AAPS PharmSciTech, Vol. 10, No. 2, June 2009 (© 2009)
DOI: 10.1208/s12249-009-9259-5

Research Article

Preparation and Evaluation of Differently Sulfonated Styrene–Divinylbenzene Cross-linked Copolymer Cationic Exchange Resins as Novel Carriers for Drug Delivery

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Received 22 December 2008; accepted 23 April 2009; published online 19 May 2009

Abstract. The differently sulfonated styrene–divinylbenzene cross-linked copolymer cationic exchange resins were prepared by oil-in-water polymerization and varied degrees of sulfonation. Several characteristics of the obtained resins were evaluated, i.e., Fourier transform infrared spectra, the ion-exchange capacity, microscopic morphology, size, and swelling. The resin characteristics were altered in relation to the degree of sulfonation, proving that differently sulfonated resins could be prepared. The behavior of chlorpheniramine (CPM) loading and *in vitro* release in the USP simulated gastric (SGF) and intestinal fluids (SIF) of the obtained resins were also evaluated. The CPM loaded in the resinates (drug-loaded resins) increased with the increasing degree of sulfonic group and hence the drug binding site in the employed resins. The CPM release was lower from the resins with the higher degree of sulfonic group due to the increase in the diffusive path depth. The CPM release was obviously lower in SGF than SIF because CPM, a weak base drug, ionized to a greater extent in SGF and then preferred binding with rather than releasing from the resins. In conclusion, the differently sulfonated resins could be utilized as novel carriers for drug delivery.

KEY WORDS: cationic exchange resin; chlorpheniramine maleate; different sulfonation; drug loading; drug release; oil-in-water polymerization.

INTRODUCTION

Ion-exchange resins are swellable cross-linked copolymers that can reversibly interchange counterions. The resins are organized into two main types depending upon the charge of the counterions with which they exchange. The cationic exchange resin contains the negatively ionizable group such as a sulfonic group, which is capable of interchanging the positively charged or cationic counterion. The anionic exchange resin interchanges the negatively charged or anionic counterion due to the existence of the positively ionizable group such as a quaternary ammonium group (1,2).

The preparation of these two resins is quite similar, consisting of two stages (2). First, the cross-linked copolymer bead is synthesized, to which the ionizable or ion-exchangeable group is added later. The cross-linked copolymer between styrene and divinylbenzene is commonly tailored in both resin types. The spherical bead can be obtained using oil-in-water emulsion polymerization. In this method, the monomer mixture containing styrene, divinylbenzene, and benzoyl peroxide (as a catalyst) is gradually added into a well-stirred aqueous phase of a stabilizing agent. Then, the polymerization is begun after the drops of the monomer mixture are formed. Having received the bead, the negatively ionizable group (i.e., sulfonic group) is simply added by a treatment with concentrated sulfuric acid, dubbed "sulfonation." The addition of the positively ionizable group (i.e., quaternary ammonium group), however, is somewhat complex, requiring multiple steps. Up until present time, when preparing a resin, the ion-exchangeable group is always added until the maximum capacity of the resin is reached.

In pharmaceutics, the resins have diversified applications, the primary among which is as carriers for drug delivery. A drug that ionizes into either a positively or negatively charged molecule can act as an incoming counterion, replacing the counterion and electrically interacting with the oppositely charged ionized group of the resins. This drug and resin combination is interchangeably referred to as the "drug resin complex" or "resinate" (1). The loaded drug will substantially release from the resinate on exposure to a like-charge ion (another counterion) present in the gastrointestinal tract. The drug release can be tuned to a desired rate by selecting suitable cross-linked resins (3), entrapping (4), or coating the resinate with suitable polymers (5). However, the above application employs only the commercial resins with the ion-exchangeable site fully filled. To the best of our knowledge, the characteristic and behavior of different partially sulfonated resins in delivering a drug has never been presented.

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Table I. Assignment, IEC, and Yield Weight of Differently Sulfonated Resins

Sulfonation time (min)	0	15	28	35	40	90	210
Assigned code	R/0	R/15	R/28	R/35	R/40	R/90	R/210
IEC (meq/g)[a]	0.000±0.000	0.000±0.000	0.480±0.001	2.057±0.007	3.586±0.002	4.138±0.046	4.144±0.012
Resin weight (g)[b]	3.000	3.115	3.303	4.178	5.159	6.220	6.410
% Weight increase[c]	0	3.8	10.1	39.3	72.0	107.3	113.7

[a] Mean ± SD from triplicate measurements
[b] After drying at 50°C for 6 h
[c] 100 × (resin weight − bead weight)/bead weight , where bead weight = 3.000 g

As a novel approach, this work was aimed at preparing and characterizing the differently sulfonated resins. The behavior of the obtained resins in terms of drug (chlorpheniramine maleate) loading and *in vitro* release were evaluated and discussed. Chlorpheniramine maleate was used as a representative of a low-dose drug. The different partially sulfonated resins had lower ion exchange than the usual resins with the full ion-exchange capacity; thus, they were feasible for use in delivering the low dose drug.

MATERIALS AND METHODS

Materials

Styrene (Sigma-Aldrich, Germany), divinylbenzene (Sigma-Aldrich), polyvinyl alcohol (M_W 85,000–124,000, 87–89% hydrolyzed, Sigma-Aldrich), benzoyl peroxide (Sigma-Aldrich), concentrated sulfuric acid (Mallinckrodt Baker Inc., USA), chlorpheniramine maleate (Green Chemical Company Ltd., Japan), dichloromethane (Ajax Finechem, Australia), sodium chloride (Ajax Finechem), potassium chloride (Ajax Finechem), sodium hydroxide (Ajax Finechem), potassium dihydrogen orthophosphate (Ajax Finechem), and concentrated hydrochloric acid (Mallinckrodt Baker Inc.) were purchased from various suppliers and used as received. Deionized water prepared by a water purifier (Barnstead/Thermolyne D 4745, USA) was used entirely in this work.

Methods

Preparation of Differently Sulfonated Resins

The cross-linked copolymer bead was prepared by oil-in-water emulsion polymerization in a 2-l Erlenmeyer flask fitted with a mechanical agitator (IKA-RW20, Germany) in a temperature-controllable oil bath (IKA-Werke). The aqueous phase (1.5 l) of a 0.5% (*w*/*v*) polyvinyl alcohol solution was added to the flask, and the temperature was raised to around 65°C. Under a fixed stirring (400 rpm), the monomer mixture containing styrene (75 ml), divinylbenzene (3 ml), and benzoyl peroxide (3 g) was gradually poured into the aqueous phase. Then, the temperature was raised to around 85°C and maintained at that temperature until the polymerization was terminated (4 h). Thereafter, the bead was washed several times with deionized water (totally 2 l) and methanol (totally 400 ml) and then sieved. The fraction in the range of 74–149 μm (100–200 mesh) was collected, dried at 50°C for 6 h in a hot air oven, kept in a tightly closed container, and used for sulfonation. This bead fraction (25.7 g) approximately corresponded to 60% of the whole beads (42.5 g) and 33% of the employed monomers (78 g), respectively.

Prior to sulfonation, the dried copolymer bead (3 g) was swollen by contacting with dichloromethane (12 ml) for 30 min. The swollen bead was then sulfonated with a fixed volume (30 ml) of concentrated sulfuric acid (H_2SO_4) in the oil bath maintained at 70°C. The slurry was periodically shaken during the sulfonation. The degree of sulfonation was

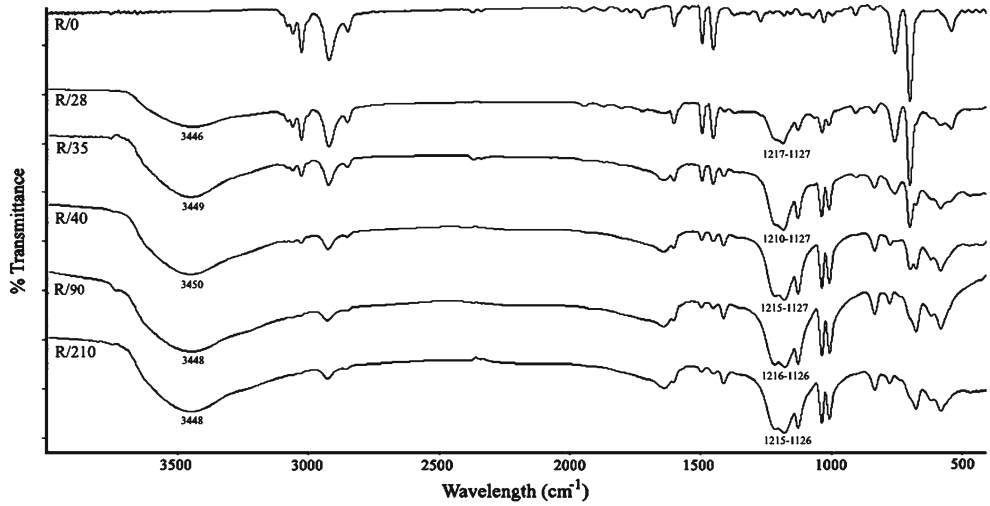

Fig. 1. Fourior transform infrared spectra of differently sulfonated resins

regulated by varying the reaction times from 0 (no sulfonation) to 210 min. The sulfonated resin was filtered, washed with excess deionized water until neutral pH, and finally dried at 50°C for 6 h. The final resin was kept in a tightly closed container until further investigation.

Characterizations of Copolymer Bead and Differently Sulfonated Resins

Fourier Transform Infrared Spectroscopy. The resins that were previously dried at 100°C until reaching a constant weight were crushed and pressed into KBr pellets. The infrared (IR) spectra of the obtained pellets were recorded over the range 400–4,000 cm^{-1} by a Fourier transform infrared spectrophotometer (Nicolet Magma-IR system 750, USA).

Ion-Exchange Capacity. The ion-exchange capacity of resins was determined by the salt splitting titration (2). An accurate amount (0.1 g) of the resins was weighed and added into a 125-ml Erlenmeyer flask containing a 2 N sodium chloride solution (25 ml). The slurry was swirled periodically and left for 3 h to allow for the displacement of H^+ from the resins. Thereafter, the slurry was titrated slowly with a 0.1 N standardized sodium hydroxide (NaOH) solution using phenolphthalein as the indicator. The ion-exchange capacity of the resins (IEC, meq/g) was calculated from:

$$\mathrm{IEC} = \frac{c \times v}{w} \tag{1}$$

where c is the standardized concentration (N), v is the volume (ml) at an endpoint of the NaOH solution, and w is the weight (g) of determined resins.

Microscopic Morphology. The dried resins (the dry state) and those put into a drop of excess deionized water (the wet state) were photographed by a microscope (Olympus, Japan) equipped with a digital camera (AnMo AM-423X DinoEye, Taiwan). The dried resins were also viewed by a scanning electron microscope (CamScan MX 2000, UK). Before viewing, the samples were fixed on stubs and sputter-coated with gold in a vacuum evaporator (Cressington Sputter Coater 108, UK).

Size and Swelling. The resins dried at 50°C for 6 h and those suspended in deionized water for 3 h were photographed with the digital microscope. Feret's diameter of 200 particles on the images was randomly measured with a calibrated digital micrometer of the image analysis program (AnMo DinoCapture version 2.3.0.0, Taiwan). Then, the average diameter of the dried (d_{dry}) and swollen (d_{swell}) resins was determined, and the swelling (%) of the resins was calculated using the following equation (6):

$$\mathrm{Swelling} = \frac{d_{swell} - d_{dry}}{d_{dry}} \times 100. \tag{2}$$

Behavior of Differently Sulfonated Resins as Drug Carriers

CPM Loading. Chlorpheniramine (CPM) loading into the differently sulfonated resins was carried out by the batch method. In this process, 0.5 g of resin was placed into a 1.0% (*w*/*v*) CPM solution in water (100 ml). The preliminary test showed that this selected drug solution could provide maximum drug loading for the resins. The mixture was allowed to come to equilibrium for drug exchange (24 h) at 35°C under constant agitation (BioSan Environmental shaker-incubator ES-20, Latvia). A preliminary study proved that 24 h was sufficient for achieving equilibrium. Thereafter, the obtained resinate was washed with deionized water to remove the unloaded drug. The resinate was dried overnight in a hot air oven at 50°C and then stored in a tightly closed container. The drug content was determined by eluting 50 mg of each resinate with a 1 N KCl solution

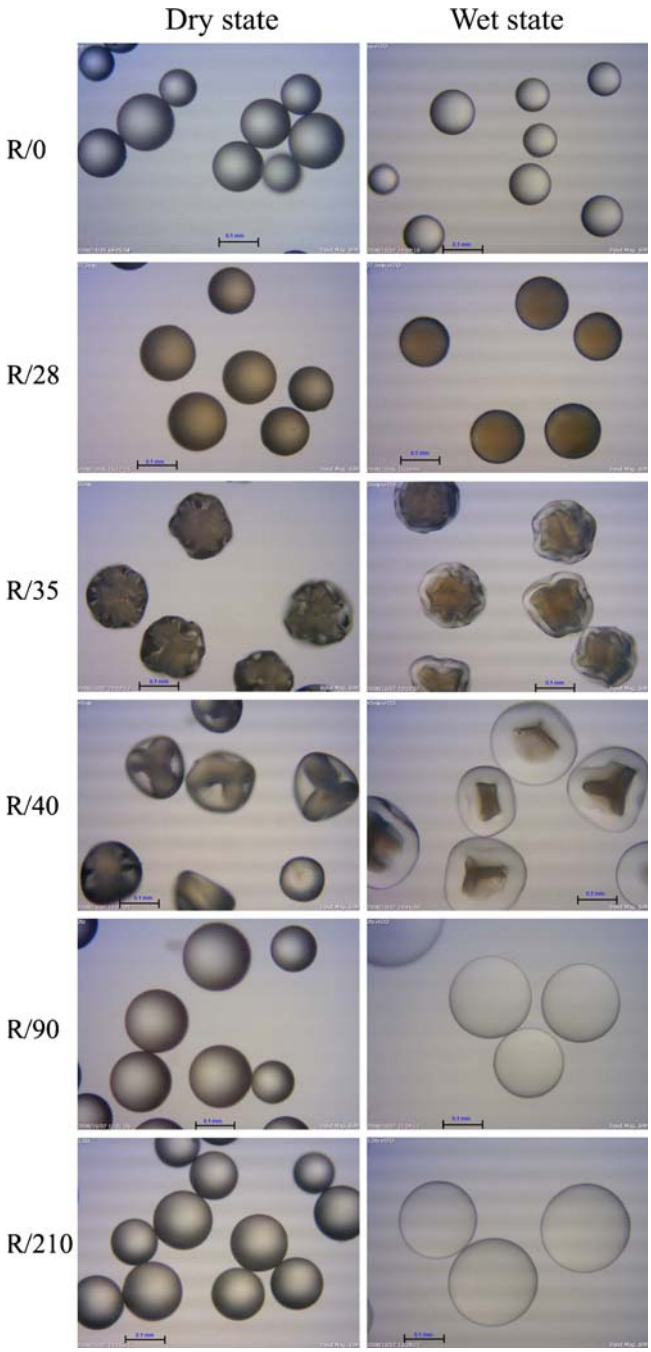

Fig. 2. Photomicrographs of differently sulfonated resins

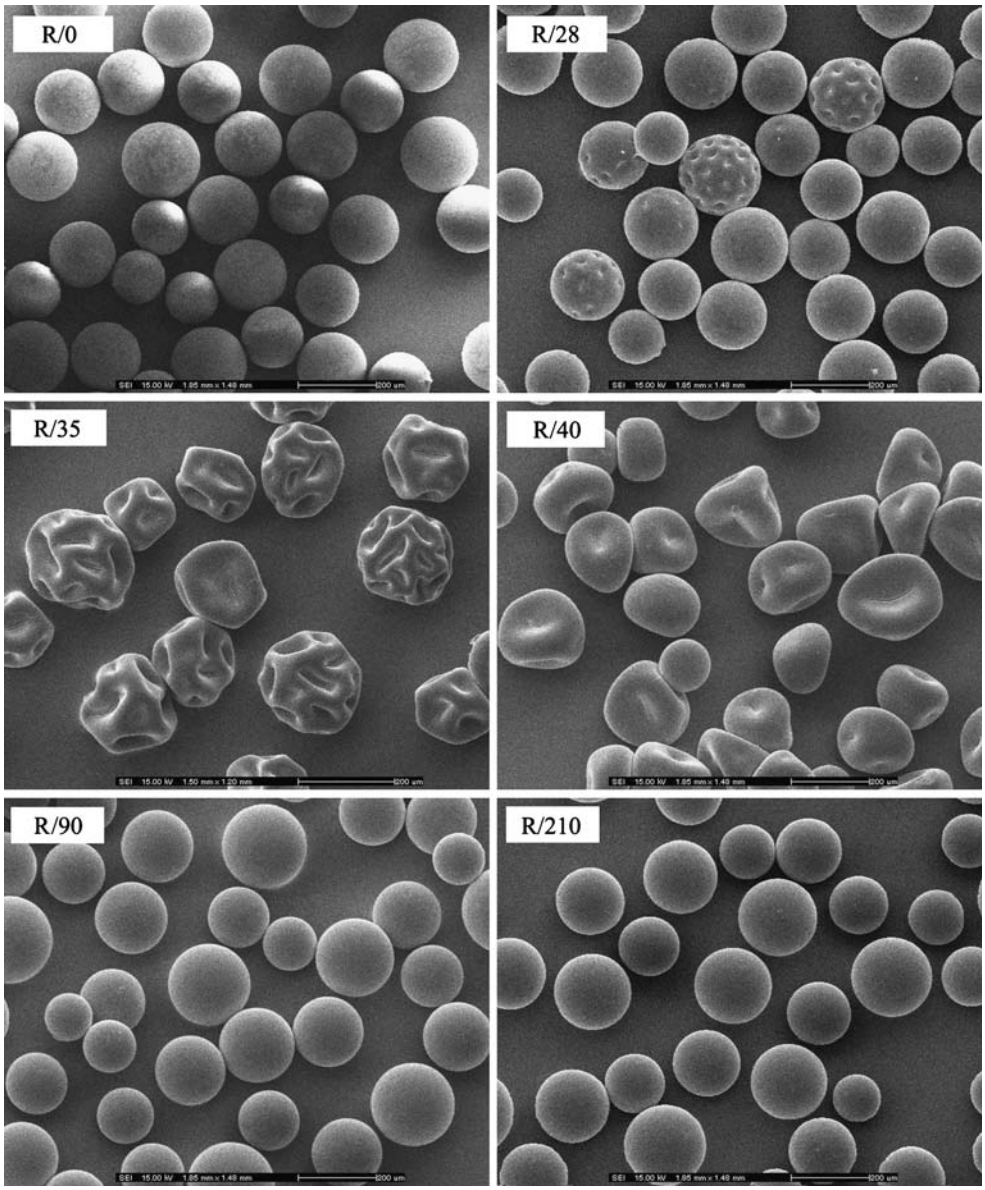

Fig. 3. Scanning electron micrographs of differently sulfonated resins

(200 ml) and then calculated in % *w*/*w* as the (amount of drug/amount of resinate) × 100 (7). The eluted drug was assayed by a UV spectrophotometer (Perkin-Elmer Lambda 2, Germany) at 261 nm.

CPM Release. In vitro CPM release was investigated in the USP simulated gastric and intestinal fluids (450 ml) by a USP release testing apparatus I (Prolabo Dissolutest, France) (8). Each resinate prepared from the differently sulfonated resins was weighed to obtain an equivalent of 24 mg CPM and then added into the release vessel. The rotation and temperature were set at 50 rpm and 37±1°C, respectively, throughout testing. At the predetermined times, small portions (5 ml) of the medium were withdrawn through a filter and assayed by the UV spectroscopic method. The same volume of fresh medium was returned to maintain the volume entirely constant. The release testing was conducted in triplicate.

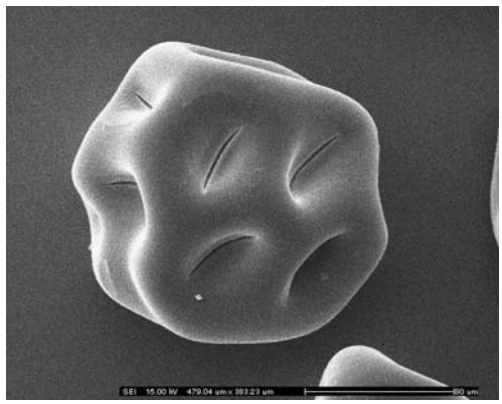

Fig. 4. Scanning electron micrograph showing fractures found in R/35

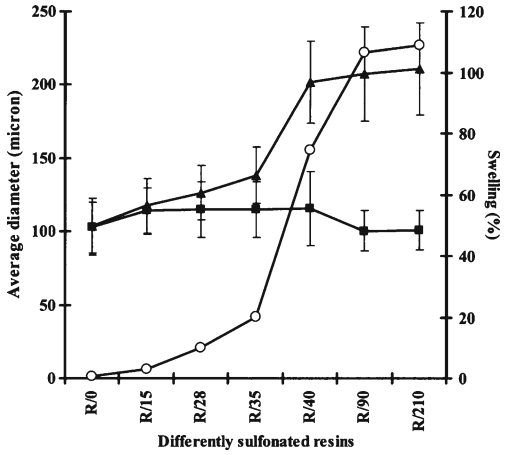

Fig. 5. Average diameter in dry (*square*) and wet (*triangle*) states and swelling (*circle*) of differently sulfonated resins

RESULTS AND DISCUSSION

Preparation and Characterizations of Differently Sulfonated Resins

The copolymer beads were prepared by oil-in-water emulsion polymerization and then sulfonated for varied reaction times to transform into the differently sulfonated resins, the codes of which are displayed in Table I. To evaluate the success of this process, the IR spectra and the ion-exchange capacity of the obtained resins were determined. The IR spectra of the differently sulfonated resins were shown in Fig. 1. There were significant new peaks around 1,126–1,217 and 3,450 cm^{-1} in the IR spectra of the copolymer beads after sulfonation or, in the other words, the differently sulfonated resins. These peaks were attributed to the stretching vibrations of the S=O and O–H of the sulfonic group ($–SO_3H$), respectively (9,10). The peaks obviously appeared more prominently in the IR spectra of the resins treated with the longer sulfonation periods, demonstrating the higher degree of sulfonic group introduced into the resins. In addition, the IR spectra of the obtained resins resembled those of identical or commercial sulfonated styrene–divinylbenzene (DVB) copolymer resins reported elsewhere (9,11). This evidence indicated that the differently sulfonated styrene–DVB cross-linked copolymer resins could be successfully prepared.

To determine the ion-exchange function of the introduced sulfonic group, the IEC of the prepared resins as well as the copolymer beads were determined (Table I). The copolymer beads showed no ion-exchange property (IEC = 0 meq/g) due to the absence of sulfonic group. In contrast, the ion-exchange property and hence IEC were found in the sulfonated resins. The IEC increased as the resins were treated with the longer sulfonation periods. This evidence confirmed the successful addition of varied degrees of sulfonic group into the resins. The sulfonic group was the ion-exchangeable site of the resins. In an ionic solution (e.g., NaCl as an ionic solution used in the determination of IEC), the sulfonic group ionized and interchanged its counterion (i.e., H^+) with another cationic counterion (i.e., Na^+). The greater degree of sulfonic group added in the resins, the greater interchange of the counterions, thus providing the higher IEC.

Also, it was found that the weight and hence the percent weight increase of the obtained resins in relation to the employed copolymer bead was increased as the sulfonation time was increased (Table I). This was due to the more sulfonic group introduced into the resins. However, this work could not provide the percent yield of the resins in relation to the used reactants because the actually reacted amount of sulfuric acid, which was added in excess for sulfonation, was not determined.

The photomicrographs of the differently sulfonated resins in the dry and wet states are shown in Fig. 2. The figure depicted, especially from the wet state, the progress of the sulfonation, proceeding from the outside into the center of the copolymer beads. The beads without sulfonation (R/0 in Fig. 2) were seen to be totally unchanged between the dry and wet states. In contrast, the outer region, which was already reacted, of the different partially sulfonated resins (R/15, /28, /35, and /40 in Fig. 2) significantly swelled, which clearly distinguished it from the remaining unreacted core. The virgin cores were of irregular shapes, demonstrating the uneven rates of sulfonation proceeding toward the bead center in each direction. Nevertheless, the irregular-shaped cores became smaller as the sulfonation further progressed and eventually disappeared in the completely sulfonated resins (R/90 and /210 in Fig. 2). The fully sulfonated resins swelled evenly throughout the beads and then returned to a uniformly spherical shape. The swelling occurrence helped confirm the success of the introduction of sulfonic group into the resins. The embedded sulfonic group had strong hydrophilicity and affinity for water, enabling it to transform the rigid cross-linked copolymer into water swellable but insoluble gelled beads (9).

The scanning electron micrographs of the resins supported the finding obtained from the photomicroscopic study presented above (Fig. 3). The surfaces and shapes of the different partially sulfonated resins were wavy and irregular

Table II. CPM Loading and Resinate Formulation Obtained from Differently Sulfonated Resins

Resin	R/0	R/28	R/35	R/40	R/90	R/210
CPM loaded in resinate (% *w*/*w*)	0	12.8	37.6	48.9	55.0	56.7
Amount of resinate formulation (mg)[a]	0	187.5	63.8	49.1	43.6	42.3
Amount of employed resin (mg)[b]	0	163.5	39.8	25.1	19.6	18.3

[a] Containing equivalently 24 mg CPM
[b] The amount of resinate formulation minus 24 mg CPM

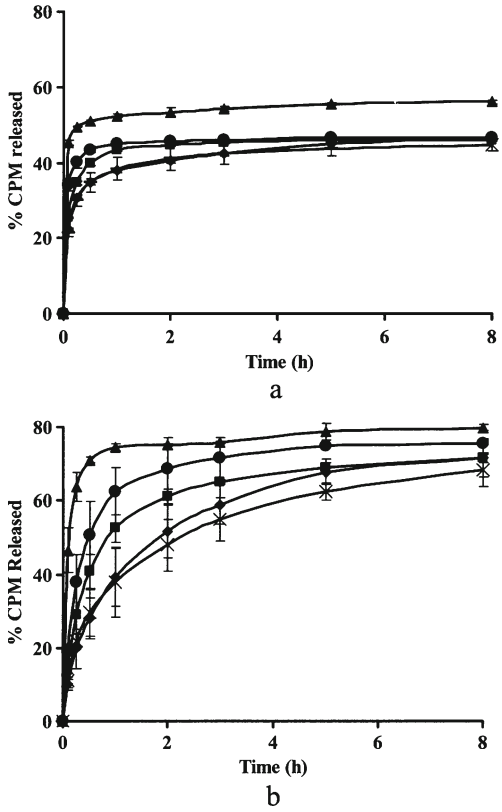

Fig. 6. CPM release from various resinate formulations prepared from (*triangle*) R/28, (*circle*) /35, (*square*) /40, (*diamond*) /90, and (*multiplication sign*) /210, respectively, as determined in **a** SGF and **b** SIF

due to the shrinkage of the outer sulfonated region superimposed upon the rigid irregular unreacted core. They reverted to uniformly smooth and spherical shapes in the completely sulfonated resins. However, according to the scanning electron microscopy study, fractures were observed on the hollow surface of moderately sulfonated resins, i.e., R/35 (Fig. 4) and /40. The fully (R/90 and /210) and poorly (R/28) sulfonated resins had no such fractures. This evidence might indicate that the fractures did not occur during the sulfonation step but rather during the post treatment, i.e., the washing step where the swelling of resins occurred. During swelling, the hollows in R/35 and /40 were the point of highest swelling (Fig. 2 and 3). Because of uneven swelling, these regions were likely to be stretched by a greater force or, in other words, had a greater internal tension than the adjacent or other regions, thus making them prone to fracture (12). On the other hand, the fully sulfonated resin beads (R/90 and /210) swelled evenly, keeping the internal tension small enough that no fractures occurred. Additionally, no fractures were found in R/28 and R/0 owing to the very low and no swelling, respectively. In fact, the fractures and breakages could be observed even in commercial resins if treated improperly during use; nevertheless, they did not significantly influence on the ion-exchange property of the resins (9).

The average diameters in the dry and wet states as well as the swelling of the resins are illustrated in Fig. 5. In the dry state, the average diameters of the differently sulfonated resins were comparable (100–115 μm), whereas those in the wet state progressively increased from 103 to 211 μm in relation to the increased degree of sulfonic group introduced in the resins. As described above, the sulfonic group brought about the increased hydration, thus resulting in the larger wet size and hence the higher swelling of the resins.

Behavior of Differently Sulfonated Resins as Drug Carriers

After the resin was placed in the drug solution, CPM dissociated into a cationic molecule would exchange with the resin counterion (H^+) and then form the resinate. The CPM loading (% *w*/*w*) in the resinates prepared from the differently sulfonated resins are presented in Table II. As expected, the drug loading was greater in the resins treated with the longer sulfonation times and hence the higher degree of sulfonic group. This is due to the fact that the sulfonic group is the ion-exchangeable or drug-binding site of the resins. As it increased, the drug loading in the resinates accordingly increased.

According to the aforementioned trend, the different partially sulfonated resins had the lower ion exchange and hence the drug loading than the resins with the full ion-exchange capacity. Therefore, to deliver the same amount of CPM (24 mg), greater amounts of resins were necessary, thus requiring higher amounts of resinate formulations than the resins with the full ion-exchange capacity (Table II). This point could be considered to be an advantage of the partially sulfonated resins for use in delivering especially low dose drugs. The increased amount of the resinate formulations may facilitate dispensing and weighing. Additionally, it might

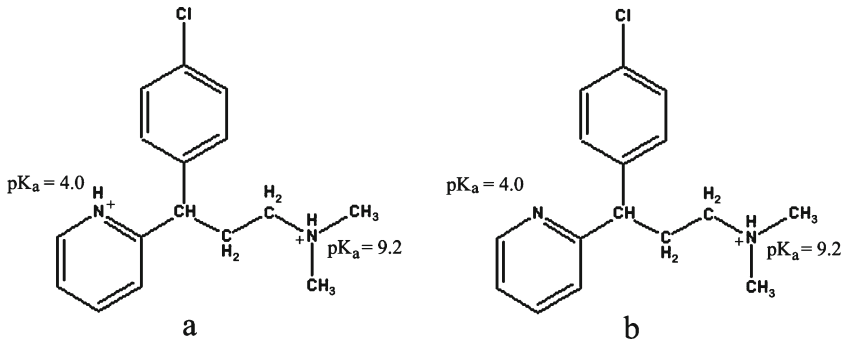

Fig. 7. Ionization of CPM in **a** SGF (pH 1.2) and **b** SIF (pH 7.5)

reduce the use of fillers when the resinate is further prepared in certain dosage forms, e.g., capsules.

The *in vitro* release of CPM from various resinates in SGF and SIF is illustrated in Fig. 6. In both media, a similar pattern was observed of the drug release being slower from the resins with the higher degree of sulfonic group. This behavior may be attributed to several causes. The first cause resulted from the sulfonation process, which began at the outer shell and proceeded toward the resin center (Fig. 2). Therefore, the resins with the higher amount of sulfonic group would have a wider diffusive path depth (or length) for drug passage. It should be noted that the wet size of the resins with the higher sulfonic group was larger because of the greater swelling (Fig. 2), simultaneously expanding the diffusive path depth. In terms of distances, the drug located at the deeper site near the resin center would require more time to diffuse out. Moreover, it was less releasable as compared with that located at the region near the resin surface (3), which would be described in more detail below. These effects thus led the resins with the higher degree of sulfonation to provide a slower rate of drug release. The other reason might be linked to the amount and hence the surface area of the resinate formulation exposed to the release medium. As presented in Table II, the resins with the higher sulfonic group were correspondingly employed in lower amounts than those with the smaller sulfonic group, offering, qualitatively speaking, lower numbers of resinate particles in the obtained formulation. As the number of resinate particles in the formulation was decreased, the surface area exposed to the release media would decrease, thus providing a slower release rate.

The CPM release in both SGF and SIF was not complete (Fig. 6) because it was driven by the ion-exchange process toward equilibrium (13). From surveying existing literature, it was found that the equilibrium release of a drug was apparently not constant but instead was likely to vary with various factors, namely, the cross-linkage and particle size of resin (3,13,14), the amount of loaded drug (11), the type of release medium (13), and the sampling procedure of release testing (15). Nevertheless, the effect of the degree of resin sulfonation on equilibrium release has never been mentioned. As seen in Fig. 6, the equilibrium release from the resinates seemed to decrease with increasing degree of sulfonic group in the employed resins. This behavior could potentially be explained by the heterogeneous nature of the cross-linked copolymer matrix. Irwin *et al.* (3) reported that not all ion-exchangeable sites (sulfonic group) were in the same accessible and releasable locations within a resin. The sulfonic group located at the deeper site near the center was less accessible and less releasable than that at the outer shell of the resin, offering a limitation for diffusion and release of the loaded drug. This effect was reportedly more pronounced with an increase in the cross-linkage and the particle size of the resin. As with this case, the resins with the higher degree of sulfonic group had both larger diffusive path depth and larger wet size (Figs. 2 and 5). Therefore, the extent of the drug loaded in the less releasable site was likely to be higher in the resins with the higher degree of sulfonic group, thus providing the lower equilibrium release.

In existing literature, the type of release medium always affects the drug release from resinates. In the present case, the CPM release determined in SGF was obviously lower than that in SIF (Fig. 6), although the total cation concentration in SGF (104.2 mN) was higher than that in SIF (87.0 mN), which was similar to the previous work (13). This might indicate that the difference in the release observed was primarily caused by the ionization of the drug rather than the total cation concentration in the release media (SGF and SIF). For CPM (Fig. 7), two pK_a values (9.2 and 4.0) were reported, corresponding to the ionization of the tertiary amino group and the pyridine ring, respectively (16). In SIF (pH 7.5), only the tertiary amino group of the drug ionized. In contrast, not only the tertiary amino group but also the pyridine ring of the drug was able to ionize in SGF (pH 1.2). Therefore, the drug in SGF ionized and then preferred to bind with the resin to a greater extent than that in SIF, thus allowing a smaller amount of the drug to be available for release.

CONCLUSION

In this study, the differently sulfonated resins were successfully prepared. The resin characteristics, CPM loading, and *in vitro* release were clearly affected by the degree of sulfonic group in the prepared resins. In addition, the release also depended on the ionization of the drug in the release medium. The different partially sulfonated resins are novel carriers for drug delivery and can be used for application in a controlled drug delivery system. In spite of experiencing surface fracture, the resins could be utilized as carriers, especially for delivering low-dose drugs, which provided the increased amount of the resinate formulation. However, further experiments should be performed to eliminate the surface fracture of the resins.

ACKNOWLEDGMENTS

The authors wish to thank the Thailand Research Fund and the Commission on Higher Education, Ministry of Education, Thailand for its funding of this work (MRG5280242), the Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand for its instrument support, and also the Faculty of Science, Silpakorn University for its assistance in the SEM study.

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