Preparation and Characterization of a Novel pH-Sensitive Ion Exchange Resin

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Methylacrylic acid/styrene cross-linked with divinylbenzene is a novel pH-sensitive ion exchange resin. Microspheres of this resin were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The microspheres showed a pulsatile swelling behavior when the pH of the media changed. The pH-sensitive microspheres were loaded with salbutamol sulfate and the drug-release characteristics were studied under both simulated gastric and intestinal pH conditions. The results obtained showed that the drug release also depended on the pH of the release media.

Key words ion exchange resin; pH-sensitive; poly(methylacrylic acid/styrene); pulsatile release

Ion exchange resins are high-molecular weight polyelectrolytes, which can exchange mobile ions of similar charge with the surrounding medium. Recently, they have been used in the investigation of drug delivery systems.[1—4] They have a number of improved properties, such as better stability, better taste, fewer side effects, and more uniform absorption and sustained release.

Many studies involving the use of ion exchange resins are currently being carried out.[5—7] However, to our knowledge, few investigations have been published on the modification of the structure of the ion exchange resins to obtain additional advantages beyond the inherent improved properties of the ion exchange resin itself. In this article we will describe the incorporation of ionic functional groups onto the cross-linked ion exchange resin to produce a novel pH-sensitive ion exchange resin.

All pH-sensitive polymers respond to a pH exchange of the surrounding environment.[8] The pH-sensitive properties of polymers are due to the ionization of weakly acidic and /or basic functional groups on their backbones. In particular, synthetic polymers like poly(methyl methacrylate), poly(acrylic acid), poly(*N*,*N*-isopropylacrylamide) and chitosan have been used as pH-sensitive drug delivery systems.[9]

Salbutamol sulfate is a short-acting beta-2 agonist[10] which is used to treat diseases such as asthma, emphysema and bronchitis. According to the human circadian rhythm,[11] asthma and related conditions often occur in the early hours of the morning and so prove very disturbing to the patient. So, if salbutamol sulfate can be released after a 2—3 h lag-time, this will greatly benefit the patients. In this article we have used salbutamol sulfate as a model drug to prepare resinates with pH-sensitive ion exchange resins. The aim was to achieve pulsatile drug release according to the pH sensitivity of the novel ion exchange resins used.

The purpose of this study was to incorporate MAA into the styrene backbone to obtain a novel pH-sensitive ion exchange resin. The copolymers prepared were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Then, the pH-sensitive ion exchange resins were loaded with salbutamol sulfate. Swelling and drug release *in vitro* were allowed to take place under gastric and intestinal pH conditions to investigate the pH sensitivity of the microspheres prepared.

Experimental

Materials The two monomers used in the study, namely methylacrylic acid (MAA) and styrene (St) were obtained from the ShenYang chemical reagent factory. Divinylbenzene (DVB) was purchased from Tokyo Kasei, Japan. Benzoyl peroxide (BPO), dichloroethane, concentrated sulfuric acid, methanol and PVA having a mol wt of 125000 were obtained from the Tian Jin chemical reagent factory. All reagents were of analytical grade.

Preparation of pH-Sensitive Ion Exchange Resins MAA/St microspheres cross-linked with DVB were prepared by free radical polymerization.[12] All monomers were vacuum distilled prior to use in order to remove the polymerization inhibitors. The mixture of MAA and styrene (MAA/styrene mol ratios, 30 : 70, 50 : 50, 70 : 30) was mixed with 0.7 wt% DVB (as a cross-linking agent) and 0.5 wt% BPO (as an initiator). The mixture was then added drop-wise to PVA solution, and nitrogen was bubbled through the mixture for 30 min to remove any dissolved oxygen that would inhibit the reaction. The polymerization was carried out at 70 °C for 12 h under vigorous stirring. The polymer obtained by this procedure was then filtered and washed thoroughly with methanol and water to extract any unreacted components. Finally, the polymer was air-dried at room temperature overnight followed by a vacuum-drying cycle at 60 °C for 24 h.

The above microspheres were firstly allowed to swell in dichloroethane for 30 min, then 93 wt% concentrated sulfuric acid was added to the mixtures and the sulfonation reaction was carried out at 75 °C with constant stirring for 10 h. The mixture was then slowly diluted with water until it became neutral. NaOH was then used to adjust the pH to 10—12 for 2 h. Finally, the ionic microspheres were dried in an oven at 60 °C.

Fourier Transform Infrared Spectra (FTIR) The miscrospheres were crushed to make the KBr pellets under a hydraulic pressure of 600 kg/cm^2. The FTIR (BRUKER, IFS55, Switzerland) spectra were recorded over the range 400 to 4000 cm^{-1}.

Differential Scanning Calorimetric (DSC) Studies DSC analysis was performed using the pure drug and the drug-loaded microspheres.[13] The temperature was increased at a rate of 10 °C/min up to 350 °C and the analysis was carried out on a DSC Analyzer (Perkin Elmer, U.S.A.).

Particle Size Analysis The mean particle size of the microspheres prepared with different amounts of MAA was measured using a laser light scattering particle size analyzer (LS230, Beckman Coulter, U.S.A.). A sample of about 500 mg of the microspheres was suspended in 100 ml distilled water. This suspension was stirred under sonication to avoid agglomeration of the particles during measurement.

Preparation of the Drug–Resin Complexes The drug–resin complex was prepared by the batch method. In this process, 1 g prepared ion exchange resin was slurried in 500 ml deionized water. Then, 1 g salbutamol sulfate was added to the water with agitation until the amount of salbutamol sulfate in the water remained stable, and the drug–resin complex had been formed by the ion exchange reaction. Then, the drug–resin complex was

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washed with deionized water to remove any unexchanged drug.

Swelling Study The pH-dependent equilibrium swelling of the crosslinking microspheres was studied when the pH increased from 1.2 to 7.4. The microspheres were allowed to swell completely for about 4 h to attain equilibrium at 37 °C.[14] Excess surface liquid was removed by blotting and the swollen microspheres were weighed using an electronic balance (Mettler, Model 20, Switzerland). The microspheres were then dried in an oven at 60 °C for 5 h until there was no change in the dry mass of the samples. The equilibrium degree of swelling (Q) was measured as follows:

$$Q=(W_\infty-W_0)/W_0 \quad (1)$$

Where W_∞ is the mass of the swollen microspheres after taking up water, and W_0 is the dry mass of the microspheres.

***In Vitro* Drug Release** *In vitro* drug release investigations were carried out using the USP paddle (apparatus II) method and a ZRS-8G Intelligent Dissolution Tester Apparatus (Tian Jin University Radio Factory, Tian Jin, China) at a speed of 50 rpm. For this, 900 ml simulated gastric fluid (0.1 M HCl) and intestinal fluid (pH 6.8 phosphate buffer) at 37±0.1 °C were used as the dissolution media. Microcapsules of the drug–resin complex were accurately weighed to obtain an equivalent of 9.6 mg salbutamol sulfate. Then, 5 ml dissolution medium was sampled at predetermined time intervals. These samples were passed through a 0.45 μm membrane filter, and the amount of drug released was measured by UV spectrophotometry at 276 nm.

Results and Discussion

FTIR Spectroscopic Study The formation of ionic MAA/styrene microspheres was confirmed by FTIR. The FTIR spectra of the ionic microspheres are presented in Fig. 1 and the results show that the carbonyl functional groups of the acrylate appear as an apparent peak at 1680 cm^{-1}. An absorption band at 2921 cm^{-1} is due to the C–H stretching of the CH_2 groups formed due to the crosslinking reaction with DVB. The absence of a peak for the alkenyl groups shows that the copolymer was formed as a result of the reaction between MAA and styrene. The peak at 1128 cm^{-1} is attributed to the stretching of the sulfonic group. However, a broad peak at 3438 cm^{-1} is due to the presence of residual water.

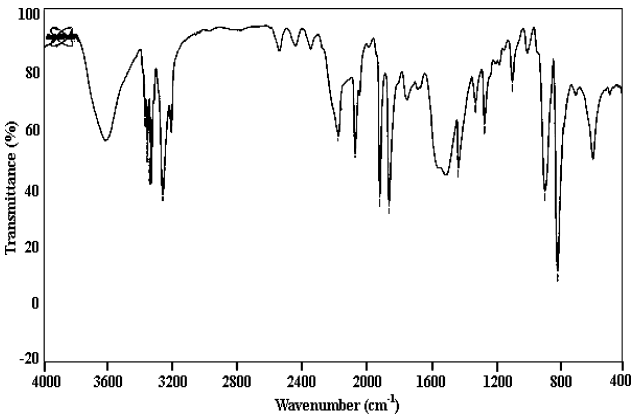

Fig. 1. FTIR Spectrum of Ionic Microspheres of MAA/Styrene

Differential Scanning Calorimetric (DSC) Studies The DSC graphs of salbutamol sulfate and salbutamol sulfate-loaded microspheres are presented in Figs. 2 and 3. The DSC curve of pure drug shows a sharp peak at about 248 °C, which is due to the melting of pure drug. The DSC curve of salbutamol sulfate-loaded microspheres shows broad peaks from 290 to 310 °C which is due to the glass transition temperature (Tg) of the microspheres with crosslinking structure. The drug-loaded microspheres showed no peak at 248 °C as observed in the curve of the drug. This indicates that the drug is connected to the crosslinking structure of the microspheres by chemical bonds, and so no separate peak was observed.

Particle Size Analysis The particle sizes of microsphers with different amounts of MAA are presented in Fig. 4 and a nearly standard normal distribution was observed. On increasing the MAA content of the microspheres, the mean

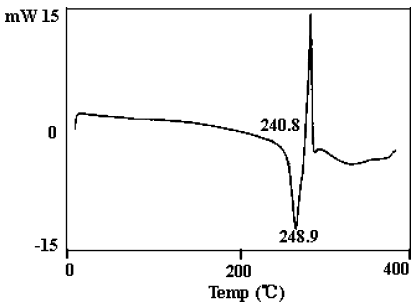

Fig. 2. DSC Curves of the Salbutamol Sulfate

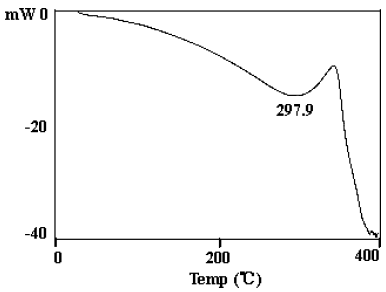

Fig. 3. DSC Curve of Salbutamol Sulfate-Loaded Microspheres (MMA-70)

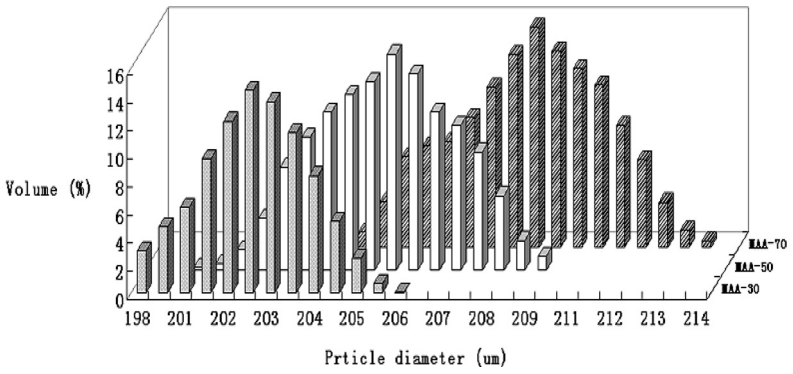

Fig. 4. Histogram of the Size Distribution of the Microspheres

Each value is the mean of three determinations.

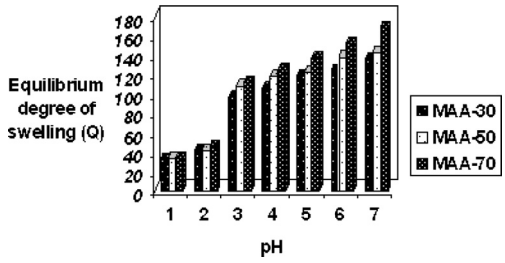

Fig. 5. Effect of pH on the EDS of P (MAA/St) Microspheres
Each value is the mean of three determinations.

particle sizes of these microspheres increased from 180 to 220 μm. This was attributed to the fact that, as the amount of MAA in the microspheres increased, the mean molecular weight also increased.

Swelling Study In order to investigate the effect of pH on the swelling of the microspheres, we studied the equilibrium degree of swelling: Q. Figure 5 shows the equilibrium swelling data of the prepared microspheres at 25 °C in buffer solution from pH 1.2 to 7.4. The results show that, on increasing the pH from 1.2 to 7.4, a considerable increase in water uptake occurs for all the microspheres. For a polymer containing ionic groups, the swelling forces may be greatly enhanced as a result of electrostatic repulsion among charges present on the polymer chains. At low pH values, the carboxyl groups of MAA would be protonated and the polymer chains would be in the form of aggregates through hydrogen bonding, and the microspheres would undergo shrinkage. At high pH values, the carboxyl groups of MAA would be partially or completely ionized, and the resulting decomplexation would lead to swelling of the microspheres.

***In Vitro* Drug Release** To understand the drug release from the salbutamol sulfate-loaded microspheres, *in vitro* release experiments were carried out under conditions of gastric and intestinal pH. Figures 6 and 7 show the cumulative drug release data of microspheres at pH 1.2 and 6.8. This shows that, at pH 6.8, salbutamol sulfate is rapidly released in 15 min and is completely released within 30 min while, at pH 1.2, the fraction of drug released is almost negligible.

At pH 1.2, a little drug is released from the microspheres, possibly due to the exchange of drug with ions in the dissolution process at the surface of the microspheres, although the microspheres were not swollen at this pH.

In contrast, a pronounced difference was observed in the release data at pH 6.8. This was attributed to the presence of the carboxyl groups that are responsible for the greater swelling in media of higher pH. As the pH of the media increased, the ionization of the carboxyl groups resulted in swelling of the microspheres, which then led to increased opening of the pores. Then, the ions in the media entered *via* the microchannels of the pores and exchanged with the drug combined with the sulfonic groups. Finally, the drug was released from the polymer.

The results in Figs. 6 and 7 show that on increasing the MAA content of the microsphere, the amount of drug released fell at pH 1.2 and the release speed increased at pH 6.8, that reflects an improved pH-sensitivity. Therefore, we

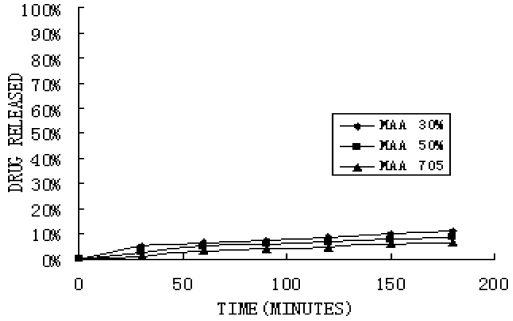

Fig. 6. Drug Release from the Resinates in Gastric Dissolution Medium
Each value is the mean of three determinations.

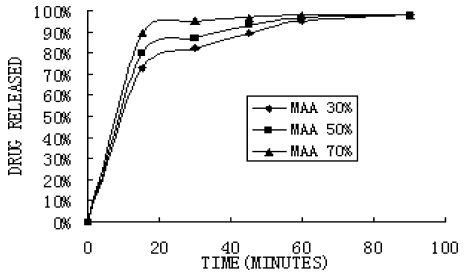

Fig. 7. Drug Release from the Resinates in Intestinal Dissolution Medium
Each value is the mean of three determinations.

finally used 70% MAA to prepare the pH-sensitive ion exchange resins.

Conclusions

A novel pH-sensitive ion exchange resin was prepared by incorporating MAA into a styrene backbone. The results of Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) showed that a pH-sensitive ion exchange resin had been obtained. The swelling and drug dissolution results exhibited an obvious pH-sensitivity. The salbutamol sulfate resinates exhibited clear pulsatile release characteristics.

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