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Drug loading and release properties of ion-exchange resin complexes as a drug delivery matrix

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ABSTRACT

Complexes of ion-exchange resins and dextromethorphan (DM), a model drug, were prepared using different methods including a batch and a column method with different functional groups, ion-exchange capacity, degree of crosslinking, and resin particle size. Drug loading efficiency, release profiles, and scanning electron micrographs were also investigated. Most of the functional groups of resins were loaded with DM after the completion of a double batch method and it was recommended for drug loading into the ion-exchange resin. Using a column method, drug loading could be monitored by simply measuring changes in the pH of the reaction medium since as complex formation reached completion, the pH returned to the initial pH of the eluent due to the limited amount of functional groups available for the exchange. DM could be loaded up to the ratio of 3 (drug): 1 (resin), depending on the physicochemical properties of the resin. As the crosslinking ratio and particle size increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. Assuming that the resin particles are uniform spheres of radius r, release mechanism was evaluated using plots of a $Bt - t$ relationship, where $B\,(=\pi^2 D_i/r^2)$ and t are the rate constant and time, respectively. D_i represents the effective diffusion coefficient of DM inside the resin. The $Bt - t$ plots displayed a straight line indicating that the diffusion of DM in the resin matrix is the rate-controlling step.

1. Introduction

Ion-exchange can be defined as an electrostatic interaction of ions between ions in solution and ion-exchange resins without significant change in the structure and properties of the resins (Anand et al., 2001). The ionic interactions are strongly dependent on the pH and the competing ions in the reaction medium. If the medium has many ionic species, it may decrease the electrostatic interaction between the resin and the ionic drug due to shielding and competitive binding effect. However, the interaction can be exploited in oral drug delivery since the resin can carry the drug and release it in the gastrointestinal (GI) tract due to the pH change or the presence of competing ions (Kim, 2000). The ion-exchange resins can be synthesized or purchased depending on their applications. Generally, ion-exchange resins for ion-exchange chromatography and deionization of water are suitable ones for the purpose of drug delivery systems. Many studies have shown that ion-exchange resins can have a good role as drug delivery systems (Motycka and Nairn, 1978, 1979; Motycka et al., 1985; Raghunathan et al., 1981).

First of all, in order to be loaded in the ion-exchange resin, a drug needs to have charged groups. Generally, the loading is accomplished using two well-known methods. The one is a batch method, and the other is a column method (Borodkin and Sundberg, 1971; Zhang et al., 2000). In the batch method, a specific amount of resin is added to a drug solution and mixed until equilibrium is obtained. In the column method, a concentrated drug solution is passed through a resin-packed column until the effluent concentration is the same as the eluent concentration.

For the efficient drug loading, it is important to know the time it takes to reach equilibrium and how much drug will be loaded into the resin, which depends on resin-type and loading method. The time to reach equilibrium and drug loading are dependent on many variables, such as the molecular weight and charge intensity of both the drug and resin, degree of crosslinking and particle size of the resin, nature of the solvent, and mixing conditions. If the molecules diffusing into ion-exchange particles are large or if the polymers in the resin are highly crosslinked, it will take more time to reach the equilibrium condition. Particle size is another important factor, which can influence the time required to establish equilibrium conditions. Fine particles have more surface area and less internal volume for ions to diffuse, and so less time might be required to reach equilibrium.

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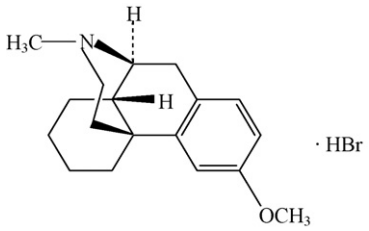

Fig. 1. Molecular structure of dextromethorphan (3-methoxy-17-methyl-9α,13α,14α-morphinan) hydrobromide monohydrate.

The ion-exchange resins to test in this study are crosslinked gel-type resins and their release kinetics are controlled mainly by drug diffusion through the gel. It has been reported that the kinetics of drug release from drug/resin complexes are dependent upon the amine moieties of the drugs used, such as NH_2, –NH–, –N–, and $–N^+–$; and the order of decreasing complex strength among the amine drugs follows: –N– > –NH– > NH_2 (Borodkin and Yunker, 1970).

In this experiment, dextromethorphan hydrobromide was selected as a model drug and batch and column methods were investigated to prepare drug/resin complexes to find the best preparation method for the complex preparation. Ion-exchange resins with different particle sizes, various degrees of crosslinking, and different functional groups were also examined to optimize drug/resin complexes. Drug release kinetics of the resin complexes was evaluated using Boyd model to get information on the rate-limiting step.

2. Materials and methods

2.1. Materials

Dextromethorphan hydrobromide monohydrate, a model drug, was obtained from the Sigma–Aldrich Co. (Lot# 013K1428, Sigma–Aldrich Co., St. Louis, MO). Fig. 1 shows the molecular structure of dextromethorphan hydrobromide (DM). Ion-exchange resins (Dowex® 50WX series, polystyrene sulfonate, H^+ form, Batch# 07120BB and 15019TB; Amberlite® IRP-69, polystyrene sulfonate, Batch# 08511HA) were purchased from the Sigma–Aldrich Co. Amberlite® IRP-69 is a cation-exchange resin with a cation exchange capacity of 5 mequiv./g and a particle size mostly less than 150 μm. All the resins were purified by rinsing three times with distilled water, two times with 95% ethanol, and then two times with distilled water again. Each treatment takes at least 8 h by a batch process. After filtration, the resin was dried in an oven, and the moisture content was measured using a Karl Fischer titrator (Model 270, Denver Instrument Co., Arvada, CO). Table 1 lists the ion-exchange resins investigated in this experiment.

2.2. Preparation of DM-loaded resin complexes

The DM/resin complexes were prepared by a batch and a column processes. For the batch method, the previously purified resin particles (0.95 g dry weight, Dowex® WX2-400) were dispersed in a 1.9% (w/v) drug solution (50 mL) under magnetic stirring at room temperature for 5 h (single batch). After decanting the clear supernatant of the above carefully, another 50 mL of fresh drug solution was added and stirred again for 5 h at room temperature; this procedure is an alternative method called as a modified batch method (double batch). In a triple batch method, an additional batch procedure was accomplished. The complex was separated from the supernatant by filtration, washed with water to remove any uncomplexed drugs, and then dried in an oven.

In order to investigate how quickly equilibrium could be reached, 0.1 mL of supernatant was collected at predetermined intervals during complex formation at room temperature, diluted with water, and then the drug amount was quantified by HPLC. After the first batch, the same procedure was applied for the double and the triple batch methods.

For the column process, a luer-lock and non-jacketed glass liquid chromatography column (size: 1.0 cm × 20 cm, bed volume: 16 mL, Sigma–Aldrich Co.) was used. A certain amount of the ion-exchange resin (Dowex® WX2-400) was slurred with water and transferred to a glass column equipped with a coarse-fritted glass disk at the bottom. To stabilize the packing, the resin was backwashed with water using a peristaltic pump (Minipuls 2, Gilson, France) and then 1.9% drug solution was pumped upward at a rate of 70 mL/h. As the complex formation occurred at room temperature, glass test tubes were used to collect the effluent at predetermined time intervals, and the drug concentration and pH of the effluent were measured using HPLC and a pH meter (Model 601A, Orion Research Inc., Cambridge, MA), respectively.

2.3. Drug release tests

Drug release tests from the drug/resin complexes were conducted according to USP 27 Apparatus 2 guidelines (paddle method) (Vankel® VK 7000, Vankel, Edison, NJ) with 900 mL dissolution medium maintained at 37 ± 0.5 °C and mixed at 100 rpm. The dissolution medium used in this study was 0.1N HCl (pH 1.1–1.2). During the release tests, samples were withdrawn at predetermined times and analyzed for drug content using an HPLC system (Agilent 1100 Series with a diode array wavelength detector, Agilent Technologies, Waldbronn, Germany) at a wavelength of 280 nm. Samples were filtered with 0.2 μm nylon or PVDF filters and then 20 μL of sample was injected. The column used for the analysis was a Symmetry® C_{18} 5 μm (3.9 mm × 150 mm) (Waters Corporation, Milford, MA) with a Sentry™ guard column (Symmetry® C_{18} 5 μm, 3.9 mm × 20 mm). The mobile phase contained a mixture of aqueous buffer (10 mM KH_2PO_4 adjusted to pH 2.6 with phosphoric acid) and acetonitrile in a volume ratio of 26:74. The retention time of DM was 3.1 min.

Table 1
Basic properties of the ion-exchange resins used in this experiment

Ion-exchange resin	Particle size (μm)	Crosslinking (DVB%)	Ionic form	Manufacturer
Dowex® 50WX4-50	300–840	4	H^+	Dow Chemical Co.
Dowex® 50WX4-100	150–300	4		
Dowex® 50WX4-200	75–150	4		
Dowex® 50WX4-400	50–75	4		
Dowex® 50WX2-400	50–75	2	H^+	
Dowex® 50WX4-400	50–75	4		
Dowex® 50WX8-400	50–75	8		
Amberlite® IRP-69	50–150		Na^+	Rohm and Haas Co.
Amberlite® IRP-64	50–150		H^+	

2.4. Scanning electron microscopy (SEM)

The morphologies of the resin and the drug/resin complexes were examined using SEM. Dried samples were attached to specimen stubs using double-sided copper tape and sputter coated with gold–palladium in the presence of argon gas using a Hummer I sputter coater (Anatech Ltd., Denver, NC). The samples were imaged with a JEOL JSM-840 scanning electron microscope (JEOL USA Inc., Peabody, MA) using a 5 kV accelerating voltage, 26–28 mm working distance, and a probe current of 3×10^{-11} A.

2.5. Drug release kinetics

A commonly used mathematical relationship (Boyd model) was applied to understand the drug release kinetics from the resin particles (Boyd et al., 1947). As already suggested earlier (Boyd et al., 1947; Reichenberg, 1953), drug release from a resin complex can be controlled by two well-known mechanisms. One is the diffusion of free drug in the resin matrix. The other is the diffusion of drug across the thin liquid film at the surroundings of the resin particle. Both diffusion mechanisms are sequential steps so the slower one can be a rate-limiting step. Assuming all the resin particles are uniform spheres with radius r and the diffusion of a drug in the matrix is the rate-limiting step, the fraction of drug released, F, was given by the following equation (Boyd et al., 1947):

$$F = \frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{e^{-n^2Bt}}{n^2} \quad (1)$$

M_t and M_∞ are the amounts of drug released after time t and after infinite time, respectively. B is the rate constant, D_i represents the effective diffusion coefficient of the exchanging ions inside the resin particle, and n is the summation variable. For F values higher than 0.85, a first term approximation can be used and the equation can be reduced to (Reichenberg, 1953):

$$F = 1 - \frac{6}{\pi^2}e^{-Bt} \quad \text{or}$$

$$Bt = -\log_e\frac{\pi^2}{6}(1-F) = -2.303\ \log_{10}(1-F) - 0.498 \quad (2)$$

If the F value is lower than 0.85, the equation can be:

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi\left(1 - \frac{\pi F}{3}\right)^{1/2}$$

$$= 6.283 - 3.290F - 6.283(1 - 1.047F)^{1/2} \quad (3)$$

At a value of $F = 0.85$, Eqs. (2) and (3) gave values of Bt agreeing to within 0.005, corresponding to a variation in F of less than 0.001 (Reichenberg, 1953). If the plot Bt corresponding to the F value against time gives a straight line, it can be assumed that drug diffusion within the resin matrix is the rate-limiting step (Atyabi et al., 1996; Ichikawa et al., 2001; Motycka and Nairn, 1978, 1979; Jeong et al., 2007).

3. Results and discussion

3.1. Methods of drug loading

The solubility of DM in distilled water was found to be around 2.0% (w/v). The drug solution used was almost saturated (1.9%, w/v) and the weight ratio between the drug and resin was 1:1 for the loading. Dowex® WX2-400 was the resin used for this study and its crosslinking and particle size are 2% and 38–75 μm, respectively.

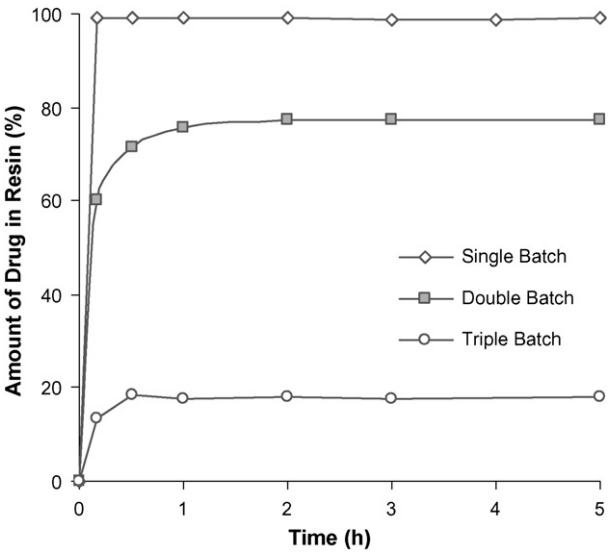

Fig. 2. Equilibrium of DM loading into Dowex® WX2-400 with various drug loading methods.

For the single batch method, equilibrium was achieved in less than 5 min and most of the drug was loaded into the resins (Fig. 2). Moreover, in the case of double batch, about 80% of the drug was loaded and equilibrium was achieved in less than 1 h, which means that many binding sites of the resins were still available for complex formation even after the single batch method was implemented. However, when the triple batch method was carried out, less than 20% of the drug was loaded.

When loading drugs into ion-exchange resins, it is desirable to increase the loading efficiency while reducing the loss of the drugs in order to minimize the size of the final dosage form and reduce the effect of the active ingredient and drug delivery device on the dosage form properties. Therefore, implementing only a single batch method may not be enough to get highly drug-loaded resin complexes. Most of the functional groups seemed to be occupied by the ionic drug following completion of the double batch method. Based on this data, the double batch method could be recommended for loading drugs into the ion-exchange resin.

The functional group of the cation-exchange resin used in this experiment is SO_3^- H^+. As complex formation progresses, acidic by-products can be produced more. If not removed from the system, the by-products would change the pH of the reaction medium, compete with the counter ionic drugs in the bulk solution, and affect equilibrium and also drug loading efficiency (Sprockel and Price, 1990). However, the pH change can be exploited to monitor the endpoint of the reaction in column process. As complex formation approached equilibrium, the drug concentration of the effluent increased to that of the eluent (Fig. 3). Moreover, when complex formation reached completion, the pH returned to the initial pH of the eluent due to the limited amount of H^+ available for the exchange (Fig. 3). Instead of analyzing the amount of drug in the effluent with HPLC, drug loading into the resin may be monitored by simply measuring changes in the pH of the reaction medium. This pH measurement can be a much easier way to determine the endpoint of complex formation.

Fig. 4 shows how much drug was loaded into the resin with various complex formation methods. The drug was almost fully loaded after the double batch process, which was comparable to the column process. In terms of drug loading, modified batch methods such as the double batch and triple batch method yielded

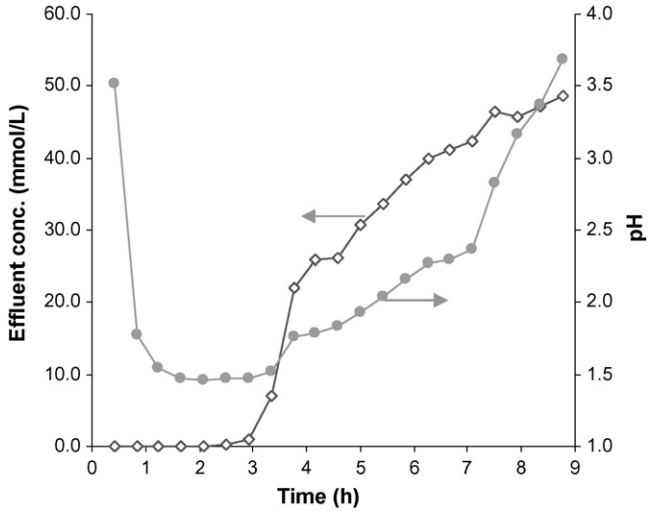

Fig. 3. Equilibrium of DM loading into Dowex® WX2-400 using the column method and based on the drug concentration of the effluent and pH of the effluent.

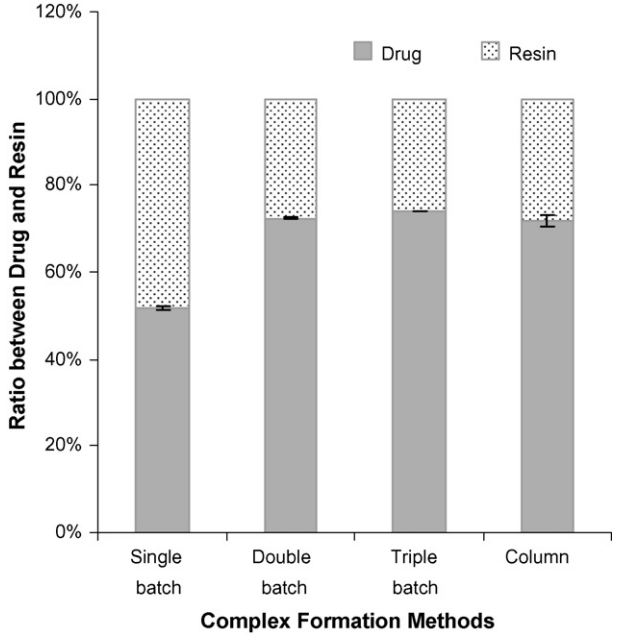

Fig. 4. Ratio between DM and the resin when DM was loaded into the Dowex® WX2-400 resin using various complex formation methods.

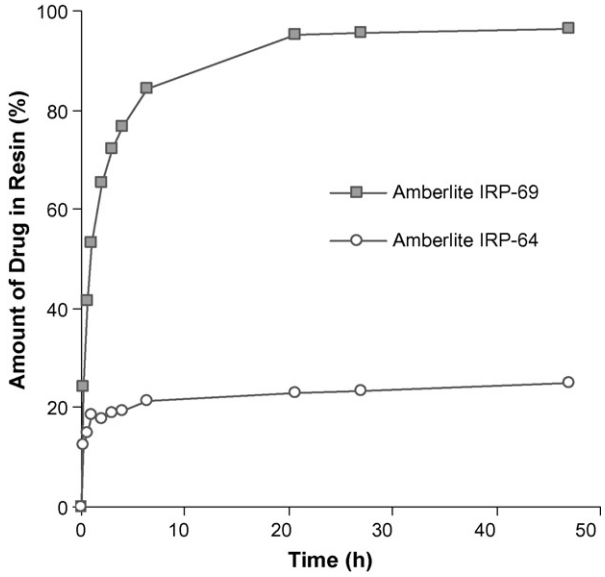

Fig. 6. Equilibrium profiles of drug incorporation into the ion-exchange resins with weakly and strongly acidic functional components.

much better results than the single batch method. The slightly reduced DM loading using the column method might be due to the incomplete contact between the DM in solution and the packed resins when the drug solution was pumped through the column. Since the double batch method was easier to prepare the resin complexes than the column process with similar efficiency, the double batch method might be more practical way to prepare drug/ion-exchange resin complexes.

Scanning electron micrographs of Dowex® 50WX2-400 resin (Fig. 5A), and drug/resin complexes with the single (Fig. 5B) and double batch method (Fig. 5C) showed that the resins had spherical shape before and after drug loading, and the particle size was very small, most of them were less than 80 μm. No porous structures could be observed in the resins. Moreover, drug loading affected particle size of the complexes. Since the crosslinking of the resin is just 2%, the mechanical strength of the resin was probably not strong enough, so some resin debris could be observed in the pictures.

3.2. Effect of functional groups on the equilibrium rate

Fig. 6 shows the equilibrium profiles of drug loading into the ion-exchange resins with weakly and strongly acidic functional groups using the single batch method without any pH modification to confirm the effect of functional groups. The strong acid had a higher affinity for ionic drugs, and this increased the amount of drug in the resulting complex. Moreover, unlikely to Dowex® resins, it took

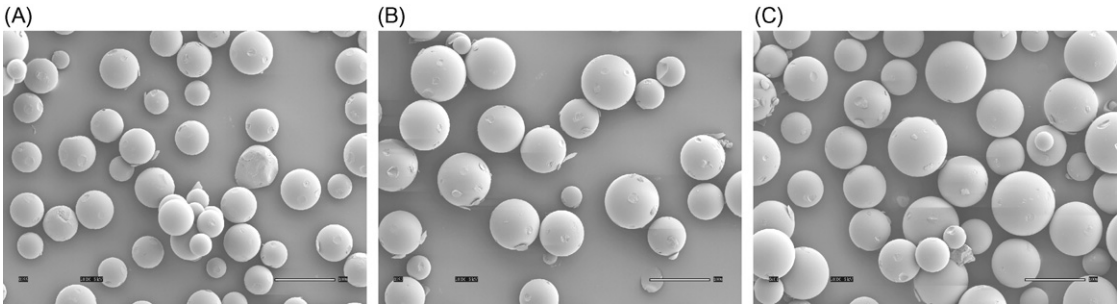

Fig. 5. Scanning electron micrographs of Dowex® 50WX2-400 resin and drug/resin complexes generated using the single batch and double batch method.

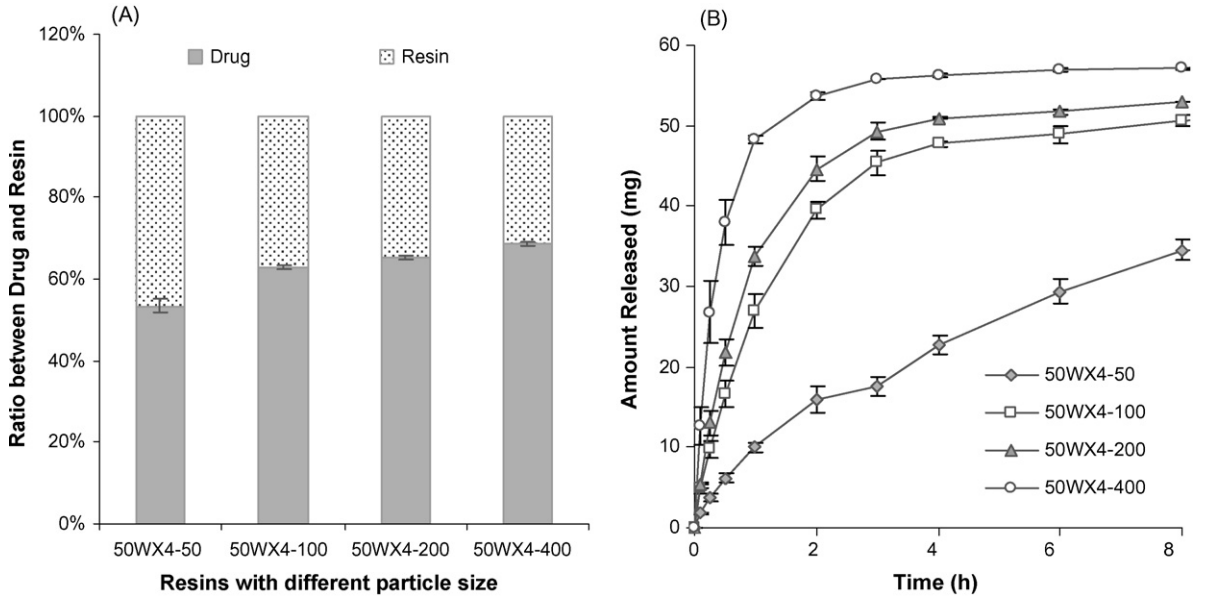

Fig. 7. Effect of particle size of ion-exchange resins on drug loading (A) and *in vitro* drug release profiles in 0.1N HCl (pH 1.2) (B). The particle size distribution of 50WX4-50 is 300–840 μm, 50WX4-100 is 150–300 μm, 50WX4-200 is 75–150 μm, and 50WX4-400 is 50–75 μm.

much more time for the Amberlite® IRP69 resin to reach equilibrium, which was almost 24 h.

Ion-exchange resins are composed of two main groups. One is polymer matrix, which can give structural integrity in the resin, and the other is functional group where the counter ions can bind. The polymer matrix consists of an acrylic styrene-divinylbenzene copolymer and the functional group can be acidic or basic. To make it acidic, sulfonic (strong) or carboxylic (weak) acid is usually used, as tested in the experiment. These two types of functional groups can affect the drug incorporation efficiency, equilibrium rate, and release kinetics. Strong acid type resins showed greater sustained release than weak acid type resins in *in vitro* dissolution tests (Pongpaibul et al., 1989). Sulfonic acid cation-exchange resins with a pK_a value of 2 can be significantly dissociated at all the pH ranges in the GI environment. Amberlite® IRP64 is a weakly acidic, hydrogen form cation-exchange resin with a particle size mostly less than 150 μm. The high affinity of Amberlite® IRP64 to hydrogen ions can yield fast desorption of bound ions when they are exposed to an acidic environment such as the stomach. When the pH is lower than 4, the resin exists in the free state. Therefore, drug/resin complex formation needs to be carried out at pH 6 or higher.

3.3. Effect of particle size and crosslinking

Fine particles have more surface area than coarse particles and less internal volume for ions to diffuse, so less time can be required to establish equilibrium. Similarly, desorption of bound drug from the complex will be faster in fine particles. Moreover, when an

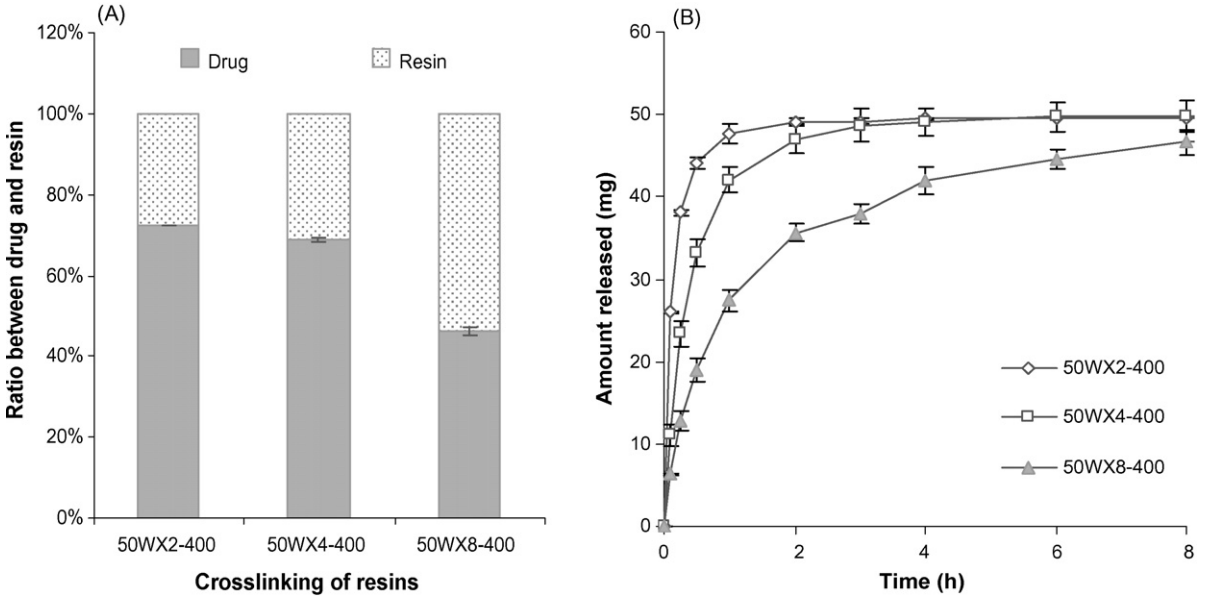

Fig. 8. Effect of crosslinking of ion-exchange resins on drug loading (A) and *in vitro* drug release profiles in 0.1N HCl (pH 1.2) (B). The crosslinking ratio (DVB percentage) of 50WX2-400 is 2 %, 50WX4-400 is 4 %, and 50WX8-400 is 8%.

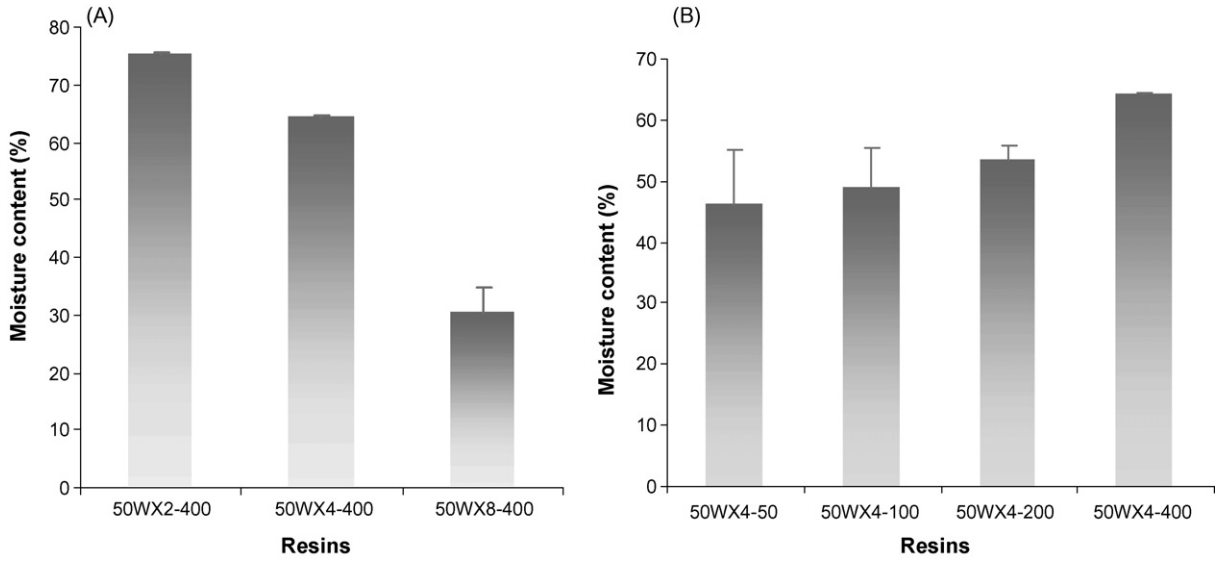

Fig. 9. Moisture content of ion-exchange resins depending on various crosslinkages and particle sizes.

ion-exchange resin is highly crosslinked, the diffusion of various ions can be impeded, and this will increase the time required to reach equilibrium and reduce the amount of loaded drug.

Various particle sizes of Dowex® 50WX4 resins were used to investigate the effect of particle size on drug loading (Fig. 7A) and drug release profiles (Fig. 7B). The particle size distribution of 50WX4-50 is 300–840 μm, 50WX4-100 is 150–300 μm, 50WX4-200 is 75–150 μm, and 50WX4-400 is 50–75 μm (Table 1). Generally, the size of the resin particles is controlled during the polymerization step. However, smaller resins are sometimes obtained by milling larger particles. As the particle size decreased, the drug loading increased significantly. For the drug release profiles, 50 mesh particles showed almost zero order release. Thus, these particles could be directly incorporated into drug delivery formulations without the application of additional drug release controlling technologies, such as coating or microencapsulation.

Resins of various degrees of permeability are dependent on the divinylbenzene (DVB) content, which is the degree of resin crosslinkage, and the number after *X* is the percentage of DVB in the resin polymer. Practical ranges are considered to be between 2 and 16%. For example, Dowex® 50WX2-50 contains 2% DVB with a particle size larger than 50 mesh. Resins with low crosslinkage tend to be watery and change dimensions a great deal depending on which ions are bound as shown in Fig. 5. The total capacity of ion-exchange resins is defined as the total number of chemical equivalents available for exchange per unit weight or unit volume of the resin. This capacity can be expressed in terms of milliequivalents per dry gram of resin or milliequivalents per milliliter of wet resin. The total exchange capacity of resins with a crosslinkage of 2, 4 and 8% used in this experiment are 0.6, 1.1, and 1.7 mequiv./mL, respectively. As the crosslinkage increased up to 8%, the drug loading ratio decreased by a significant amount (Fig. 8A). If a resin is highly crosslinked, it is more difficult to generate additional func-

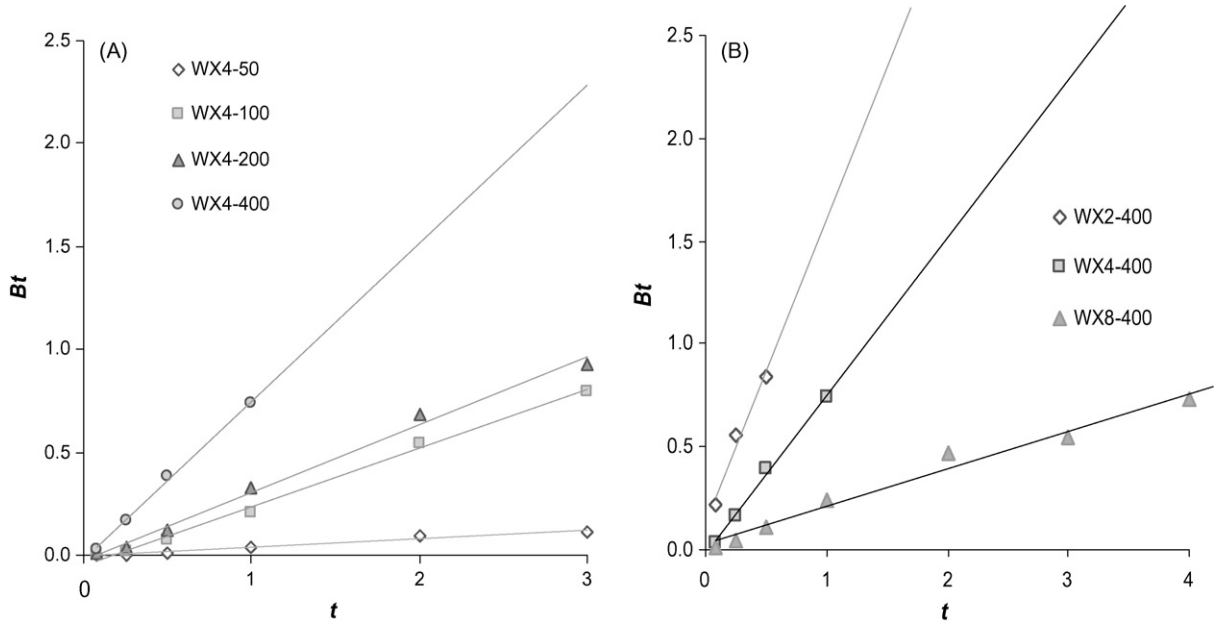

Fig. 10. Plots of *Bt* versus *t* for the drug release using the data of Figs. 7 and 8.

tional groups, because sulfonation is generally accomplished after the crosslinking reaction. Sulfonation can introduce sulfonic acid groups inside the resin particles as well as on its surface. When the resin is highly crosslinked, fewer functional groups are available inside the particle, resulting in low ion-exchange capacity. However, higher crosslinked resins display a more sustained release effect than lower crosslinked resins, as can be noticed from the release profiles (Fig. 8B).

3.4. Moisture content with different crosslinking and particle size

Moisture content is another important property of the ion-exchange resins when there is difference in crosslinkage and particle size. Resins with low crosslinkage can hold a lot of water and can change dimensions easily. For example, sulfonic acid cation-exchange resins, tested in this experiment, tend to attract water strongly holding inside the particles. As shown in Fig. 9A, as the crosslinkage increased up to 8%, moisture content of the resin decreased more than half when compared to that of 2%. In the case of particle size (Fig. 9B), the difference of moisture content was not so significant compared to that of crosslinkage. High swelling properties can be exploited into different application such as polymethacrylic carboxylic acid ion-exchange resins (Amberlite® IRP-88, Rohm and Haas Co.) which were investigated as tablet disintegrants (Borodkin and Sundberg, 1971).

Temperature can be one of the variables, which can be modified to control the drug loading and the drug release in the complex. It was already disclosed that as the temperature increased, the extent of drug incorporation into the resin also increased (Irwin et al., 1988). High temperature can make resin particles swell more as a result of thermal and hydration effect. The swelling can give better access to the center of the particles deep within the matrix. As the temperature drops on cooling the resin particles can shrink and hold the drug within the matrix resulting in an increased load and sustained release.

3.5. Drug release kinetics from ion-exchange resin complex

As shown in Fig. 10, the release rate of DM gave linear $Bt - t$ plots when Eq. (3) was used, showing that drug diffusion within the resin matrix is probably the rate-controlling step, even though the slopes of the plots were strongly dependent on the different types of ion-exchange resins. Even though the above relationships were claimed to fail when considering a moving boundary layer, occurring when the ions in solution come in contact with the attached ions in the resin (Holl and Sontheimer, 1977; Selim and Seagrave, 1973a,b), they can give a good information regarding the drug release properties. To explain the drug release from these ion-exchange resins (Kim, 1996), a pseudo-steady state shrinking-core model was also suggested, which is based on a non-catalytic gas–solid reaction, or chemical leaching process, within the nonporous particles.

4. Conclusions

DM loaded ion-exchange resins were prepared using different methods including a batch and a column process with different functional groups, ion-exchange capacity, degree of crosslinking, and resin particle size. Most of the functional groups of the resins were loaded with DM after the completion of a double batch method and it was recommended for the drug loading into the ion-exchange resin. When a column method was applied, simply measuring changes in the pH of the reaction medium could monitor drug loading, because as complex formation reached completion, the pH returned to the initial pH of the eluent. DM could be loaded up to the ratio of 3 (drug): 1 (resin), depending on the physicochemical properties of the resin. As the crosslinking ratio and particle size increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. Fine particles required less time to establish equilibrium because of more surface area and less internal volume for ions to diffuse. Similarly, desorption of bound drug from the complex was faster in fine particles. Moreover, when an ion-exchange resin is highly crosslinked, the diffusion of various ions was impeded, and this increased the time to equilibrium and reduced the amount of loaded drug. When the drug release profiles were applied into the Boyd model, linear $Bt - t$ plots were obtained suggesting that drug diffusion within the matrix is the rate-limiting step.

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