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Original Research Article

Development, optimization, and *in vitro/in vivo* evaluation of ranitidine hydrochloride- resinate sustained-release suspension

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Abstract

Purpose: *To prepare ranitidine hydrochloride (RH) sustained-release suspension aimed at improving its safety, effectiveness and convenience of administration.*
Methods: *The RH resinate suspension was prepared using bath method, with a cation- exchange resin as carrier. To obtain an ideal sustained release effect, RH resinates were coated with Eudragit®RS100 using the surface coating method, followed by optimization through a single-factor experiment and response surface analysis. The optimized RH suspension was characterized using accelerated stability test. Moreover, it was pharmacokinetically evaluated in vivo.*
Results: *The optimized RH resin microcapsules showed relative mean deviation between the predicted and measured release values that was < 10 %, ($p < 0.05$) and demonstrated good reproducibility. Accelerated stability test results showed that the optimized RH suspension exhibited good stability over a period of 6 months ($F > 0.9$; drug content: 97 – 100 %, drug release: $f_2 > 50$; drug leakage < 0.5 %), with good redispersibility. Results from pharmacokinetics showed that values of T_{max} for RH sustained-release suspension and RH common tablet were 4.00 and 2.5 h, respectively ($p < 0.05$), while the corresponding C_{max} values were 2545.78 and 3245.97 ng/mL, respectively ($p < 0.05$). Results of analysis of AUC_{0-24} showed that they were equivalent in terms of AUC_{0-24} ($p < 0.05$) and bioavailability of 101.05%.*
Conclusion: *The optimized ranitidine hydrochloride (RH) sustained-release suspension has been successfully prepared using ion-exchange resin as a carrier and Eudragit® RS100 as a coating material.*

Keywords: *Ion exchange resins, Ranitidine hydrochloride (RH), Surface coating method, Sustained-release suspension, Pharmacokinetics, Bioavailability*

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INTRODUCTION

Ranitidine hydrochloride (RH) is a second generation high-performance H_2-receptor antagonist developed after cimetidine. It is widely used for treating gastric and duodenal ulcers, reflux esophagitis, and other digestive system diseases e.g., high gastric acid secretion [1]. It

was listed in 1981 by Glaxo, UK, after which it became one of the top ten best-selling drugs in the world, as an effective drug for the treatment of peptic ulcer. However, the solid oral dosage forms such as tablets and capsules are the most common RH dosage forms which are very difficult for the elderly and children to ingest. In addition, due to its biological half-life of 2 - 3 h, there is need for frequent administration of the drug for it to be effective. Moreover, the drug does not maintain a stable plasma level of ranitidine, and it does not produce sustained release effect *in vivo* [2]. Recently, studies have shown that RH is slightly bitter, astringent and smelly, leading to poor compliance by patients [3]. Therefore, it is imperative to develop a dosage form that reduces the number of daily doses of ranitidine and also maintains a sustained-release effect for stable plasma levels *in vivo*.

Conventional oral liquid preparations such as syrups and suspensions ensure prompt drug release. However, they usually fail to maintain drug concentrations within the therapeutically effective range for the required period. Therefore, to a certain extent, the emergence of the oral controlled drug delivery system is aimed at overcoming the aforementioned problems [4]. Sustained-release suspension mixed with coated ion exchange resin produces the desired release profile over a long period of time, maintains the stability of the drug, and even overcomes the unpleasant taste of the drug [5]. Ion-exchange resin (IER) [6] is an organic polymer with a three-dimensional network structure that adsorbs ionized substances, and they are particularly useful as drug carriers for extended-release liquid formulations. They exchange with ionic drugs which they attract through electrostatic action [7]. Thus, the drug permeates the IER skeleton, resulting in masking of its bad odor, thereby improving patient compliance [8].

Surface coating based on drug resin complexes, is also used for coating particles and pellets to obtain microcapsules with sustained-release effects [9]. Unlike the emulsion– solvent evaporation method [10], the particle size of the microcapsules prepared using the surface coating method is relatively small, and it is also suitable for subsequent preparations, in addition to having low residual organic solvent. The process of surface coating is simple, when compared with fluidized bed coating, and the equipment involved is also simple and cheap. In addition, surface coating has the advantages of good process reproducibility and easy industrialization.

In this study, RH and ion exchange resin were combined into RH resin using ion exchange reaction. The RH resin microcapsules were prepared by coating the coating material (Eudragit® RS100) on the capsule core (RH resin). The relevant coating parameters were optimized to obtain satisfactory sustained-release effect. Then, the RH-coated microcapsules and blank matrix were evenly mixed to prepare RH sustained-release suspension. Subsequently, the pharmacokinetics of the RH sustained-release suspensions were evaluated in rats.

EXPERIMENTAL

Materials

Suzhou Hongsen Pharmaceutical Co. Ltd. China. Supplied the ranitidine hydrochloride. Rohm and Haas Company, USA. Supplied Amberlite® IRP69. Eudragit® RS100 and Eudragit® RL100 were products of Rohm Pharma (Germany). The use of all other reagents, which were of analytical quality, was done without additional purification.

Animals

Mature rats weighing 180 to 220 g were purchased from Jiangsu University Animal Center. All animal studies were carried out in strict accordance with the standard protocol approved by Jiangsu University Animal Center, (approval no. UJS-IACUC-202004101) and in compliance with the Guide for the Care and Use of Laboratory Animals [11].

Preparation and characterization of drug resin complexes

The RH resin complex was prepared using the bath method [12]. The cation-exchange resin (Amberlite® IRP69. 500 mg) was placed in a beaker containing 100 mL of 5 mg/mL RH solution. Then, the mixture was stirred at room temperature until the ion exchange between the drug and the resin in the water was balanced. Thereafter, the RH resin complex was filtered and the residual drugs on the surface of the complex were washed with purified water, followed by overnight drying at 55 ^{o}C. The dried RH resin complex was filtered through an 80-mesh screen, prior to use in subsequent experiments.

The drug concentration was measured at a wavelength of 314 nm using UV-Spector S600 spectrophotometer (Analytik Jena AG, Germany) so as to determine the drug loading capacity.

The drug resins were characterized using SEM, x-ray diffraction (BRUKER, Germany), differential scanning calorimetry (DSC) (NTZCH, Germany), and infrared spectroscopy (IR) (AVATAR370 DTGS Japan). These techniques were applied to investigate the mechanism of reaction between RH and Amberlite® IRP69.

Treatment of drug resin complexes with PEG 4000

Since Amberlite® IRP69 is a gel type resin, when the dried drug resin is exposed to air or water for a long time, the functional group of the resin becomes strongly hydrated and swells, implying that direct coating of the drug resin complex causes the coating layer to rise and break [13]. Therefore, before coating the drug resin, there is need to treat it with an anti-swelling impregnating agent so that the prepared coated microcapsules are intact for stable drug release. The impregnant used in this study was PEG 4000. An aqueous solution of PEG 4000 (15 % w/v), an anti-swelling impregnating agent, was prepared and maintained at a temperature of 40 ºC to enhance its solubility. Then, the RH resin complex was added, and the mixture was stirred for 1 h. The final product was suction-filtered and dried.

Microencapsulation of pretreated RH resinate and optimization of parameters

Preparation of RH resin microcapsules

The RH resin microcapsules were prepared using surface coating method. Selection of Eudragit® RS100 and Eudragit® RL100 as coating materials. Coating solutions were prepared by dissolving the Eudragit® RS100 and RL100 in ethanol. An appropriate amount of RH resin complex was added to the coating solution and stirred at a suitable temperature for 4 h. Thereafter, the product was washed with distilled water, filtered, and dried at 50 ºC. The sample was then passed through an 80-mesh drug screen, prior to use in further experiments.

Single-factor investigation

Relevant coating parameters such as type and amount of coating material, drug loading, coating temperature, and volume of reaction medium were optimized since they have potential impacts on sustained drug release profiles.

The optimization of preparation of RH resin microcapsules involved the use of different percentages of drug loading of RH resin complex (25, 35, and 42 %); different types and amounts of coating materials (*Eudragit® RL100 and Eudragit® RS100*), and various volumes of aqueous ethanol (60, 90, 120 and 200 mL). In addition, coating temperature (20, 45, and 50 ºC) was optimized.

Box-Behnken response surface experiment

Based on the outcome of the single factor test, three key factors that had significant impact on the preparation of RH resin microcapsules were used for the optimization via response surface experiments [14]. Three factors-levels Box-Behnken test design (BBD) were composed of seventeen groups of experiments were designed, as shown in Table 1.

Data analysis

Data were analyzed using the response surface regression program of the Statistical Analysis System (SAS) and Design Expert (version 8.0.6) software. The experimental data were fitted to a second-order polynomial model (Eq 1) to obtain regression coefficients.

$$L = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 \quad \ldots (1)$$

where L (predicted response) represents the *in vitro* release of RH resin microcapsules at different times. The decision coefficient(R^2) was used to represent the fitting quality of the polynomial model equation, and its statistical significance was checked using F-test.

Table 1: Independent variables and their coded and actual values used for BBD-RSM experiment

***Inde*pendent variable**	***Unit***	***Symbol***	***Coded levels***		
			-1	***0***	***1***
Percentage of coating material	% (v/v)	A	5	10	15
Reaction medium volume	mL	B	100	150	200
Temperature	℃	C	25	37.5	50

The significance of the regression coefficient was tested using t-test. Statistical significance was assumed at $p < 0.01$, $p < 0.05$ and $p < 0.1$.

Based on the "Guidelines for Research on the Release Rate of Oral Sustained-Release Preparations of Chemical Drugs" issued by the Drug Evaluation Center of the Chinese Food and Drug Administration [15], this study focused on the release at 1 (L_1), 5 (L_5), and 12 (L_{12}) hours, and used them as the response values. The optimum cumulative percent of drug release were set at 15 - 25 % (L_1), 45 - 55 % (L_5), and 80 - 90 % (L_{12}).

Verification of model

After the prescribed optimization, the RH resin microcapsules were prepared under the optimal conditions. The measured and predicted values were compared to determine the validity of the model. Then, three batches of RH resin microcapsules were prepared in line with the optimized prescription, and their technical stabilities were studied using in vitro drug release. The predicted and experimental values of these parameters were also compared to determine the validity of the model.

The release mode of RH resin microcapsules was formulated in line with the second method (paddle method) of determination of release in Chinese Pharmacopoeia (2020). Furthermore, 300 mg of RH resin microcapsules was dispersed in 0.15 mol/L KCl solution (900 mL) with mechanical stirring at 50 rpm for 24 h at 37 ℃. Samples were drawn at pre-determined time, then assayed using UV spectrophotometer. At the same time, an equivalent volume of KCl solution (0.15 mol/L) was added to the release medium. The concentration of the released drug was calculated from absorbance value measured at 314 nm in UV spectrophotometer. Finally, the percent drug release was determined as average of three measurements at each predetermined time.

Preparation of RH sustained release suspension

Referring to related literature [16,17], this study screened suspending agents, wetting agents, fillers, and preservatives using sedimentation volume ratio and re-dispersibility as indicators. Formulations of optimized suspensions were produced based on the results of the screening. The compositions of the optimized suspension are shown in Table 2.

Table *2*: Formulation of RH suspension

RH drug-resin microcapsules	100 mL of suspension medium equivalent to 300 mg of RH drug
Sucrose	0.50 g
Propylene glycol	0.40 mL
Tragacanth	0.04 g
HFCS	40 mL
EDTA	0.005 g
Propyl para-hydroxybenzoate	0.06 g
Orange flavor	0.03 g

The process used in the preparation of the RH suspension was as follows: propyl para-hydroxybenzoate was added to propylene glycol solution in a beaker, and the solution was stirred and dissolved at 45 °C. When the dissolution was complete, the solution was cooled to normal room temperature, and Tragacanth was added and stirred evenly to obtain solution 1. Prescribed amounts of sucrose, HFCS, orange flavor and EDTA were stirred and dissolved in a beaker with an appropriate amount of deionized water at room temperature to obtain solution 2. Solution 1 and solution 2 were mixed thoroughly in a 100-mL volumetric flask, followed by addition of 300 mg of RH drug resin microcapsules. Then, the volume of the flask content was brought up to 100-mL mark with deionized water. The RH suspension was successfully prepared after stirring for 30 minutes.

The stability of the RH suspension was assessed using accelerated testing. Three batches of RH suspension were placed in a stabilization chamber at 40 ± 0.2 ºC, and the corresponding sedimentation rate (*F*), redispersibility index (*RI*) and drug content were investigated at pre-determined times of 1, 2, 3 and 6 months.

***In vivo* pharmacokinetic study**

The study was performed in mature male SD rats weighing 180 - 220 g. Twelve SD rats were randomly split into two groups (A and B).

Group A was fed with RH sustained-release suspension, while group B was fed with ranitidine hydrochloride conventional tablets. The tablets were crushed and administered orally as a suspension at a dose of 27 mg/kg.

After gavage administration, 0.3 mL of blood sample was collected in heparinized centrifuge tubes from the retroorbital axis of each rat at pre-determined intervals of 0.5, 1, 1.5, 2, 2.5, 3, 4, 5,

6, 8, 10, 12, and 24 h. The blood samples were immediately centrifuged at 4000 rpm for 10 min to obtain plasma samples. Then, 50 µL of plasma sample was thoroughly vortexed with an equal volume of 7 % perchloric acid for 20 sec. The mixture was centrifuged at 20,000 rpm for 10 min to obtain a supernatant for final pharmacokinetic studies via HPLC analysis. The plasma concentrations of RH were measured using HPLC. The HPLC conditions were as follows: Unitary (CN) chromatographic column of dimensions 4.6 mm x 250 mm, 5µm; ultraviolet detector wavelength of 314 nm; injection volume of 20 µL; column temperature of 30 ^{o}C; flow rate of 1 ml/min; running time of 30 min; the mobile phase comprising a mixture of methanol (A), 1 % glacial acetic acid solution (B) and triethylamine in a volume ratio of 14:85:1.

RESULTS

Characterization of drug-resin complexes

Morphological changes in the cation exchange resin (a) and the RH resinates (b) were observed using SEM, as shown in Figure 1. The results displayed that the morphology of RH resin did not change distinctly after drug loading, and no free drug was found on the surface of RH resinates. These results succinctly revealed that the drug was successfully bound to the ion exchanger resin through ion exchange, rather than physical surface adsorption.

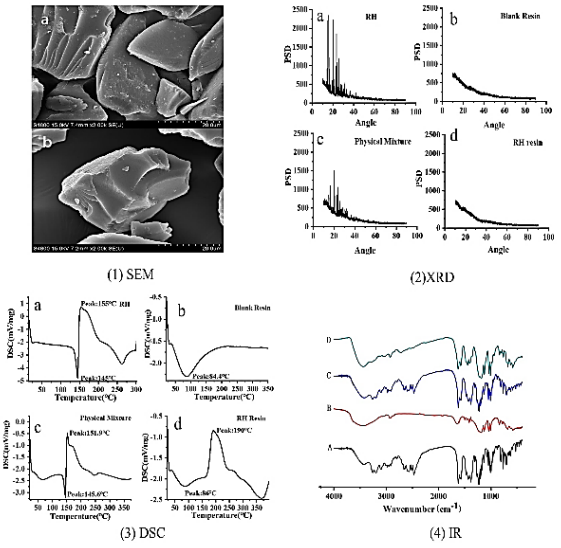


Figure 1: (1) SEM images of cation-exchange resin. (a) RH resinate, and (b) free RH. (2) XRD images of RH (a), cation-exchange resin (b), physical mixture of RH and resin (c), and RH resinates (d). (3) DSC images of RH (a), cation-exchange resin (b), physical mixture of RH and resin (c), and RH resinates (d). (4) Images of IR spectra of RH (A), cation-exchange resin (B), physical mixture of RH and resin (C), and RH resinates (D)

Similarly, the mechanism involved in loading of RH drug in ion exchange resin was evaluated with IR, DSC, and XRD. The X-ray pattern of RH drug shows several crystalline peaks (Figure 1(2)). The X-ray spectrum of Amberlite® IRP69 resin showed no crystalline peaks, which indicated the amorphous nature of Amberlite® IRP69. Based on the X-ray spectrum of the simple physical mixture of RH and Amberlite® IRP69, the crystallization peaks of the RH drug and their locations were not changed. These results showed that the physical mixture of RH drug and Amberlite® IRP69 did not result in changes in their structures. In the X-ray spectrum of RH drug-loaded resin, the RH drug crystallization peak disappeared, and the structure remained the same, just as the blank resin Amberlite® IRP69, which indicated that the RH was not simply adsorb onto the Amberlite® IRP69 but rather the ion exchange might have caused the spectrum to change.

In the DSC experiment, the endothermic peak of RH appeared at 145 °C (close to its melting point of 137-143 °C). while Amberlite® IRP69 showed an endothermic peak at 84.5 ^{o}C (Figure 1(3)). The endothermic peak at 145 ^{o}C also appeared for the physical mixture of RH drug and Amberlite® IRP69 resin. It was similar to the characteristic peak of RH, but it was clear from the DSC image of RH drug-loaded resin that the endothermic peak of RH at 145 ^{o}C disappeared, while that of the resin at 86 ℃ remained. These observations were different from the corresponding images of the simple physical mixture of RH drug and resin. These results clearly indicate that the RH drug and Amberlite® IRP69 were not simple physical mixtures, but might have undergone ion exchange, thereby resulting in spectral changes.

The infrared spectrum of the simple physical mixture(C) revealed a simple superposition of the spectra of RH and Amberlite® IRP69, but the RH drug-loaded resin had no such weak peak of RH at 3100 - 3500 cm^{-1} N-H bond (Figure 1(4)). However, there was a benzene ring peak of Amberlite® IRP69 at 3000 - 3100 cm^{-1}, which indicated that the drug and resin were combined into drug-loaded resin through the ion exchange, rather than physical absorption. All the aforementioned analyses showed that RH drug ionically combined with the resin through ion exchange.

Single factor investigation

Effects of relevant coating parameters

The RH resin microcapsules with different types of quaternary ammonium salt resins (Eudragit® RL100 and Eudragit® RS100) produced some levels of sustained release effect, with drug release level from Eudragit® RS100 being higher than that from Eudragit® RL100 (Figure 2 a) [21]. As a result, Eudragit® RS100 was selected as the coating material for the preparation of RH resinates.

The *in vitro* release of RH resin microcapsules was slower as the concentration of Eudragit® RS100 was increased (Figure 2 b) [22]. This implied that the higher the level of Eudragit® RS100 in the same volume of reaction medium, the more the quaternary ammonium salts combined with the sulfonic acid group of the drug-loaded resin, thereby making the drug to penetrate deep into the resin. The end result was that the release rate from the resin became slower.

The release rate of RH resin microcapsules slowed down with decreasing drug loading (Figure 2 c). Thus, the lower the drug loading,

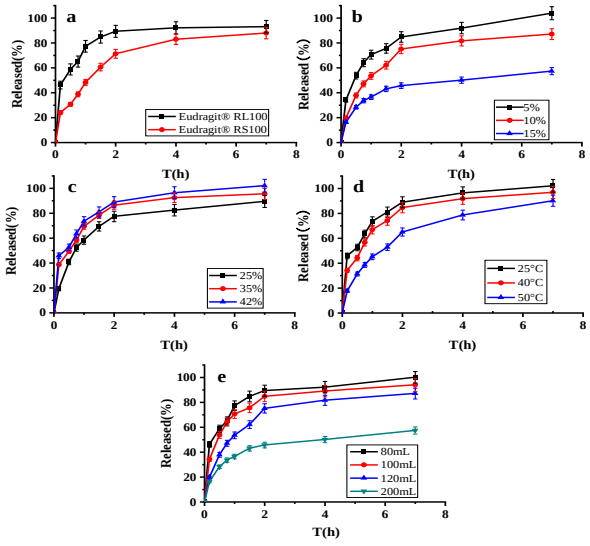


Figure 2: (a) Effect of different coating materials on RH release from microcapsules; (b) effect of different amounts of coating material (Eudragit® RS100) on RH release from microcapsules; (c) effect of different % drug loadings on RH release from microcapsules; (d) effect of coating temperatures on RH release from microcapsules; (e) effect of reaction medium volume on RH release from microcapsules

the more sulfonic acid groups remained on the resin. In this regard, the quaternary ammonium salt groups on Eudragit® RS100 were bound to more sulfonic acid groups, leading to the slower drug release. Therefore, drug loading of the resin played an important role in the sustained release effect of the drug delivery system [10].

Coating temperature and volume of reaction medium also affected drug release rate, as shown in Figure 2 d. The reaction of Eudragit® RS100 with RH resin complex is an endothermic process, because the higher the reaction temperature, the slower the RH release. The elevated temperature promoted further binding of Eudragit® RS100 to the RH resin complex, which resulted in slow drug release. In addition, as the volume of the reaction medium increased, the surface area of the entire reaction system increased, leading to a slower drug release rate from the coated microcapsules (Figure 2 e).

Box-Behnken response surface experiment

Results from the aforementioned optimization studies revealed that factors that greatly influenced in vitro drug release from the formed *RH resin* microcapsules were the amount of coating material (A), volume of the reaction medium (B), and temperature (C).

The results shown in Table 3 were analyzed with Design-Expert 8.0.6 software. The analysis showed that the quadratic polynomial was the best model (Table 3) [23]. The respective and appropriate model equations were:

$L_1 = 27.34-2.64A+2.23B-4.52C-1.74AB+1.15AC+0.14BC+1.57A^2+3.92B^2-1.90C^2$ ….. (2)

($R^2 = 0.9703$; model: p = 0.0002, significant)

$L_2 = 74.59-7.95A-8.62B-2.61C-1.69AB-2.24AC+0.62BC+2.53A^2-4.54B^2-2.27C^2$….. (3)

($R^2 = 0.9982$; model: p < 0.0001, significant)

$L_3=89.51-3.14A+3.77B-1.71C+1.93AB+1.28AC+0.14BC+2.20A^2-51.08B^2+0.19C^2$ … (4)

($R^2 = 0.973$; model: P < 0.0001, significant)

It can be seen that the reliability of the experimental design was due to the good fitting between the predicted data and the actual data, as well as the reliability of the experimental design (Figure 3). Through the linear coefficient of the fitting equation, the release at the early and late periods showed

Table 3: Results of BBD-RSM experiment

A (%)	B (mL)	C (°C)	L_1 (%)	L_2 (%)	L_3 (%)
5.00	100.00	37.50	36.67	87.76	95.14
15.00	100.00	37.50	32.85	74.73	89.36
10.00	100.00	25.00	36.67	79.92	91.52
10.00	100.00	50.00	27.11	72.79	91.37
10.00	150.00	37.50	27.11	74.70	89.46
15.00	150.00	50.00	22.13	62.62	88.6
5.00	200.00	37.50	36.29	73.8	92.76
5.00	150.00	50.00	23.09	82.52	91.97
10.00	150.00	37.50	26.92	75.08	89.08
10.00	150.00	37.50	28.64	74.71	89.85
15.00	150.00	25.00	28.64	71.65	89.26
10.00	150.00	37.50	26.92	73.74	90.6
5.00	150.00	25.00	34.19	82.58	97.77
15.00	200.00	37.50	25.5	54.02	82.26
10.00	200.00	25.00	31.32	61.52	89.24
10.00	200.00	50.00	22.33	56.88	84.8
10.00	150.00	37.50	27.10	74.70	88.51

Note: [1] A: Amount of coating material; [2] B: Volume of the reaction medium; [3] C: Temperature; [4] L_1: Dissolution of RH resin microcapsules in the first hour; [5] L_2: Dissolution of RH resin microcapsules at the 5th hour; [6] L_3: Dissolution of RH resin microcapsules at the 12th hour

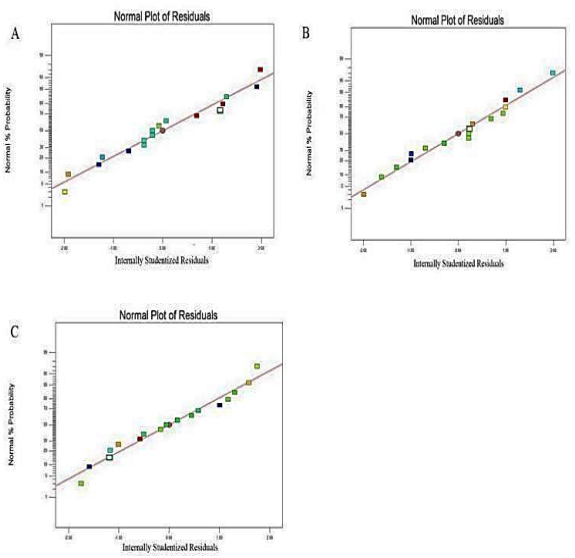


Figure 3: Fitting curve of actual and predicted data. **A:** release degree L_1; **B:** release degree L_2; **C:** release degree L_3

that the coefficients of A and C were negative, while the coefficient of B was positive. These results indicated that the effects of the amount of coating material and temperature on the release rate were in the same direction, whereas the volume of the reaction medium had an opposite effect on the drug release rate. However, in the mid-term release, the coefficients of A, B and C were all negative numbers, which indicated that the amount of coating material, the volume of the reaction medium and the temperature had opposite effects on the release. The p-value of the three fitting models was used as one of the evaluation indicators, and the difference was significant ($p < 0.05$), while the lack of fit term was not significant ($p > 0.05$).

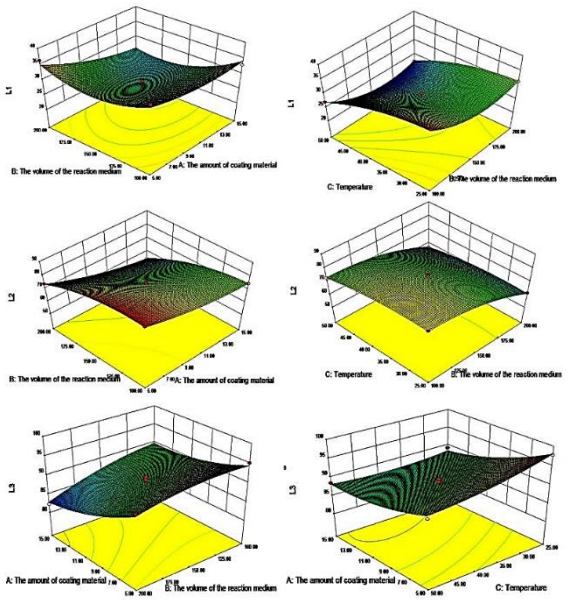


Figure 4: 3D response surface graph of the first hour cumulative release (L_1); 3D response surface graph of the fifth hour cumulative release (L_2); 3D response surface graph of the twelfth hour cumulative release (L_3)

The drug release rate in the first hour was greatly affected by the coating material and the volume of the reaction medium (Figure 4 L_1). The 3D response surface also showed a large slope with its change, but it was not affected by temperature. This observation meant that temperature did not regulate drug release appreciably at 1 h (L_1).

From Figure 4 L_2 can be seen that at the fifth hour, the drug release rate first increased, and then decreased with increases in drug loading and temperature (Figure 4). In contrast, the amount of coating material and the volume of reaction medium had less than 1 h effect on the drug release rate.

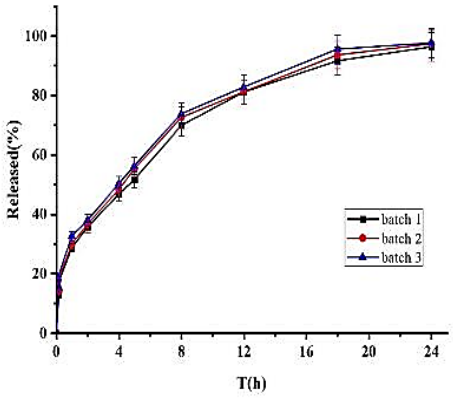
From Figure 4 L_3, it can be seen that changes in temperature in the later release became larger, and the slope of the 3D response surface also increased. These results indicated that temperature effectively regulated drug release.

Using the aforementioned analysis, the conditions for optimal formulation were: 14% coating material, reaction volume of 190 mL, and temperature of 49 ^oC. The predicted first, fifth-, and twelfth-hour cumulative drug releases were 21.02, 53.80, and 83.97 %, respectively.

Verification of model

Three batches of RH resin microcapsules were prepared under the optimized process conditions, and *in vitro* release experiments were also carried out. The correlation between the predicted and the measured values was determined (Figure 3). The results from the three batches of RH resin microcapsules were analyzed, as presented in Figure 5. The relative average deviation between the predicted value and the measured value for the prepared RH resin microcapsules under the optimal conditions was less than 10 %. This indicated that the BBD-RSM was effective in designing optimal preparation conditions for the microcapsules. The conditions for preparation of the microcapsules were accurately optimized and predicted. The results also showed that the process used in preparation of the RH resin microcapsules via the optimized conditions had good reproducibility (Figure 5 a).

a



b

Responses	Predicted value (%)	batch			DEV (%)		
		1	2	3	1	2	3
L_1	21.02	21.94	20.98	21.34	4.38	-0.19	1.52
L_2	53.80	55.12	54.92	54.12	2.45	2.08	0.59
L_3	83.97	82.45	85.09	84.47	-1.81	1.33	0.60

Figure 5: (a) *In vitro* drug release profiles from 3 batches of RH resin microcapsules prepared under optimized conditions; (b) comparison of predicted and measured values for RH resin microcapsules

Evaluation of sustained release suspension

The results of assessment of stability of RH suspension using accelerated test are shown in Table 4.

Pharmacokinetics of *in vivo* sustained drug release from suspension

The linear range of RH concentration was 50 to 5000 ng/mL ($R^2 > 0.99$), with 15 ng/mL as the detection limit of RH. At the same time, the results for precision, stability, recovery and reproducibility showed that the method met the analytical requirements.

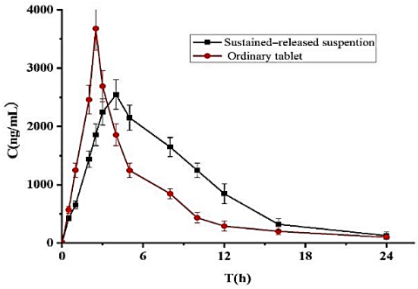
The pharmacokinetics of the two doses were compared based on the plasma concentrations of the drug in the suspension and in the ordinary tablet. The pharmacokinetics of the RH obtained from the suspension showed a pronounced sustained-release behavior, when compared to

Table 4: Stability of RH suspension

Time (month)	*F*	*RI*	Drug leakage (%)	Content (%)	Drug release (%)
1	0.96	***	0.32	98.74	$f>50$
2	0.94	***	0.34	99.12	$f>50$
3	0.93	**	0.49	98.12	$f>50$
6	0.95	**	0.52	97.46	$f>50$

the ordinary tablet (Figure 6 a). In addition, the DAS2.0 software (the non-compartmental model) was used to process the *in vivo* data from rats, and the corresponding pharmacokinetic parameters were calculated as shown in Figure 6 b. The results also depicted sustained drug release from RH suspension.

a



b

Parameter	Ordinary tablet	Sustained-released suspension
$t_{1/2}$ (h)	3.25	4.32
T_{max} (h)	2.50	4.00
C_{max} (ng/mL)	3245.97	2545.78
MRT_{0-24} (h)	6.34	7.60
AUC_{0-24} (ng·h·mL^{1})	22521.53	22757.71

c

T (h)	0.5	1	2	4	6	8	12	18	24
F (%)	16	29	36	47	52	70	81	92	96
Fa (%)	10	21	38	54	75	89	94	99	103

Figure 6: (a) Plasma concentration-time profiles of RH with respect to RH sustained-release suspension and RH ordinary tablets; (b) pharmacokinetic parameters of RH ordinary tablets and RH sustained-release suspension; (c) data for *in vitro* sustained drug release from RH suspension

The T_{max} of RH from suspension was longer than that of the ordinary tablets, while the C_{max} value was lower than that of the ordinary tablets ($p < 0.05$; Figure 6 b). These data suggest that RH sustained-release suspension had obvious sustained-release characteristics. Results of analysis of AUC_{0-24} showed that they were equivalent in terms of AUC_{0-24} ($p < 0.05$).

Moreover, a linear regression on the percentage F for *in vitro* cumulative release using the *in vivo* absorption fraction (Fa) was performed, and the corresponding regression equations and correlation coefficients obtained (Figure 6 c) were Fa = 1.1714F - 0.0244 and r = 0.953.

These results demonstrated that the drug release curve of RH suspension had excellent correlation *in vitro* and *in vivo*. The absorption fraction (Fa) of ranitidine hydrochloride at different times was calculated using the W-N method, as shown in Eq 5.

$$F_a(\%) = \frac{(X_A)_T}{(X_A)_\infty} = \frac{c_T + k\int_0^T c\,dt}{k\int_0^\infty C\,dt} \quad \text{..... (5)}$$

DISCUSSION

Ion exchange resins (IERs) have now gained much attention as carriers for the development of sustained- and controlled-release drug delivery systems, taste masking and stability improvement. In this study, RH resinate suspension was prepared using ion exchange resin, and sustained RH release was achieved by optimizing relevant the coating parameters. Previous studies have shown that drugs may be loaded onto ion exchange resins due to their structural characteristics [18,19]. The UV measurement of the drug loading of the ion exchange resin revealed a value of 0.679 mg/mg, which meant that 0.679 mg RH drug was successfully loaded onto 1mg ion-exchange resin. Thus, the ion exchange resin was a good drug carrier.

Although the RH resinate produced appreciable sustained-release effect due to ion exchange, it did not satisfy the target requirements [20]. Therefore, it is necessary to use appropriate coating materials and coating techniques to further delay the release and absorption of RH *in vivo*. The coating material Eudragit® RS100 was used in this study. The mechanism involved in the surface coating method involves the combination of quaternary ammonium salt groups on the coating material Eudragit® RS100 with free sulfonic acid groups on the pharmaceutical resins. The results showed that the coated microcapsules prepared with Eudragit® RS100 had good sustained-release effect.

The RH sustained-release suspension was safe, and it is expected to reduce the number of times patients took medicine while improving patients' compliance. The Chinese Pharmacopoeia recommends that the sedimentation volume ratio (F) should be greater than 0.9. Thus, the larger the F value, Therefore, the larger the F value, the more stable the self-made suspension. The good stability of RH suspension was also verified through redispersibility (RI), which meant that microcapsules in the suspension could be uniformly dispersed again by shaking for a few seconds [24]. The drug content further confirmed the stability of RH suspension because the drug content of RH suspension after being placed for 6 months was more than 95 %. In summary, all indices remained stable in the RH suspension within 6 months, thereby meeting the requirements of the Chinese Pharmacopoeia.

This finding shows that the RH suspension had good stability.

Compared with ordinary tablets, the RH sustained release suspension had stable blood concentration and sustained release *in vivo*. At the same time, the bioavailability of RH sustained-release suspension and RH ordinary tablet was 101.05 %, which indicated that RH sustained release suspension and RH ordinary tablet had biological equivalence. Indeed, in terms of clinical practice, RH sustained-release suspension deserved to be studied in depth.

CONCLUSION

Ranitidine hydrochloride sustained-release suspension has been successfully prepared using ion-exchange resin as a carrier and Eudragit® RS100 as a coating material for the sustained-release microcapsules. The accelerated stability test confirms that the best RH suspension not only have good stability but also high drug content.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Meiping Han and Yi Du designed the experiments, and Xiaowen Wu conducted the experiments. Xin Zhang and Quanzhu Yang analyzed and interpreted the data, while Caleb Kesse Firempong, Hongfei Liu, Dongli Li prepared the manuscript with contributions from all co-authors.

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