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Dual ambroxal and chlorpheniramine resinate as an alternative carrier in concurrent resinate administration

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Two classical resinates, ambroxal (AMX) resinate and chlorpheniramine (CPM) resinate, and a novel formulation of dual AMX and CPM resinate were prepared by the batch method. The dissolution behavior of the drug from the classical resinates, a mixture of two classical resinates, and the dual-drug resinate in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) was examined and compared. The equilibrium of drug on to the resin and the re-exchange of the drug on to the resinate were also investigated. The drug release pattern from the resinate followed the particle diffusion process. The type of dissolution medium affected the amount of drug released from the resinate. The amount of drug released from the dual AMX and CPM resinate was not significantly different from that from the classical AMX resinate or CPM resinate ($p < 0.05$), but was considerably higher than that from the concurrent administration of two classical resinates ($p > 0.05$). These results indicated that the concurrent administration of the resinates affected drug release from the resinate, and the dual-drug resinate can be used as an alternative carrier for an ion-exchange delivery system.

1. Introduction

Resinate is a drug-resin complex prepared from an ionized drug loaded on to a resin by a chemical ion-exchange reaction [1, 2]. It has superior properties over its original drug such as better stability, better taste, fewer side effects and more uniform absorption [3–5]. It is used for formulating certain sustained release pharmaceutical products [6, 7]. Resinate products on the market can be classified into single-resinate products and multiple-resinate products [8].

The concurrent administration of pharmaceuticals causes a high incidence of pharmaceutical interactions, which can alter the therapeutic efficacy of the pharmaceuticals [9–10]. The concurrent administration of resinates with other resinates or with other drugs is found in clinical therapy. Theoretically, such administration may possibly affect the rate and amount of drug release from the resinates, although, this pharmaceutical interaction has not been proven, and no attempt to solve this disadvantage has yet been reported.

The objectives of this study were to examine *in vitro* drug release from the resinate in cases where they were administered separately and concurrently and to introduce a novel resinate formulation called a dual-drug resinate as an alternative carrier for concurrent admistration of the resinates. Two classical resinates, ambroxal (AMX) resinate and chlorpheniramine (CPM) resinate, and a resinate containing AMX and CPM (dual AMX and CPM resinate) in equivalent doses were prepared. The dissolution behavior of drug released from the classical resinates, the mixture of classical resinates and the dual-drug resinate was examined and compared. Finally, we clarified the interactions of the drugs released when the resinates were administered concurrently.

2. Investigations, results and discussion

2.1. Preparation of resinates

The AMX resinate, the CPM resinate, and the dual AMX and CPM resinate containing equivalent doses of AMX and CPM were obtained using the batch method. The resinates were rounds free flowing spheres. The amounts of drug in the loading solution and in the resinate during preparation are presented in Table 1. The small difference in the percentage of drug before and after the washing the process at equilibrium (0.02–0.56%) indicated that the washing process did not significantly affect the amount of drug. The content of AMX and CPM in the solution kept under the preparation conditions was not changed in our preliminary study. In a previous report, we determined that AMX or CPM were dispersed monomolecularly in their resinates, and an ionic association was formed between the sulfonate groups of the resin and the NH^+ group of AMX or CPM [11, 12]. Thus, two classical resinates, AMX resinate and CPM resinate, and the dual AMX and CPM resinate were successfully prepared.

2.2. In vitro release study

Figure 1 shows the dissolution profiles of AMX and CPM from AMX resinate or CPM resinate compared with those

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

Type of resinate	Amount of the drugs in the solution (mg)						Amount of drug loading (mg)					
	Initially		At equilibrium				At equilibrium				Difference[1]	
			Before washing		After washing		Before washing		After washing			
	AMX	CPM	AMX	CPM	AMX	CPM	AMX	CPM	AMX	CPM	AMX (%)	CPM (%)
AMX resinate	625	–	17.75	–	17.63	–	607.25	–	607.37	–	0.12 (0.02)	–
CPM resinate	–	105	–	9.13	–	9.11	–	95.87	–	95.89	–	0.02 (0.02)
Dual AMX and CPM resinate	750	120	136.14	20.75	132.73	20.47	613.86	99.25	617.27	99.53	3.41 (0.56)	0.30 (0.28)

[1] Amount of the drugs after washing minusbefore washing

from a mixture of AMX and CPM resinates and the dual-drug resinate in SGF and SIF. The retarded release profiles of the drugs from all types of resinates were observed. The sustained release property of Dowex® 50W X2, a strongly cationic exchange resin, with various drugs has been reported, and it has been proposed that their crosslinked structure resists drug diffusion through the resin beads [13–16].

Figure 2 shows the Bhaskar plots of drug release from the resinates in SGF and SIF. A high linear regression analysis coefficient ($r > 0.9$) was obtained from the plot between $-\ln(1 - F)$ and $t^{0.65}$, and therefore the drug liberation mechanism was shown to be particle diffusion control [17].

The apparent amount of AMX and CPM released from various resinates at 8 h in SGF and SIF is presented in Table 2 and 3, respectively. The amount of AMX released in SGF was somewhat greater than that in SIF for all types of resinates (1.1 times, Table 2). However, the amount of CPM released in SGF was considerably lower than that in SIF (2.6 times for CPM resinate and dual-drug resinate, and 4.7 times for concurrent administration of CPM resi-

Table 2: Apparent amount of AMX released at 8 h from the AMX resinate, the mixture of AMX resinate and CPM resinate and the dual-drug resinate in simulated gastric fluid and simulated intestinal fluid

Resinates in dissolution systems	Type of resinates	Percent of apparent amount of AMX released (S.D.)	
		Gastric fluid	Intestinal fluid
AMX resinate	Classical	87.22 (0.77)	76.37 (1.38)
AMX resinate concurrent with CPM resinate	Mixture	71.14 (0.96)*	62.89 (0.96)*
Dual-drug resinate	Dual	86.07 (2.04)	71.73 (1.53)

* $p < 0.05$ compared with the AMX resinate and the dual-drug resinate

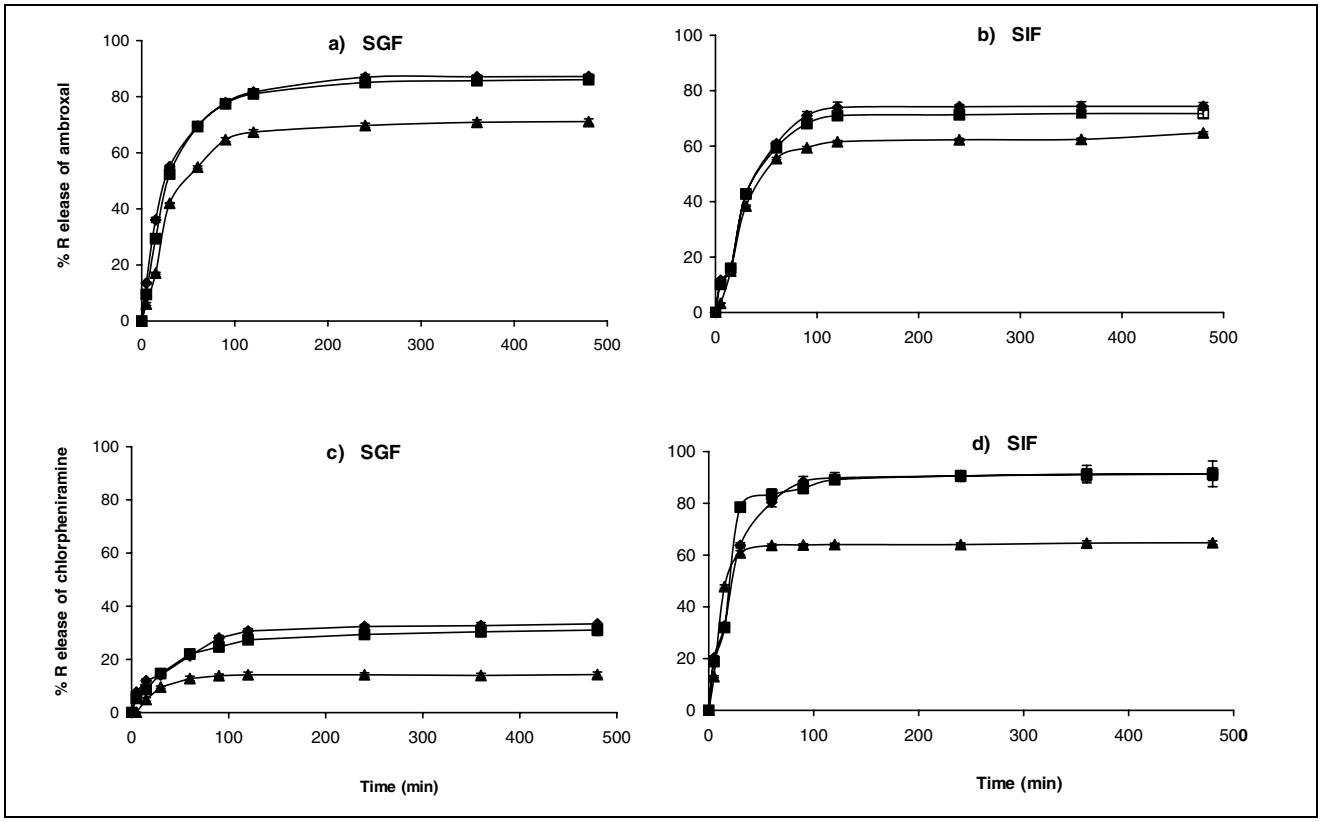

Fig. 1: Profiles of AMX and CPM released from the resinates in SGF (a, b) and SIF (b, d). ◆, AMX resinate (a, b) or CPM resinate (c, d); ■, dual-drug resinate containing AMX and CPM; ▲, the mixture of AMX resinate and CPM resinate. Each point represents the mean ± S.D. of three experiments

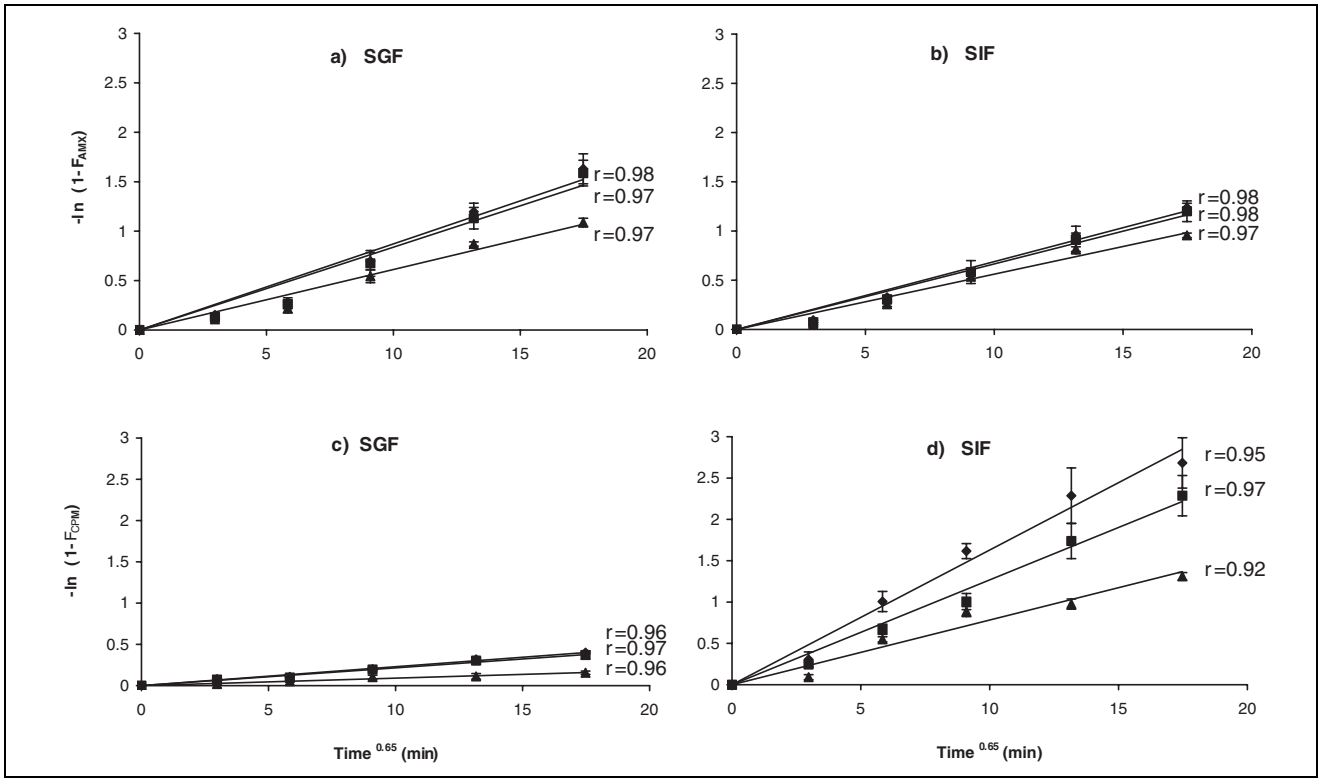

Fig. 2: Bhaskar's plots of AMX and CPM released from the resinates in SGF (a, c) and SIF (b, d). ◆, AMX resinate (a, b) or CPM resinate (c, d); ■, the dual-drug resinate containing AMX and CPM; ▲, the mixture of AMX resinate and CPM resinate. Each point represents the mean ± S.D. of three experiments

nate and AMX resinate, Table 3). Table 4 shows the equilibrium of the drug exchange on to the resin in SGF and SIF. The percentage drug exchange on to the resin in SGF and SIF was similar for AMX, but was significantly different for CPM.

The type of dissolution medium considerably influenced the apparent amount of the drug released from the resinates. However, the magnitude of this effect depended on the type of drug. To clarify the effect of the dissolution medium, we focused on the solubility of the drug, particle size of the resin and equilibrium constant of the exchange reaction. The solubilities of AMX and CPM in SGF and SIF are different [18], however, a sink-like condition was provided for AMX and CPM in these dissolution systems. It is generally accepted that sink conditions exist provided that the concentration of solute in the dissolution media does not exceed 10% of its saturated solubility [19]. Therefore, the solubility of the drug in each medium may not affect the amount of drug released. Although no significant difference was found in the particle size of the resinate after immersion in SGF and SIF (181 ± 22 micron in SGF, and 179 ± 24 in SIF, data not shown), the percentage exchange of the drug on to the resin, which directly related to the equilibrium constant of the exchange reaction [20] was different in SGF and SIF, especially for CPM (Table 4). The type and concentration of ion in SGF and SIF is different [21], and this might cause the difference in the equilibrium constant of the exchange reaction. The percentage exchange of the drug on to the resin is inversely related to the apparent amount of the drug released. Therefore, the difference in the amount of the drug released in different media may be due to the variability of the equilibrium or exchange constant.

The rate limiting step of drug release from the resinate depends mainly on the feasibility of movement or diffusibility of the drug molecule through the tight pore structure of the resin. The diffusion coefficients of the drug within the resin calculated from Bhaskar's expression are shown in Table 5. The diffusion coefficients of AMX and CPM in classical resinates were similar to those in the dual-drug resinate, but were considerably higher than those in the mixture of two classical resinates. The amount of AMX and CPM released at 8 h from the concurrent administration of AMX resinate and CPM resinate was also signifi-

Table 3: Apparent amount of CPM released at 8 h from the CPM resinate, the mixture of AMX resinate and CPM resinate and the dual-drug resinate in simulated gastric fluid and simulated intestinal fluid

Resinates in dissolution systems	Type of resinates	Percent of apparent amount of CPM released (S.D.)	
		Gastric fluid	Intestinal fluid
CPM resinate	Classical	33.37 (1.12)	91.41 (4.95)
AMX resinate concurrent with CPM resinate	Mixture	14.30 (0.96)*	64.78 (0.73)*
Dual-drug resinate	Dual	31.04 (2.04)	91.30 (2.41)

* $p < 0.05$ compared with the CPM resinate and the dual-drug resinate

Table 4: Equilibrium of the drugs exchanged on to the resin in simulated gastric fluid and simulated intestinal fluid

Drugs	Type of media	Amount of the drugs in the solutions			% Exchange
		Initial	Equilibrium	Exchanged	
AMX	Gastric	37.5	19.34	18.16	48.43
	Intestinal	37.5	18.52	18.98	50.61
CPM	Gastric	6.0	0.92	5.08	84.67
	Intestinal	6.0	3.52	2.48	41.33

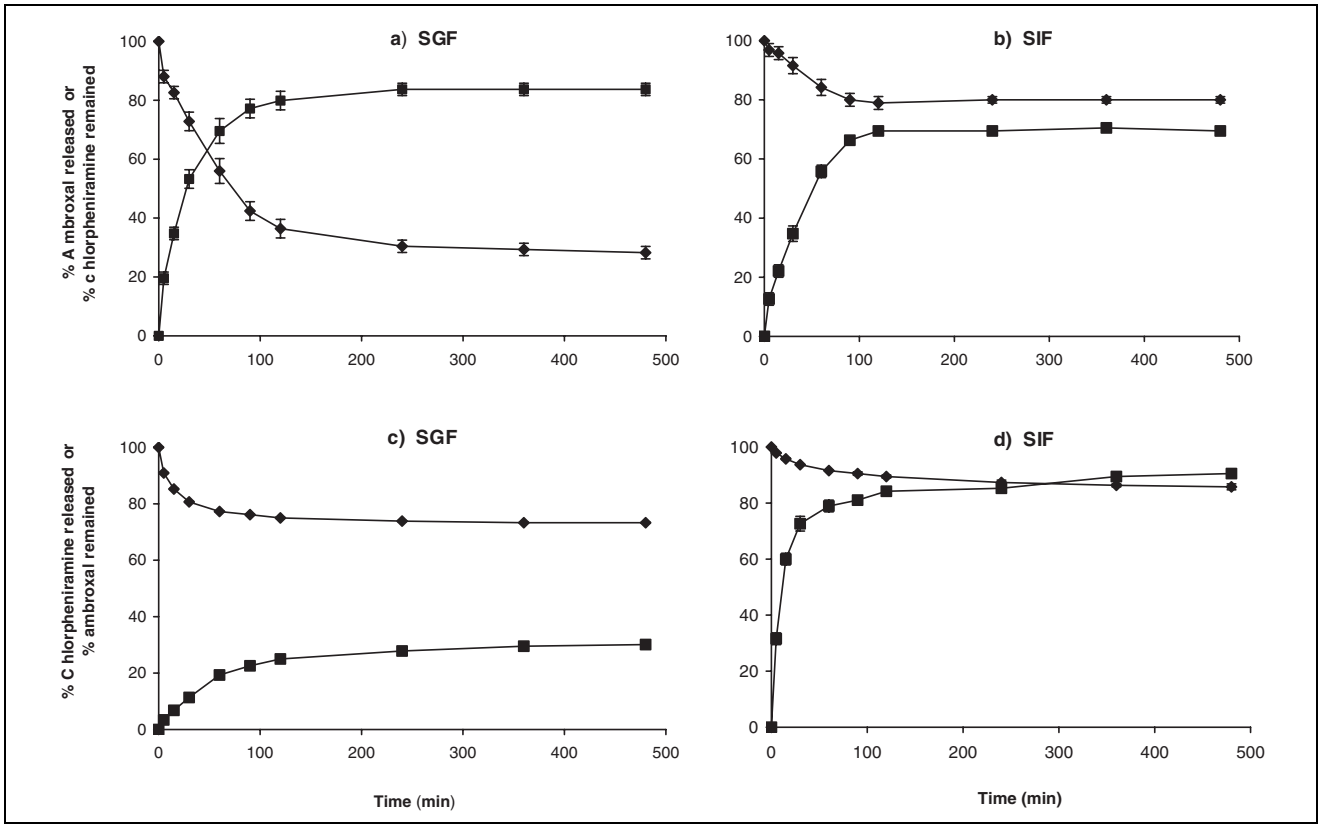

Fig. 3: Concentration profile of AMX remaining and CPM released after adding CPM resinate (a, b) and that of CPM remaining and AMX released after adding AMX resinates (c, d) in SGF (a, c) and (SIF) (b, d). ◆, AMX released (a, b) or CPM released (c, d); ■, CPM remaining (a, b) or AMX remaining (c, d). Each point represents the mean ± S.D. of three experiments

cantly lower than that from the classical AMX resinate and CPM resinate, and the dual AMX and CPM resinate ($p < 0.05$) (Tables 2, 3). Figure 3 shows the concentration profile of AMX remaining and CPM released after adding CPM resinate and CPM remaining and AMX released after adding AMX resinates to SGF and SIF. The reduction of AMX or CPM after adding the resinate containing CPM resinate or AMX resinate was observed in both dissolution media. It might be caused by the fact that when the resinate released the drug, it has the capability of exchanging another ionized drug on to itself. These results indicated that the re-exchange phenomenon of the dissolved drug on to the resinate was taking place.

The apparent amount of drug released was similar between the dual-drug resinate and the corresponding classical resinate (Tables 2, 3). It might be that the dual-drug resinate behaved as if two drugs were molecularly dispersed in the same resin which was similar to the classical type of resinate [11]. Therefore, each drug could be released independently by its own driving force into the dissolution medium, and was equilibrated at a certain proportion of free drug in the solution and bound drug on the resinate. However, a reduction in the amount of drug released and diffusion coefficients was observed in the case where one drug was added to the medium with the resinate containing the other drug (Tables 2, 3, 5). These results can be explained by the re-exchange of the drug on to the resinate (Fig. 3). The exchange property of ion exchange is a consequence of Donnan exclusion [22]. That is, the counter ion in the resin can be exchanged for an other counter ion from the surrounding medium. The mixture of two classical resinates behaved as if each drug occupied the resinate separate. The re-exchange of the released drug from one resinate to the other resinate might occur. Both AMX and CPM have the same positive charge [23], so the first ionized drug which released from one resinate could function as an effective counter-ion in exchanging for the second drug which is bound on the other resinate. This phenomenon finally caused the lower diffusion coefficient and the lower apparent amount of drug released.

Table 5: Diffusion coefficient of AMX and CPM released from the resinates in simulated gastric fluid and simulated intestinal fluid

Resinates	Initial amount of drug (Q_0, mg)	D_B of AMX $\times 10^{-6}$ (mm^2/min)		D_B of CPM $\times 10^{-6}$ (mm^2/min)	
		Gastric fluid	Intestinal fluid	Gastric fluid	Intestinal fluid
Classical	75.1	9.16	6.15	1.28	24.4
AMX resinate concurrent with CPM resinate	75.1	5.50	4.35	0.353	9.22
Dual	74.9	9.16	6.15	1.170	17.8

2.3. Conclusion

The present study verified the reduction of AMX and CPM released in the case of concurrent administration of classical AMX resinate and CPM resinate. An alternative carrier was introduced to deliver two resinates concurrently using a dual AMX and CPM resinate. The dual AMX and CPM resinate would be suitable and efficient for the concurrent administration of AMX resinate and CPM resinate. In conclusion, a dual-drug resinate can be used as an alternative carrier for an ion-exchange delivery system utilized

for concurrent administration of pharmaceuticals. However, the influence of concurrent administration of resinate on bioavailability and the utilization of the dual-drug resinate as an alternative carrier should be investigated further *in vivo*.

3. Experimental

3.1. Materials

The cation exchange resin, Dowex® 50W X2, (lot 23H0245, Sigma Chemical Co., USA), CPM maleate BP 88 (lot 6630 P.C. drugs, Thailand) and AMX hydrochloride (lot. 24790, Kunze Indopharm, Holland) were used as received.

3.2. Preparation of resinates

Prior to use, the resin (20 g) was placed in a 250 ml beaker and 200 ml distilled water were 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 twice more according to the above procedure. The washed resin was collected by filtration and dried overnight in a hot air oven at 50 °C. The dried resin was kept in a sealed vial until preparation of the resinates.

The classical type of resinates, AMX resinate and CPM resinate, were prepared. 500 mg of resin was added to 100 ml of each loading solution, containing 625 mg of AMX hydrochloride and 105 mg of CPM maleate, respectively. 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 sealed vial. The drug content of each final filtrate, which consisted of the filtrate and washing water, was analyzed by UV spectrophotometer (Hitachi, U-2000, Japan) at 261 nm for CPM and 307.4 nm for AMX.

The dual-drug resinate containing two drugs, AMX and CPM, was prepared by the simultaneous exchange of the drugs and resin. The resin (500 mg) was added to a loading solution composed of 750 mg AMX hydrochloride and 120 mg CPM maleate. The resinates were isolated, washed, dried and stored by the same method as the classical resinates. The final filtrate, which consisted of the filtrate and washing water, was analyzed by the simultaneous derivative UV spectrophotometry (Hitachi, U-2000, Japan) at wavelengths 261 nm and 307.4 nm. The amount of drug loaded on both the classical and the dual-drug resinate was obtained by subtracting the amount of drug remaining in the final filtrate from the initial amount.

3.3. In vitro release study

The dissolution behavior of the drug released from the classical resinate, the mixture of two classical resinates, and the dual-drug resinate was investigated. The release profile was studied using the dissolution apparatus II [24]. The sample was accurately weighed to obtain the equivalent of 75 mg of AMX or 12 mg of CPM and added to 900 ml of dissolution media, simulated gastric fluid with no enzyme (SGF) and simulated gastric fluid with no enzyme (SIF) [21]. The temperature and paddle speed were set at 37 ± 1 °C and 50 ± 1 rpm, respectively. At suitable times, the amount of drug released was analyzed by an UV spectrophotometer. The dissolution profiles of drugs released from the resinate were plotted, and the amount of drug released from the resinates at 8 h was compared.

The release process from the resinate was examined using Bhaskar's expression [17] as eq. (1):

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

F represents the fraction of drug released from the resinate at time t, Q_0 is the initial drug content of the resinate ($g \cdot g^{-1}$), Q_t is the drug content of the resinate at time t ($g \cdot g^{-1}$), D is the diffusion coefficient of the drug within the resin ($mm^2 \cdot min^{-1}$), 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 released from the resinate ($-\ln(1 - F)$) was plotted against $t^{0.65}$. F_{AMX} represents the fraction of AMX released, and F_{CPM} represents the fraction of CPM released. The regression coefficient was examined, and D was also calculated from the slope of this plot.

3.4. Equilibrium of drug exchanged on to resins study

The resin (31 g) was weighed and added to dissolution media containing 37.5 mg of AMX hydrochloride or 6 mg of CPM maleate inspectively. The mixtures were kept in a water bath at 37 °C and periodically shaken. The supernatants were withdrawn at 48 h, and the content of AMX or CPM was determined by UV spectrophotometer.

3.5. Re-exchange of drug on to resinates study

The re-exchange of CPM on to the AMX resinate and AMX on to the CPM resinate were studied using dissolution apparatus II. The AMX resinate was accurately weighed to obtain the equivalent of 75 mg of AMX and added to 900 ml of the dissolution medium containing 12 mg of CPM. Correspondingly, the CPM resinate was accurately weighed to obtain the equivalent of 12 mg of CPM and added to 900 ml of the dissolution medium containing 75 mg of AMX. The temperature and paddle speed were set at 37 ± 1 °C and 50 ± 1 rpm, respectively. At suitable times, the amount of drug released was analyzed by UV spectrophotometer.

3.6. 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.

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