doi.org/10.36721/PJPS.2022.35.3.REG.721-729.1

Preparation, characterization of clonidine hydrochloride resinates and investigation of the kinetics and thermodynamics of the ion exchange process

Hongfei Liu[1,4], Xiangping Lai[1], Chao Chen [1], Yingshu Feng[3], Yang Yu [4], Xuezhi Yin[2]* and Haibing He[5]*

[1]College of Pharmacy, Jiangsu University, Zhenjiang, China
[2]Zhejiang Tianyu Pharmaceutical Co., Ltd, Zhejiang, China
[3]School of medical technology, Zhenjiang college, Zhenjiang, Jiangsu, China
[4]Jiangsu Sunan Pharmaceutical Industry Co., Ltd, Zhejiang, China
[5]Jiangsu haizhihong biomedical Co., Ltd, Nantongm P.R. China

Abstract: Clonidine Hydrochloride (CH) resinates were prepared by plating solution with strong acid cationic-exchange resin as the carrier. The drug resinate's combination mode was characterized by SEM, DSC and X-ray diffraction. The reaction at different temperatures and the influence of different ion exchange resins on the ion exchange process were studied, The kinetics and thermodynamics of ion exchange resins under different temperatures were studied. The *In vitro* drug liberate from the drug-resinates was investigated in different mediums. The study proved that the combination of CH and resin was not a simple physical mixture but ionic bonded. With the increase of temperature and ion exchange and Amberlite®IRP69 had a higher affinity for ionic drugs. The results of *In vitro* release experiment showed that temperature, medium volume, stirring speed, the ionic strength and type. The *In vitro* release of CH resin was fitted with Viswanathan equation, it conformed to the process of particle diffusion. Also, the results showed that further coating of CH resin is necessary to achieve a significant continued release effect.

Keywords: Clonidine hydrochloride, ion exchange resin, kinetics, thermodynamics, characterization, *in vitro* release.

INTRODUCTION

Ion exchange resin is a new type of medicinal polymer material, which is a kind of cross-linked polymer with reticular stereoscopic structure that is insoluble in water and can exchange ions with other ions in solution(Doraswamy and Ramana, 2014; Pande *et al.,* 2011). Resins have diversified applications in chemical and pharmaceutical industries. The same charged active ion in the solution will diffuse to the active group on the surface of the resin, then exchange with the ion exchange resin to form a new compound (Upadhye *et al.,* 2008). The application of ion-exchange technology in drug-controlled release systems can improve the efficacy and safety of drugs, reduce the incidence of side effects, extend the duration of drug action and reduce the frequency of drug administration (Davis, 2005). It also helps reduce oral olfactory perception of the drug, effectively masking the drug odor (Bhoyar *et al.,* 2011; Aman *et al.,* 2014). Meanwhile, some studies also show that small particles of resin can delay the hydrolysis of drugs in gastrointestinal tract and improve the stability of drugs (Halder and Sa, 2006; Yuan *et al.,* 2014). The emergence of ion exchange resin as a new excipient provides a new idea and development opportunity for the development of a new drug delivery system.

CH is a chemical synthetic drug with the structure of imidazoline-derivative (Saito *et al.,* 2021). Research suggests that CH is a partial agonist of the α_2-receptors. Its major pharmacological effects involve of Changes in heart rate and reduce blood press and relieve pain (Kuldeep KR and Anil KS, 2011). CH is clinically used in the treatment of hypertension and acute hypertension, as a drug for moderate and severe hypertension, CH acts through the central nervous system to elicit a hypotensive response (Saito *et al.,* 2021). In the treatment of children, CH is principally used as a sedative in commixture with other drugs and to prevent withdrawal after long-term use of sedatives (Merino-Bohorquez *et al.,* 2019).

At present the domestic and foreign already marketed Clonidine Hydrochloric acid preparation as tablet, drop pills, injection, etc. There are many defects in oral fast-release preparations, such as large fluctuation of blood concentration and short duration of drug efficacy. In recent years, the oral sustained-release tablet of CH has been approved for market in the United States, which can effectively make up for the defects of ordinary quick-release preparation. Therefore, the preparation of CH sustained-release suspension may be an alternative method to overcome the above disadvantages and provide a new method for clinical application. Many researches on ion exchange resin delivery systems are being carried out (Singare *et al.,* 2008; Lokhande *et al.,* 2008; Inui *et al.,* 2011). However, most of reports only involve the

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

parameters affecting the preparation of the microencapsulated ion-exchange resins and the drug release from microencapsulated resinates (Ichikawa *et al.,* 2001). Very few investigations have focused on the drug loading process and the kinetics and thermodynamics of the ion-exchange process.

In this research, CH was used as model drug and strong acid cation exchange resin was used as carrier to prepare drug-resin complexes. Then the investigations were carried out to optimize the factors which influence the drug load and *in vitro* release process. The kinetic and thermodynamic constants of the ion exchange process under different conditions are calculated.

MATERIALS AND METHODS

Materials

CH was obtained from Hubei Kangbaotai fine Chemical Co., Ltd., China; the cation exchange resin was obtained from Dow Chemical Company. Other reagents were purchased from Sino pharmaceutical Reagents Co., Ltd.

Methods

Preparation of the Drug-Resin Complexes

CH-resinates were prepared by bath method. Firstly, 250 mg CH is dissolved in 50mL deionized water. Then 250 mg resin is added into the CH solution. The ion exchange process ended when the amount of drug in the solution was stable. The drug-resin complexes were repeatedly rinsed with deionized water and then dried in a vacuum dryer of 323~333 K. All preparations of drug resinates were performed six times.

Kinetics research for the ion-exchange process

During the ion exchange process, samples were obtained at given interval and the drug concentration was measured. The drug-loading rate (Q_t) and the utilization ratio of drug (E) were calculated according to Eq. 1 and Eq. 2.

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

$$E = \frac{(C_0 - C_t)}{C_0} \quad (2)$$

Here, Q_t (mg•mg^{-1})is the drug-loading rate of ion-exchange resin at a particular sampling time, V (mL) is the volume of the drug solution, C_0 (mg•mL^{-1}) is the initial concentration of the drug, C_t (mg•mL^{-1}) is the drug concentration sampled at a certain time, and W_R (mg) is the total amount of ion-exchange resin..

Different type of ion-exchange resin (Amberlite®IRP69, Amberlite®IRP64, Amberlite®IRP88) and different reaction temperature (298, 310 and 318K) were investigated.

Thermodynamics research for the ion-exchange process

In the thermodynamics research, the ion exchange resin (Amberlite®IRP69) was used with agitation at 298, 310, and 318 K. The solutions were stirred until the amount of CH remained stable, and the quantity exchanged (Q) was calculated from Eq. 3.

$$Q = (C_0 - C_\infty) * V \quad (3)$$

Here, Q (mg) is the drug amount exchanged, C_0 (mg•mL^{-1}) is the initial concentration of the drug, C_∞ (mg•mL^{-1}) is the drug concentration at the time when the ion exchange reaction reaches equilibrium, and V (mL) is the total volume of the drug solution.

Scanning electron microscopy (SEM)

The surface morphology of ion exchange resin and Drug-Resin Complexes by the scanning electron microscopy (SEM) (Hitachi S-4800, Tokyo, Japan). Samples were gold sputtering coated by a high-vacuum sputter coating device (BAL-TEC SCD500, Austria) (Liu *et al.,* 2017).

Powder X-ray diffraction properties

Ion exchange resin, CH, CH-resinates and physical mixture of CH and ion exchange resin were investigated by an X-Ray Diffractometer (D8 ADVANCE, BRUKER company, The Germany). P-XRD was area from 5° to80 °(2θ) at a sweep speed of 10°/ min. PW3123/00 curved Ni-filtered Cu-Ka radiation at 40 kV/40mA was used as the X-ray source (Qu *et al.,* 2019).

Differential scanning calorimetry

Ion exchange resin, CH, CH-resinates and physical mixture of CH and ion exchange resin were assessed by differential scanning calorimetry analysis (NETZSCH DSC 204 F1, The Germany). The samples were dried overnight in a vacuum drying oven at 60°C. Different samples were taken from 10mg alumina crucible and heated at a heating speed of 10°/min at a temperature range of 20~400°C to assess the vitrification transition behavior under the static air (Liu *et al.,* 2018).

In vitro drug release

In vitro drug release investigations were carried out using the USP paddle (apparatus II) method and a ZRS-8G Intelligent Dissolution Tester Apparatus (Tian Jin University Radio Factory, Tian Jin, China) at 310 K, different dissolving media were 900mL with a speed of 50 rpm, accurately weigh a certain amount of CH resin. Take 5mL dissolution medium within the set time interval. The sample was filtered through a 0.45μm membrane and the amount of drug released was determined by high performance liquid chromatography.

Different ion intensity (0.15mol·L^{-1}, 0.5mol·L^{-1}, 1.0 mol·L^{-1} NaCl); different reaction temperature (310 K, 318 K); different medium volume (250mL, 500mL, 900mL); different stirring speed (50 rpm, 75 rpm, 100 rpm) and different ion species (NaCl, KCl, HCl) were investigated.

RESULTS

Kinetics of the ion-exchange process

Effect of resins type on the ion exchange process

The influence of the resin type on the kinetics of the ion-exchange process is shown in the fig. 1.

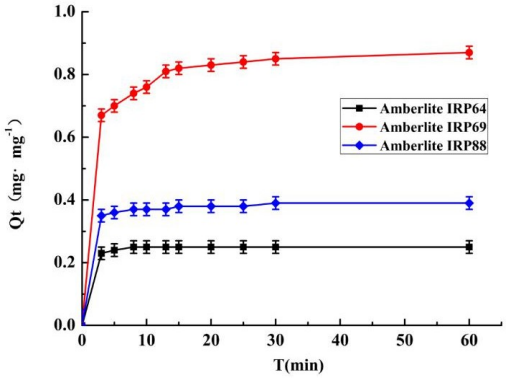

Fig. 1: Effect of Resin Type on the Ion-exchange Kinetics

Effect of temperature on the ion exchange process

The influence of the temperature on the kinetics of the ion-exchange process is shown in the fig. 2 and table 1, and the results showed that on increasing the temperature, the reaction reached equilibrium faster, and Q and E added slightly.

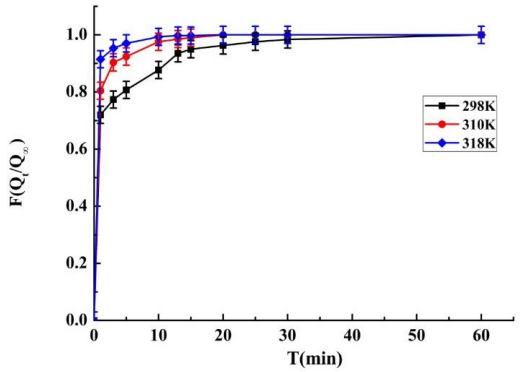

Fig. 2: Effect of Temperature on the Kinetics of Ion-exchange

The kinetic constants of the ion-exchange using the bath method were calculated as Eq. 4 (Du , 2019).

$$-\text{In}\ (1\text{-}F) = K_t \quad (4)$$

Here, F is the exchange ratio at the particular sampling time; F was calculated according to Eq. 5.

$$F = \frac{Q_t}{Q_\infty} \quad (5)$$

Here, Q_t (mg•mg^{-1}) is the drug-loading rate of ion-exchange resin at a particular sampling time, Q_∞ (mg•mg^{-1}) is the drug-loading rate of ion-exchange resin when the concentration of CH in the water was steady. K is the reaction kinetics constant. Linear regression of -In (1-F) versus t, allows calculation of the kinetic constant of the ion exchange reaction.

Table 1: The effect of temperature on the kinetics of Ion-exchange

T(K)	298	310	318
Q_∞(mg•mg^{-1})	0.87	0.90	0.90
E (%)	86.53	89.05	89.80

The kinetics results are given in tables 2 and 3. The results showed that the ion exchange rate of Amberlite IRP69 was accelerated with the increase of temperature, and Amberlite IRP69 had a high affinity for ionic drugs.

Table 2: Ion exchange rate constant for different resin types

Resin Type	Amberlite® IRP64	Amberlite® IRP69	Amberlite® IRP88
K(hr^{-1})	0.3121	0.0929	0.0979
r^2	0.9774	0.9948	0.9412

Table 3: The k_1 and Q_∞ (at different temperatures)

T/K	Regression equation	r	k_1 (h^{-1})	Q_∞ (mg• mg^{-1})
298	ln(1-F) = -0.1018t	0.982	0.1018	0.879
310	ln(1-F) = -0.2073t	0.9894	0.2073	0.895
318	ln(1-F) = -0.2729t	0.987	0.2729	0.899

Thermodynamics of the ion exchange process

The effect of temperature on the thermodynamics of the ion exchange process is shown in table 4. The consequences showed that the amount of drug exchange increased with the increase of temperature.

The thermodynamic constants of the ion exchange reaction using the bath method were calculated as follows: when ion exchange process reached equilibrium, the equilibrium constant Ka could be calculated from Eq. 6.

$$\text{Ka} = \frac{[D]_r[A]_s}{[D]_s[A]_r} \quad (6)$$

Here, $[D]_r$ (mmol•g^{-1}) is the drug concentration in the ion-exchange resin,$[D]_s$ (mmol•mL^{-1}) is the drug concentration in the solution,$[A]_r$ (mmol•g^{-1}) is the OH^- ion concentration in the ion-exchange resin, and $[A]_s$ (mmol•mL^{-1}) is the OH^- ion concentration in the solution. The Ka of the ion exchange reaction is also called the selection coefficient, and it shows that the ion exchange exhibited selectivity to different ions. When Ka increased, the drug exchange with the resin became easier. When Ka was reduced, the drug exchange with the resin became more difficult. The equilibrium constant Ka is shown in table 5 under different conditions.

Table 4: The amount of exchange at different temperatures

T(k)	C_0(mg•mL^{-1})	C_∞(mg•mL^{-1})	Q(mg)
298	5.00±0.03	0.66±0.04	217±7
310	4.99±0.02	0.51±0.02	224±4
318	5.02±0.01	0.50±0.04	226±5

Table 5: Ka of CH -resin Preparation (at different temperatures)

T (K)	298	310	318
$[Na^+]_s$ (mmol·L^{-1})	16.23	16.87	17.07
$[Drug^+]_s$ (mmol·L^{-1})	2.53	1.89	1.69
$[Na^+]_r$ (mmol·g^{-1})	2.31	2.18	2.14
$[Drug^+]_r$ (mmol·g^{-1})	3.25	3.37	3.41
K_e	9.03	13.79	16.12

The results show that on increasing the temperature, the equilibrium constant increased.

And with the obtained equilibrium constant, the enthalpy change could be obtained using the van' t Hoff isochore (Smith, 1990).

$$InKa = -\Delta H_{r,m}/RT + C \quad (7)$$

Here, *R* is constant (8.314 J/K·mol). Plotting InKa against 1/T can give a linear plot of the slope $-\Delta H_{r,m}/R$.

The Gibbs free energy at each temperature was obtained from Eq. 8.

$$\Delta G^{\theta}_{r,m} = -RT\ In\ Ka \quad (8)$$

Here, $\Delta G^{\theta}_{r,m}$ is the exchange of free energy when 1mol ion exchange occurs under standard conditions. *Ka* is the equilibrium constant of the ion exchange reaction.

Finally, the entropy change at each temperature could be obtained from the Gibbs Eq. 9 (Du, 2019).

$$\Delta G^{\theta}_{r,m} = \Delta H_{r,m} - T\Delta S_m \quad (9)$$

The thermodynamics constants of the ion exchange reaction are given in table 6.

Table 6: Thermodynamic Parameters at Different Temperatures

T (K)	298	310	318
Ke	9.03	13.79	16.12
$\Delta H^{\theta}_{r,m}$ (KJ·mol^{-1})	23.20	23.20	23.20
$\Delta G^{\theta}_{r,m}$ (KJ·mol^{-1})	-5.45	-6.76	-7.35
$\Delta S^{\theta}_{r,m}$ (KJ·mol^{-1}·K^{-1})	0.096	0.097	0.096

From the results given in table 6, at different temperatures, the thermodynamics constants $\Delta G^{\theta}_{r,m}$ is < 0 and $\Delta S^{\theta}_{r,m}$ is > 0, it indicates that when the resin reacts with CH, the free energy decreases, the entropy increases. Also, the reaction is not a spontaneous process, and the $\Delta H_{r,m}$ >0 shows that the ion exchange reaction is endothermic.

Scanning electron microscopy

The morphological changes of blank anion resin and CH resin after drug loading were observed using SEM (Liu, 2014). As shown in fig. 3, the results showed that the morphology of the resin before and after drug loading was basically unchanged. No free drug traces were found on the surface of the resin.

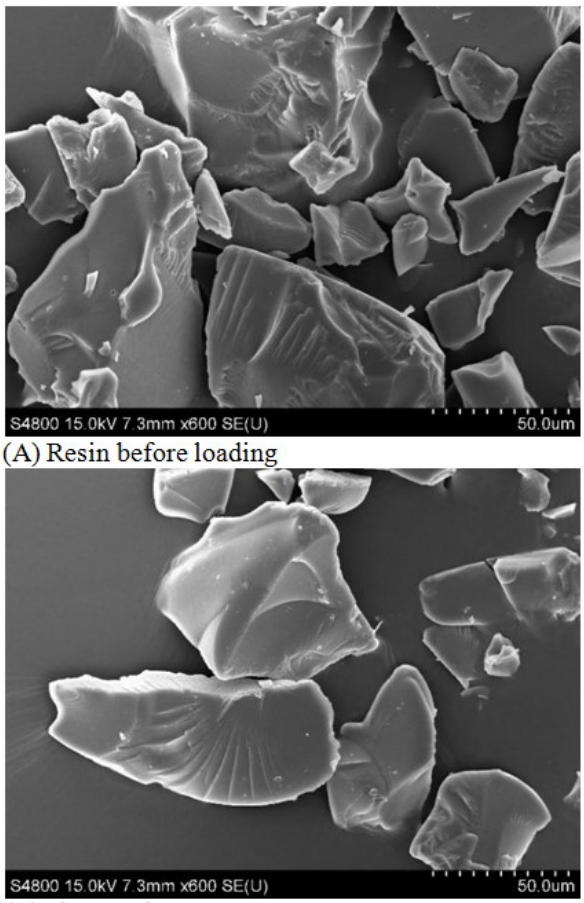

Fig. 3: The SEM of Resin and Drug-Resin

Powder X-ray diffraction properties

The genre of bonding between CH and ion-exchange resin was investigated by powder X-ray diffraction analysis in figure 4.

Differential scanning calorimetry

The thermal behavior of the CH, Resin, physical mixture of CH and ion-exchange resin and CH drug resin complex were investigated by DSC and the result was shown in figure 5.

In vitro release of drug resinates

Effect of temperature in drug release

The consequence are shown in fig. 6, we can see that the effect of temperature was not obvious.

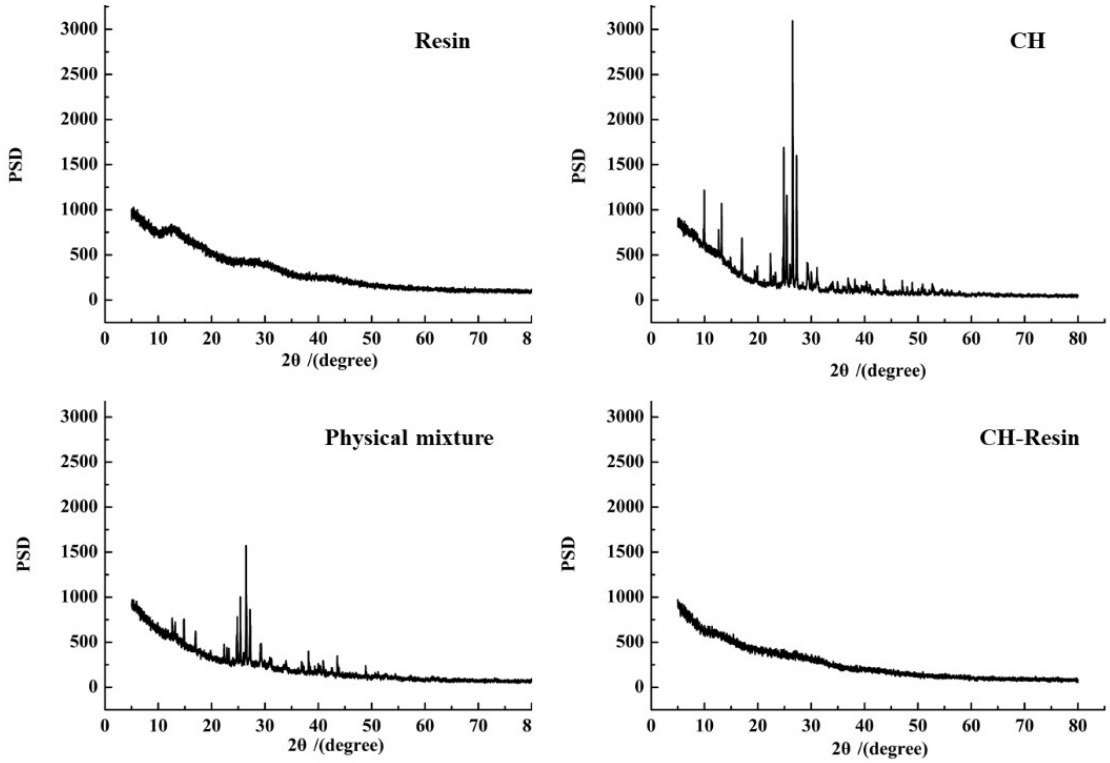

Fig. 4: The spectra of CH and other samples by XRD

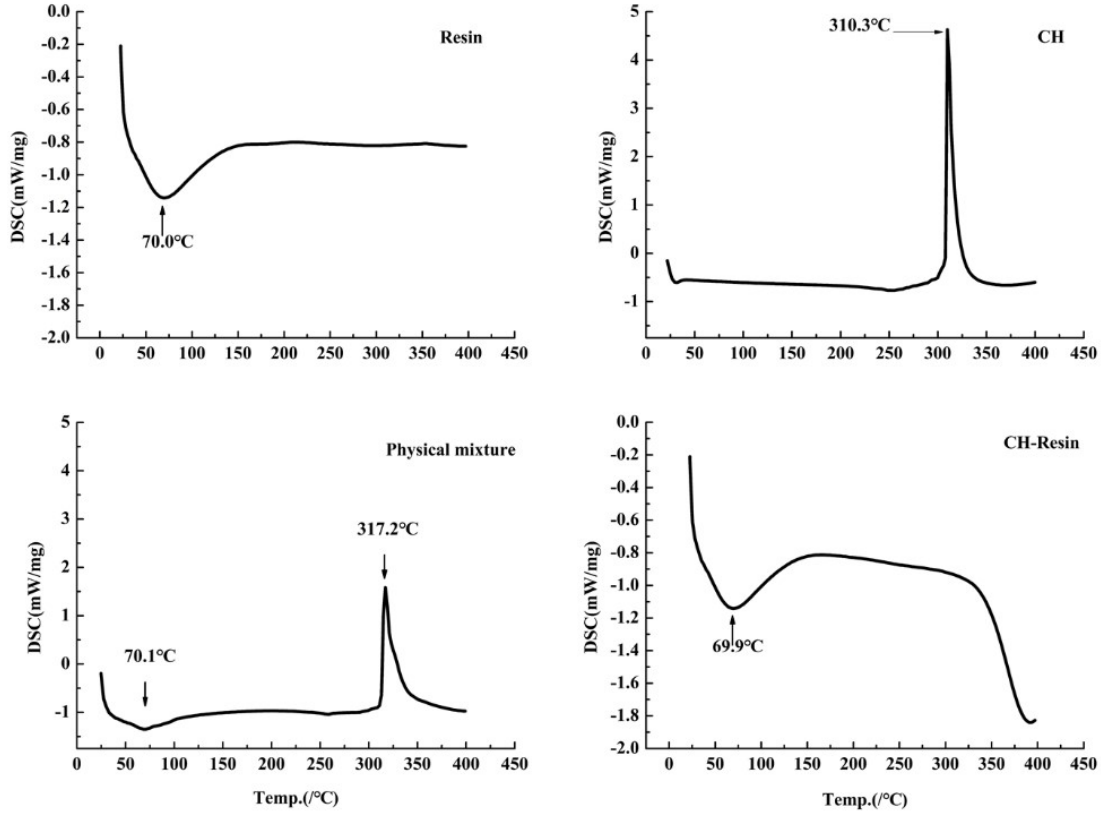

Fig. 5: The curve of resin and CH samples by DSC

Table 7: The release kinetics equation in different conditions

Factors	Conditions	The drug release kinetics	D_r ($m^2 \cdot min^{-1}$)	R
Temperature	298K	y = 1.4644x + 0.4457	$2.44747E^{-08}$	0.9866
	310K	y = 2.5097x + 0.9731	$5.60607E^{-08}$	0.983
	318K	y = 3.4483x + 0.693	$9.13988E^{-08}$	0.9916
Ionic concentration (Na^+)	0.15 $mol \cdot L^{-1}$	y = 2.5097x + 0.9731	$5.60607E^{-08}$	0.983
	0.5 $mol \cdot L^{-1}$	y = 2.5804x + 1.2864	$5.85087E^{-08}$	0.9643
	1.0 $mol \cdot L^{-1}$	y = 6.572x + 0.5891	$2.4652E^{-07}$	0.9852
Medium volume	250 mL	y = 2.0412x + 0.1702	$4.07946E^{-08}$	0.9889
	500 mL	y = 2.3939x + 0.3985	$5.2131E^{-08}$	0.9497
	900 mL	y = 3.535x + 0.5986	$9.49581E^{-08}$	0.9718
Stirring speed	50 rpm	y = 3.8986x + 0.5325	$1.10176E^{-07}$	0.9791
	75 rpm	y = 4.6564x + 0.9562	$1.45086E^{-07}$	0.9759
	100 rpm	y = 4.9747x + 1.0734	$1.60622E^{-07}$	0.9942
Ion species	Na^+	y = 2.07x + 1.0433	$4.16835E^{-08}$	0.9965
	K^+	y = 2.1526x + 0.9773	$4.42697E^{-08}$	0.9651
	H^{+-}	y = 2.9969x + 1.1971	$7.36542E^{-08}$	0.9857

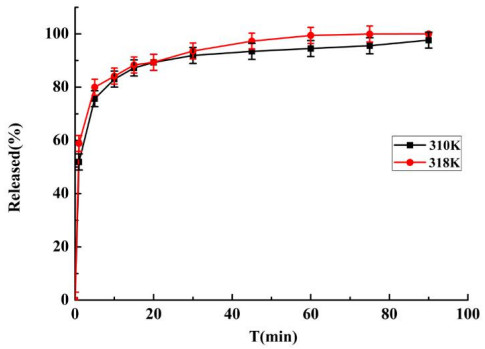

Fig. 6: The effect of temperature on the CH resin release

Effect of the Medium volume in drug release

The results are shown in fig. 7 and we can see that, the medium volume has a great influence on drug release. The total amount of drug release increased significantly with the increase of medium volume.

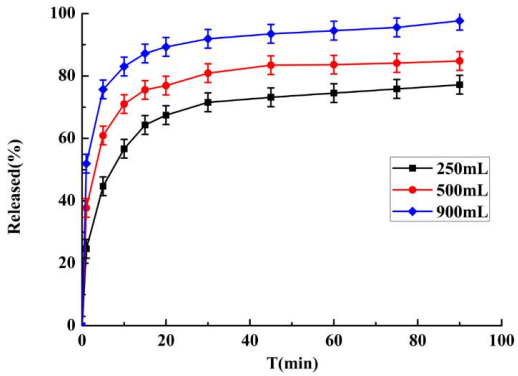

Fig. 7: The effect of medium volume on the CH resin release

Effect of the* stirring speed *in drug release

The results are shown in fig. 8, and we can see a certain relationship between the release speed and the stirring speed.

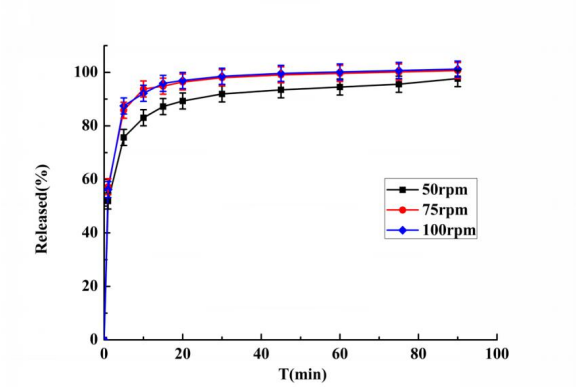

Fig. 8: The effect of stirring speed on the CH resin release

Effect of the kind of counter-ion in drug release

The results are shown in fig. 9, and we can see those different types of counter ions had little influence on the *In vitro* dissolution of CH resin.

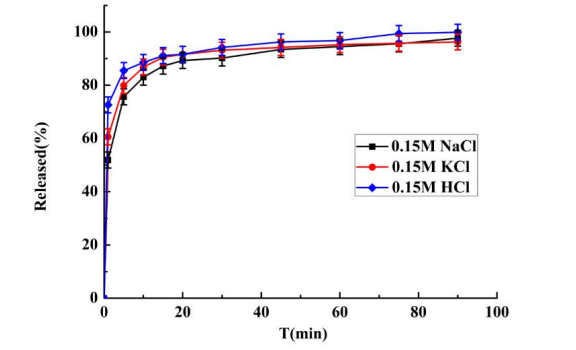

Fig. 9: The effect of Ionic type on the CH resin release

Effect of ion intensity in drug release

The consequences are shown in fig. 10, and we can see that the release speed augmented with the increase of ion intensity.

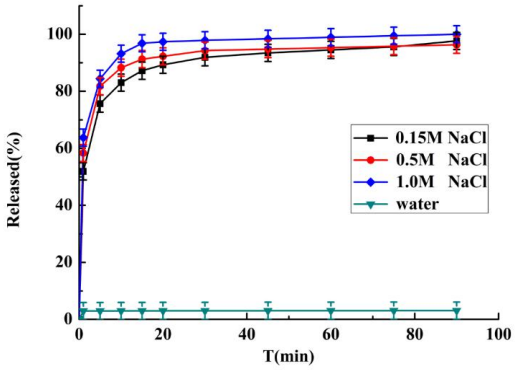

Fig. 10: The effect of ion intensity on the CH resin release

DISCUSSION

Kinetics of the ion-exchange process

Effect of resins type on the ion exchange process

The results showed that compared with Amberlite®IRP64 and IRP88, the Amberlite®IRP69 resin has a higher affinity for ionic drugs, and the speed and degree of ion exchange reaction are also higher. Therefore, the Amberlite®IRP69 resin could be selected to prepare CH resin.

Effect of temperature on the ion exchange process

As the reaction temperature augment, the membrane diffusion rate of drug ions and the rate of drug diffusion into the resin structure also increased, which sped up the ion exchange reaction between CH and resin. However, the experimental data showed that the increase was not too much. Considering all factors of the experiment comprehensively, in order to facilitate the operation of the experiment, the experiment was carried out at the temperature of 298 K.

Thermodynamics of the ion exchange process

In general, the calculation results show that the ion exchange process is an endothermic process, and the increase of temperature is beneficial to the reaction. Therefore, the increase of temperature is beneficial to the preparation of CH resin, which is consistent with the experimental results.

Powder X-ray diffraction properties

There are no crystal characteristic peaks in the X-diffraction pattern of the blank resin, but the diffraction patterns from a physical mixture contained sharp diffraction peaks corresponding to the crystalline drug molecules present in the mixture. However, the characteristic peak of CH disappeared in the X-ray spectrum of CH resin, indicating that CH existed in an amorphous form at this time. It showed that there was no simple physical adsorption between the drug and the resin.

Differential scanning calorimetry

The results are shown in fig. 5, The blank resin and CH had a single peak at 70.0°C and 310.3°C, respectively. The atlas obtained by the physical mixture of blank resin and drug is a simple superposition of the peak patterns of the two substances, while CH drug resin only has a blunt peak at 69.9°C. This indicated that CH crystal changed, the drug existed in amorphous form and there was not a simple physical adsorption between the drug and resin.

In vitro release of drug resinates

Effect of temperature in drug release

Temperature had no obvious effect on drug release, Considering that the normal body temperature is 310 K, 310 K could be chosen as the temperature of dissolution test.

Effect of the Medium volume in drug release

From figure 7, we can see that CH is soluble in 0.15 mol·L^{-1} NaCl, it can reach the condition of leakage in three different volumes of solution. When the volume of solution reaches 900 mL, the number of exchangeable ions in the solution is the largest, and the drug in the resin can be basically released completely.

Effect of the* stirring speed *in drug release

As can be seen from Figure 8, When the stirring speed increases, the *In vitro* dissolution rate of the drug increased slightly at the same time point, and when the reaction finally reached equilibrium, the total dissolution rate of the drug was basically the same. To simulate gastrointestinal conditions, 50 rpm could be selected as the dissolution condition of CH resin.

Effect of the kind of counter-ion in drug release

Different types of counter ions had little influence on the *In vitro* dissolution of CH resin. To simulate gastrointestinal conditions, 0.15 mol·L^{-1} NaCl could be selected as the dissolution condition of CH resin.

Effect of ion intensity in drug release

As can be seen from Figure 10, When water was used as the dissolving medium, the drug could not be released because there were no counter ions. The release rate and amount of CH resin are in direct proportion to the ion intensity. However, with the aggrandize of ion intensity, the impact on the release speed and amount will be reduced. And 0.15 mol·L^{-1} NaCl is the concentration of normal saline, which is similar to the ionic strength in human body fluid. As a dissolution medium, it can better simulate the drug release environment in human body.

From the *In vitro* release results, we can see that the dissolution process of drug-coated resin was influenced by the temperature, stirring speed, medium volume, the strength and type of the ion. The research of drug liberate kinetics from drug resinates mainly uses the grain diffusivity equation (Boyd equation)[1], index equation and logarithm equation (Viswanathan equation), among which Viswanathan Eq was suitable for *In vitro* drug release process of all drugs resin composites.

$$- \ln(1 - F) = -\ln(\frac{Q_t}{Q_0}) = 1.59(6/d)^{1.3} Dr^{0.65} t^{0.65} \quad (10)$$

The *F* represent the release speed of the drugs from the drug-resin complexes; Q_0 is represent the drug content in drug resonates($mg \bullet mg^{-1}$) at the starting time; Q_t was for the drug content in drug resinates ($mg \bullet mg^{-1}$) at time *t*; D_r was for diffusion coefficient of drugs in the resin ($m^2 \cdot min^{-1}$); *d* was for the medial particle size of resin(m); the constant 0.65 and 1.59 was apply to all drugs resin composites. The data of CH release from drug resinates was fitted with Viswanathan equation and the drug release kinetics curve was shown in table 7, the diffusion coefficient Dr in different release medium can be gained the slope of the linear equation.

The results showed that the release of CH -resin accords with Viswanathan equation. The linear relationship is good, indicating that the release process of CH -resin *In vitro* is a granular diffusion process.

CONCLUSION

CH resin were prepared by bath method using cationic-exchange resin as the carrier. The characterization study showed that the combination of CH and resin was a kind of ionic bonded by SEM, DSC, XRD. The influence of the reaction temperature and resin type on process of ion-exchange were investigated, The results showed that The speed of ion exchange increases with the increase of temperature and Amberlite®IRP69 had a higher affinity for ionic drugs.

The kinetic and thermodynamic results showed that the ion exchange reaction between CH and cationic resin conformed to the first order reaction model, the process was an endothermic process and the reaction was spontaneous to the right. In conclusion, the preparation of CH drug resin can be improved by increasing reaction temperature and selecting appropriate ion exchange resin. The *In vitro* liberate test proved that the process of drug release was influenced by the temperature, medium volume, stirring speed, the strength and form of the ion. The drug released by the resin conforms to viswanathan's equation. The results showed that it conformed to the process of particle diffusion. The results of *In vitro* release of CH resin showed that the release equilibrium of CH could be achieved within a relatively short time. Therefore, further coating of CH resin is necessary to achieve a significant sustained release effect.

ACKNOWLEDGEMENTS

This manuscript was supported by 2020 Haimen Dongzhou talent project, Jurong Science & Technology program (Grant No. YF202004, No.ZA42109), 2021 Zhenjiang sixth “169 project” scientific research project, Jiangsu Planned Projects for Postdoctoral Research Funds (No 2020Z209), China postdoctoral science foundation (No 2020 M681532), Zhenjiang science and technology project (No SH2020048), Youth special project of Zhenjiang College in 2019 (No GZQNZX2019017)

REFERENCES

Saito J, Hanawa T and Matsumoto T (2021). Stability of clonidine hydrochloride in an oral powder form compounded for pediatric patients in Japan. *J. Pharm. Health Care and Sci.*, **7**(1): 31.

Aman RM, Meshali MM and Abdelghani GM (2014). Ion-exchange complex of famotidine: sustained release and taste masking approach of stable liquid dosage form. *Drug Discoveries Ther.,* **8**(6): 268-275.

Pande SV, Kshirsagar MD and Chandewar AV (2011). Ion exchange resins Pharmaceutical applications and recent advancement. *Int. J. Advances in Pharm. Sci*., **2**(1): 8-16.

Merino-Bohorquez V, Delgado-Valverde M and Garci-Palomo M (2019). Physicochemical and microbiological stability of two news oral liquid formulations of clonidine hydrochloride for pediatric patients. *Pharm. Dev. Technol.*, **24**(4): 465-478.

Bhoyar PK, Morani DO, Biyani DM, Umekar MJ, Mahure JG and Amgaonkar YM (2011). Encapsulation of naproxen in lipid-based Matrix Microspheres: Characterization and Release Kinetics. *J. Young Pharm*., **3**(2): 112-118.

Davis SS (2005). Formulation strategies for absorption windows. *Drug Discov. Today*, **10**(4): 249-257.

Doraswamy KP and Ramana V (2014). Controlled drug release studies of atenolol using differently sulfonated acryloxyacetophenone and methyl methacrylate copolymer resins as drug carriers. *Chinese J. Polym. Sci*., **32**(3): 280-291.

Du Y, Li DL, Liu XH, Ding XY and Liu HF (2019). Preparation, characterization of trazodone hydrochloride resinates and investigation of the kinetics and thermodynamics of the ion exchange process. *Lat. Am. J. Pharm.*, **38**(7): 1436-1445.

Halder A and Sa B (2006). Sustained release of propranolol hydrochloride based on ion-exchange resinentrapped within polystyrene microcapsules. *J. Microencapsulation*, **23**(8): 899-911.

Ichikawa H, Fujioka K, Adeyeye MC and Fukumori Y (2001). Use of ion-exchange resins to prepare 100 μm-sized microcapsules with prolonged drug-release by the Wurster process. *Int. J. Pharm.*, **216**(1-2): 67-76.

Inui T, Abe W, Kitano M and Nakamura T(2011). Determination of Cr (III) and Cr (VI) in water by wavelength-dispersive X-ray fluorescence spectrometry after preconcentration with an ion-exchange resin disk. *Spectrometry*, **40**(4): 301-305.

Liu HF, Jiang FR, Ding H, Que Y, Xu M and He Y (2018). Preparation and *in vitro*/*in vivo* evaluation of trazodone hydrochloride drug-resin sustained-release suspension. *Lat. Am. J. Pharm*., **37**(9): 1888-1898.

Liu HF, Liu D, Chen C, He Y, Zhu FQ and Zhang P (2017). Preparation and evaluation of carbinoxamine maleate sustained release suspensions with ion exchange resin as the carriers. *Lat. Am. J. Pharm*., **36**(4): 797-809.

Liu HF, Shi SS, Pan WS, Sun CS, Zou XM and Fu M (2014). Biocompatibility research of a novel ph sensitive ion exchange resin microsphere. *Iran. J. Pharm. Res*., **13**(3): 835-842.

Lokhande RS, Singare PU and Kolte AR (2008). ion exchange equilibrium for some uni-univalent and uni-divalent reaction system using strongly basic anion exchange resin Duolite A-102 D. *Bull. Chem. Soc. Ethiop.,* **22**(1): 107-114.

Qu Y, Lai WL, Yin YR, Zhu FQ, Zhu Y and Wang L(2019). Development, optimization and evaluation *in vitro*/*in vivo* of oral liquid system for synchronized sustained release of levodopa/benserazide. *AAPS PharmSciTech*, **20**(8): 312.

Singare PU, Lokhande RS and Prabhavalkar TS (2008). Thermodynamics of ion exchange equilibrium for some uni-univalent and divalent reaction systems using strongly basic anion exchange resin Indion FF-IP. *Bull. Chem. Soc. Ethiop.*, **22**(3): 415-421.

Smith EB(1990). Basic Chemical Thermodynamics. Clarendon Press, Oxford.1990.ISBN 0-19-8555564-4.

Upadhye AA, Ambike AA, Mahadik KR and Paradkar A(2008). Application of ion exchange resin in floating drug delivery system. *Drug dev. Ind. Pharm*., **34**(10): 1117-1124.

Kuldeep KR and Anil KS (2011). Structural basis for the [beta]-adrenergic receptor subtype selectivity of the representative agonists and antagonists. *J. Chem. Inf. Model.,*51(6): 1405.

Yuan J, Liu TT, Li H, Shi T, Xu J and Liu HZ (2014). Oral sustained-release suspension based on a novel taste-masked and mucoadhesive carrier-ion-exchange fiber. *Int. J. Pharm*., **472**(1-2): 78-81.