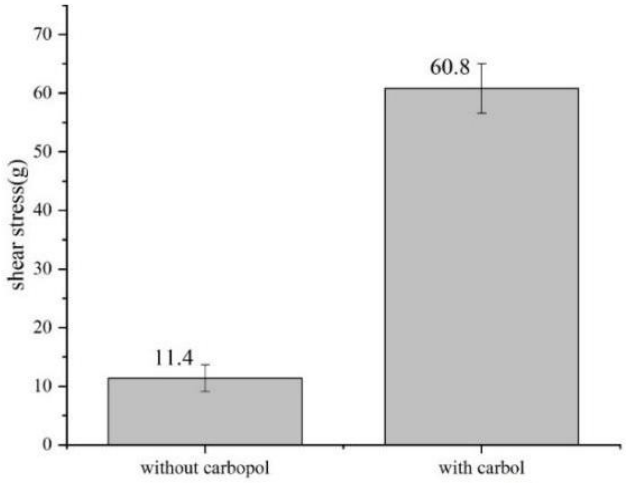

Fig. 10: *In vitro* shear stress activity (n=5)

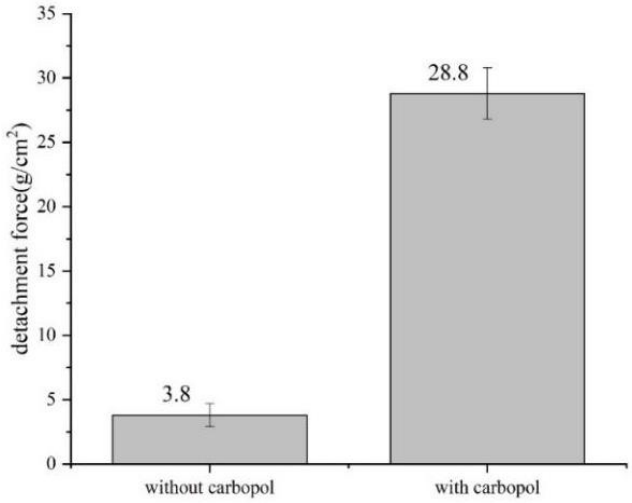

Fig. 11: *In vitro* detachment force activity (n=5)

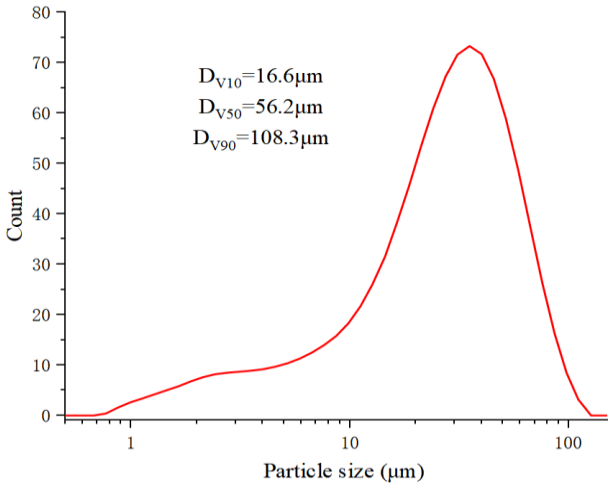

Fig. 12: Particle size distribution of FAM-CM

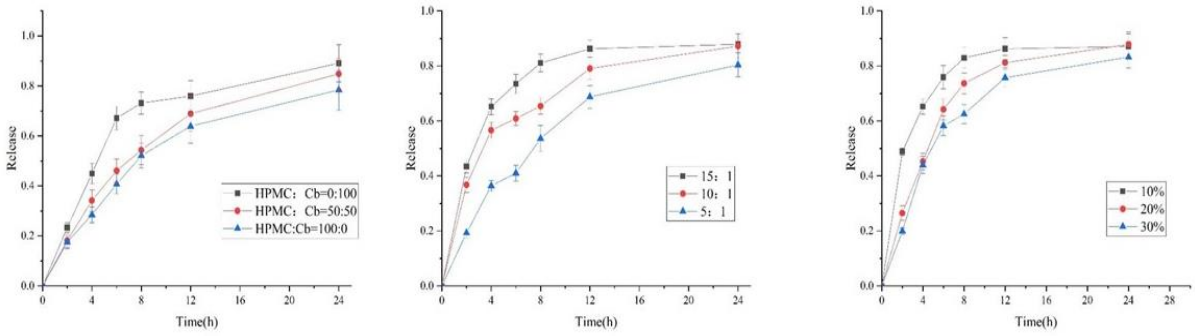

Fig. 13: Effects of different factors on the *in vitro* release behavior of drug resin complexes

The final suspension agent was prepared based on the screened materials and appropriate ratio, with other auxiliary materials remaining unchanged. According to the requirements of Chinese Pharmacopoeia 2020, the sedimentation volume ratio, redispersibility and drug leakage of the suspension were determined. The samples were placed in a stability chamber with the temperature set at 40℃±2℃ and the relative humidity set at 75%±5%. The caps of the brown plastic bottles containing the samples were unscrewed and stored. Samples were taken at 1, 2, 3 and 6 months after placement to be tested and evaluated for various indicators and stability tests were conducted (table 6).

Pharmacokinetics of sustained release suspension

SD rats were used as model animals for the *in vivo* studies. HPLC (Shimadzu LC-20AT Liquid Chromatograph and Shimadzu SPD-M20A Manual Sampler) method was used to determine the content of the drugs in the rats. The difference between the commercially available FAM tablets and the homemade adhesive sustained-release suspension was compared using pharmacokinetic parameters such as drug time curves. The *in vivo* data of the rats were processed based on the non-atrioventricular model with the help of DAS pharmacokinetics software. Commercially available FAM tablets were used as reference preparation, while the homemade FAM bioadhesive sustained-release suspension was used as test preparation to investigate the bioavailability of the drug.

Animals and analytical method

Twelve Specific Pathogen Free (SPF) male SD rats weighing 180~220 g were obtained from the Laboratory Animal Center of Jiangsu University (Qualification certificate number NO.202215334).

In vivo experiments were performed using HPLC on the Diamonsil C18 (4.6mm×250 mm, 5μm) column. The mobile phase comprised 80% 0.05% triethylamine solution and 13% acetonitrile mixture. The detection wavelength was 266 nm with a liquid flow rate of 1.0 mL/min, a sample size of 20μL and a column temperature of 27℃.

Preparation of FAM standard solution: FAM (1mg) was added to a small amount of methanol in a 100 ml volumetric bottle to form a mixture. The mixing agent was rinsed using ultra-pure water and the solution was added to the mixture to dissolve the FAM completely. Methanol was used to adjust the volume to obtain a 0.01 mg/mL concentration.

Preparation of FAM blank plasma: The orbital blood of the rats stored at -20℃ was removed from the refrigerator and allowed to stand at room temperature. Some amount of the blood sample (0.5 mL) was taken when it turned into liquid. The transparent supernatant was collected into a 1.5 mL EP tube using a pipette gun after 15 min vortex at 12000 r/mi. Perchloric acid solution (300μL) was added to the supernatant. The two substances then combine and precipitate. The obtained supernatant was centrifuged at 12000 r/min for 20 min and used as a blank reserve.

Preparation of FAM plasma samples: Blood was collected from the untreated mouse orbit and centrifuged. An appropriate amount of FAM solution was added to the supernatant and thoroughly mixed. Perchloric acid solution (200μL) was added to the mixture and swirled for 1min. The sample was centrifuged at 10000 r/min for 15 min to obtain the FAM plasma samples for use.

The chromatograms of the three samples were as follows (fig. 3):

Pharmacokinetic study in rats

This study compares the pharmacokinetics of FAM suspensions and commercially available FAM preparations. Twelve male SD rats were randomly divided into groups labeled Group 1 and Group 2. Group 1 was administered with commercially available regular FAM tablets, while Group 2 was administered with homemade FAM bioadhesive sustained-release suspension. All the rats were administered via intragastric administration according to the dose. Blood was collected in the orbital eye area of the rats with capillaries within a certain period after administration. Perchloric acid is added to the extracted plasma sample to precipitate impurities such as protein, vortex and centrifuge. The supernatant was filtered by a membrane and the drug content was

determined by HPLC, and pharmacokinetic data were analysed using DAS 2.0.

STATISTICAL ANALYSIS

Data were obtained at least in triplicate and expressed as mean + standard deviation (SD). Statistical differences were determined by student's two-tailed t test. Differences are considered statistically significant at $p < 0.05$.

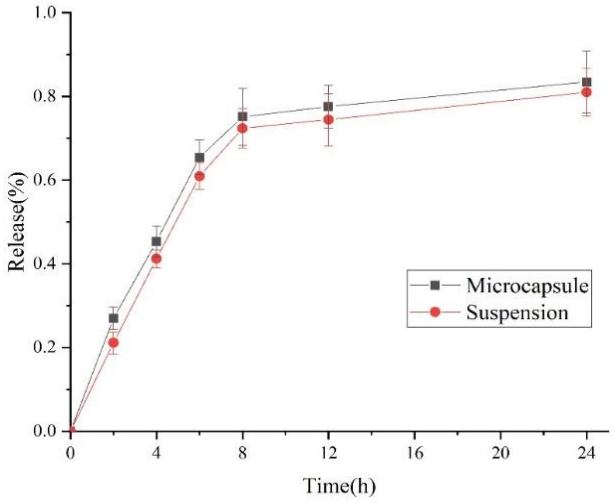

Fig. 14: *In vitro* release profile of coated microcapsules and suspension (n=3)

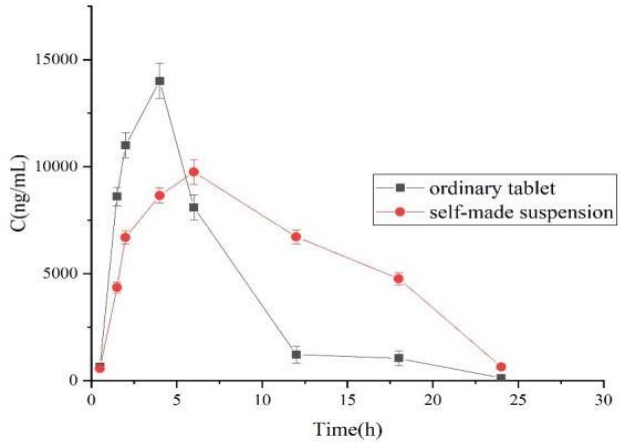

Fig. 15: FAM blood concentration time curve.

RESULTS

Characterization of drug-resin complexes

SEM

The morphology of the coating resin was smoother and more rounded than the drug-carrying resins (fig. 4). The surface had a noticeable coating (fig. 4b) and the coating film was continuous, dense and complete on coating resin. The surface of the resin microcapsule after coating was smoother than the drug resin before coating.

XRD

Fig. 5 demonstrated the X-ray spectrum of RH, Amberlite® IRP69, physical mixture of FAM and ion-exchange resin and FAM drug resin complexes.

FTIR

The FTIR spectrum of RH (b), Amberlite® IRP69(a), physical mixture of FAM and ion-exchange resin(c) and FAM drug resin complexes(d) was shown in fig. 6.

In vitro release of Famotidine-loaded resin

The optimal in vitro release factors were obtained from the comparison in fig. 7.

The FAM-loaded resin had similar release behavior before and after dipping with the impregnated drug-loaded resin (fig. 8). The results indicated that the dipping was only a preparation procedure before coating, which was a guarantee against the sudden release of drugs and therefore, did not interfere with other properties.

Optimization of famotidine bioadhesive resin coating

The coated resin had a good slow-release effect and the microcapsules with gastric adhesion function generally had a time-lag effect caused by adding hydroxypropyl methylcellulose and carbomer to the coating material. Hydroxypropyl methylcellulose was used as a coating material to slow the release of the drug, while carbomer was used as a binding material to wrap the coating surface. The formulation formed a gel that adhered firmly to the coating, thus further hindering the release of the drug when it interacts with water. We usually evaluate the properties of bioadhesion using several *in vitro* and *in vivo* experimental methods. This study used the *in vitro* animal retention, shear and separation forces tests.

The amount of FAM that remained on the mucosa about the coated microcapsules with carbomer was about 8 times that of the coated microcapsules without carbomer (fig. 9; table 2).

More weights were added to separate the two glass plates when the glass plate was coated with the microcapsule with added carbomer (fig. 10, table 3).

The glass sheet with microcapsules plus carbomer for the mucous membrane needed more water in the plastic bag to separate than the microcapsules without carbomer (fig. 11, table 4).

The experimental data for optimizing the coating parameters are shown in fig. 13.

Screening and evaluation of suspension prescriptions

Four prescriptions were discussed and the final prescription of the FAM suspension was determined as prescription B by prescription screening (table 1).

The release and dissolution curves of coated microcapsules and sustained release suspension were similar in vitro (fig. 14).

Under the set experimental conditions, the leaked amount of the sample was 0.51% after standing for 6 months, which accounted for a small proportion (table 5).

Pharmacokinetics

The blood concentrations of homemade sustained-release suspension and FAM ordinary tablets were measured, respectively and the blood collection time was plotted in horizontal coordinate (fig. 15).

DISCUSSION

Preparation of the drug resin complexes

The final preparation process was selected: FAM (500 mg) was added to 100 mL of 0.1 mol/L hydrochloric acid. Amberlite® IRP69 of the same weight was also added to the sample after the drug was completely dissolved. The reaction was thoroughly stirred at room temperature for 4 hours. FAM-DRC's final drug loading (Q_∞) was 0.787 mg/mg with a drug utilization rate (E) of 78.87%.

Characterization of drug-resin complexes

XRD

The findings showed that the drug had crystallinity and from the microstructure perspective, the crystal morphology changed after the formation of the drug-resin complex. The complex was not a simple physical change but a chemical change.

FTIR

Famotidine had a guanidine peak at 3505-3237cm^{-1}, while drug-resin complex had no characteristic peak at 3505-3237cm^{-1}. Benzene ring peaks were found at 3000~ 3100cm^{-1} between the resin and the drug-resin complex, which further confirmed the chemical ion exchange binding between the drug and resin.

In vitro release of famotidine-loaded resin

Considering all the factors and better simulating the in vivo environment (Zhao *et al*., 2015), the optimal in vitro release conditions were selected: 900 mL of 0.1mol /L HCl, 50 rpm and 37.0 ℃±0.5 ℃. Thus, FAM was released almost entirely under these conditions (fig. 7).

Optimization of famotidine bioadhesive resin coating

The results indicated that the coated microcapsules had increased adhesion performance on the gastric mucosa thus, resulting in longer residence time in the stomach after adding carbomer.

In vitro shear stress activity shows that, the more the applied external forces, the greater the shear force and the stronger the adhesion performance.

In vitro detachment force activity shows that, the external force required to separate the two pieces of glass was greater; thus, the required separation force was greater with good adhesion performance.

The effect of different encapsulation methods on the in vitro release of microcapsules were investigated and finally, the emulsified solvent coating method was selected. Ethanol was continuously extracted from the dispersed phase with liquid paraffin as a continuous phase. The content of ethanol then became very small. The products were filtered and dried to form stable microcapsules. Carbomer 934 was also chosen as the biological bonding material because it had the most robust bonding properties compared to other materials. In the gastric environment, carbomers can interact with glycoproteins in the stomach to form hydrogen bonds, which was the main guarantee of adhesion (El-Zahaby SA et al, 2014; Fu J et al, 2002; Hongfei LIU et al, 2018). At the same time, the mucosal surface and moist conditions of the gastric fold created favorable conditions for drug adhesion and longer retention. The slow-release properties of carbomer were negatively correlated with the adhesion properties. In order to achieve the desired effect, the ratio of HPMC to Cb was set at 1:1. The quality of the microcapsule itself also has a significant influence on the release behavior. Considering factors such as material consumption and release curve, the ratio of drug resin to sustained-release capsule material was set at 10:1 with a plasticizer concentration of 30% by studying isolated animal's retention, shear force, separation properties. It was proven that carbomer was a good binding material with good bonding properties.

After our tests, the D_V (10) of FAM-CM was 16.6μm, the D_V (50) was 56.2μm and the D_V (90) was 108.3μm, which meets the requirement of less than 200μm for suspension particles. The zeta potential of FAM-CM was -33.23 mV (fig. 12). The stability of microcapsules is tested alongside the stability of the suspension, the microcapsules were found to be well stabilized (table 5).

Screening and evaluation of suspension prescriptions

Experimental results shown that, the preparation of the suspension does not affect the release of the coating resin itself.

The stability test shown that, the quality requirements were all in line with the quality requirements of pharmacopoeia, which indicated that the FAM sustained-release suspension had good stability (Tong *et al*., 2010; Hongfei *et al.*, 2018).

Pharmacokinetics

The C_{max} value of self-made sustained-release suspension was about half of the commercially available preparations (fig. 15, table 6). The peak time of drug concentration of

the homemade preparation was delayed with more minor fluctuation in blood drug concentration and significantly increased area under the curve compared with the commercially available preparations, the results showed that the homemade preparations had a pronounced sustained-release effect.

The homemade FAM bioadhesion sustained-release suspension took longer to reach the peak concentration, about one and a half times that of the commercial preparation. Therefore, the homemade FAM sustained-release suspension had a noticeable sustained-release effect compared to the ordinary tablets. The area under the curve and MRT_{0-24} of the self-made sustained-release agent were also significantly higher than the commercially available FAM, which supported the excellent bio-adhesion performance of the new formulation (Jorapur *et al.,* 2018).

The relative bioavailability of homemade sustained-release suspension to ordinary tablets was 146.44%; hence, the bioavailability of homemade bioadhesive sustained-release suspension increased by about 50% compared with the ones sold on the market.

FAM is mainly absorbed in the upper middle part of the small intestine. Ordinary tablets break up into powder when they enter the body, so they pass quickly through the upper and middle parts of the small intestine to the lower part of the small intestine, which is not so well absorbed. In suspension, the presence of bioadhesion causes it to adhere to the upper middle part of the small intestine, increasing the absorption capacity of the drug. The AUC of the homemade suspension was greater than that of the commercially available formulation, indicating that the homemade suspension is superior to the commercially available formulation. All these results showed that FAM sustained release suspension had great potential for more comprehensive clinical applications.

CONCLUSION

This study successfully prepared a sustained-release FAM-DRC suspension with biological adhesion using its *in vitro/in vivo* slow-release ability confirmed in various active substances. FAM was fixed on the surface of cation exchange resin through ion exchange and the drug resin microcapsules were prepared using HPMC and carbomer. The drug resin microcapsules' release rate was slowed by optimizing the coating parameters. The suspension prepared by the best drug resin microcapsules obtained by screening had high drug content within 6 months. The biological adhesion of the drug resin microcapsules had good performance, which achieved the purpose of slow release.

Finally, FAM tablets and slow-release suspension were administered by gavage to SD rats as a model animal and in groups, and the drug time profiles and related pharmacokinetic parameters were analysed.The $t_{1/2}$ of self-made suspension was one hour later than that of commercially available suspension. The T_{max} was 4h and 6h, respectively. The AUC_{0-24} of commercially available FAM tablets was 95085.75ng·h/mL and the AUC_{0-24} of homemade FAM sustained-release suspension was 139245.00ng·h/mL. The relative bioavailability of the two was calculated to be 146.44%.Overall, the self-made drug-time curve is smoother, indicating that the blood drug concentration does not fluctuate significantly and shows a pronounced and good sustained release effect. Moreover, the MRT_{0-24} of the homemade FAM suspension was significantly higher than that of the commercial one, indicating that the expected adhesion effect was achieved. The findings showed that FAM sustained-release suspension provided a good and novel drug prescription for certain patients with gastroesophageal reflux disease, including children and the elderly.

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