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Preparation and In Vitro Release of Dual-Drug Resinates Containing Equivalent Content Dextromethorphan and Diphenhydramine

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ABSTRACT The dual-drug resinate containing equivalent content of dextromethorphan hydrobromide (DTM) and diphenhydramine hydrochloride (DPH) was developed and characterized. To achieve this specific resinate, a procedure of simultaneous dual-drug loading using loading solutions composed of different proportions of DTM and DPH was performed and a dual-drug loading diagram was constructed to determine the equivalent drug loading solution (ELS) and also the estimated equivalent drug content (EQC). The effects of resin crosslinkage, overall drug concentration of the loading solution, and temperature during drug loading on the values of ELS and EQC were assessed. The increased overall drug concentration from 0.25 to 1.0% w/v elevated the EQC values from 18 to 35% w/w for low crosslinked resins (Dowex 50W × 2 and × 4), and from 18 to 27% w/w for high crosslinked resin (Dowex 50W × 8). It also changed the values of ELS from 0.50 to 0.48 for the low crosslinked resins, and 0.50 to 0.55 for the high crosslinked resin. For the high crosslinked resin, the applied heat from 35 to 65°C further increased the values of EQC from 27 to 32% w/w, and changed the values of ELS in the reverse direction from 0.55 to 0.48. However, the heat did not exert significant effects on the values of EQC and ELS for the low crosslinked resins. Different batches of dual-drug resinates prepared from the determined ELS provided the resultant resinates with equivalent contents of DTM and DPH which were very close to the estimated EQC. The drug release from the resinates was performed in 0.05, 0.1, 0.2, and 0.4 N of KCl solutions. The increased ionic strength generally accelerated the release of both drugs except for 0.4 N KCl solution in which the drug release from the resinates of high crosslinkage was decreased. The congestion on the outward movement of drugs through the high crosslinked matrix might cause the delay of drug release. In conclusion, the release study demonstrated that the dual-drug resinate using a suitable crosslinked resin could be used for extended delivery of two combined drugs with the equivalent therapeutic dose.

KEYWORDS Ion exchange resin, Dual-drug resinate, Dextromethorphan hydrobromide, Diphenhydramine hydrochloride, Equivalent drug content, Drug release

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INTRODUCTION

Ion exchange resins have been used as an effective carrier for oral drug delivery systems (Borodkin, 1993). In contact with a drug solution, the resin will reversibly interchange its counter ions versus the like-charge drug until the establishment of equilibrium forming the drug resin complex commonly referred as "resinate." In the digestive system, the resinate will liberate the bound drug on exposure to the like-charge ion present in the gastrointestinal tract. The behavior of the resin to provide gradual drug dissolution offers the resinate achievable to make extended-release formulations. The resin has been considered an ideal carrier for the extended-release suspension since there is no considerable drug leached out from the resinate suspending in the ion-free vehicle during a storage period (Amsel et al., 1984; Sriwongjanya & Bodmeier, 1997). The resinate can be further coated with polymeric membrane to make drug release more controllable (Cuna et al., 2000; Zhang et al., 2000). In addition, the resinate can protect the liberated drug from the burst exposure to mouth, hence avoiding its unwanted taste before swallow (Borodkin & Sundberg, 1971).

Generally, the resinate is prepared by loading only single drug onto a resin. Therefore, a product of combined drugs is produced by blending the resinates of each drug (Amsel et al., 1984; Ogger et al., 1991). Recently, an alternative resinate, so called the "dual-drug resinate," was introduced for the concurrent delivery of two combined drugs (Akkaramongkolporn & Ngawhirunpat, 2003). It was found that the dual-drug resinate could provide similar drug release characteristics to the individual of single drug loaded resinates. Since both drugs were simultaneously loaded to form the resinate, the preparation required only a single batch process to produce a combined drug product. In comparison with the blending approach, the delivery of two combined drugs in the form of the dual-drug resinate practically reduces the step of production.

In the previous investigation, two drugs were loaded onto resinates in different amounts (Akkaramongkolporn & Ngawhirunpat, 2003). Therefore, it is of interest to develop dual-drug resinates in cases where the loaded drugs have the same therapeutic dose and require the same loading amount. A method of preparation was developed to achieve this specific formulation. The effects of loading variables on the behavior of equivalent content dual-drug loading were also investigated. Dextromethorphan hydrobromide (DTM) and diphenhydramine hydrochloride (DPH) were chosen as the model drugs. They have similar ranges of dose with a short half-life each, and can potentially be formulated in combined preparations for allergy and cough suppression (Jack, 1992; McEvoy, 2001).

Strategy to Prepare Equivalent Content Dual-Drug Resinates

The loading process of a cationic drug onto a cationic exchange resin follows the ion-exchange reaction below (Borodkin, 1993).

$$RNa + A^+ \rightleftharpoons RA + Na^+$$

where

RNa = resin in Na form,
A^+ = ionized drug A in loading solution,
RA = resin containing drug A, called "resinate," and
Na^+ = Na^+ in loading solution.

The extent of drug loading onto the resin is governed mainly upon the inherent affinity of the drug with the resin and the concentration of the drug in the loading solution.

Likewise, the ion exchange reaction for dual-drug loading onto the resin is as follows.

$$R2Na + A^+ + B^+ \rightleftharpoons RAB + 2Na^+$$

where

B^+ = ionized drug B in loading solution, and
RAB = resin containing drug A and B, called "dual-drug resinate."

In this situation, both drug A and B are simultaneously loaded onto the resin. Which drug species will prevail in binding with the resin mainly depends on domination of two parameters, the inherent affinity of each drug with the resin, and the proportion of each drug in the loading solution. A drug with higher affinity with the resin will exhibit a greater extent of drug loading than the other drug with lower affinity. However, the latter drug can have the same, or even

greater, drug loading if the proportion of this drug in the loading solution is increased until it outweighs the effect contributed by the superior affinity of the former drug. For any pair of drugs to be loaded, the inherent affinity of each drug with the resin is constant. Indeed, this parameter engages with the drug structure; it can not be modified without risk in changes of the drug properties, for example the physicochemical and the pharmacological properties. Therefore, the required equivalent dual-drug loading will be achieved by mean of modulating the proportion of each drug in the loading solution.

Based on the above concept, the equivalent drug loading solution is obtained by the following procedures. Firstly, a series of loading solutions (under a fixed overall drug concentration) containing various proportions of drug A to B is prepared. Then each loading solution is agitated with a certain quantity of resins until the equilibrium is reached. Having known the content of drug loading from each loading solution, a dual-drug loading diagram is constructed as depicted in Fig. 1. The left and right y-axis represent the content (calculated as % w/w of drugs in the resinate) of drug A and B loaded, respectively. The x-axis represents the proportions of drug A to B in the loading solution. The left and right ends of the x-axis locate the loading solution containing only drug A and B, respectively. Then, across from the left to right end on the x-axis indicates declining proportions of drug A to B in the loading solution, and vice versa toward the opposite direction. In this regard, the content of drug A loaded (solid line) is highest at the left end and then will decrease as the proportion of drug A in the loading solution is decreased. On the other hand, the content of drug B loaded (dash line) increases from the left end and will be highest at the right end of the x-axis, corresponding to the increased proportion of drug B in the loading solution. These two crossing lines, no matter whether they are linear or not, yield the intersecting point where drug A and B are equally loaded in the resinate. From this point, the equivalent drug loading solution (ELS), which is used to prepare the equivalent content dual-drug resinate, as well as the estimated equivalent content (EQC) of both drugs loaded can be determined by solving two equations of the crossing lines (see appendix for method of calculation).

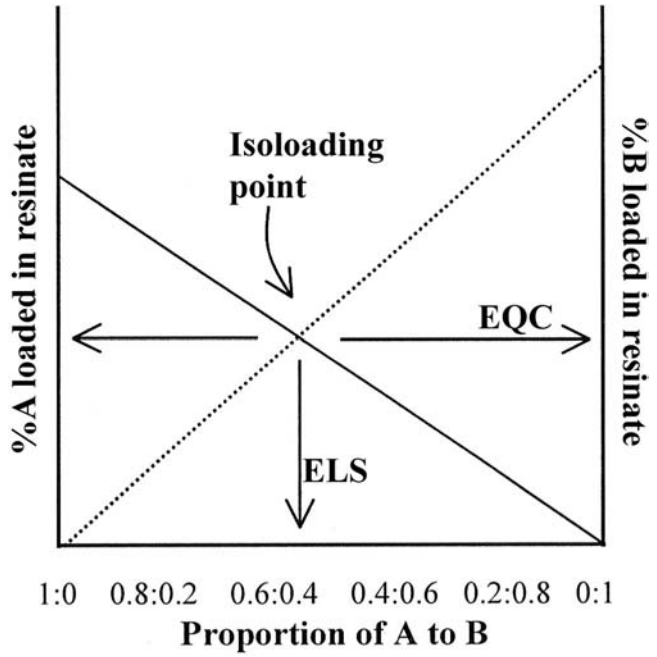

FIGURE 1 A Typical Dual-drug Loading Diagram.

MATERIALS

The following materials were purchased and used as received: strong cationic exchange resins (Dowex 50W × 2–200, × 4–200, and × 8–200, Sigma-Aldrich, St. Louis, MO, USA), dextromethorphan hydrobromide USP/BP (Wockhardt Ltd., Gujarat, India), diphenhydramine hydrochloride USP/BP (Shuanglao Pharmaceutical Co., Beijing, China), potassium dihydrogen orthophosphate (Fisher Scientifics, UK), orthophosphoric acid (Ajax Finechem, Australia), triethylamine (Fluka Chemika, Switzerland), acetronitrile (Lab Scan, Ireland), methanol (Lab Scan, Ireland), sodium hydroxide (Ajax Finechem, Australia), sodium chloride (Merck, Germany), potassium chloride (Ajax Finechem, Australia), and potassium hydrogen phthalate (Farmitalia Carlo Erba, Italy). The chemicals were analytical grade; the solvents used for HPLC analysis were HPLC grade. Deionized water was used throughout this study.

APPARATUS AND PROCEDURE

Treatment of Resins

About 20 g of resins was consecutively washed with 3 × 100 mL of deionized water, 100 mL of 95% ethanol, 100 mL of 50% ethanol, and 100 mL of deionized water. Removal of the supernatant was made

consecutively by sedimentation and decantation after agitation on a magnetic stirrer. The washed resin was converted to Na form by equilibrating with 2 × 120 mL of 2 N NaOH (Cuna et al., 2000). The resin (in Na form) was collected by filtration and thoroughly washed with deionized water until the pH value of the filtrate was neutral. The final resin was dried overnight at 50°C in a hot air oven and kept in a closed vial. The moisture content of the final resins was determined using a moisture analyzer balance (Sartorious MA 30, Germany).

Determination of Resin Properties

The total exchange capacity of resins was determined by the salt splitting titration (Salmon & Hale, 1959; Harland, 1994). The received resins (in H form) were cleaned, dried, and determined for moisture content as mentioned above. An accurate amount (0.2 g) of the resins was weighed and added into a 250 mL Erlenmeyer flask containing 50 mL of 1 N sodium chloride solution. The slurry was swirled gently and was left overnight to assure complete exchange reaction. Thereafter, the slurry was titrated slowly with 0.1 N sodium hydroxide solution standardized with potassium hydrogen phthalate. Phenolphthalein was used as an indicator for the titration. The total exchange capacity of the resin in H form (MC_H, meq/g) was calculated from c × v × 1000/w where c is the actual concentration (N) of sodium hydroxide solution, v is the volume (mL) of sodium hydroxide solution at end point, and w is the dry weight of resins (g). Based on the fundamental law of mass action, the total exchange capacity of the resin in H form could be transformed into that in Na form (MC_{Na}, meq/g) by the following equation.

$$MC_{Na} = \frac{MC_H}{(1 + 0.001 \times MC_H \times (AW_{Na} - AW_H))}$$

AW_H and AW_{Na} are the atomic weight of H and Na, which are 1 and 23, respectively. The total exchange capacity was determined in triplicates at ambient condition.

The particle size of resins was determined using Mastersizer 2000 (Malvern, UK). The final resins were suspended in deionized water for 6 h, and then were measured for particle size; $d_{10\%}$, $d_{50\%}$, and $d_{90\%}$, are the volume-number diameters where the given percentage of the resin particles is under that size. The measurement of particle size was conducted in triplicates. The appearance of the resins was examined by using an optical microscope (Nikon Eclipse E2000, Japan) connected with a digital camera (Nikon Coolpix4500, Japan).

Dual-Drug Loading

Effect of Resins with Different Crosslinkage and Overall Drug Concentrations

The dual-drug loading onto each resin was studied under varying overall drug concentrations of 0.25, 0.50, 0.75, and 1.00% w/v. For an overall drug concentration, six loading solutions comprising various proportions of DTM and DPH in the ratio of 1:0, 0.8:0.2, 0.6:0.4, 0.4:0.6, 0.2:0.8, and 0:1 were prepared. Then, 100 mL of each loading solution was agitated with 0.5 g (dry weight) of the final resins. The drug loading was conducted in a temperature-controlled shaking bath at 35 ± 1°C for 24 h. It was proved that this equilibrating time was adequate for the reaction to reach the equilibrium. At equilibrium, the remainder of both drugs in the loading solution was assayed using High Performance Liquid Chromotography (HPLC) method. The amount of drug loading onto the resinate was the difference of the initial and the remainder of drugs in the loading solution at the equilibrium, and was calculated as percnt w/w of drugs in the resinate. A preliminary work showed no considerable degradation of both drugs occurring in the drug loading process (less than 1% of the initial amount). Having known the amounts of drug loading at varying proportions of the loading solution, the dual-drug loading diagram was constructed, and then the values of EQC and ELS were determined. Each study was made in triplicates.

Effect of Temperatures During Drug Loading

At a fixed overall drug concentration (1.00% w/v) of the loading solution, the dual-drug loading was conducted at varying temperatures from 35 to 55 ± 1°C for Dowex 50W × 2 and × 4, and extended to 65 ± 1°C for Dowex 50W × 8, respectively. The rest of processes and determination of EQC and ELS were performed as above described. No significant degradation of both drugs in the loading solution was observed at the temperatures employed.

Preparation of Equivalent Content Dual-Drug Resinates

Several batches of selected equivalent content dual-drug resinates were prepared by equilibrating the resins with the corresponding ELS obtained from the above study. After equilibrium, the resinates were collected by filtration and washed thoroughly with deionized water. The remainder of both drugs in the filtrate was assayed using HPLC method. The amount of drug loading was determined by the subtraction method and presented as percent w/w of drugs in the resinate. The obtained resinates were dried overnight in a hot air oven at 50°C and then were kept in closed vials. The moisture content of the resinates was determined by a moisture analyzer balance.

In Vitro Release Evaluation

Drug release was evaluated using USP dissolution apparatus type II (Erweka DT6R, Germany) (USP 25/NF 20, 2000). The release media were 900 mL of 0.05, 0.1, 0.2, and 0.4 N potassium chloride solutions in order to investigate the effect of ionic strength on drug release. The rotating speed and maintained temperature were set at 50 ± 1 rpm and 37 ± 1°C, respectively. Each produced resinate was accurately weighed to have the equivalent content (60 ± 1.5 mg) of both drugs, and directly transferred into the release vessels. At a predetermined time, 3 mL of the release medium was withdrawn through a filter and then was analyzed by HPLC method. The fresh medium was equally returned into the vessels. The release study was done in triplicates.

HPLC Conditions for Drug Analysis

Drug analysis of all experiments was done on HPLC with UV detector (Shimadzu 10AVP, Japan) using a 4 × 250 mm column containing 5 μm Betasil C8 (Thermo Electron Corporation, UK). The mobile phase was a 65:35:003 mixture of 75 mM potassium dihydrogen orthophosphate (adjusted to pH 3.5 with orthophosphoric acid), acetronitrile, and triethylamine. The HPLC conditions were operated at a constant flow rate of 1.0 mL/min, injection volume of 20 μL, and detection wavelength at 257 nm. For each assay, a daily calibration curve was generated and used within the assay. The validation had shown that this method was specific (Fig. 2), linear ($R^2 > 0.9995$), and reproducible.

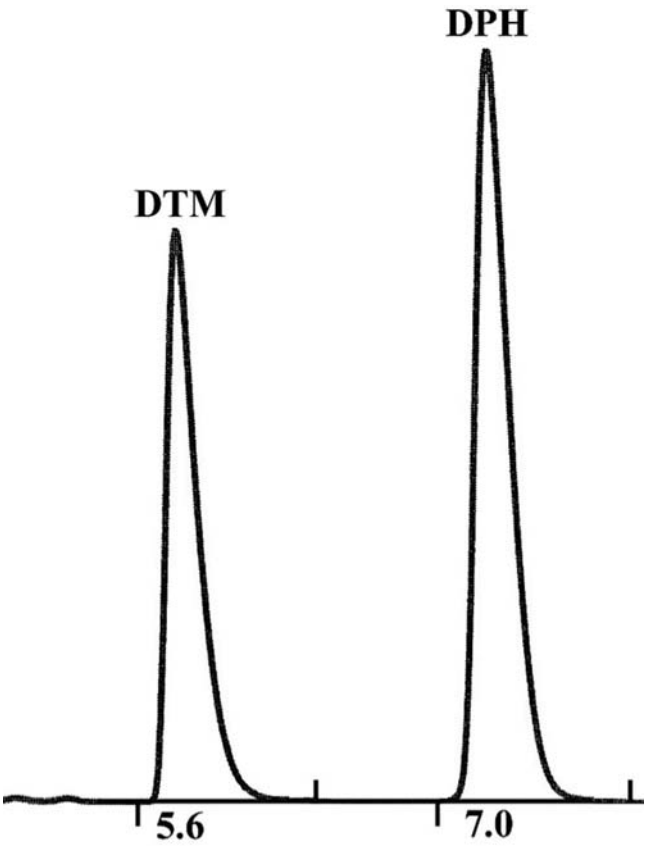

FIGURE 2 HPLC peaks of DTM and DPH.

Molar Volume of Drugs

The molar volume of DTM and DPH was estimated using the following relationship (Molar Volume, 2005).

$$V_{molar}(mL/mole) = \frac{MW}{\rho}$$

MW and ρ are the molecular weight and true density of drugs, respectively. The molecular weight of DTM and DPH is 370.3 and 291.8, respectively. The true density of drugs was determined by helium displacement method (Quantachrome Ultrapycnometer 1000, USA). From five replicate measurements, the true density of DTM and DPH was 1.3548 ± 0.0022 and 1.1634 ± 0.0015 g/mL, and the calculated molar volumes were 273.3 and 250.8 ml/mole, respectively.

RESULTS AND DISCUSSION

Properties of Resins

All resins were spherical (Fig. 3). The total exchange capacity among the resins was similar (Table 1), indicating that the crosslinking within the resins did not affect the function of exchangeable groups. Even though specified in the same 200 mesh size, the particle size of Dowex 50W × 2 was found to be bigger than that of Dowex 50W × 4 and × 8 while they had a comparable size distribution (SPAN).

Equivalent Dual-Drug Loading

Effect of Crosslinkage Degree and Overall Drug Concentrations

Figure 4 shows the dual-drug loading diagrams of each resin prepared under various overall drug concentrations of the loading solution. Interestingly, the percent of each drug loaded in the resinate linearly related to the proportion of that drug in the loading solution ($R^2 \geq 0.996$). Then, the EQC and ELS values were obtained by determining the crossing point of these two linear plots (see appendix for method of calculation).

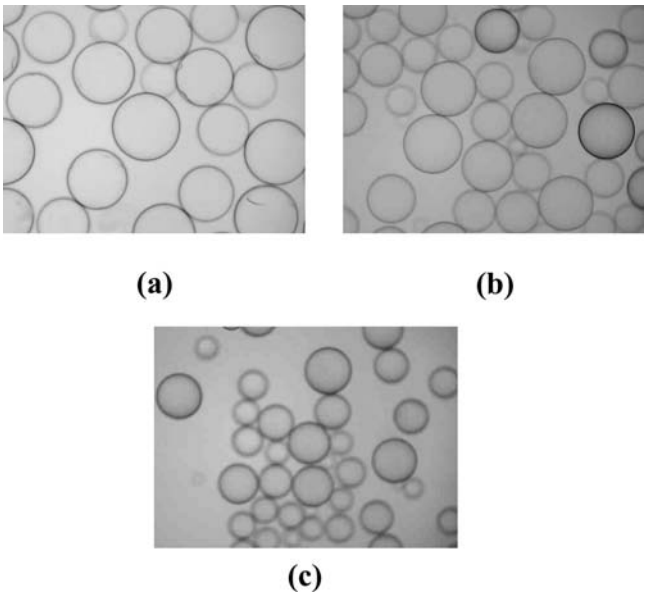

FIGURE 3 Photomicrographs of Dowex 50W × 2 (a), × 4 (b) and × 8 (c) (10 × 10 magnification).

The calculated EQC values at various overall drug concentrations of the loading solution are depicted in Fig. 5 and presented in Table 2. For all resins, the values of EQC increased with increasing the overall drug concentrations, and then leveled off. However, the EQC values of Dowex 50W × 8 reached the plateau earlier and were less than those of Dowex 50W × 2 and × 4. When the values of EQC on the plateau at 1% w/v overall drug concentration were transformed into the term of exchanged capacity (Table 3), it demonstrated that almost binding sites of Dowex 50W × 2 and × 4 were occupied with the loaded drugs while Dowex 50W × 8 had nearly half of the total binding sites unoccupied. These vacant binding sites might locate in the deep and narrow pore region where the drugs could not access to the binding sites in the normal condition. Dowex 50W × 8 had more tortuous structure of matrix so that it had greater extents of the inaccessible binding sites (Irwin et al., 1987).

Equivalent drug loading solution (ELS) was the proportion of DTM and DPH in the drug loading solution employed to obtain an equivalent content dual-drug resinate (see appendix for ELS definition). Moreover, it could be indicative of competition between DTM and DPH in binding with resins. The calculated values of ELS are presented in Table 2. At the overall drug concentration of 0.25% w/v, it was found that the ELS values of all resins were around 0.50 indicating no considerable competition of the drugs in binding with the resins. It might be caused by the sufficiency of the accessible binding sites for most of the loaded drugs as the traces of unloaded drugs were found in the final loading solution. However, the values of ELS for Dowex 50W × 2 and × 4 decreased

TABLE 1 The Total Exchange Capacity (meq/g) and the Particle Size (μm) of Each Resin[a]

Resins[b]	MC_H	MC_{Na}	$d_{10\%}$	$d_{50\%}$	$d_{90\%}$	SPAN[c]
Dowex 50W × 2	5.27 (0.02)	4.72 (0.01)	137.588 (0.611)	188.446 (0.583)	257.590 (0.598)	0.637 (0.002)
Dowex 50W × 4	5.34 (0.00)	4.78 (0.00)	108.444 (0.305)	149.294 (0.571)	204.700 (0.920)	0.645 (0.005)
Dowex 50W × 8	5.18 (0.01)	4.65 (0.01)	107.628 (0.511)	148.119 (0.699)	202.570 (1.154)	0.641 (0.001)

[a]Values are presented in mean (s.d.).
[b]× 2, × 4, and × 8 expresses the degree of crosslinkage within the resin matrix.
[c]Polydispersity (size distribution) of resin particles calculated from $(d_{90\%} - d_{10\%})/d_{50\%}$.

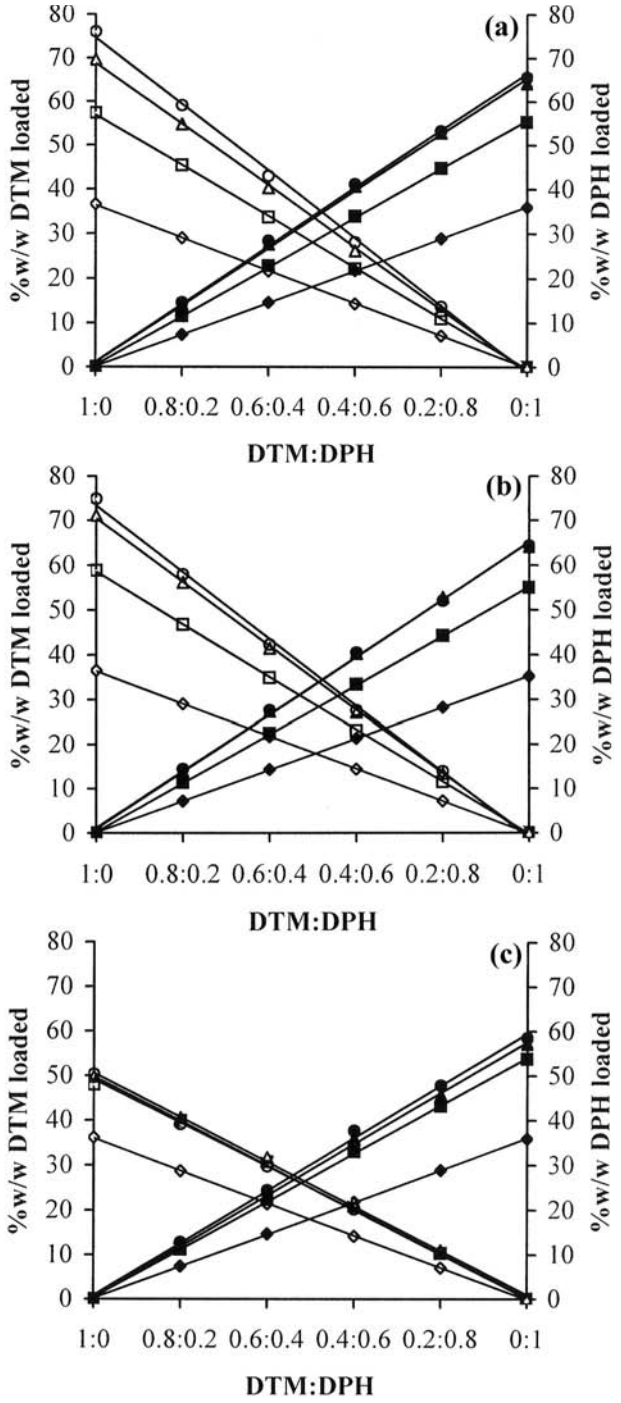

FIGURE 4 Dual-drug Loading Diagrams of Dowex 50W × 2 (a), × 4 (b), and × 8 (c), Obtained Under Varying Overall Drug Concentrations; 0.25 (◇), 0.50 (□), 0.75 (Δ), and 1.00% w/v (○), Respectively, Where Open Symbols Represent DTM and Closed Symbols Represent DPH.

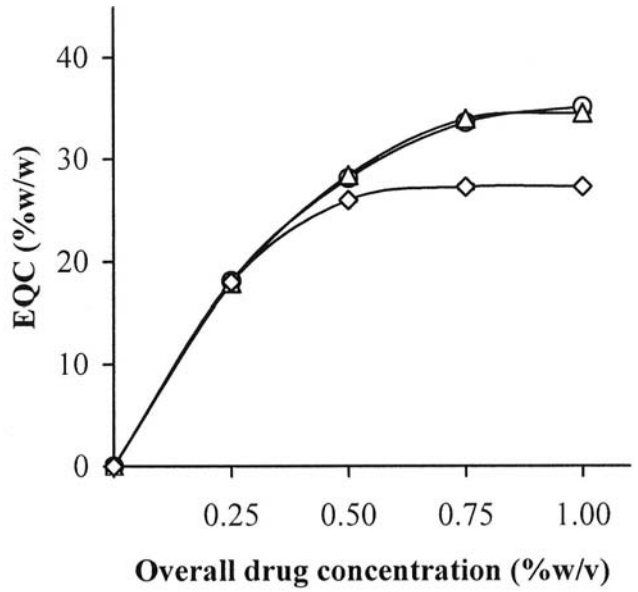

FIGURE 5 Effect of Overall Drug Concentrations on EQC of Dowex 50W × 2 (○), × 4 (Δ), and × 8 (◇), Respectively.

when the overall drug concentration was increased. This behavior might indicate the competition occurring between the drugs to share the binding sites in the resins which was due to the insufficiency of the binding sites. The decreased values of ELS far below 0.50 indicated that DTM was more competitive than DPH to bind with the resins. A reverse trend was observed in case of Dowex 50W × 8; the values of ELS increased with increasing the overall drug concentration. An increase of the ELS values above 0.50 demonstrated that DPH was predominant in binding with this resin.

Most likely different mechanisms governing drug loading between low (Dowex 50W × 2 and × 4) and high (Dowex 50W × 8) crosslinked resins provided different effects of the overall drug concentration on ELS values. It is recognized that the drug loading is driven through electrostatic interaction between the opposite charges. Nevertheless, the magnitude of this interaction, and hence drug loading, is closely associated with the hydrophobicity and the molecular weight or size of loaded drugs (Hale et al., 1953; Farag & Nairn, 1988; Kril & Fung, 1990). For similar charged drug molecules, the drug loading will increase as the hydrophobicity of drugs increases owing to an additional van der Waals force generated from the hydrophobic portions between the loaded drug and resin. Moreover, high drug loading is preferable to a smaller molecular weight drug which is easier to introduce into the binding sites especially for the resin with high degree of crosslinkage. DTM is a sparingly water soluble drug while DPH is very soluble in water with the partition coefficient (Log P) of 4 and 3.3, respectively (Moffat, 1986; Jack, 1992). Therefore, DTM is likely

TABLE 2 **Effect of Overall Drug Concentrations (%w/v) on Values of EQC and ELS[a]**

Resins	0.25	0.50	0.75	1.00
On EQC				
Dowex 50W × 2	18.130 (0.001)	28.154 (0.002)	33.586 (0.024)	35.122 (0.029)
Dowex 50W × 4	17.931 (0.001)	28.408 (0.003)	33.915 (0.030)	34.493 (0.024)
Dowex 50W × 8	18.016 (0.003)	26.031 (0.184)	27.295 (0.264)	27.347 (0.042)
On ELS				
Dowex 50W × 2	0.500 (0.000)	0.498 (0.000)	0.494 (0.002)	0.480 (0.001)
Dowex 50W × 4	0.494 (0.000)	0.488 (0.000)	0.486 (0.001)	0.479 (0.000)
Dowex 50W × 8	0.503 (0.000)	0.522 (0.003)	0.530 (0.002)	0.548 (0.006)

[a]Values are presented in mean (s.d.).

TABLE 3 **Exchanged Binding Sites of Resins When Using 1.00% w/v Overall Drug Concentration in Drug Loading**

	35°C		45°C		55°C		65°C	
Resins	meq/g	%[a]	meq/g	%	meq/g	%	meq/g	%
Dowex 50W × 2	4.62	97.88	4.58	97.03	4.57	96.82	—[b]	—[b]
Dowex 50W × 4	4.45	94.00	4.77	99.79	4.61	96.44	—[b]	—[b]
Dowex 50W × 8	2.87	61.72	3.14	67.53	3.74	80.43	3.86	83.01

[a]Values were calculated from $100 \times (\text{meq/g})/MC_{Na}$.
[b]Did not perform.

to be more hydrophobic than DPH. DTM (MW = 370.3) has greater molecular weight than DPH (MW = 291.8). Additionally, the molar volumes of drugs emphasized that DTM (273.3 mL/mole) has relatively bigger size than DPH (250.8 mL/mole). In this work, DTM was found to be more competitive than DPH to bind with Dowex 50W × 2 and × 4 (ELS < 0.5, Table 2). It was obvious that the hydrophobicity of drugs was the determining factor on drug loading onto the resins. As these resins have a low crosslinked matrix, the drugs could be loaded to nearly reach the total exchange capacity (Table 3), revealing that the moieties of DTM and DPH were capable of filling most vicinity of the resins. With this regard, the difference in the molecular size of drugs therefore exhibited minor effect. In contrast, Dowex 50W × 8 has a high crosslinked matrix; therefore, the passage of drugs through the narrow pore matrix structure to interact with the binding sites should determine drug loading. Diphenhydramine hydrochloride (DPH) has a smaller molecular size so that it has a higher accessibility into the resin. This might outweigh its inferior hydrophobicity. Accordingly, DPH was more competitive than DTM to bind with the high crosslinked resin.

Effect of Temperatures

The effect of heat on dual-drug loading is shown in Fig. 6. The plots of the percent of each drug loaded against the proportion of that drug in the loading solution were in good linearity ($R^2 \geq 0.994$). Therefore, the values of EQC as well as ELS were calculated by the same method as described previously (Table 4). It could be concluded that an increase in the loading temperatures from 35 to 55°C had no significant effect on the equivalent dual-drug loading of Dowex 50W × 2 and × 4. It might be attributed to the exhaust of the binding sites (Table 3) and the inherently large pores inside these resins. On the other hand, the heat considerably affected the equivalent dual-drug loading of Dowex 50W × 8. The values of EQC increased when more heat (35 to 65°C) was applied. This finding agreed with the previous work which illustrated the promotion of heat on single drug loading onto this resin (Irwin et al., 1988). It was explained that the heat expanded the centered narrow pore region affording the drugs accessiblity to deeper binding sites of the resin.

It was evident that the heat exhibited a more enhancing effect on DTM absorbed onto Dowex 50W × 8 than on DPH (Fig. 5c). The decrease in the values

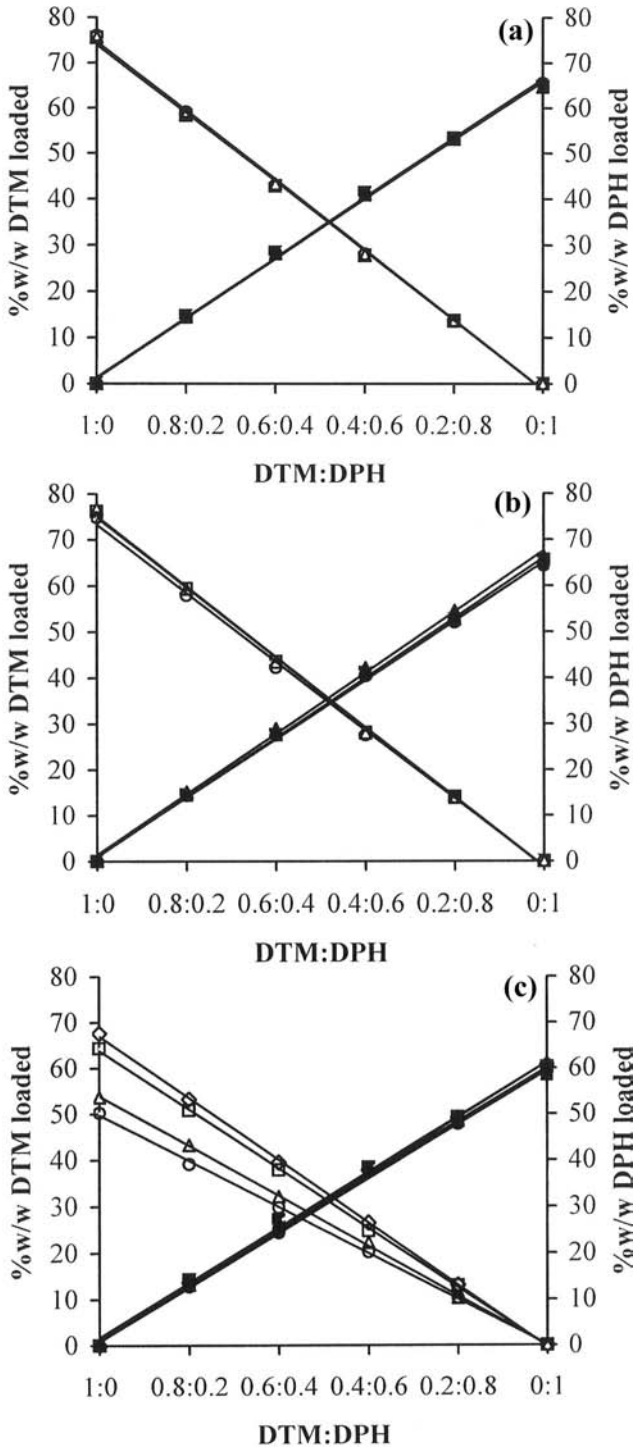

FIGURE 6 **Dual-drug Loading Diagrams of Dowex 50W × 2 (a), × 4 (b), and × 8 (c), Obtained Under Varying Temperatures; 35 (○), 45 (△), 55 (□), and 65°C (◇), Respectively, Where Open Symbols Represent DTM and Closed Symbols Represent DPH.**

of ELS from 0.548 to 0.483 was observed (Table 4). This suggested that the preference of this resin to absorb DPH at low temperatures (35°C) was gradually changed to bind preferentially with DTM at higher temperatures. This could be explained by the fact that the heat induced expansion of the narrow pore region of the resin where DTM was unable to enter at low temperature condition. Once without limited accessibility through the resin structure, DTM, which has superior hydrophobicity, then was more competitive than DPH to bind with this resin. In conclusion, the factor governing dual-drug loading onto Dowex 50W × 8 at high temperature changed from the accessibility to the hydrophobicity of the loaded drugs.

In Vitro Release Characteristics

The resinates with similar values of EQC were employed for drug release study in order to avoid any confounding effects from different levels of drug loading (Chen et al., 1992; Akkaramongkolporn et al., 2001). As presented in Table 2, the resinates of Dowex 50W × 2 and × 4 prepared using 0.50% w/v overall drug concentration (ELS = 0.498 and 0.488, respectively) and that of Dowex 50W × 8 prepared using 1.00% w/v overall drug concentration (ELS = 0.548) gave similar values of EQC (about 27–28%); then they were selected for release evaluation.

Several batches of each selected resinate were prepared using the same loading condition, and the resultant resinates are summarized in Table 5. It was seen that all prepared resinates contained the similar contents of DTM and DPH. Moreover, the obtained drug contents were very close to the calculated values of EQC (Table 2). The data confirmed the reproducibility and practicality of the proposed procedure in preparing the equivalent content dual-drug resinate.

Release profiles of the resinates are shown in Fig. 7. It is known that drug release from resinates occurs via particle diffusion controlled process (Boyd et al., 1947; Reichenberg, 1953; Irwin et al., 1987). Accordingly, the release rate from the resinates could be obtained by treatment of the release profiles with the following mathematical expressions.

$$F = 1 + \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{e^{-n^2Bt}}{n^2}$$

where F is the fraction of drug release, B is the exchange rate constant (h^{-1}), n is the summation variable, and t is time (h). The above expression was later

TABLE 4 Effect of Temperatures on Values of EQC and ELS[a]

Resins	35°C	45°C	55°C	65°C
On EQC				
Dowex 50W × 2	35.122 (0.029)	34.958 (0.027)	34.941 (0.019)	—[b]
Dowex 50W × 4	34.493 (0.024)	35.632 (0.017)	35.088 (0.036)	—[b]
Dowex 50W × 8	27.347 (0.042)	28.814 (0.033)	31.650 (0.059)	32.174 (0.057)
On ELS				
Dowex 50W × 2	0.480 (0.001)	0.479 (0.000)	0.482 (0.000)	—[b]
Dowex 50W × 4	0.479 (0.000)	0.483 (0.000)	0.477 (0.001)	—[b]
Dowex 50W × 8	0.548 (0.006)	0.535 (0.002)	0.498 (0.001)	0.483 (0.001)

[a]Values are presented in mean (s.d.).
[b]Did not perform.

TABLE 5 percent w/w of Drugs in Resinates from Repeated Preparations[a]

Resins	Total batches	DTM	DPH
Dowex 50W × 2	11	28.280 (0.515)	28.203 (0.569)
Dowex 50W × 4	8	27.734 (0.509)	28.489 (0.285)
Dowex 50W × 8	11	27.741 (0.739)	28.330 (0.461)

[a]Values are presented in mean (s.d.).

simplified to the following equations depending upon the magnitude of F value.

$$Bt = 6.28318 - 3.2899F - 6.28318\,(1 - 1.0470F)^{1/2} \quad \text{when } F \leq 0.85$$

$$Bt = -2.30258\log(1 - F) - 0.49770 \quad \text{when } F > 0.85$$

When the Bt value corresponding to the F value is plotted against time, a straight line will be obtained if the particle diffusion controlled process governs drug release from the resinates. The slope of the line yields the B value, and then the diffusion coefficient can be obtained by the following equation.

$$D = \frac{Bd^2}{4\pi^2}$$

Where D is the diffusion coefficient (m^2h^{-1}) and d is the diameter of swollen resin particles (m, $d_{50\%}$ in Table 1). Indeed, the Bt-t plots were not entire linearity, but were leveled-off at high time periods where drug release began toward an equilibrium (Borodkin, 1993; Akkaramongkolporn et al., 2001). With this regard, the linear portions were determined by doing stepwise linear regressions, and then backwards selecting the first linear portion with $R^2 \geq 0.970$. The relevant parameters of drug release obtained from the above kinetic treatment are summarized in Table 6.

As illustrated in Fig. 7, the drug release from the resinates of Dowex 50W × 2 and × 4 was rapid and reached plateaus within 2 h. At the same ionic strength, the resinates of Dowex 50W × 4 showed slightly slower drug release (Table 6). The drug release from the resinates using Dowex 50W × 8 was obviously slowest, and showed considerably extended action up to 6 h. This finding supported the influence of the structural characters of resins on drug release as reported in previous works (Schacht et al., 1982; Irwin et al., 1987). The retardation of drug release from the resinates would increase with increasing degree of crosslinkage within the resins.

With regard to the drug delivery based on ion exchange, the ionic strength plays an important role on drug release. An increase in the ionic strength enhances the influx of eluting ions, and will increase the liberation of the bound drug. This results in an increased concentration gradient of the liberated drug diffusing outwardly from the resin, and hence, greater drug release (Irwin et al., 1987; Sprockel & Prapaitrakul, 1988; Ogger et al., 1991; Pisal et al., 2004). In this work, the drug release from the resinates of Dowex 50W × 2 and × 4 was found to be increasing with an increase in the ionic strength of release media in accordance with the previous reports (Table 6). Interestingly, the increase of ionic strength might not produce faster drug release as it is always expected. In the

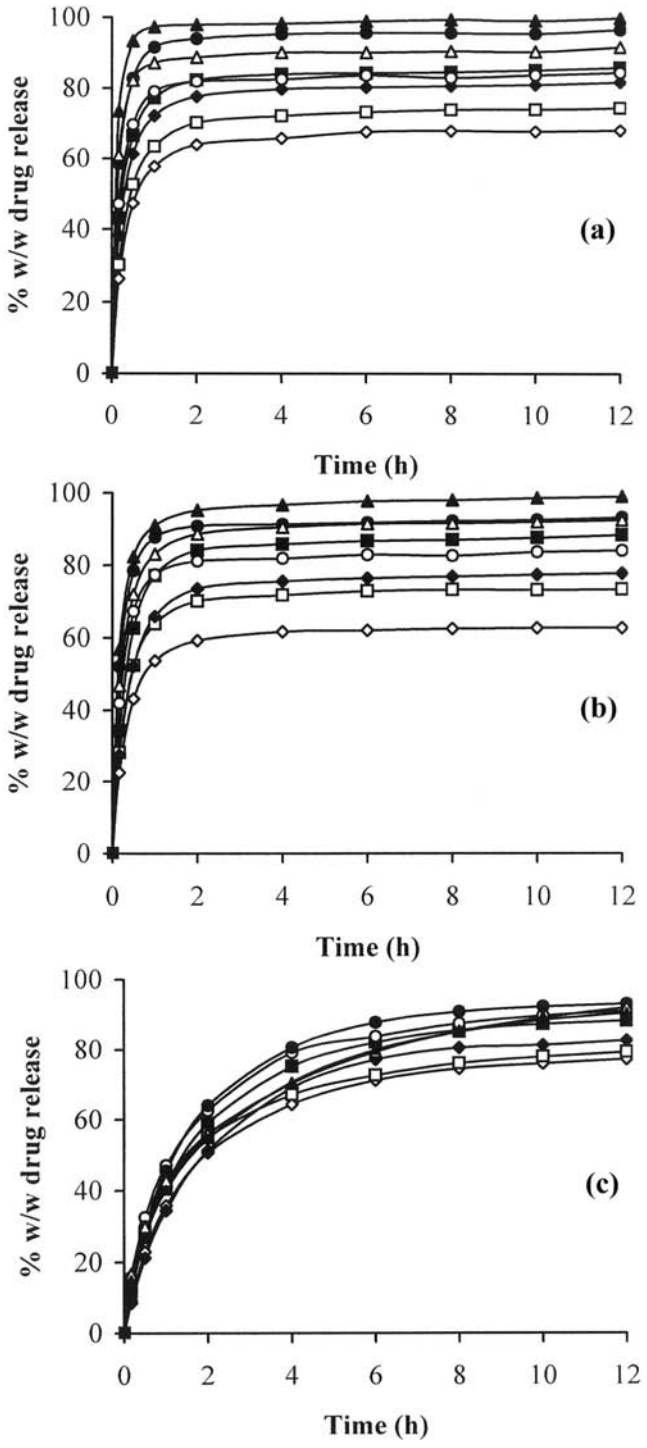

FIGURE 7 **Release Profiles of the Resinates of Dowex 50W × 2 (a), × 4 (b), and × 8 (c), Performed in 0.05 (◇), 0.1 (□), 0.2 (○), and 0.4 N (Δ) KCl, Respectively, Where Open Symbols Represent DTM and Closed Symbols Represent DPH.**

case of the resinates prepared using Dowex 50W × 8, the ionic enhancing effect on drug release occurred only with increasing ionic strength in the range from 0.05 to 0.2 N of KCl while the drug release performed in 0.4 N KCl was considerably slower than that in the lower ionic strengths (Table 6). A similar result had been reported in a previous work (Ogger et al., 1991). The cause for this unexpected result might associate with the narrow pore matrix structure of this resin. Due to the potassium ion having a very small size (atomic weight = 39), it was likely that further increasing the influx of eluting ions from 0.2 to 0.4 N extensively liberated the bound drugs. The burst extents of the free drugs whose molecular weights are about seven to eight times larger than the eluting ions probably exceeded the capacity of diffusive pathways within this resin. This might cause the congestion on the outward movement of drugs from the resin which consequently resulted in the delay of drug release.

Release of DPH was mostly in faster rate and greater extent than that of DTM (Table 6) which might be explained by attribution of the hydrophobicity and the molecular size of the loaded drugs. Dextromethorphan hydrobromate (DTM) having greater hydrophobicity exerted stronger van der Waals force with the resins. Therefore, it was allowed less liberation than DPH. Moreover, the larger molecular size might be responsible additionally for the less release of DTM. However, a unique character of drug release from the resinates of Dowex 50W × 8 was found. The difference in the release between DTM and DPH tended to decrease when the ionic strength was increased. It was, perhaps, a direct impact from the gradually increased congestion on the drug movement like the situation of traffic congestion slowing all running vehicles down to a certain speed.

CONCLUSION

This study showed that dual-drug resinates containing the equivalent content of DTM and DPH were successfully prepared by the proposed method. The behavior of equivalent dual-drug loading onto resins was affected by the loading variables including the degree of resin crosslinkage, overall drug concentration of the loading solution, and temperature during drug loading. Development of this novel resinate required a specific loading condition for a desired equivalent dual-drug content of each resin. Dowex 50W × 8 provided satisfactory extended release from its resinate. The resinates produced from Dowex 50W × 2 and × 4 gave somewhat rapid drug release so they need further coating to accomplish the extended action. The present work demonstrated that the dual-drug resinate using a

TABLE 6 **Relevant Parameters of Drug Release from Resinates**

Resins	Ionic strength (N)	DTM					DPH				
		B (h^{-1})	D ($\times 10^{-10}$ m^2/h)	R^2	Release of linear portion (%)	12 h released (%)	B (h^{-1})	D ($\times 10^{-10}$ m^2/h)	R^2	Release of linear portion (%)	12 h released (%)
Dowex 50W × 2	0.05	0.441	1.293	0.985	0–58	68.207	0.566	1.660	0.985	0–64	74.524
	0.10	0.810	2.379	0.981	0–72	81.864	0.997	2.925	0.979	0–77	86.024
	0.20	1.443	4.234	0.999	0–70	84.648	1.969	5.779	0.977	0–92	96.645
	0.40	2.446	7.178	0.994	0–82	91.756	4.524	13.277	0.998	0–93	99.935
Dowex 50W × 4	0.05	0.369	0.680	0.988	0–54	62.755	0.581	1.070	0.986	0–64	73.337
	0.10	0.634	1.168	0.995	0–66	77.718	1.012	1.864	0.995	0–77	88.268
	0.20	1.012	1.864	0.974	0–77	83.986	1.603	2.952	0.972	0–88	93.094
	0.40	1.286	2.369	0.983	0–83	92.396	1.903	3.505	0.974	0–91	98.876
Dowex 50W × 8	0.05	0.119	0.215	0.977	0–75	77.264	0.155	0.281	0.986	0–81	82.706
	0.10	0.143	0.259	0.978	0–73	79.344	0.192	0.348	0.983	0–86	88.256
	0.20	0.208	0.377	0.972	0–86	91.031	0.224	0.406	0.972	0–92	93.016
	0.40	0.170	0.309	0.998	0–92	92.002	0.162	0.294	0.991	0–90	90.483

suitable crosslinked resin (for example Dowex 50W × 8) could be an option for extended delivery of two combined drugs with the equivalent therapeutic dose.

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APPENDIX

From dual-drug loading diagrams (Figs. 4 and 6), the percent of DTM and DPH loaded in the resinate linearly relates against the proportion of that drug in the loading solution which can be written in linear equations as follows.

$$X_{DTM} = M_{DTM} P_{DTM} + Y_{DTM} \quad (1)$$

$$X_{DPH} = M_{DPH} P_{DPH} + Y_{DPH} \quad (2)$$

where X_{DTM} and X_{DPH} are the percent of DTM and DPH in the resinate, and P_{DTM} and P_{DPH} are the proportion of DTM and DPH in the loading solution. The values of M_{DTM} and M_{DPH} are the slopes, and the values of Y_{DTM} and Y_{DPH} are the intercepts of the lines of DTM and DPH, respectively. Since $P_{DPH} = 1 - P_{DTM}$, Eq. 2 will be transformed into the following equation.

$$X_{DPH} = M_{DPH} P_{DTM} + (Y_{DPH} + M_{DPH}) \quad (3)$$

The equivalent content is the point where X_{DTM} in Eq. 1 equals X_{DPH} in Eq. 3. Having known the values of M_{DTM}, M_{DPH}, Y_{DTM}, and Y_{DPH} from the regression analysis, equalizing Eq. 1 with Eq. 3 can thus estimate the value of P_{DTM}.

$$P_{DTM} = ELS = \frac{(M_{DPH} + Y_{DPH} - Y_{DTM})}{(M_{DTM} + M_{DPH})} \quad (4)$$

Equivalent drug loading solution (ELS) is defined to have the same value as P_{DTM}, but its meaning is exclusive. If the value of ELS is, for example, any X, meaning that the proportions of DTM (P_{DTM}) and DPH (P_{DPH}) in the loading solution used to prepare the resinate are X and (1–X), respectively, then the value of EQC can be calculated by substituting either X in Eq. 1, or (1 – X) in Eq. 2 which gives the same result.