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INTRODUCTION

Ion exchange resins are applied widely in various fields including pharmaceutical such as taste masking, ionic drug delivery[1]. Recently, increasing attention has been focused on ion exchange fibers due to advantage of them over ion exchange resins such as more efficient drug loading and release into/from the ion exchange fibers, easier incorporation of large sized molecules and more straightforward controllability of the loading/release[2]. Ion exchange fibers consist of polymeric frameworks and ion exchange groups. Nanofibers are used mostly as polymeric frameworks because of amazing characteristics such as a very large surface-to-volume ratio and good mechanical properties. The introduction of ionic functional groups into the nanofibers is a promising option to provide novel ion exchangers with a high exchange capacity. Electrospinning is widely used to produce nanofibers because of simple and easy way to control the morphology of ultrafine fibers[3]. Polystyrene (PS) is widely used to produce cation exchange fibers[4]. Sulfonation is required to produce cation exchange fibers. However, the sulfonation of PS nanofibers cannot be successfully performed because the PS nanofibers dissolve during the sulfonation reaction[5]. Therefore, crosslinking of the PS nanofibers prior to sulfonation is required. Ion exchange fibers can be used in controlled release for both topical and oral routes. However, few studies have reported the use of ion-exchange fibers in oral drug delivery. Therefore, the aim of this study was to prepare cation exchange fibers from PS and to evaluate the drug loading and release behavior.

MATERIALS AND METHODS

Material: The polystyrene resin (PS, Mw = 2.99×10^5 Da, Mn = 1.19×10^5 Da, 685 D) (Dow Plastics, USA), dextromethorphan hydrobromide (DXM), propranolol hydrochloride (PPL), diphenhydramine hydrochloride (DPH), silver sulfate, dimethylacetamide (DMAc, $\geq$ 99.5%, Sigma-Aldrich Chemical Company, USA), tetrabutylammonium bromide (TBAB) (Bio Basic Inc., Canada), concentrated sulfuric acid (98%, Mallinckrodt Baker Inc., USA), formaldehyde (40% w/v, Carlo Erda Reagents) were purchased from various suppliers and used as received. Deionized water was used entirely in this work.

Preparation of polystyrene nanofiber ion exchangers (PSNIE)

Electrospinning process: 15% w/v PS solution was prepared by dissolving PS in DMAc with the addition of 0.025% w/v TBAB. The electrospinning process was conducted at 25 °C with the fix applied voltage, the distance between the tip and the collector, and the feeding rate as 15 kV, 15 cm and 0.4 ml/h, respectively.

Crosslinking and sulfonation: PS nanofibers (2×2 cm^2) were immersed in a mixture of 98% sulfuric acid and formaldehyde at a volumetric ratio of 90/10 with 0.1% w/v silver sulfate with stirring for 10 min at 70 ± 0.5 °C to allow crosslinking, and then immersed in a mixture of 98% sulfuric acid with 0.2% w/v silver sulfate at 70 ± 0.5 °C; the mixture was left to stir for 30 min for the sulfonation reaction.

Characterization: The morphologies, diameters and chemical structures of PS nanofibers, crosslinked PS nanofibers and PSNIE were characterized using a scanning electron microscope (SEM), and a Fourier Transform Infrared spectrophotometer (FT-IR), respectively.

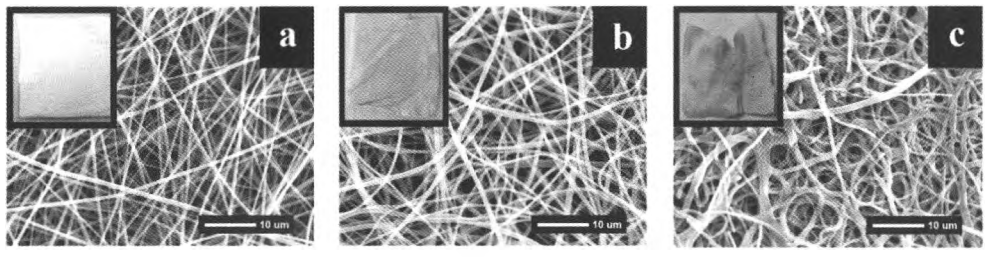
Drug loading: PSNIE were loaded with DXM, PPL and DPH by a batch process. Briefly, the PSNIE were placed in drug solution at the optimized drug/PSNIE ratios (i.e. 5:1), and allowing each mixture to stir on a magnetic stirrer for 6 h. After equilibrium, the drug loaded PSNIE were washed several times with copious amounts of deionized water, and dried at 60 °C overnight in a hot air oven. Drug content in the PSNIE was determined by an elution method. A portion of the drug-loaded PSNIE was accurately weighed and placed in a volumetric flask that contained 50 mL of 2 N KCl solution. The mixture was stirred for 24 h, and the eluted drug was assayed by a UV spectrophotometer at wavelengths of 218, 278 and 289 nm for DPH, DXM and PPL, respectively.

Drug release: In vitro drug release was investigated in the simulated gastric (SGF) at pH 1.2 for 8 h, in the simulated intestinal fluids USP (SIF) at pH 6.8 for 8 h, and in SGF for 2 h, followed by SIF for 6 h. The drug-loaded PSNIE (7.0 mg) were accurately weighed, placed into 30 ml of release medium and incubated at 37±1 °C with stirring at 100 rpm. At a predetermined time, samples of release medium (1 ml) were collected and replaced with a fresh medium. The amount of released drug was analyzed with a

UV spectrophotometer at the same wavelengths. The release testing was conducted in triplicate. The release kinetics of drug loaded PSNIE were investigated using zero order model, first order model, higuchi model and particle diffusion model.

RESULTS AND DISCUSSION

The electrospun PS nanofibers were successfully prepared by electrospinning process[6]. The SEM image of PS nanofibers (376 ± 36 nm) was shown in Fig. 1a. These PS nanofibers were completely crosslinked with 90/10 (v/v) of sulfuric acid/formaldehyde and sulfonated in sulfuric acid to obtain the PSNIE. The crosslinked PS nanofibers and PSNIE appeared visibly darker than the starting fibers, shrank and moved into closer under SEM and also the diameters increased to 456±45 nm and 464±35 nm, respectively (Fig 1b and 1c).



376±36 nm 456 ± 45 nm 464 ± 35 nm

Fig. 1 The SEM images (1000x), the visual appearance and the diameter of a) electrospun PS nanofibers b) crosslinked PS nanofibers c) PSNIE

A possible structure for PSNIE was shown in Fig. 2, which was confirmed by the FT-IR spectra in Fig. 3. The asymmetric and symmetric stretching vibration peaks of sulfone group appeared at 1306 cm^{-1} and 1091 cm^{-1}, respectively. In addition, a stretching vibration peak of methylene group was observed at 1412 cm^{-1}. These might indicate that the sulfone and methylene bridges were responsible for the crosslinking of PS nanofibers. Relevant peaks corresponding to the aromatic sulfonic acid groups were also found, which included the asymmetric stretching and symmetric stretching of O=S=O at 1188 and 1130 cm^{-1}, S-O at 670 cm^{-1} and O-H at 3449 cm^{-1}, respectively[7]. It confirmed the successful incorporation (sulfonation) and hence the presence of sulfonic groups in PSNIE.

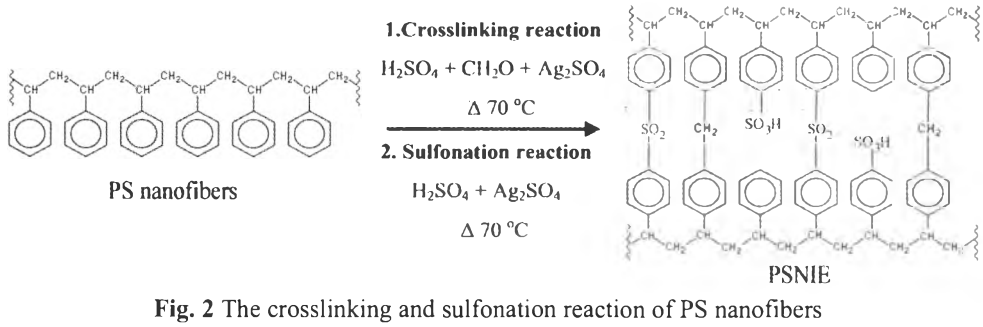


Fig. 2 The crosslinking and sulfonation reaction of PS nanofibers

DXM, DPH and PPL were loaded in PSNIE. DXM showed the highest drug content of 3.96 ± 0.2 mmol/g, followed by DPH (3.67 ±0.4 mmol/g) and PPL (3.43±0.1 mmol/g). This observed order of drug loading generally corresponded to the lipophilicity (Log P) of drugs loaded. Similarly, a previous study revealed that the drug content increased with increasing the lipophilicity of drug (tarcrine > propranolol > nadolol)[8]. Moreover, with its tertiary amine groups, DXM and DPH had a higher affinity to sulfonic acid groups than did PPL, which have secondary amine groups[9].

In vitro releases of DXM, DPH and PPL in SGF (Fig.4a), the ranking of the percentages released after 8 h was DPH (77 %) > DXM (61 %) > PPL (53 %). These results may be attributed to three reasons. First, the release rate of DPH was the highest (0.0251 $min^{-0.65}$). Second, the low lipophilicity of DPH caused the low affinity of drugs towards the ion exchange fibers; therefore, the release was higher for DPH than for the more lipophilic drugs. Third, the lowest molecular weight of DPH caused the faster diffusion rates of the smaller drug-ions compared to those of the larger ones[2]. In SIF (Fig.4b), the ranking of the percentage released was similar to that in SIF, but the amount of drug released was slightly lower

than in SGF. Except for DXM, the amount of drug released in SIF was higher than in SGF. Similarly, a previous study revealed that the PPL release in SGF from strong ion exchange resins is higher than that in SIF[10]. Our previous study also revealed that the releases of DPH from cation exchange resins (Amberlite IRP-69) in SGF are higher than those in SIF[11]. This result may be due to the greater total amount of cationic ions in SGF than in SIF and the higher ionic size of K^+ ions in SIF as compared to H^+ ions in SGF[12]. However, the releases of DXM from cation exchange resins in SIF were higher than that in SGF because DXM are weak base drugs, which ionize to a greater extent in SGF and then prefer binding with the resins rather than releasing from them[9]. Among the model drugs, PPL showed the lowest drug release both in SGF and SIF mediums. In SGF for 2 h, followed by SIF for 6 h (Fig. 4c), the percentage of drug release was larger than the percentage released in SGF or SIF after 8 h except for PPL in SGF. In all cases, the drug release in both SGF and SIF was incomplete because it was driven by the ion-exchange process towards equilibrium[9].

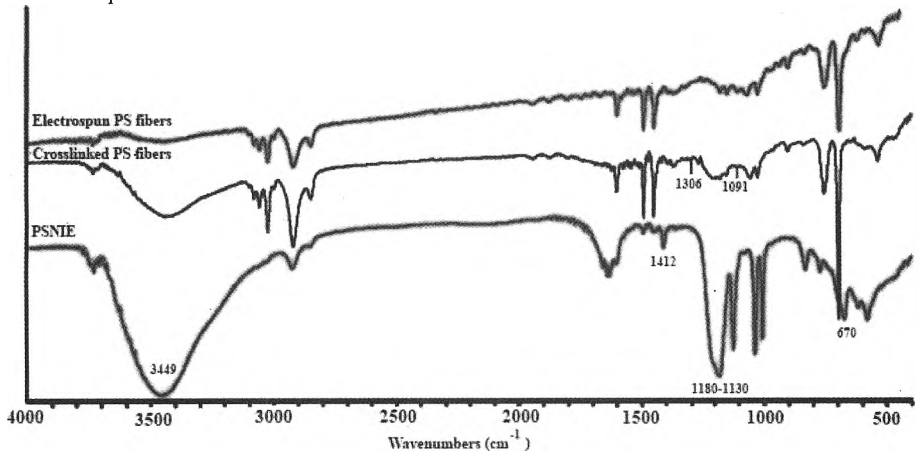


Fig. 3 FT-IR spectra of the electrospun PS fibers, crosslinked PS fibers and PSNIE

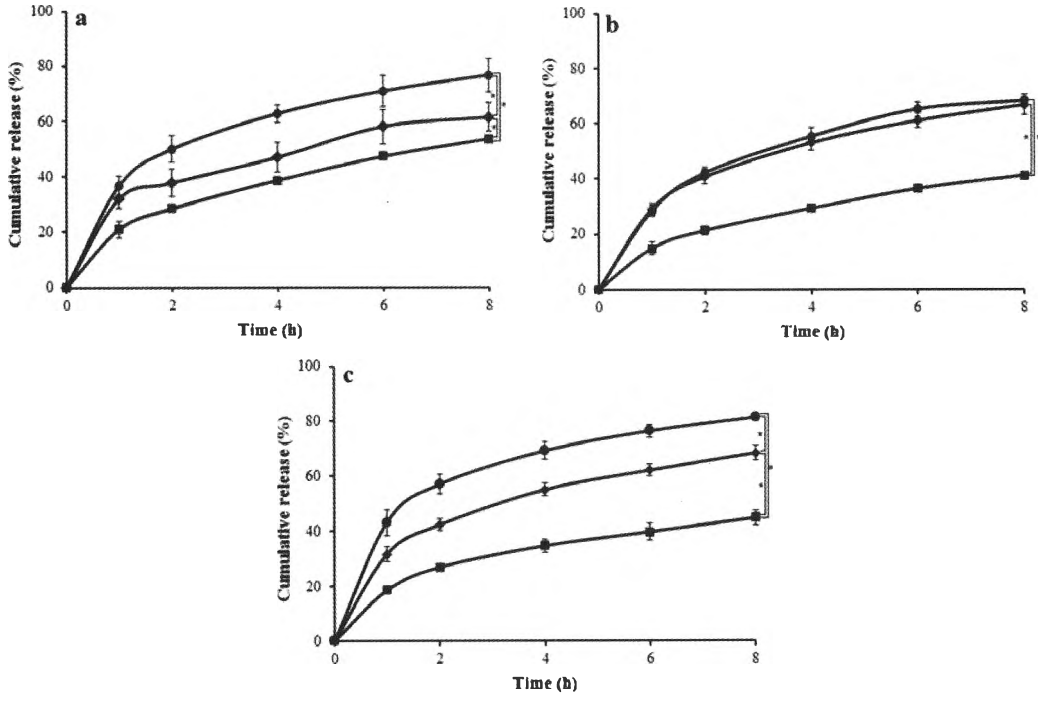


Figure 4 Release profiles in (a) SGF 8 h, (b) SIF 8 h, (c) SGF 2 h and SIF 6 h with drugs: (●) DPH, (◆) DXM and (■) PPL.

Release kinetics of the three model drugs from PSNIE was examined by fitting with the zero order, first order, Higuchi and particle diffusion controlled model. In all release media, it was found that the release profiles of all drugs in SGF 8 h, SIF 8 h and SGF 2 h, followed by SIF for 6 h provided the best fit with the particle diffusion model ($R^2 > 0.98$) as shown in Table 1. It indicated that the release

kinetics of drugs from PSNIE was governed by the particle diffusion controlled model. The result was in agreement with the release kinetic from resinates, which was mostly governed by the particle diffusion controlled model. This model indicated that drug diffusion through the fiber matrix was the determining process in controlling the drug release from PSNIE.

Table 1 Release kinetics of drugs in SGF, SIF and SGF+SIF

Release kinetic	Dextromethorphan			Propranolol			Diphenhydramine		
	SGF	SIF	SGF+SIF	SGF	SIF	SGF+SIF	SGF	SIF	SGF+SIF
Zero order									
R^2	0.8447	0.8843	0.7936	0.9319	0.9208	0.8663	0.8262	0.8528	0.7639
First order									
R^2	0.9285	0.9603	0.9189	0.9737	0.9549	0.9142	0.9505	0.9449	0.9294
Higushi									
R^2	0.9743	0.9911	0.9695	0.9987	0.9973	0.9832	0.9731	0.9843	0.9424
Particle diffusion controlled									
R^2	0.9906	0.9968	0.9921	0.9986	0.9880	0.9981	0.9951	0.9943	0.9913
k ($min^{-0.65}$)	0.0179	0.0196	0.0199	0.0134	0.0094	0.0105	0.0251	0.0206	0.0288
Diffusion coefficient (nm^2/s)	3.9474	4.5387	4.6460	2.5284	1.4654	1.7374	6.6404	4.8998	8.2048

CONCLUSION

PSNIE were successfully prepared by electrospinning, crosslinking and sulfonation techniques. All drugs could be loaded in PSNIE; the maximum (3.96 mmol/g) and minimum (3.43 mmol/g) of drug content were DXM and PPL, respectively. DPH gave the highest percentage release in both SGF and SIF. However, the release of all drugs was not complete. The release kinetics of all drugs in SGF and SIF provided a good correlation to the particle diffusion model. This finding presented a novel drug delivery system for controlling drug release.

ACKNOWLEDGEMENTS

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