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ORIGINAL ARTICLE

Preparation and in vitro release of dual-drug resinate complexes containing codeine and chlorpheniramine

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Abstract

Objective: To develop the dual-drug resinate complexes containing codeine and chlorpheniramine with a novel batch processing, characterize the dual-drug resinate complexes, and study its drug release behavior in vitro. *Methods*: A procedure of simultaneous dual-drug loading using combination solutions composed of different proportions of codeine phosphate and chlorpheniramine maleate was performed to achieve the specific resinate, and the dual-drug loading content was determined by high-performance liquid chromatography method. The dual-drug resinate complexes were characterized by a scanning electron microscope, and the formation mechanisms were confirmed with X-ray diffraction analyses and differential scanning calorimetric analyses. The release behavior of the two drugs from the dual-drug resinate complexes in vitro was studied in the media simulating in vivo environments (simulated gastric fluid: pH = 1.2 HCl, simulated in vivo ionic strength: 0.15 M NaCl, and simulated intestinal fluid: pH = 6.8 buffer solution containing KH2PO4–NaOH). *Results*: Scanning electron microscopic analyses proved that the dual-drug resinate complexes had the same appearance and characters as the initiative ion exchange resins (IERs). Via X-ray diffraction and differential scanning calorimetric analyses, it is found that the two drugs in dual-drug resinate complexes were combined with IERs by chemical bond. The drug-resinate complex, like IER, was in amorphous state. More than 90% of codeine phosphate was released in 15 minutes in three different media, whereas little amount of chlorpheniramine maleate was released in all the release time in the medium pH = 1.2 HCl, and the release equilibrium time was about 5 minutes, only 40% was released in the medium 0.15 M NaCl, and the equilibrium time was 40 minutes, and about 90% was released in the medium pH = 6.8 KH2PO4–NaOH. The increased ionic strength generally accelerated the release of the two drugs from the dual-drug resinate complexes. *Conclusion*: The dual-drug resinate complexes were formed through the reaction between the drugs and the IERs by chemical bond. The release behavior of the drug from the dual-drug resinate complexes in vitro was mainly correlated with the drug molecular structure, the eluting ionic strength, composition, and ionic strength of the release media. The novel dual-drug resinate complexes could be used to deliver two drugs in one therapeutic dose.

Key words: Characterization, chlorpheniramine maleate, codeine phosphate, dual-drug resinate, ion-exchange resin, preparation, release

Introduction

Ion-exchange resins (IERs) are cross-linked water-insoluble polymers carrying ionizable functional groups, which have different abilities to exchange oppositely charged ion. IERs, as new drug-delivery vehicles, have been extensively studied in the development of novel drug-delivery systems because of its versatile properties[1–4].

The IER binds a drug to form a drug–resin complex, known as a resinate, the drug delivery from which is consequently based on an ion-exchange process at the desired site or in the dissolution media[5–8]. It could be used as a carrier to avoid drug unwanted taste and

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further coated with polymeric membrane for drug's extended release or controlled release[9,10].

Resinate complexes can be prepared by two different procedures called a batch technique and a column technique. Both methods are carried out by mixing the drug solution with the selected IER. In particular, in the batch technique, a specific amount of the IER is mixed with the drug solution until the equilibrium is established, whereas in the column technique, resinate complexes are formed by passing a concentrated solution of drug through the IER-packed column until the effluent concentration equals the eluting one. The resinate complexes obtained by both methods must thus be collected, dried, and can be used to prepare the final pharmaceutical form.

Generally, the resinate is prepared by loading only a single drug onto a resin. Therefore, a product of combined drugs is produced by blending the resinates of each drug. Recently, an alternative resinate, the so-called dual-drug resinate, is introduced for the concurrent delivery of two combined drugs by loading two drugs onto the same resin with different amounts or equivalent content. It is found that the dual-drug resinate could provide similar drug release characteristics to the sole drug–resinate. Because both drugs are simultaneously loaded to form the resinate, the preparation process of the combined drug product is simple and the production cost is reduced.

Codeine phosphate (CDP) is chemically 7,8-didehydro-4,5-α-epoxy-3-methoxy-17-methyl-morphinan-6-α-ol phosphate salt. In pharmaceutical preparations, it is used as a sedative, an analgesic, and an antitussive agent. Chlorpheniramine maleate (CPM) is chemically 2-pyridinepropanamine,γ-(4-chlorophenyl)-*N*,*N*-dimethyl, (*Z*)-2-butenedioate maleate salt. It is an antihistamine and is widely used as an ingredient in antitussive formulations. These two drugs are the pharmacologically active constituents found in most conventional cough-cold pharmaceutical preparations[11,12].

In this article, CDP and CPM had been selected as model drugs, the dual-drug resinate complexes containing CDP and CPM were prepared by a novel batch technique, and the formulations were optimized and characterized. The dual-drug resinate complexes can be used to prepare taste-good dual-drug suspension or dual-drug sustained-release preparation.

Materials and methods

Materials and apparatus

The following materials were purchased and used as received: strong cationic exchange resins (Amberlite IRP 69, Rohm and Haas Corporation, Midland, MI, USA); codeine phosphate (Qinghai Pharmaceutical Factory Co., Ltd., Qinghai, China); chlorpheniramin maleate (Guangdong Pharmaceutical Industry Company, Guangdong, China); KCl, HCl, NaOH, and KH_2PO_4 (Guangzhou Chemical Reagent Co., Ltd., Guangdong, China); purified water used throughout this study (Shenzhen Zhijun Pharmaceutical Co., Ltd., Guangdong, China). Methanol and acetonitrile used for high-performance liquid chromatography (HPLC) analysis were HPLC grade, and other chemicals used were of analytical grade.

Blast Air Over (Model: YSEF, Chongqing Yongsheng experiment instrument factory, Chongqing, China), Moisture Analyzer Balance (Model: HG63, METTLER-TOLEDO corporation, Greifensee, Switzerland), pair stirrer (Model: RS-1000, EYELA corporation, Tokyo, Japan), HPLC (Model: 1200, Agilent Technologies Co., Ltd., Santa Clara, CA, USA), HPLC columns (Ph-3, 5 μm, 4.6 × 250 mm, GL Science Corporation, Tokyo, Japan), dissolution apparatus (Model: RC-806, Tianjing University Precision Corporation, Tianjing, China), thermal analyzer (Model: DSC204, Netzsch Company, Selb, Germany), Thermal FE Environment Scanning Electron Microscope (Model: Quanta 400, FEI Company, Philips, Hillsboro, OR, USA), Powder X-ray Diffractometer (Model: D/Max-IIIA, Rigaku Corporation, Tokyo, Japan) were used.

Preparation of dual-drug resinates

Specified amount of CDP and CPM was accurately weighed and put into a flask with specified amount of purified water. Specified amount of Amberlite IRP 69 resin was added and suspended when the two drugs were dissolved under stirring at room temperature, and then the suspension was continuously agitated on a magnetic stirrer for 4 hours to assure complete exchange reaction. The dual-drug resinate complexes obtained were washed with purified water, dried in hot air at 50°C for 12 hours, and kept in closed vials. The washing process, removing the free drugs, was repeated until the drug concentration in the supernatant became negligible (below 10 μg/mL for codeine and 4 μg/mL for CPM).

Drug assay of dual-drug resinates

About 200 mg of dual-drug resinate complexes was added into 1000 mL of 0.7 M KCl under magnetic stirring at 500 rpm for 12 hours, and then aliquot was filtered through a 0.45 μm membrane filter and 10 μL of the filtrate was directly injected for HPLC analysis (as shown in Figure 1). Separation was achieved by using a HPLC column at 30°C. Elution was performed as follows:

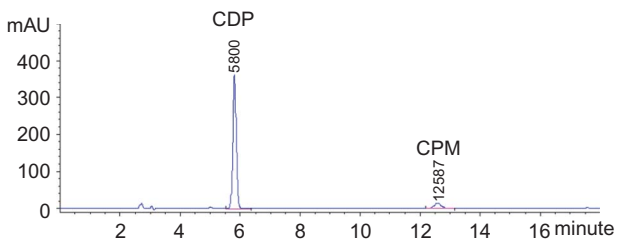


Figure 1. HPLC peaks of CDP and CPM.

flow rate 1.0 mL/min, 0–20 minutes, eluent acetonitrile/phosphate buffer (potassium dihydrogen phosphate, 6.8 g; sodium 1-hexanesulfonate, 0.5 g; triethylamine hydrochloride, 0.5 g, made into 1 L, pH 2.5) (20:80). Both the active pharmaceutical ingredients were detected by absorbance at 220 nm with UV detector. Peak areas were directly proportional to mass of standards injected. The drug concentrations were determined by interpolation from a standard curve. The drug assay of the dual-drug resinate complexes was performed as described above. Throughout this study, the ratio of CDP and CPM were calculated individually by $C_{18}H_{21}NO_3$ and $C_{16}H_{19}ClN_2{\cdot}C_4H_4O_4$.

Optimization of process factors

To investigate the effect of the preparation process on drug loading, loading capacity, amount of resin used, and dual-drug concentration were studied to optimize the dual-drug resinate complexes, as shown in Tables 1–3.

Characterization of dual-drug resinates

SEM was used to observe the morphological characteristics of the dual-drug resinates. The samples were sputter-coated with Au/Pd using a vacuum evaporator and examined using a SEM at 10 kV accelerating voltage.

X-ray diffraction analyses of both drugs, blank resin, dual-drugresinate, and physical mixture were carried out for validation of the formation of dual-drug resinate complexes. Usually, the character of drug–resinate complex is similar to the original blank resin, but very different from their physical mixtures (drugs' crystalline feature peak appearance), and the drug in the drug–resinate complex is amorphous.

Differential scanning calorimetry was performed to ascertain the formation of dual-drug resinate complexes. The samples were heated at a rate of 10°C/min from 0°C to 200°C under a dry nitrogen gas purge. All measurements were conducted in sealed nonhermetic aluminum pans. Typical sample weights ranged between 5 and 10 mg.

Table 1. The effect of dual-drug competitive combination onto the same resin.

Formulation number	CDP (g)	CPM (g)	Amberlite IRP 69 (g)	Purified water (mL)
Formulation (1)	3.5	0.612	8.0	60
Formulation (2)	3.5	1.20	8.0	60
Formulation (3)	3.5	2.45	8.0	60
Formulation number	**Designed ratio of codeine/CPM**	**CDP adsorbed (%)**	**CPM adsorbed (%)**	**Assayed ratio of codeine/CPM**
Formulation (1)	4/1	94.17	95.85	3.92/1
Formulation (2)	2/1	89.30	97.92	1.82/1
Formulation (3)	1/1	84.32	95.16	0.88/1

Table 2. The effect of amount of resin used on dual-drug resinate complexes.

Formulation number	CDP (g)	CPM (g)	Amberlite IRP 69 (g)	Purified water (mL)
Formulation (1)	3.5	0.612	8.0	60
Formulation (4)	3.5	0.612	12.0	60
Formulation (5)	3.5	0.612	16.0	60
Formulation number	**Designed ratio of codeine/CPM**	**CDP adsorbed (%)**	**CPM adsorbed (%)**	**Assayed ratio of codeine/CPM**
Formulation (1)	4/1	94.17	95.85	3.92/1
Formulation (4)	4/1	95.94	97.17	3.95/1
Formulation (5)	4/1	96.97	97.29	3.98/1

Table 3. The effect of dual-drug concentration on dual-drug resinate complexes.

Formulation number	CDP (g)	CPM (g)	Amberlite IRP 69 (g)	Purified water (mL)
Formulation (1)	3.5	0.612	8.0	60
Formulation (6)	7.0	1.23	8.0	60
Formulation (7)	1.76	0.30	8.0	60
Formulation number	**Designed ratio of codeine/CPM**	**CDP adsorbed (%)**	**CPM adsorbed (%)**	**Assayed ratio of codeine/CPM**
Formulation (1)	4/1	94.17	95.85	3.92/1
Formulation (6)	4/1	88.11	96.16	3.65/1
Formulation (7)	4/1	96.81	90.84	4.30/1

Release of dual-drug resinates

Drug release was evaluated using USP dissolution apparatus type II. To investigate the effect of in vitro milieu on drug release, the release media chose were 900 mL of three media (simulated gastric fluid: pH = 1.2 HCl, simulated in vivo ionic strength: 0.15 M NaCl, and simulated intestinal fluid: pH = 6.8 KH_2PO_4–NaOH). The rotating speed and maintained temperature were set at 75 rpm and 37 ± 0.5°C, respectively. Each dual-drug resinate complex was accurately weighed to have the same content (equivalent to codeine 32 mg and CPM 8 mg) and directly transferred into the release vessels. Aliquot equal to 5 ml was withdrawn at specific time interval and it was filtered through 0.45 μm filter; the solution was analyzed by HPLC method and quantity of drug release was determined periodically. The fresh medium was equally returned into the vessels. The release study was carried out in triplicates.

Results and discussion

Preparation of dual-drug resinates

Loading capacity, amount of resin used, and dual-drug concentration had great effects on the dual-drug ratio; the results are shown in Tables 1–3.

Because of the different loading capacity of CDP and CPM, the designed ratio was 4/1 for codeine/CPM in Formulation (1), but the assayed ratio in the obtained dual-drug resinates was 3.92/1, and the drug adsorbed percentage of CDP and CPM was 94.17% and 95.85%, respectively. In the Formulation (3), with the same equivalent concentration for codeine and CPM, the drug adsorbed percentage of CDP and CPM was 84.32% and 95.16%, respectively, and the assayed ratio in the obtained dual-drug resinates was 0.88/1 for codeine/CPM.

Results showed that CDP and CPM had competitive relationship on the same IER Amberlite IRP 69, and the bonding ability of CPM was stronger than CDP, because of their different molecular structure (as shown in Figure 2). Both their active group were tertiary amine in their molecular structures, but the tertiary in CDP was cyclized in a cyclohexane and the tertiary in CPM was free, so CPM was bonded to the sulfonic group of the resin Amberlite IRP 69 more easily.

To adjust the amount of resin used or dual-drug concentrations, the designed ratio of CDP and CPM in the dual-drug resinate could be obtained as shown in Tables 2 and 3. The results showed the CDP and CPM drug adsorbed percentage increased with increase in the amount of resin used, and the CDP and CPM drug adsorbed percentage decreased with the increase of the dual-drug concentration. Based on the results of Formulations (1)–(7), new formulations were designed as in Table 4, and the application curve of formulation optimization could be fitted as in Figure 3, and then according to the application curve, the optimized formulation could be obtained, and the results of validation were conformable as in Table 5.

Characterization of dual-drug resinates

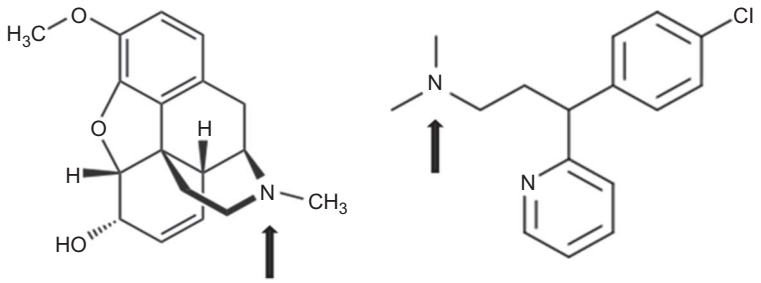
The morphology of the blank resin and the dual-drug resinates was examined by a thermal field emission environmental SEM. Samples were mounted onto stubs using double-sided adhesive tape and vacuum coated with gold film using a sputter coater. Both were of irregular shape with some arris (as shown in Figure 4) from the view of SEM, the dual-drug resinates were similar to the original blank resin in the morphology.

From the results of the X-ray (as shown in Figure 5) and the differential scanning calorimetry, the character of dual-drug resinates was similar to the original blank resin, but very different from their physical mixture (drug crystalline feature peak appearance); it was obvious that both the drugs CPM and CDP in dual-drug resinate complexes were amorphous, but initially they were crystalline.

During the process of drug loading, both drugs combine and solidify to the functional sulfonic group of the resin Amberlite IRP 69 and form the dual-drug resinate complexes, so the drugs were amorphous in the dual-drug resinate complexes, but not originally crystalline.

Release of dual-drug resinates

Release profiles of the dual-drug resinate complexes were shown in Figure 6. About 90% of the CDP was



Codeine Chlorpheniramine

Figure 2. Chemical structures of codeine and chlorpheniramine.

Table 4. The effect of amount of codeine used on dual-drug resinate complexes.

Formulation number	CDP (g)	CPM (g)	Amberlite IRP 69 (g)	Purified water (mL)
Formulation (1)	3.5	0.612	8.0	60
Formulation (8)	3.6	0.612	8.0	60
Formulation (9)	3.7	0.612	8.0	60
Formulation (10)	3.8	0.612	8.0	60
Formulation (11)	3.9	0.612	8.0	60

Formulation number	Designed ratio of codeine/CPM	CDP adsorbed (%)	CPM adsorbed (%)	Assayed ratio of codeine/CPM
Formulation (1)	4/1	94.17	95.85	3.921
Formulation (8)	4.15/1	93.69	95.84	3.971
Formulation (9)	4.26/1	93.16	95.68	4.061
Formulation (10)	4.38/1	93.11	95.67	4.171
Formulation (11)	4.5/1	92.64	95.76	4.261

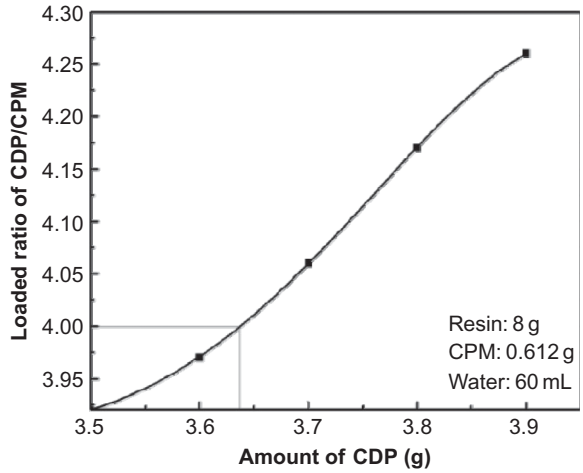


Figure 3. The effect of amount of codeine used on drug loaded ratio of CDP/CPM in dual-drug resinates.

released and reached equilibrium in 15 minutes in three different media. But the release behavior of CPM from the dual-drug resinate complexes was very different from that of CDP. For example, in the medium of pH = 1.2 HCl, little amount of CPM was released in all the release time, whereas in the medium of 0.15 M NaCl, the release equilibrium time was about 5 minutes and about 40% drug was released; however, in the medium of pH = 6.8 KH_2PO_4–NaOH, the equilibrium time was 40 minutes and about 90% drug was released.

Release of CDP from the dual-drug resinate complexes was faster than that of CPM in the same medium, which might be explained by attribution of both drugs' molecular structure (as shown in Figure 2). CPM had free tertiary amine, and the tertiary amine in CDP was cyclized, so the van der Waals force between CPM and Amberlite IRP 69 was stronger than that of CDP, and the release of CPM from the dual-drug resinate complexes was slower than that of CDP in the same medium.

With regard to the drug delivery based on ion exchange, the ionic strength played an important role on drug release. Except for the ionic strength, eluting ion type had an important effect on drug release. The release behavior of CPM from the dual-drug resinate complexes was very different in three media, because of the different eluting capabilities of the H^+, Na^+, and K^+, which corresponded to the van der Waals force; if the van der Waals force of eluting ion was stronger than the drug, the drug would be liberated easily, that is why the CDP in the dual-drug resinate was liberated easily by one of three eluting ions H^+, Na^+, and K^+. On the contrary, if the van der Waals force of eluting ion was weak, the drug would be liberated with difficulty, so the release behavior of CPM in the dual-drug resinate was different in the three media.

Table 5. The formulation of dual-drug resinate complexes.

Formulation number	CDP (g)	CPM (g)	Amberlite IRP 69 (g)	Purified water (mL)
Formulation (12)-1	3.62	0.612	8.0	60
Formulation (12)-2	3.62	0.612	8.0	60
Formulation (12)-3	3.62	0.612	8.0	60

Formulation number	Designed ratio of codeine/CPM	CDP adsorbed (%)	CPM adsorbed (%)	Assayed ratio of codeine/CPM
Formulation (12)-1	4.17/1	93.35	95.83	4.02/1
Formulation (12)-2	4.17/1	93.40	95.81	4.02/1
Formulation (12)-3	4.17/1	93.38	95.77	4.02/1

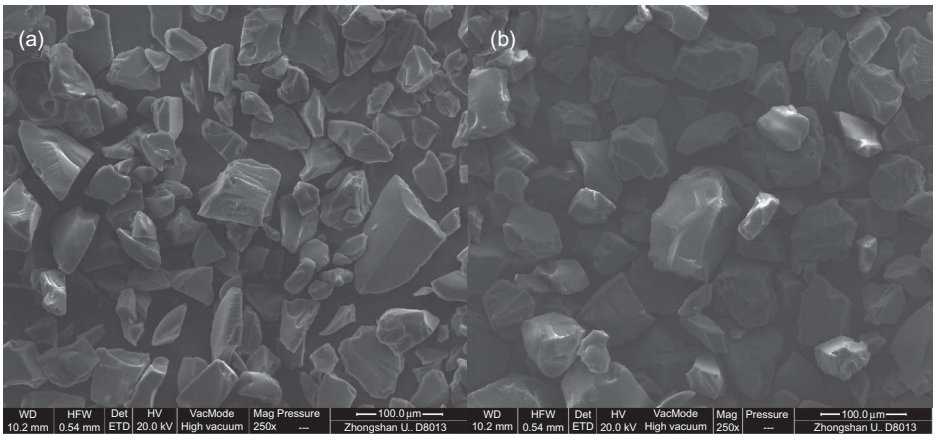


Figure 4. Micrograph of blank resin and dual-drug resinate complexes; (a) blank resin; (b) dual-drug resinate.

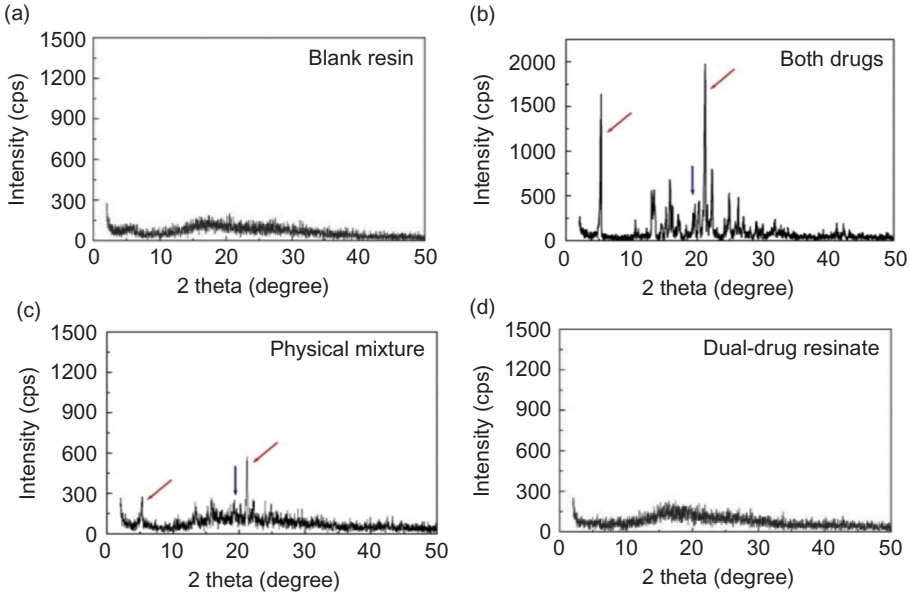


Figure 5. X-ray curves of different samples for validation of dual-drug resinate complexes; (a) blank resin; (b) both drugs; (c) physical mixture; (d) dual-drug resinate complex.

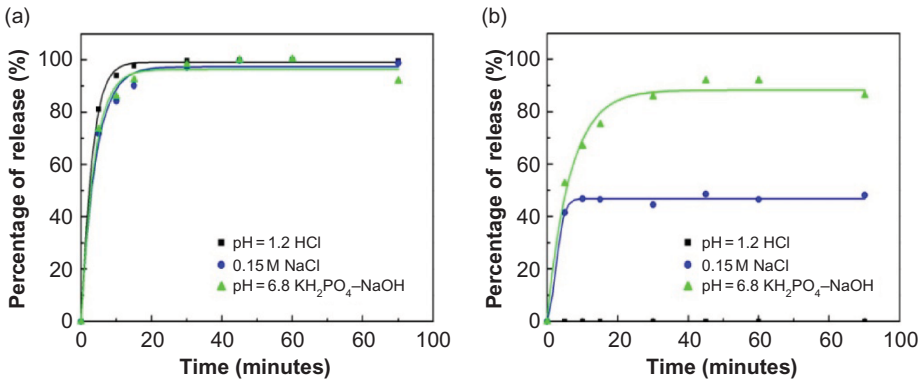


Figure 6. Drug release curves of dual-drug resinate complex in different medium; (a) CDP; (b) CPM.

The release study demonstrated that the dual-drug resinate could be used for delivery of two combined drugs with the therapeutic dose and further research on sustained or controlled release preparation.

Conclusions

The dual-drug resinate complexes containing codeine and chlorpheniramine were prepared by the novel batch method in which both drugs were loaded simultaneously onto the same resin. The behavior of dual-drug loading onto the same resin was affected by the process variables including drug molecular structure, amount of resin used, dual-drug concentration, and proportion of both drugs. As the amount of IERs increased, both CDP and CPM adsorbed percentages were improved. The application curve of formulation optimization could be used to optimize formulation design.

In clinical practice, CDP and CPM are often used as combination preparations. To achieve the dual-drug resinate complexes, a procedure of simultaneous dual-drug loading using combination solutions composed of different proportions of CDP and CPM was performed. It would not only simplify the production process, but also increase production efficiency. The novel batch method for dual-drug resinate complexes is simple and useful for the preparation of a combined drug product. Furthermore, the studies suggested that the dual-drug resinate complexes would be useful alternative for combination pharmaceutical application with good taste and sustained release.

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Declaration of interest

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