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Fabrication and evaluation for the novel ranitidine hydrochloride resinates and calculation of the kinetics and thermodynamics parameter for the ion exchange process

Yongjian Yang[1], Yi Du[1], Haibing He[4,5], Yang Yu[3], Dongli Li[1,2*] and Hongfei Liu[1, 2*]

[1]School of Biotechnology and Health Sciences, Wuyi University, Jiangmen, PR China
[2]International Healthcare Innovation Institute (Jiangmen), Jiangmen, PR China
[3]Jiangsu Sunan Pharmaceutical Industry Co., Ltd, Zhenjiang, PR China
[4]Department of Pharmaceutics, College of Pharmacy, Shenyang Pharmaceutical University, Shenyang, PR China
[5]Jiangsu Haizhihong Biomedical Co., Ltd., Nantong, PR China

Abstract: Ranitidine hydrochloride (RH) resinates were prepared by bath method using a highly acidic cation-exchange resin as the carrier. The drug-resinates combination pattern was characterized by DSC and X-ray diffraction. The influences of the types of the ion-exchange resin, initial RH concentration and the reaction temperature on the process of ion exchange were investigated. Three empirical kinetics models and thermodynamics equations were studied to the ion exchange process under different temperatures. The results showed that RH combined with ion-exchange resin not simple physical mixture but by ion bond, and the rate of ion exchange increased on increasing the initial drug concentration and reducing the temperature the resin. The *in vitro* drug release test showed that the release process was affected by the kind of countra-ion, ionic strength and temperature. Thermodynamics results showed that the ion exchange reaction between RH and cation-exchange resin was exothermic ($\Delta H^{\theta}_{r,m<}<0$), and the drug release process could preferably be fitted with the first order equation. In conclusion, RH resinates were prepared by the bath method with strongly acidic cation-exchange (Amberlite® IRP69) with 5 mg/mL RH solution(100mL) stirred at 298K for 1h. Drug release from resinates was fitted with Viswanathan equation, and to achieve obvious sustained-release effect, the RH-resin complex should be further coated with a semipermeable membrane.

Keywords: Ranitidine hydrochloride, ion exchange resin kinetics, thermodynamics, characterization, *in vitro* drug resin.

INTRODUCTION

Ion exchange resin is a new type of pharmaceutical polymers, which can exchange their active ions with ionizable drugs in the surrounding medium (Doraswamy and Venkata, 2014; Liu *et al*, 2017). In recent years, its versatile properties such as good taste, good stability, less side effects, more uniform absorption and sustained release have been widely used as a new form of drug carrier[8] in chemical and pharmaceutical industries. Ion exchange resins can be combined with the drug through the ion exchange process to form drug-resin complexes. After oral administration, it takes time for the drugs to be released from the drug-resin complexes to be absorbed by the body and play curative efficacy with the help of some ions in the gastrointestinal tract (Zhang *et al*, 2011). So in order words, the drug-resin complexes can play a sustained-release role. In addition, due to the properties of ionizable and activated groups, ion exchange resins can be used to cover the unpleasant odor of drugs by ion exchange or electrostatic adsorption with ionic drugs through wrapping the drug inside the resin (Shweta *et al*, 2010).

Ranitidine hydrochloride (RH) is a safe drug used for treating stomach ulcers (Bourder *et al.*, 2005), and acts as a reversible histamine inhibitor for histamine H_2 receptors located on gastric cells. RH is widely used clinically such as in treatment of esophagitis, esophageal reflux disease, and Zollinger Ellison's syndrome (the production of too much acid) (Li *et al*, 2019). But as some research reported, RH is a kind of white to light yellow crystalline powder with abnormal odor and slight bitter acerbity, which can reduce patient compliance (Wu *et al*,2018). In addition, most RH products are tablets and capsules and these can make them difficult for children and elder patients to swallow. With the short half-life, RH should be taken for several times a day, which lead to the large plasma concentration fluctuations in body, the poor medication compliance of the dosage forms and side effects followed by (Mohammed *et al*, 2020). Therefore, preparation of RH liquid sustained release dosage form with the ion exchange resin technique might be an alternative method which can overcome the above stated shortcoming.

Nowadays with the development of the refinement of ion exchange resin synthesis techniques and the ion exchange theory, ion resins as a carrier of liquid sustained-release preparations have played more and more important part in controlled drug delivery system. Many studies have reported how to improve the rate from resinate during the ion exchange process. To same regret, there are very few

*Corresponding author: e-mail: articlepharmacyliu@163.com

investigations about mechanism and actions of how this process works.

The aims of this study were to use ranitidine hydrochloride as a model drug, and cation-exchange resin as the drug carrier to prepare drug-resin complexes. Then an investigation was carried out of the factors that influence the drug load and release process. And the constants of the kinetics and thermodynamics of the ion-exchange process were calculated under different conditions to study mechanism and actions of the ion exchange process. Also the X-ray diffraction analysis and DSC were used to investigate the type of bonding between RH and ion-exchange resin.

MATERIALS AND METHODS

Materials

Ranitidine hydrochloride was obtained from Suzhou Hongsen pharmaceutical Co., Ltd., China; Amberlite® IRP69 (sodium polystyrene sulfonate), Amberlite® IRP88 (polacrilin potassium), Amberlite® IRP64 (polacrilex resin) were purchased from Rohm and Haas Company, USA.

Methods

Sodium Content

The equivalent of 1g of accurately weighed ion exchange resin was washed with a slight excess of sulfuric acid. This was followed by the addition of 1mL of nitric acid and some water to the residue. After warming to enhance dissolution, the solution was transferred into a volumetric flask, then diluted with water to the mark and mixed thoroughly. Then 10 mL of this solution was pipetted into a 100 mL volumetric flask. Then 1 mL of low-sodium, low-potassium, non-ionic surfactant solution (1: 50) was added, followed by dilution with water to the mark, and mixing. The solution was then analyzed (ICP eradiate spectrum instrument, Thermo Elemental. USA). The sodium concentration was determined, and the percentage of sodium (P) was calculated from equation 1: P= A/W(1) (Wipada *et al*, 2013).

Here, A is the weight, in mg, of sodium found per liter and W is the weight, in g, of the ion-exchange resin used.

Preparation of the drug resin complexes

The RH drug-resin complexes were obtained by the bath method. First, the cation-exchange resins were added to RH solution. After the concentration of RH in the water was stable, the RH-resin complexes were separated by vacuum filtration, washed with deionized water several times and dried in an oven. All preparations of drug resinates were performed six times. The drug concentration was analyzed with UV-Specord S600 spectrophotometer (Analytik Jena AG, Germany) at 314 nm.

The drug loading (Q_t), the availability of drug (E) and the exchange ratio (F) of the resin were calculated according to the formulas 2,3 and 4, respectively.

$$h2 = \frac{rc\gamma c\gamma tco}{2\eta} \quad (2)$$

$$\rho = \frac{m_1 - m_0}{m_2 - m_0} \quad (3)$$

Where, V (mL) is the volume of the drug solution;
Q_t is the exchange amount per ion-exchange resin at different sampling time;
C_0 (mg/mL) is the initial concentration of RH;
C_t (mg/mL) is the drug concentration at the different sampling time;
W_R (mg) is the amount of ion-exchange resin.

Different RH concentration (1 mg/mL, 3 mg/mL, 5 mg/mL and 6 mg/mL) RH solution, ion-exchange resin type (Amberlite® IRP69, IRP64 and IRP88) , *the ratio of resin to RH* (2:1, 5:1, 1:1, 1:2) and different ion exchange process temperature (298K, 310K, 318K) were investigated.

Dynamic and thermodynamic

Zero-order model, First-order kinetic model and second order kinetic model were used to analyze the ion exchange dynamic process. Thermodynamic parameters such as enthalpy change ($\Delta H^{\theta}_{r,m}$),Gibbs free energy change ($\Delta G^{\theta}_{r,m}$) and entropy change ($\Delta S^{\theta}_{r,m}$) were determined to analyze the ion exchange thermodynamic process (Marta *et al*, 1999).

Characterization of the bonding mechanism of RH resins

The ion exchange mechanism of RH and Amberlite® IRP69 was investigated by X-ray diffraction (*BRUKER,* Germany) and Differential Scanning Calorimetry (DSC) (NTZCH, Germany) (Omar L and Sprockel, 1989).

X-ray diffraction (XRD)

RH, Amberlite® IRP69, physical mixture of RH and ion-exchange resin and RH drug resin complex were investigated. The samples were scanned in increments of 5°/ min from 10° to 90° (diffraction angle 2θ) at room temperature and detected by the semiconductor array detector.

Differential scanning calorimetry (DSC)

The RH, Amberlite® IRP69, physical mixture of RH and ion-exchange resin and RH drug resin complex were examined by DSC. The blank aluminum plate was used as a control. The heating rate was 10°C/min and temperature range for each sample was set from 30 to 300°C, under atmosphere of static air and the sample weight was 10 mg.

In vitro drug release from the drug resinates

The *in vitro* release test was investigated according to the Chinese Pharmacopoeia (2015 edition) Appendix XC

Dissolution Determination Second Method. The release test was performed using 900 mL of different dissolution media, at 310K and 50 rpm with 300 mg RH resinates. 5 mL dissolution medium was sampled at predetermined time intervals. These samples were passed through a 0.45 µm membrane filter and the same volume dissolution medium was added to the dissolution container in time, and the amount of drug released was measured by UV spectrophotometry at 314 nm.

Different ion intensity (H_2O, 0.15 mol/L KCl，0.4 mol/L KCl，1 mol/L KCl); different temperature (298K, 310K, 318K) and different countra-ion (Na^+, K^+) were investigated.

Statistical Analysis was as follows: The date was expressed as mean±SD. The orthogonal experiment results were statistical evaluated by ANOVA. P-value of <0.05 was considered to represent a statistically significant difference. F2 factor was used to evaluate the similarity of release curves.

RESULTS

Sodium content

The sodium content of cation-exchange resin is given in table 1. The results showed that the sodium content of cation-exchange resin conformed to the USP standard. The sodium content reflects the exchange capacity of the ion exchange resin.

Table 1: Sodium content of cation-exchange resin

cation-exchange resin	Amberlite® IRP69	USP standard
Sodium content	9.52%	9.4%~11.5%

Preparation of the drug resin complexes

Effect of resins type on the ion exchange process

The effect of ion-exchange resin types on the ion-exchange progress (drug loading progress) was presented in fig. 1 and table 2, where it is showed Amberlite®IRP69 resin can increase the amount of drug onto the resins, and had a higher drug availability.

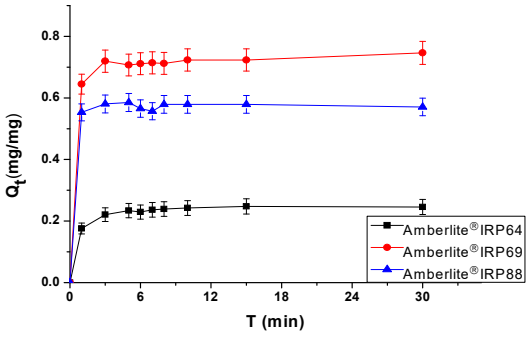

Fig. 1: The effect of resin type on bath method

Table 2: The effect of resins type on bath method

Resins type	Amberlite® IRP64	Amberlite® IRP69	Amberlite® IRP88
Q_∞ (mg/mg)	23.77	69.61	57.07
E (%)	12.55	69.51	29.68

Effect of temperature on the ion exchange process

The effect of temperature on ion-exchange process was presented in fig. 2 and table 3. This showed that the drug loading rate of the resin can be enhanced when the temperature increased (Zhang and Ping, 1999; Che *et al.*, 2005).

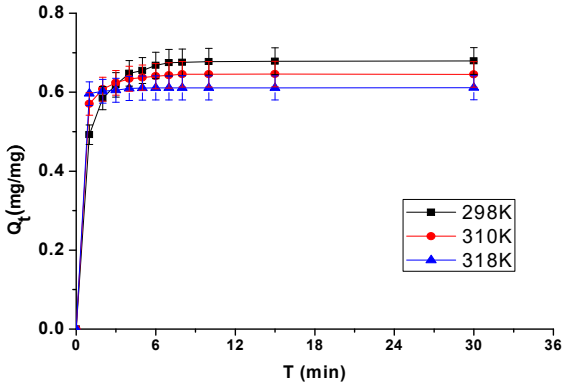

Fig. 2: The effect of temperature on bath method

Table 3: The effect of temperature on bath method

T(K)	298	310	318
Q_∞(mg·mg^{-1})	0.675	0.645	0.611
E (%)	67.54	64.54	61.10

Effect of initial RH concentration on the ion exchange process

The effect of concentration of RH on ion-exchange progress was presented in fig. 3 and table 4. This showed that the optimal drug concentration for this experiment was 5 mg/mL.

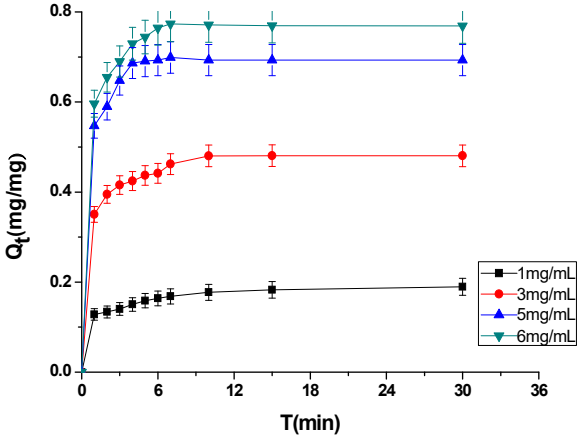

Fig. 3: The effect of initial RH concentration

Table 4: The effect of initial RH concentration

Concentration (mg/mL)	1	3	5	6
Q_∞(mg/mg)	0.189	0.4805	0.6990	0.773
E (%)	94.67	80.05	69.90	57.56

The effect of the ratio of resin to RH on ion-exchange progress

The effect of the ratio of resin to RH on ion-exchange progress is shown in table 5. The results showed that the ratio of resin to RH was 1:1.

Table 5: The effect of ratio of resin and drug

Ratio of resin: drug	2:1	5:3	1:1	1:2
Q_∞(mg·mg^{-1})	0.423	0.488	0.679	0.968
E (%)	85.13	81.38	67.91	48.09

Ion exchange dynamic studies

The ion exchange dynamic process can be analyzed with Zero-order model, First order kinetic equation, and Second order kinetic model (Liu *et al.,* 2014; Du *et al.,* 2019).

Zero-order model：$1-F = k_0t+a$ (4)

First-order model：$\ln(1-F) = -k_1t$ (5)

Second order model：$1/(1-F) = k_2t+b$ (6)

The drug loading curves at 298K were fitted according to the above models. The model fitting equation is shown in table 6. The result showed that the combination of RH and Amberlite® IRP69 was the best fitted kinetic model to the first-order model (R^2=0.98), the second order model was the next best (R2=0.6899), and the zero-order model is the worst (R2=0.2638). It can be obtained that the preparation of RH drug resin is a first-order kinetic process, and the fitting equation is ln(1-F)=-0.6228x-0.4495 (298K).

Table 6: The kinetic profiles pattern of loading（298K)

Reaction order	Regression equation	R^2
Zero order reaction	1-*F* = 0.0072t + 0.0999	0.2638
First order reaction	ln(1-*F*) = -0.6228t - 0.4495	0.98
Second order reaction	1/(1-*F*) = 175.18t - 668.49	0.6899

The thermodynamics of the ion exchange process

The drug resin loading process itself is the ion exchange between the RH ions in solution and the sodium on Amberlite® IRP69 resin, which make the drug onto the resin. The reaction can be described as follows:

$$\text{Resin - } SO_3\,Na^+ + Drug^+ \leftrightharpoons \text{Resin- } SO_3^-Drug^+ +$$

The thermodynamic constants of the ion exchange process using the bath method can be calculated as follows: when ion exchange reaction reached equilibrium, the equilibrium constant K_e (the binding capacity of Amberlite® IRP69 to RH) could be calculated from equation 7. With the K_e value increases, the drug exchange with the resin became easier. And the effect of temperature on the thermodynamics of the ion exchange process was shown in table 8. The results showed that the amount of the drug exchanged increased when the temperature decreased，which indicated that the lower the temperature, RH with the active group of Amberlite® IRP69 had higher the affinity, and that RH drug resins are suitable for preparation at lower (or normal) temperatures.

$$K_e = \frac{[Drug^+]_r[Na^+]_s}{[Drug^+]_s[Na^+]_r} \quad (7)$$

Where $[Drug]_r$ (mol/g) is the drug concentration in the ion exchange resin;

$[Drug]_s$ (mol/mL) is the drug concentration in the solution;

$[Na^+]_r$ (mol/g) is the sodium ion concentration in the ion exchange resin;

and $[Na^+]_s$ (mol/ml) is the sodium ion concentration in the solution.

With the equilibrium constant at each temperature, Thermodynamic parameters such as Gibbs free energy change ($\Delta G^\theta_{r,m}$), enthalpy change ($\Delta H^\theta_{r,m}$) and entropy change ($\Delta S^\theta_{r,m}$) have been determined according to the following equations (Liu *et al.*, 2015)：

$$\Delta G^\theta_{r,m} = -RT\ln Ke \quad (8)$$

$$\ln Ke = -\Delta H^\theta_{r,m}/RT + C \quad (9)$$

$$\Delta G^\theta_{r,m} = \Delta H^\theta_{r,m} - T\Delta S^\theta_{r,m} \quad (10)$$

Here R [8.314 J/ (mol K)] is the gas constant; The result of thermodynamic parameters ($\Delta G^\theta_{r,m}$, $\Delta H^\theta_{r,m}$, $\Delta S^\theta_{r,m}$) at different temperatures are given in table 9.

From table 9, we can see that the Gibbs free energy change $\Delta G^\theta_{r,m} < 0$ at 298K, indicating that the exchange process proceeded spontaneously to the right under this temperature. And the $\Delta H^\theta_{r,m} < 0$ showed that the reaction was exothermic, which suggested that the increasing temperature was not conducive to the preparation of RH drug resin. In conclusion, considering the Q_∞, *E* and K_e, RH drug resin was prepared by bath method at room temperature. Activation energy E_a can be obtained by the fitting equation $\ln k_1 = -E_a/RT + A = -2096.2/T + 5.2181$. And the result showed that E_a =17.43 KJ·mol^{-1}, which indicated that RH resin loading process was easy.

Table 8: K_e of RH-resinates preparation (at different temperatures)

T (K)	298	310	318
$[Drug^+]_r$ (mmol/g)	1.94	1.84	1.26
$[Drug^+]_s$ (mmol/L)	2.74	3.03	4.76
$[Na^+]_r$ (mmol/g)	3.62	3.71	4.29
$[Na^+]_s$ (mmol/L)	5.81	5.82	3.79
K_e	1.13	0.90	0.38

Table 9: Thermodynamic parameters at different temperatures

T (K)	298	310	318
Ke	1.134	0.901	0.379
$\Delta H^{\theta}_{r,m}$ (KJ/mol)	-0.833	-0.833	-0.833
$\Delta G^{\theta}_{r,m}$ (KJ/mol)	-0.311	0.269	3.828
$\Delta S^{\theta}_{r,m}$(KJ·mol^{-1}·K^{-1})	-0.002	-0.004	-0.015

Powder X-ray diffraction properties

Fig. 4 demonstrated the X-ray spectrum of RH, Amberlite® IRP69, physical mixture of RH and ion-exchange resin and RH drug resin complexes.

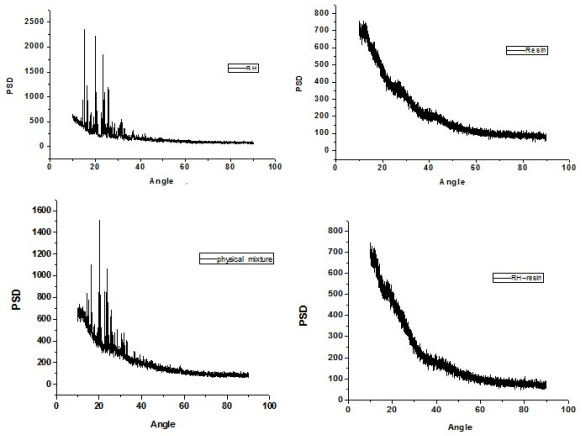

Fig. 4: X-ray spectrum of RH, blank resin, simple physical mixing, RH- resin

Differential Scanning Calorimetry (DSC)

The thermal behavior of the RH, Amberlite® IRP69, physical mixture of RH and ion-exchange resin and RH drug resin complex were investigated by DSC and the result was shown in fig. 5.

By the analysis and validation of X-ray and DSC, the combination of RH and Amberlite® IRP69 was not simple physical adsorption, but an ionic bond.

In vitro drug release from the drug resinates

Effect of the kind of countra-ion in drug release

The result was shown in fig. 6, and we could see that the drug was released quickly in NaCl、KCl solution and the drug was rarely released in deionized water.

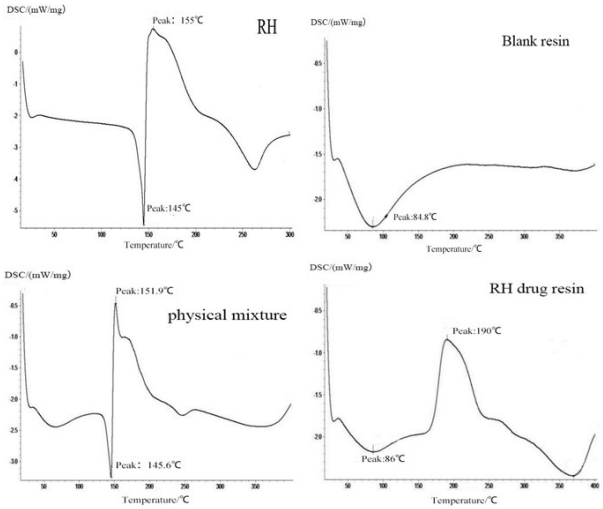

Fig. 5: DSC spectrum of RH, blank resin, simple physical mixing, RH drug resin

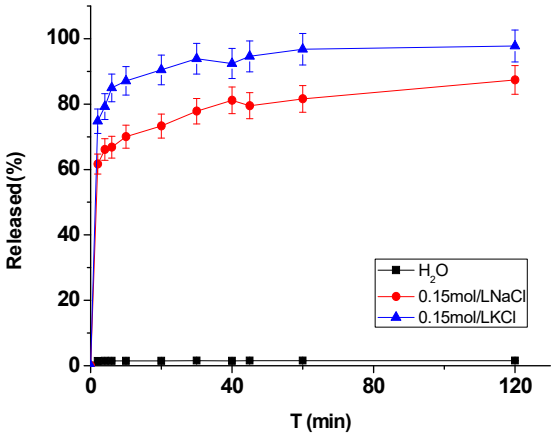

Fig. 6: The effect of counter-ion types on the RH release

Effect of ionic strength on the RH release

The results of the RH release with different ionic strength is shown in fig. 7, and we could see that with the increasing ion strength, the release rate increased.

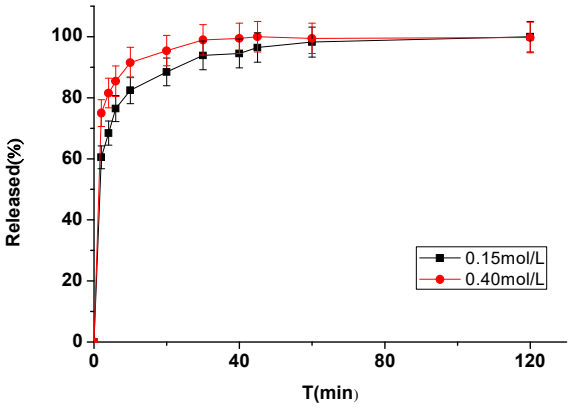

Fig. 7: The effect of ionic strength on the RH release

Effect of temperature on the RH release

The results of the RH release with different temperature was shown in fig. 8. And we can see that when the temperature increased, the time came to equilibrium was shortened.

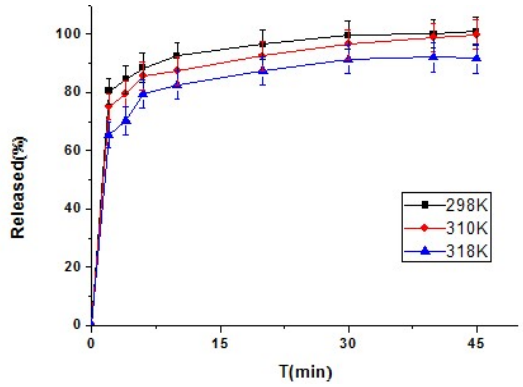

Fig. 8: The effect of temperature on the RH release

DISCUSSION

Preparation of the drug resin complexes

Effect of resins type on the ion exchange process

Compared with the strongly acidic resin (Amberlite® IRP69), the weakly acidic (Amberlite® IRP64, Amberlite® IRP88) have relatively low amount of drug loading and drug availability when reached equilibrium. Therefore, Amberlite® IRP69 was chosen as the drug loading resin (Zhang *et al.,* 2018).

Effect of temperature on the ion exchange process

With the increase of temperature, the final drug loading rate and drug availability decrease, indicating that the increase of temperature was not conducive to the forward reaction. Since the time of reaching equilibrium is so short (less than 10 minutes) that we can basically ignore the speed of the RH and resin exchange *process*. Considering the higher drug loading rate and drug availability rate and lower heat loss, 298K was adopted as the loading temperature in this study. The preparation of tramadol-resin complexes and nefopam hydrochloride complexes also have the same situation.

Effect of initial RH concentration on the ion exchange process

As the concentration of RH increased, the drug load of RH resin increased (from 0.189 to 0.773), but the drug availability rate decreased (from 94.67% to 57.56%). When the RH concentration was 5 mg/mL, there was no significant improvement of the exchange amount but the availability of drug reduced greater even less than 60%. This indicated that the resin loading was saturated there was no significance to continuously increase the initial RH concentration. Considering the drug load and drug availability of RH, the optimal drug concentration for this experiment was 5 mg/mL. The effect of drug concentration on ion exchange process was investigated in the preparation of levodopa/benserazide hydrochloride compound drug resins, as the concentration of increased, the drug load of increased, but the drug utilization rate decreased (Liu *et al.*, 2015).

The effect of the ratio of resin to RH on ion-exchange progress

Following the proportion of drug to resin increased, the drug loading increased while drug availability decreased. This because resin will reach saturated if the amount of the drug increases, and the rest drugs was stored in deionized water, and then remove with the removal solution. In conclusion, the data was taken into account, the ratio of resin to RH was 1:1.

Ion exchange dynamic studies

Using the Linear regression of -In(1-F) versus, the rate constant k_1 at different temperature could be calculated in table 7. In general, with the increase of temperature, the rate constant k_1 increases, but Q_∞ changes little, indicating that high temperature is beneficial to the combination of drugs and resins. But the result showed that although the exchange rate constant increased with the temperature, which indicated that increasing temperature can facilitate the preparation of the RH drug resin, it is not conducive to the ion exchange moving to the positive reaction, resulting in a decrease in the amount of drug loaded on the resin during equilibrium, and the ion exchange process was incomplete.

Powder X-ray diffraction properties

From fig. 4, we can see that RH has crystallization peaks, while Amberlite® IRP69 resin were amorphous. The fig. of physical mixture of RH with Amberlite® IRP69 showed a weak crystallization peak at the same position as the RH, indicating that the RH structure had not changed. The diffraction patterns from RH-resinates showed an amorphous structure with no any of the diffraction peaks, which indicated that RH is chemically bonded to Amberlite® IRP69.

Differential Scanning Calorimetry (DSC)

From fig. 5, we can see that the RH sample had obvious endothermic peak at 145℃which was close to the melting point of RH (137-143℃) and the endothermic peak of Amberlite® IRP69 appeared at 84.5℃. The endothermic peaks from a physical mixture of RH and Amberlite® IRP 69 was a simple stack characteristic peak of them. The endothermic peak of RH drug resin had endotherm at 86℃the same as resin but not the RH, indicating that chemical binding occurred between the RH and Amberlite® IRP69.

In vitro drug release from the drug resinates

Effect of the kind of countra-ion in drug release

Drug release was ion exchange process. When the process reached equilibrium, the RH drug was more completely

released in the KCl reaction medium than NaCl. Therefore, KCl was selected as the reaction medium in drug resin release.

Table 10: The drug release kinetics equations of the drug with different temperature and ionic strength

Factors	Conditions	The drug release kinetics	Dr (m^2/min)	R^2
Tempe-rature	25°C	y= 1.2624x +0.0078	7.29×10^{-11}	0.988
	37°C	y = 0.9753x +0.1218	4.90×10^{-11}	0.974
Ionic strength (K^+)	0.15 mol/L	y = 0.4501x +0.3438	1.49×10^{-11}	0.941
	0.4 mol/L	y = 1.3892x-0.0218	8.45×10^{-11}	0.999
Stirring speed	50 rpm	y = 0.1547x +1.1137	2.88×10^{-11}	0.844
	75 rpm	y = 1.0011x +0.152	5.10×10^{-11}	0.968
	100 rpm	y = 0.7321x +1.7377	3.43×10^{-14}	0.895
Medium volume	500 mL	y = 0.01x+1.7874	3.15×10^{-11}	0.854
	750 mL	y = 0.1644x +0.7898	3.17×10^{-12}	0.893
	900 mL	y = 1.2119x +0.0591	6.85×10^{-11}	0.997
Ion species	Na^+	y = 0.1111x +0.5665	5.99×10^{-11}	0.925
	K^+	y = 0.143x +1.1147	2.56×10^{-11}	0.820

Effect of ionic strength on the RH release

From fig. 7, we can see that the higher the ionic strength, the release experiment is pushed to the right, making the drug release rate increase.

Effect of temperature on the RH release

From fig. 8, we can see that higher temperature was not conducive to release completely. Considering that there was no significant difference between 298K and 310K as the fig. 8 showed, so 310K (body temperature) was selected as the temperature for in vitro release.

From the above experiments, we can see that drug release process from resinate was affected by many variables, which it couldn't simply be fitted with one-level or zero-level dynamics. The grain diffusion equation (Boyd equation), index equation and logarithm equation (Viswanathan equation) are used to study the research of drug release kinetics from drug-resin complexes, among which Viswanathan equation is suitable for *in vitro* drug release process of all drug-resin complexes.

$$\ln(1-F) = -\ln(\frac{Q_t}{Q_o}) = 1.59(\frac{6}{d})^{1.3} Dr^{0.65} t^{0.65} \quad (1)$$

Where F represents the release rate of the drug from the drug resin composites,

Q_0 refers to the content of drug in drug-resin complexes (g/g) at the starting time;

Q_t refers to the content of drug in drug-resin complexes (g/g) at the time of t;

D_r refers to the diffusion coefficient of drugs in the resin (m^2/min^{-1});

d refers to the average particle size of resin (m).

The drug release kinetics equations were calculated and shown in table 6 and the diffusion coefficient D_r in different release medium could be obtained from the slope of the linear equation which is also shown in table 10. From table 10，-ln(1-F) had a good linear relationship with $t^{0.65}$, which showed that the data of TRDH released from the drug-resin complexes was fitted with Viswanathan equation.

CONCLUSIONS

RH resinates were prepared by the bath method using an acidic cation-exchange resin under different initial RH concentration, resins type, and temperature. The results showed the strongly acidic cation-exchange (Amberlite® IRP69) had a higher affinity for ionic drugs. And the ion exchange rate increased with increased temperature and initial RH concentration. In the thermodynamic study of ion exchange process, $\Delta H^{\theta}_{r,m} < 0$ showed that the ion exchange reaction between RH and cation-exchange resin was exothermic， and the drug release process could preferably be modeled with first order kinetic equation, and the fitting equation is ln(1-F)=-0.6228x-0.4495 (298K). The *in vitro* release test showed that the release process of drug-resinate was affected by temperature, the kind of countra-ion and the ionic strength.

In conclusion, 298 K，Amberlite® IRP69 resins and 5 mg/mL RH concentration were suitable for the preparation of the RH resinates. RH-resin complex were studied by DSC and X-ray spectra, it was proved that the combination of RH and Amberlite® IRP69 was not simple physical mixture, but an ionic combination. The drug release from the resin be fitted with Viswanathan equation. The drug-resin complex need to be further coated with a semipermeable membrane to achieve satisfying sustained-release effect.

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