International Journal of Pharmacy and Pharmaceutical Sciences
Vol 2, Issue 2, 2010

Research Article

CONTROLLED RELEASE OF CHLORPHENIRAMINE FROM RESINATES THROUGH SURFACE COATING WITH EUDRAGIT® RS 100

TANASAIT NGAWHIRUNPAT[a], EVRIN GOEGEBAKAN,[a,b], SUREEWAN DUANGJIT[a], PRASERT AKKARAMONGKOLPORN[a], MONT KUMPUGDEE-VOLLRATH[b,*]

[a] Faculty of Pharmacy, Silpakorn University, Sanamchan Palace Campus, Thailand, [b] Faculty of Pharmaceutical and Chemical Engineering, University of Applied Sciences Berlin, Germany, E mail: vollrath@beuth-hochschule.de

Received: 26 Dec 2009, Revised and Accepted: 28 Jan 2010

ABSTRACT

The purpose of this study is to investigate the effect of Eudragit® RS 100 as a surface coating for controlled release of chlorpheniramine (CPM) resinate. CPM resinate was prepared by the batch method using Dowex® 88 as the resin. The resinates was coated with Eudragit® RS100 solutions at different concentrations (1%, 5%, 10% and 20% w/w) by a dipping method. The release behavior of the drug from the resinate in deionized water (DI), simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and various concentrations of KCl (0.05-0.6 N) was examined and compared. The morphology of the resinates was observed by scanning electron micrograph (SEM). In various dissolution media, the amount of CPM released from CPM uncoated resinate can be ranged as follows: 0.6 N KCl > SIF > 0.2 N KCl >0.05 N KCl > SGF > DI. In Eudragit® RS100 coated resinate, the higher the Eudragit® RS 100 concentrations used for coating the resinate, the slower the release of CPM was observed. Increasing in the amount of polymer increased the coating thickness of the resinates. This increased the path length through which the drug molecule had to diffuse and the time required to transverse the membrane and, hence, made the drug release slower from the resinates. Kinetic studies revealed that the desorption of drug from the resinate obeyed the typical particle diffusion process, whereas the drug release from the coated resinate followed the diffusion controlled model in accordance with the Higuchi equation. These results indicated a simple method using for coating the resinate. In addition, Eudragit® RS 100 appeared to be a suitable polymer to provide prolonged release of chlorpheniramine resinates.

Keywords: chlorpheniramine, Resinates, Coating, Eudragit® RS100

INTRODUCTION

Resinate is a drug-resin complex yielded from the ionized drug loaded onto a resin by chemical ion-exchange reaction[1]. It has superior properties over its original drug such as better stability, better taste, less side effect and more uniform absorption[2]. It is applied for formulating in forms of sustained release pharmaceutical products[3-5]. Resinate products in the market can be classified into single-resinate products and multiple-resinate products[6-7]. Modification of the surface by coating of resinate is one method for controlling the drug release. The resinate can be coated with different polymeric materials such as waxes, ethylcellulose, cellulose acetatebutyrate, Eudragit® RS and nylon[8-10]. However, those coating techniques require the equipment such as spray drying machine or fluid bed coater for producing the products.

Eudragit®, an acrylates/ammonium methacrylate copolymer acrylic polymer, is one of the most popular polymers using for coating of the pharmaceutical products. The aim of this present study is to investigate the effect of Eudragit® RS100 (trimethyl-[2-(2-methylprop-2-enoyloxy)ethyl]azanium; chloride) as a surface coating by dipping method for controlled release of chlorpheniramine (CPM) resinate. CPM resinate was prepared by the batch method using Dowex® 88 as the resin. The resinates were coated with Eudragit® RS100 solutions at different concentrations (1%, 5%, 10% and 20%). The drug release from the resinate in deionized water, simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and various concentrations of KCl (0.05-0.6 N) was examined and compared. The morphology of resinates was observed by scanning electron micrograph (SEM).

MATERIALS AND METHODS

Materials

Dowex® 88 was obtained from Dow Chemical Company (Tokyo, Japan). Chlorpheniramine maleate (CPM) was purchased from Kongo Chemical Co., LTD (Toyama, Japan). Eudragit® RS 100 (ERS) was purchased from Röhm AG (Darmstadt, Germany). Potassium chloride and sodium chloride from Ajak Finechem (Sydney, Australia), Hydrochloric acid 37 % and sodium hydroxide pure pellet were obtained from P.C. Drug Center Co, LTD. (Bangkok, Thailand). All other reagents were obtained commercially and used as received.

Preparation of resinates

Prior to use, the resin (20 g) was placed in a 250 ml beaker and 200 ml distilled water was added. The slurry was stirred with a magnetic bar for 5 min, and allowed to settle for 15 min; then, the supernatant was removed by decantation. The resin was washed another two times according to above procedure. The washed resin was collected by filtration and dried overnight in a hot air oven at 50°C to a constant weight. The dried resin was kept in a tight glass vial until preparation of the resinates.

Resins about 500 mg, accurately weighed, were added to 100 ml of the loading solution of 105 mg of CPM maleate. The mixtures were left in the dark at room temperature (25°C) for 48 h and periodically shaken. The resinates were isolated by filtration and washed with an excess of distilled water which was then collected and added to the previous filtrate. The resinates were dried overnight in a hot air oven at 50 °C, and stored in a tight glass vial. The drug content in each final filtrate, which consisted of the filtrate and washing water, was analyzed by UV spectrophotometer (Hitachi, U-2000, Japan) at 260 nm, which is the maximum absorbance of CPM. The amount of drug loading onto the resinate was obtained from the initial concentration and the remainder concentration in the loading solution at the equilibrium, and was calculated as % drug loaded in Equation 1:

$$\%\,drug\ loaded = \frac{drug\ loaded\ (mg)}{drug\ loaded\ (mg) + re\sin(mg)} x100\% \qquad (1)$$

Coating of resinates with Eudragit® RS 100

The resinate was coated with Eudragit® RS 100 (ERS). ERS was dissolved in dichloromethane at various concentrations (1%, 5%, 10% and 20% w/w). Each sample of 0.9 g of CPM-Resinate was suspended in 5 ml ERS solution for 40 min in an orbital shaker. The coated particle was then isolated by vacuum filtration and air-dried for 24h. The particle sizes of microcapsules and in vitro release of drug were then examined.

Drug release study

Drug release was investigated in triplicate using a USP release testing apparatus II (Prolabo Dissolutest, France)[22]. The sample was accurately weighed to obtain the equivalent of 12 mg of CPM and added into 900 ml of dissolution media. The release medium was

900 ml of deionized water or KCl solutions (0.05–0.6 N), simulated gastric (SGF) and intestinal fluids USP without enzyme (SIF). The rotation and temperature were maintained at 50 rpm and 37±1°C, respectively, throughout testing. At predetermined times, small portions (5 ml) of medium were withdrawn through a filter (0.45 μm) and assayed by an ultraviolet spectrophotometer (Lambda 2, Perkin-Elmer, Germany) at a wavelength of 260 nm. The dissolution profiles of drugs released from the resinate were plotted between % of CPM release as Y-axis and time as X-axis, and the amount of drug released from the resinates at 8 h was compared.

The liberation process from the resinate was examined using Bhaskar's expression[11] as equation (2):

$$-\ln (1-F) = -\ln (Q_o/Q_t) = 1.59 \ (6/d_p)^{1.3} \ D^{0.65} \ t^{0.65} \qquad (2)$$

F represents the fraction of drug released from the resinate at time t (min), Q_0 is the initial drug content of the resinate ($g.g^{-1}$), Q_t is the drug content of the resinate at time t ($g.g^{-1}$), D is the diffusion coefficient of the drug within the resin ($mm^2.min^{-1}$), d_p is the mean diameter of the resin (mm), and t is the time of dissolution (min). The logarithmic of the fraction of drug release from the resinate (-ln (1-F)) was plotted against $t^{0.65}$.

Scanning electron microscopy (SEM)

The surface morphology of resinate and coated resinate was viewed by an electron scanning electron microscope (CamScan MX 2000, UK). Prior to testing, samples were fixed on stubs and sputter coated with gold in a vacuum evaporator (Cressington Sputter Coater 108, UK).

Statistics

Analysis of variance (ANOVA) with Dunnett's test in multiple comparison was used for statistical evaluation of the drug release among the resinates. *P*-values of < 0.05 were considered to represent a statistically significant difference.

RESULTS AND DISCUSSION

Preparation of resinates

The CPM resinate was obtained using the batch method. The resinates were round and free flowing. The amount of the drug in the loading solution and in the resinate during preparation are presented in Table 1. The low difference in the percent of the drug before and after washing process at the equilibrium (0.02% w/w) indicated that washing process did not significantly affect the amount of the drug. The content of the CPM in the solution kept under the preparation condition was not changed in our preliminary study. In our previous report, we found that CPM was dispersed monomolecularly in its resinate, and ionic association was formed between the sulfonate groups of the resin and the NH^+ group of CPM[12]. Therefore, the CPM resinate was successfully prepared.

In vitro release study

Uncoated CPM resinate

Figure 1a shows the dissolution profiles of CPM from CPM uncoated resinate in various dissolution media. The retard release profiles of the drugs from all types of the resinates were observed. The sustained release property of Dowex® 88, a strongly cationic exchange resin, with various drugs has been reported, and it was discussed with their crosslinked structure which resists drug diffusion through the resin beads[7,13-16]. Figure 2 shows the Bhaskar's plots of drugs released from the resinates in various dissolution media. A high linear regression analysis ($r^2 > 0.98$) was obtained from the plot between –ln (1-F) and $t^{0.65}$, therefore, the drug liberation mechanism was clarified to be the particle diffusion control[11,17,18].

Table 1: The amount of the drug in the solution and amount of drug loading during preparation of the resinate.

Conditions for preparation		Amount of CPM in the solution (mg)	Amount of CPM loading (mg)
At initial		105	105
At equilibrium	Before washing	9.13	95.87
	After washing	9.11	95.89
Difference[1]			0.02

[1] Amount of the drugs after washing minus before washing

The apparent amount of CPM released from CPM uncoated resinate in various media at 8 h was presented in Table 2. In various dissolution media, the amount of CPM released from CPM uncoated resinate can be ranged as follows: 0.6 N KCl > SIF > 0.2 N KCl >0.05 N KCl > SGF > DI. There was very low CPM released (0.2 %) in the deionized water. In the drug resin complex, the drug bound with the sulfonic group of the resin by electrostatic attraction, and was not liberated unless it was replaced by another counter-ion[1]. Since there were no counter-ions in DI, only the limited amount of drug remaining unbound was available for the release, thus explaining the smaller amount of released drug. In regard to ion exchange resin-based dosage forms, ions played an important role in the drug release[18]. Therefore, CPM released from resinate was further investigated in 0.05–0.6 N KCl solutions, SGF and SIF. As expected, it was found that the presence of ions in the release medium greatly influenced the CPM released from the resinate (Fig. 1 and Table 2). The drug release in KCl solutions was higher than that in DI. This was possible because potassium ion (K^+) acted as a cationic counter-ion, like the drug, and could exchange for Na^+ in the resin. During the release and complex formation process, the released drug (CPM) therefore competed with K^+ in exchange for Na^+ in the resin, which then formed less of the drug–resin complex (Eq. 3), meaning that a larger amount of drug remained available for release. Even in cases where the drug–resin complex was already formed, the bound drug would be replaced by K^+ and then liberated from the complex (Eq. 4), thus further promoting the release. As shown in Fig. 1, the increase in the concentration of KCl solutions dramatically increased the release. According to the equilibrium treatment of Eq. 3 and Eq. 4, the increased K^+ could more effectively both prevent the released drug (CPM) from forming the drug–resin complex and liberate the bound drug from the formed complex. Chloride ion (Cl^-), the anionic co-ion, was not involved in the cationic exchange of this resin and hence in these phenomena[8].

$$RSO_3Na + CPM^+ + K^+ \leftrightarrow RSO_3 (CPM/K) + Na^+ \qquad (3)$$

$$RSO_3CPM + K^+ \leftrightarrow RSO_3K + CPM^+ \qquad (4)$$

The gastrointestinal fluids containing a number of ions, it was also worth determining how the release behaved in SGF and SIF. Like in KCl solutions, the drug release in the SGF and SIF was higher than that in DI. This was due to the existence of cationic ions, i.e. the mixture of H^+ and Na^+ in SGF and the mixture of K^+, H^+ and Na^+ in SIF, which competed with the drug in the ion exchange process as explained above. The amount of CPM released in SGF was considerably lower than that in SIF (10.3 times, Table 2). CPM, a weak base drug, ionized to a greater extent in SGF and then preferred binding with rather than releasing from the resins. The percent exchange of the drug onto the resin, which directly related to the equilibrium constant of the exchange reaction[14] was significantly different in SGF and SIF (data not shown). As the type and concentration of ion in SGF and SIF are different, the difference in the equilibrium constant of the exchange reaction was occurred. The percent exchange of the drug onto the resin inversely related to the apparent amount of the drug release. Therefore, the difference of the amount of the drug release in different media may be due to the variability of the equilibrium or exchange constant.

Table 2: The apparent amount of chlorpheniramine released at 8 h from the CPM resinate in various dissolution media [a)]

Dissolution systems	Percent of apparent amount of CPM released (S.D.)
Deionized water	0.21 (0.03)
Simulated gastric fluid	3.72 (0.21)*
Simulated intestinal fluid	38.2 (3.1)*,**
0.05 N KCl	30.4 (2.5)*,**
0.2 N KCl	42.5 (2.8)*,**
0.6 N KCl	83.8 (4.1)*,**,***

[a)] Each point represents the mean ± S.D. of three to five experiments. * p<0.05 compared with deionized water,** p<0.05 compared with simulated gastric fluid, *** p<0.05 compared with simulated gastric fluid, simulated intestinal fluid, 0.05 N KCl and 0.2 N KCl.

Table 3: Effect of ERS concentration as coating agent on chlorpheniramine release kinetics data from coated resinates in 0.6 N KCl.

Concentration of ERS (% w/w)	Bhaskar's equation	Korsmeyer-Peppas's equation		Higuchi's equation	
	Correlation coefficient (r^2)	Correlation coefficient (r^2)	n	Correlation coefficient (r^2)	Diffusion rate ($h^{-1/2}$)
1	0.912	0.989	0.48	0.991	28.52
5	0.923	0.996	0.51	0.997	21.44
10	0.932	0.992	0.51	0.998	16.91
20	0.965	0.979	0.47	0.981	3.28

Coated CPM resinate

As the amount of CPM release from CPM uncoated resinates was the highest in 0.6 N KCl, this medium was selected to be the dissolution medium for CPM coated resinates. Figure 2a shows the dissolution profiles of CPM from CPM coated resinate in 0.6 N KCl. It is seen that the higher the ERS concentration used for coating the resinate, the slower the release and the release rate of CPM were observed (Table 3). As discussion in the previous section, even in cases where the drug–resin complex was already formed, the bound drug would be replaced by K^+ and then liberated from the complex, thus further promoting the release. At higher concentrations of ERS, the microcapsules were well formed and uniformly coated. Consequently, the typical drug release mechanism of the microencapsulated resinate became operative, resulting in a slower release. Increasing in the amount of the polymer, not only caused uniform coating but also increased the coating thickness of the microcapsules. This increased the path length through which the drug molecule had to diffuse and the time required to transverse the membrane and, hence, made the drug release slower from the resinates. This finding agreed with the SEM results in which thickness on the surface of resinates appeared progressively increased with increasing the polymer incorporation (Fig. 3a–e, right side). At 20 % w/w of ERS (Fig 3 d-e, left side), the morphology of the surface was coarser than that at 1-10 % of ERS, indicating some adhesion of the coated resinate at this coating polymer concentration. However, the slowest of CPM released from these coated resinates was observed. ERS has been utilized for the coating process in various studies [4,8,10]. However, the coating methods in these previous studies require special equipments such as a spouted bed coater or a spray dryer. The chemical reaction can be also used but it is time consuming because of o/w evaporation process. In our study, SEM of x-section of coated resinate showed the homogeneity of the polymer coating, shown by the uniformity of thickness of coated resinate (Fig. 3b-e, right side). Moreover, the shape of the resinates after the dissolution studies was found to be unaltered (data not shown). This indicates that ERS coating provided sufficient resistance to prevent the rupture of the coating film that would normally result from the rehydration and swelling of the dried resinate, and hence, that the process does not require any impregnating agent. These results indicated the suitability of the coating process using ERS in our study.

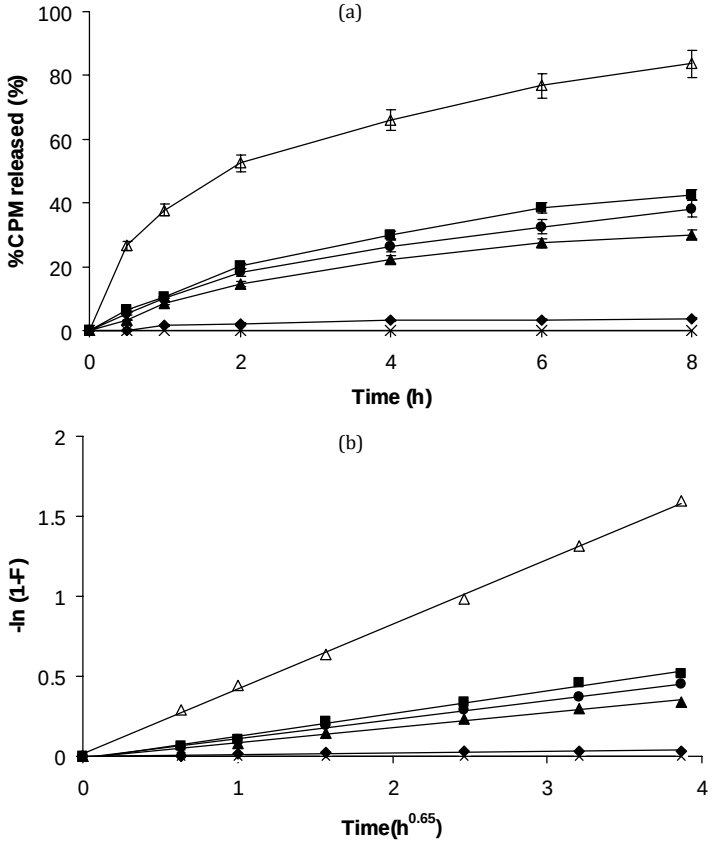


Fig. 1: a) Release of chlorpheniramine from resinates , and b) Bhaskar's plot of chlorpheniramine released from resinates in deioned water (x), simulated gastric fluid (♦), simulated intestinal fluid (■), 0.05 N KCl(▲), 0.2 N KCl (●) and 0.6 N KCl (△). Each point represents the mean ± S.D. of three to five experiments.

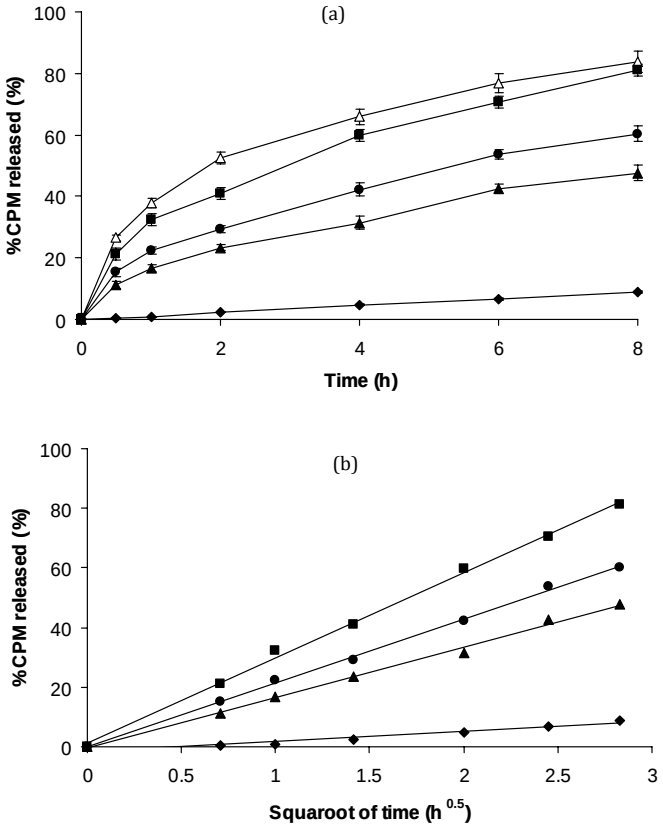
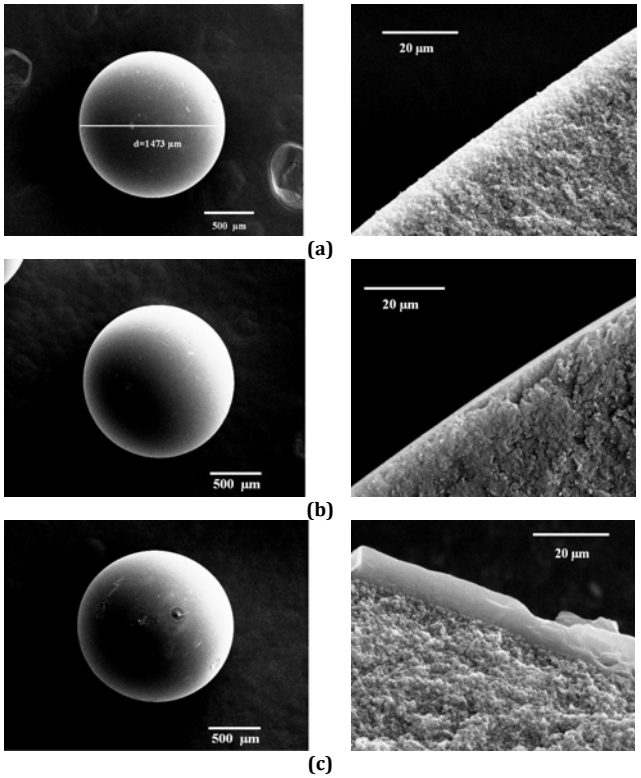


Fig. 2: a) Release of chlorpheniramine from ERS 100 coated resinate and b) Higuchi's plot of chlorpheniramine released from ERS coated resinate at ERS concentration of 0% (△),1% (■),5% (●),10% (▲) and 20%(♦). Each point represents the mean ± S.D. of three to five experiments.



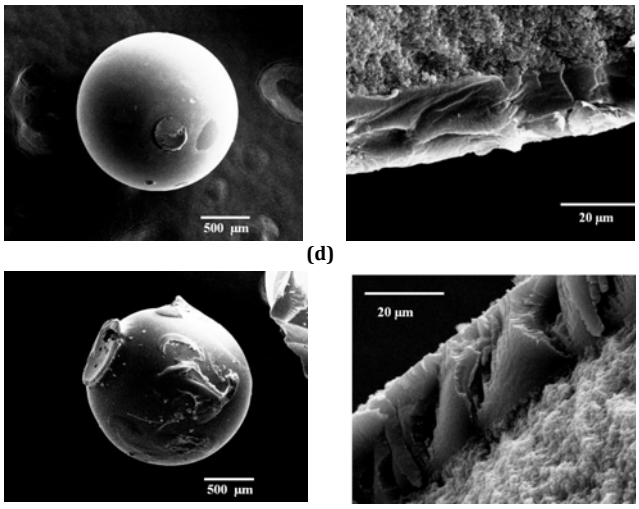


Fig. 3: SEM of ERS 100 coated resinates (left) and cross section (right) at ERS concentration of a) 0% , b) 1%, c) 5%, d) 10% and e) 20% w/w (Left, 50X, BAR=500 µm; right 2000X, BAR=20 µm).

The correlation coefficient of the plot between –ln (1-F) and $t^{0.65}$ was higher than 0.98 (Table 3), therefore the exchange of drug from the uncoated resinate was found to follow the particle diffusion process as the equation developed by Bhaskar et al.[8] in Eq.2, confirming that the release rate from the resin was controlled by particle diffusion (Fig. 1b). Drug release from the coated resinates has also been reported to follow the particle diffusion process[10,19]. However, CPM release from the ERS in our studies was found to deviate from the particle diffusion mechanism; as shown in Table 1, r^2 were between 0.91-0.96 by Bhaskar's model. Hence, the data then were fitted into the Korsmeyer-Peppas model[20] in Eq.5,

$$Mt/M\alpha = at^n \qquad (5)$$

where a is a constant incorporating structural and geometric characteristics of the dosage form; n is the release exponent, indicative of the drug release mechanism; and the function of t is Mt/Mα (fractional release of drug). Acceptable linearity was observed (r^2>0.97, Table 3), and the values of n varied from 0.47 to 0.51 (Table 3). This indicates that the Fickian type of transport mechanism might be operative in the release of CPM from the coated resinate. The release data were then fitted into the Higuchi model [21] in equation (6), and plotted in Figure 2b.

$$Q = kt^{1/2} \qquad (6)$$

where Q is the amount of drug release, k is the release rate constant and t is time. The correlation coefficient of the plot between percent of CPM release and $t^{0.5}$ was higher than 0.98 (Table 3), for all the coated resinates. The present study indicated that release of CPM from the ERS-coated resinates obeyed a diffusion controlled process because the correlation coefficient is the highest among three plotted equations.

CONCLUSION

The CPM resinate and ERS coated CPM resinate were successfully prepared. The dissolution medium affected the release of the drug from the resinate. The higher the ERS concentrations used for coating the resinate, the slower the release of CPM was observed. Kinetic studies revealed that the release of drug from the resinate obeyed the typical particle diffusion process, whereas the drug release from the coated resinate followed the diffusion controlled model in accordance with the Higuchi equation. These results indicated a simple method for coating the resinate. Moreover, ERS appeared to be a suitable polymer to provide prolonged release of chlorpheniramine.

ACKNOWLEDGEMENTS

The authors wish to thank the Thailand Research Funds through the Golden Jubilee Ph.D. Program (Grant No. PHD/0141/2550) and TRF-DAAD Research Based mobility Scheme Project 2008 (D/08/04910) for the financial support.

REFERENCES

1. Borodkin S. Ion exchange resins and sustained release. In: Swarbick J, Boylan, J.C., editors. *Encyclopedia of Pharmaceutical Technology* .Marcel Dekker, New York. P.203-216.
2. Irwin WJ, Belaid KA, Alpar, HO. Drug-Delivery ion-exchange. Part III: Interaction of ester pro-drugs of propranolol with cationic exchange resins. Drug Dev Ind Pharm 1987; 13 Suppl 9: 2047-2066.
3. Burke GM, Mendes RW, Jambhekar SS. Investigation of the applicability of ion-exchange resins as a sustained release drug delivery system for propranolol hydrochloride. Drug Dev.Ind Pharm1986; 12 Suppl 1:713–32.
4. Cuna M, Jato JLV, Torres D. Controlled-release liquid emulsions based on ion-exchange particles entrapped within acrylic microcapsules. Int J Pharm 2000; 199:151–158.
5. Zhang ZY, Ping QN, Xiao B. Microencapsulation and characterization of tramadol–resin complexes. J Control Rel 2005; 66:107–113.
6. Anand V, Kandarapu R, Garg S. Ion-exchange resins: carrying drug delivery forward. Drug Del 2001; 26 Suppl 17: 20-27.
7. Pongjanyakul T, Priprem A, Chitropas P, Puttipipatkhachorn S. Effect of polysulfonate resins and direct compression fillers on multiple-unit sustained-release dextromethorphan resinate tablets. AAPS PharmSciTech. 2005 ; 30 Suppl 6:E190-197.
8. Sriwongjanya M, Bodmeier R. Entrapment of drug-loaded ion exchange particles within polymeric microparticles. Int J Pharm 1997; 158:29–38.
9. Torres D, Seijo B, Garcia-Encina G, Mjose A., Vila-Jato J.L. Microencapsualation of ion-exchange resins by interfacial nylon polymerization. Int J Pharm 1990;59 Suppl 1:9-17.
10. Ichikawa H, Fujioka K, Adeyeyye MC, Fukumori Y. Use of ion-exchange resins to prepare 100 mm-sized microcapsules with prolonged drug-release by the Wurster process. Int J Pharm 2001; 216 Suppl 1 :67-76.
11. Bhaskar R, Murthy RSR, Miglani BD, Viswanathan K. Novel method to evaluate diffusion controlled release of drug from resinate. Int J Pharm 1986;28: 59-66.
12. Akkaramongkolporn P, Yonemochi E, Terada K. Molecular state of chlorpheniramine in resinates. Chem Pharm Bull 2000; 48: 231–4.
13. Akkaramongkolporn P, Kulvanich P, Pathipvanich M. Preparation and in vitro release of dual-drug resinates containing

equivalent content dextromethorphan and diphenhydramine. Drug Dev Ind Pharm 2006; 32 Suppl 4: 483-96.
14. Akkaramongkolporn P, Ngawhirunpat T. Dual ambroxal and chlorpheniramine resinate as an alternative carrier in concurrent resinate administration. Pharmazie 2003; 58: 195-199.
15. Jeong SH, Berhane NH, Haghighi K, Park K. Drug release properties of polymer coated ion-exchange resin complexes: experimental and theoretical evaluation. J Pharm Sci 2007; 96 Suppl 3:618-32.
16.Junyaprasert VB, Manwiwattanakul G. Release profile comparison and stability of diltiazem-resin microcapsules in sustained release suspensions. Int J Pharm 2008; 352 Suppl 1-2:81-91.
17. Gyselinck P, Steyaert H, Severen RV, Braeckman P. Drug polymer combinations. Part 2: Evaluation of some mathematic approaches to drug release from resinates. Pharmazie1982; 37:190-193.
18. Ogger KE, Noory C, Gabay J, Shah VP, Skelly JP. Dissolution profiles of resin-based oral suspensions. Pharm Tech 1991; 9:84–91.
19. Motycka S, Nairn JG. Preparation and evaluation of microencapsulated ion-exchange resin beads. J Pharm Sci 1979; 68:211-215.
20. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25-35.
21. Schwartz JB, Simonelli AP, and Higuchi WI. Drug release from wax matrices. I. Analysis of data with first-order kinetics and with the diffusion-controlled model. J Pharm Sci 1968;57:274-277.