

Controlled Drug Release Studies of Atenolol Using Differently Sulfonated Acryloxyacetophenone and Methyl Methacrylate Copolymer Resins as Drug Carriers^{*}

K. Doraswamy and P. Venkata Ramana^{**}

Department of Chemistry, Sri Krishnadevaraya University, Anantapur-515 003, India

Abstract 2-Acryloxyacetophenone (AAP) was prepared and subjected to suspension polymerization with methyl methacrylate (MMA) using azobisisobutyronitrile (AIBN) as free radical initiator. The differently sulfonated AAP-MMA cross-linked copolymer cationic exchange resins were prepared by sulfonation with concentrated sulphuric acid at 70 °C. Several characteristics of the prepared resins were evaluated, *i.e.* FTIR, the ion-exchange capacity (IEC), thermo gravimetric analysis (TGA), particle size distribution and microscopic morphology. The resin characteristics were altered with degree of sulfonation, providing that differently sulfonated resins could be prepared. The behavior of atenolol (ATL) loading and *in vitro* release in the USP stimulated gastric and intestinal fluids of the obtained resins were evaluated. The drug loaded in the resin increased with increasing degree of sulfonation and hence the drug binding site in resin employed. The drug release was lower from the resins with higher content of sulfonic group due to the increase in the diffusive path depth. The drug release was a little lower in stimulated gastric fluid (SGF) than in stimulated intestinal fluids (SIF). The basic groups, ionized to a little greater extent in SGF and preferred binding with the resin rather than releasing. Hence, the differently sulfonated resins could be utilized as novel carriers for drug delivery.

Keywords: 2-Acryloxyacetophenone; Methyl methacrylate; Different sulfonation; Cationic exchange resins; Atenolol; *In vitro* drug release.

INTRODUCTION

Ion-exchange materials are insoluble acids or bases that, when converted to salts, remain insoluble. Based on the nature of the exchangeable ion of the resin as a cation or anion, it is classified as cationic or anionic exchange resin, respectively^[1]. Cation-exchange materials contain fixed electronegative charges (associated with counter ions), *e.g.* $\text{RSO}_3^-\text{Na}^+$, and anion-exchange materials analogously have fixed electropositive charges, *e.g.* $\text{RN}^+\text{Me}_3\text{Cl}^-$. Strong-acid cation exchange materials are usually based on sulphonic acids. Strong-base anion-exchange materials may be quaternary ammonium hydrochlorides and weaker base types may be the tertiary amines themselves. Most ion-exchange resins can be regenerated with appropriate counter ions. It is not uncommon for resin beads to be continually used and regenerated over months/years before total resin replacement. Some resins are operated at elevated temperatures, *e.g.* 70 °C.

Ion exchange resins have been widely used as drug carriers in pharmaceutical dosage forms for taste

^{*} The authors wish to thank The University Grants Commission, New Delhi for its funding of this work. The authors also thank Indian Institute of Science, Bangalore for its instrumental support and Department of Physics, Sri Venkateswara University, Tirupathi, for its assistance in the SEM study. The authors also thank UGC, New Delhi for its support under SAP and DST, New Delhi for its support under FIST.

^{**} Corresponding author: Venkata Ramana, E-mail: ramanapv54@gmail.com

Received March 19, 2013; Revised October 1, 2013; Accepted November 22, 2013

doi: 10.1007/s10118-014-1406-0

masking^[2] and controlling release^[3–6]. These resins are cross linked water insoluble polymers carrying ionizable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and hence a drug-resins complex (drug resinate) is formed^[7]. Drug is released from the resinates, by exchanging with ions in the GI fluid, and followed by drug diffusion^[8]. The sustained released profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resinates^[9, 10] and by selecting a degree of cross-linking and particle size of the resins without a coating process^[11, 12].

Many studies involving the use of ion exchange resins are currently being carried out^[13–17]. However, to our knowledge, few investigations have been published on the modification of the structure of 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. 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*-isopropyl acrylamide) and chitosan have been used as pH-sensitive drug delivery systems^[18].

The purpose of this study was to incorporate MMA into the 2-methacryloxyacetophenone backbone and to obtain different partially sulfonated novel pH-sensitive ion exchange resins. The copolymers prepared were characterized by Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). Then, the pH-sensitive ion exchange resins were loaded with Atenolol. Swelling and drug release *in vitro* were allowed to take place under gastric and intestinal pH conditions to investigate the pH sensitivity of the prepared resins.

EXPERIMENTAL

Materials

Acrylic acid (Merck), benzoyl chloride (Merck), 2-hydroxyacetophenone (Merck), methyl methacrylate (Merck), polyvinyl alcohol (M_w 85000–124000, 87%–89% hydrolyzed, Merck), azobisisobutyronitrile (Merck), atenolol (ATL, Jubilant Life Sciences Ltd, Nanjangud), concentrated sulfuric acid (Merck), dichloromethane (Merck), sodium chloride (Merck), potassium chloride (Merck), sodium hydroxide (Merck), potassium dihydrogen orthophosphate (Merck) and concentrated hydrochloric acid (Merck) were purchased from various suppliers and used as received. All reagents were of analytical grade. Milli pour water prepared by a water purifier (Milli Q Gradient Century) was used entirely in this work.

Preparation of 2-Acryloxyacetophenone (AAP)

Acrylic acid (10 g) was taken in round bottom flask and benzoyl chloride (35 g) containing hydroquinone (0.15 g) was added slowly. The reaction mixer was refluxed for two hours and distilled for 85 °C fraction. The collected acid chloride again distilled at 75 °C and collected the pure acryloyl chloride.

To a solution of 2-hydroxyacetophenone (0.2 mol) in 2-butanone, triethylamine (TEA) (0.3 mol) was added and stirred at 0–5 °C. Thermometer, mechanical stirrer and dropping funnel were arranged. To this mixture, acryloyl chloride (0.2 mol) in ether was added in a period of 60 min. The condensation of acryloyl chloride with 2-hydroxyacetophenone liberates hydrochloride, which is adsorbed by TEA, which ultimately results into the quaternary salt (TEA hydrochloride). This quaternary salt is filtered and washed with ether and the filtrate is collected. The filtrate which contains the monomer is washed with aqueous 5% NaOH followed by water. Then the organic layer was collected and evaporated to get the monomer. The formation of AAP is confirmed by IR and ¹H-NMR. The spectral data are consistent with the structure of monomer. The ¹H-NMR spectrum of AAP is presented in Fig. 1.

IR (KBr) cm^{-1} : 3043 (Alkene C—H stretching); 3010 (Ar C—H stretching); 1741 (carbonyl stretching in ester); 1690 (carbonyl stretching in ketone); 1495 (C=C skeletal vibration); 1245 (CO—C stretching).

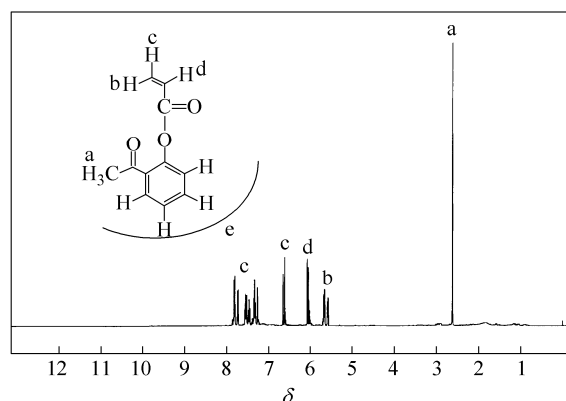


Fig. 1 Proton NMR spectrum of acryloxyacetophenone

^1H -NMR (CDCl_3 , δ): 2.62 (3H, s, $-\text{COCH}_3$); 5.65 and 6.65 (2H, dd, $\text{CH}_2=\text{C}-$); 6.03 (1H, dd, $\text{CH}=\text{CH}_2$); 7.2–7.9 (4H, Ar-H).

Preparation of AAP-MMA Cross-linked Copolymer

The cross-linked copolymer beads were prepared by suspension polymerization in a 4-necked reaction kettle fitted with a mechanical stirrer, a dropping funnel, water condenser and a nitrogen inlet in a temperature controllable oil bath. The aqueous phase (1.5 L) of a 0.5% (*W/V*) polyvinyl alcohol solution was taken into the flask, and the temperature was raised to around 65 °C. Under a fixed stirring (400 r/min), the monomer mixture containing AAP (35 g), MMA (4.57 g), and AIBN (0.5 g) was gradually added to the aqueous phase. Then, the temperature was raised to around 80 ± 1 °C and maintained at that temperature until the polymerization was terminated (12 h). Thereafter, the beads were washed several times with deionized water, petroleum ether, butanone, acetone and methanol and then sieved. The fraction in the range of 75–150 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 (15.9 g) approximately corresponded to 59.4% of the whole beads (26.73 g) and 40.1% of the employed monomers respectively.

Preparation of Differently Sulfonated Resins

Prior to sulfonation, the dried copolymer beads (3 g) were swollen in dichloromethane (12 mL) for 30 min. The swollen beads were then sulfonated with a fixed volume (30 mL) of concentrated sulfuric acid (H_2SO_4) in an oil bath maintained at 70 °C. The slurry was periodically shaken during the sulfonation. The degree of sulfonation was regulated by varying the reaction times from 0 (no sulfonation) to 220 min. The sulfonated resin was filtered, washed with excess deionized water until neutral pH, and finally dried at 60 °C for 6 h. The final resin was kept in a tightly closed container until further investigation. Schematic diagram of preparation of differently sulfonated acryloxyacetophenone and methylmethacrylate copolymer is presented in Scheme 1.

Characterization of Copolymer Beads and Differently Sulfonated Resins

Fourier transform infrared spectroscopy

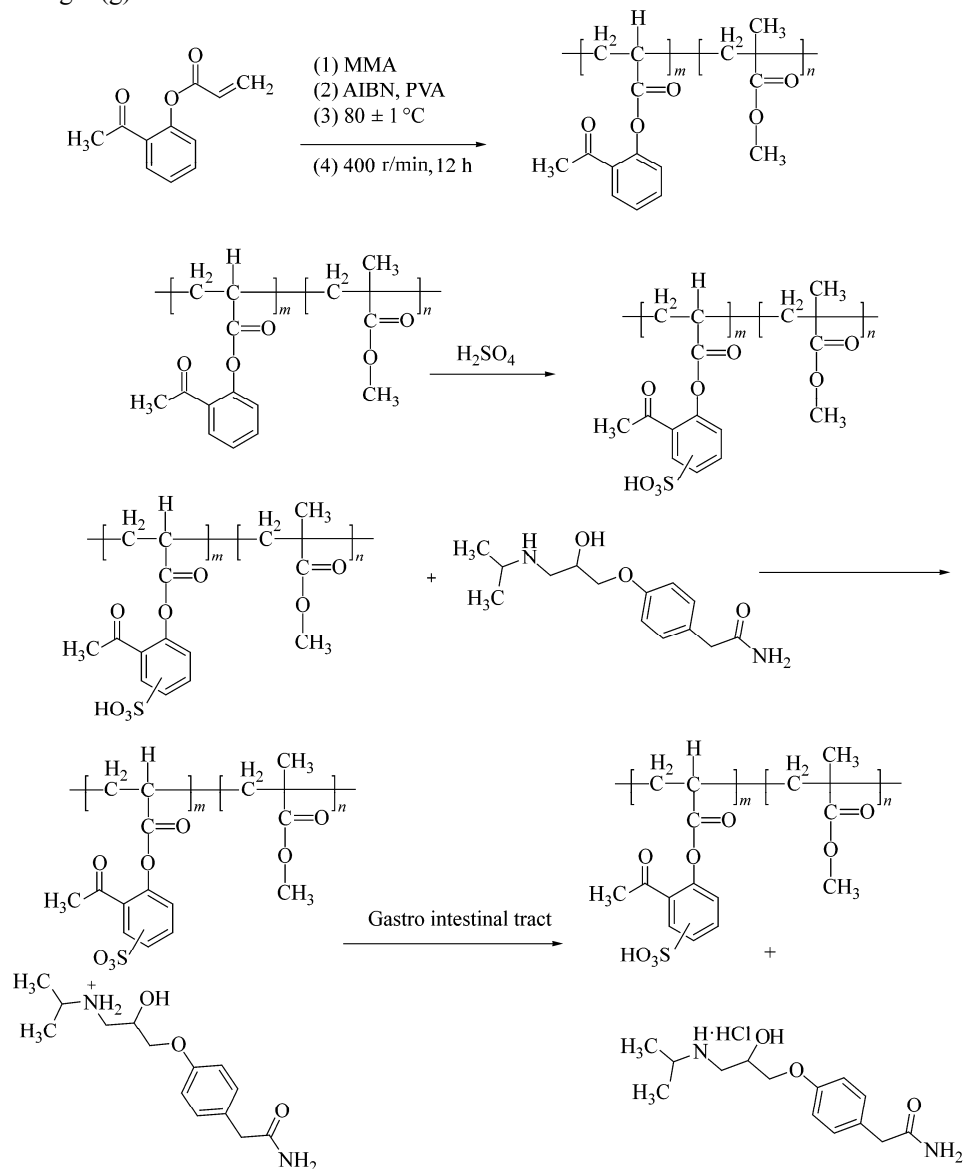
The resins that were previously dried at 60 °C until reaching a constant weight were crushed and pressed into KBr pellets. The infrared (IR) spectra of the obtained pellets were recorded over the range 4000–450 cm^{-1} by a Fourier transform infrared spectrophotometer (Perkin-Elmer spectrum 100).

Ion-exchange capacity

The IEC of resins was determined by the salt splitting titration^[19]. An accurate amount (0.1 g) of the resin was weighed and added into a 125 mL Erlenmeyer flask containing a 2 mol/L sodium chloride solution (25 mL). The slurry was swirled periodically and left for 3 h to allow for the displacement of H^+ from the resin. Thereafter, the slurry was titrated slowly with a 0.1 mol/L standardized sodium hydroxide (NaOH) solution using phenolphthalein as an indicator. The IEC (meq/g) of the resins was calculated from:

$$IEC = \frac{c \times V}{W}$$

where c is the standardized concentration (mol/L), V is the volume (mL) at an endpoint of the NaOH solution, and W is the weight (g) of determined resins.



Scheme 1 Synthesis of sulfonated acryloxyacetophenone-methyl methacrylate resins and atenolol binding

Microscopic Morphology

The dried resins were viewed by a scanning electron microscope (ZEISS, EVO MA 15 EDS Germany). Before viewing, the samples were fixed on stubs and sputter-coated with gold in a vacuum evaporator (EMITECH SC7620 Sputter Coater, Germany).

Swelling Studies

The resin dried at 60°C overnight and suspended in deionized water for 3 h. The diameter of 200 particles on the images was randomly measured with a calibrated digital micrometer of the image analysis program (An Mo

Dino Capture version 2.3.0.0, Taiwan). Then average diameter of the dried and swollen resins was determined, and the swelling (%) of the resins was calculated using the following equation^[20].

$$\text{Swelling (\%)} = \frac{d_{\text{swell}} - d_{\text{dry}}}{d_{\text{dry}}} \times 100$$

Behavior of Differently Sulfonated Resins as Drug Carriers

ATL loading

ATL 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) ATL 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 (Magnetic stirrer, vision lab equipment). 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 mol/L KCl solution (200 mL) and then calculated in wt% as the (amount of drug/amount of resinate) $\times 100$ ^[4]. The eluted drug was assayed by a UV spectrophotometer (LABINDIA, 3000⁺) at 226 nm.

ATL release

In vitro ATL release was investigated in the USP simulated gastric and intestinal fluids (600 mL) by a USP release testing apparatus (LABINDIA)^[21]. Each resinate prepared from the differently sulfonated resins was weighed to obtain an equivalent of 25 mg ATL and then added into the release vessel. The rotation and temperature were set at 50 r/min 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.

RESULTS AND DISCUSSION

Characterization of Copolymer (AAP-MMA)

Elemental analysis

The AAP-MMA copolymer was characterized by elemental analysis. The found values of C and H are consistent with calculated values. Anal. Calcd: C, 66.20; H, 6.20. Found: C, 65.73; H, 6.08.

IR spectral studies

The IR spectrum of the AAP-MMA *co*-polymer (Fig. 2, R/0) shows absorption around 2945 cm^{-1} , which has been identified as —CH back bone methylene stretching vibration. The ester carbonyl is identified by the appearance of a strong absorption band at 1737 cm^{-1} . The C—O—C stretching vibrations in the compound are confirmed by absorption at 1190 cm^{-1} . The keto carbonyl functionality is identified by a sharp absorption band at 1695 cm^{-1} .

Characterizations of Differently Sulfonated Resins

The copolymer beads were prepared by suspension polymerization and then sulfonated for varied reaction times to transform into the differently sulfonated resins, the codes of which are displayed in Table 1. To evaluate the success of this process, the IR spectra and the ionexchange capacity of the obtained resins were determined. The IR spectra of the differently sulfonated resins are shown in Fig. 2. There are significant new absorption bands around $1255\text{--}1160$ and $3452\text{--}3420\text{ cm}^{-1}$ in the IR spectra of the copolymer beads after sulfonation. These are attributed to the stretching vibrations of the S=O and O—H of the sulfonic group (—SO₃H), respectively^[16, 22]. The bands 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. The IR absorption bands indicated that the differently sulfonated AAP-MMA cross-linked copolymer resins could be successfully prepared.

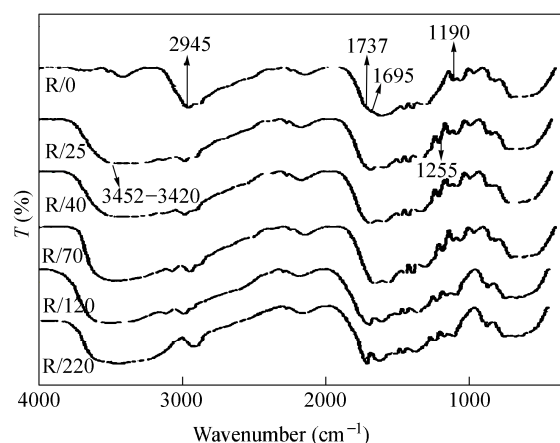


Fig. 2 Fourier transform infrared spectra of differently sulfonated resins

Table 1. Assignment, resin weight and weight increase of differently sulfonated resins

Sulfonation time (min)	Assigned code	Resin weight (g) ^a	Weight Increased (%) ^b	IEC (meq/g) ^c
0	R/0	3.000	0.000	0.000 ± 0.000
25	R/25	3.129	4.300	0.512 ± 0.002
40	R/40	3.570	19.000	2.097 ± 0.016
70	R/70	4.371	45.712	3.609 ± 0.028
120	R/120	5.550	85.023	4.474 ± 0.007
220	R/220	6.158	105.290	4.470 ± 0.031

^a After drying at 60 °C for 6 h

^b $100 \times (\text{resin wt} - \text{bead wt}) / \text{bead wt}$, where bead wt = 3.000 g

^c Mean ± SD from triplicate measurement

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 1). 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 for 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 groups into the resins. The sulfonic group is 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⁺). Greater the degree of sulfonic group added in the resins, greater is the interchange of the counterions, thus providing the higher IEC.

It was also observed that the weight and hence the percent weight increase of the obtained resins in relation to the employed copolymer beads increased as the sulfonation time was increased (Table 1). This was due to the more sulfonic groups 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 scanning electron micrographs of the resins show that the different partially sulfonated resins have smooth surface and spherical shape. The scanning electron micrographs show fractures on the hollow surface of moderately sulfonated resin, *i.e.*, R/40 (Fig. 3). The fully (R/120 and R/220) and poorly (R/25) 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/40 were the point of highest swelling (Fig. 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^[23]. On the other hand, the fully sulfonated resin beads (R/120 and R/220) swelled evenly, keeping the internal tension small enough that no fractures occurred.

Additionally, no fractures were found in R/25 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 the ion-exchange property of the resins^[22]. The scanning electron micrographs of R/0, R/70, R/120 are shown in Fig. 4.

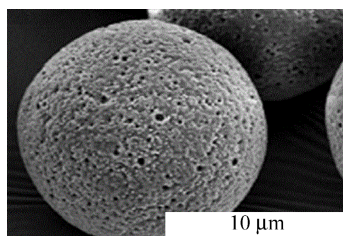


Fig. 3 Scanning electron micrograph showing fractures in sulfonated AAP-MMA resin (R/40)

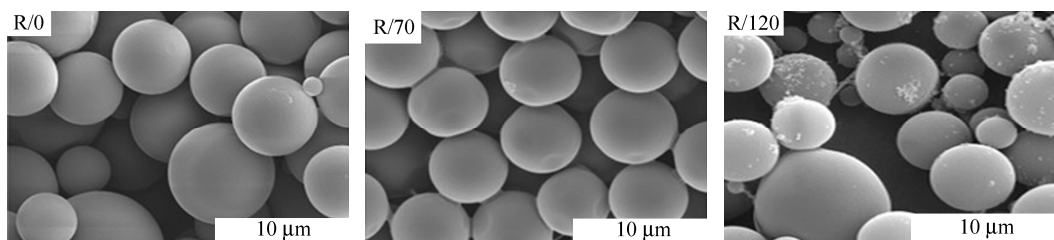


Fig. 4 Scanning electron micrographs of differently sulfonated AAP-MMA resins (R/0, R/70 and R/120)

Average diameters in the dry and wet states as well as the swelling of the resins are shown in Fig. 5. In the dry state, the average diameters of the differently sulfonated resins were comparable (42 μm to 49 μm), whereas those in the wet state progressively increased from (54 μm to 107 μm) in relation to the increased degree of sulfonic groups 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. The swelling occurrence helps to confirm the successful introduction of sulfonic groups into the resins.

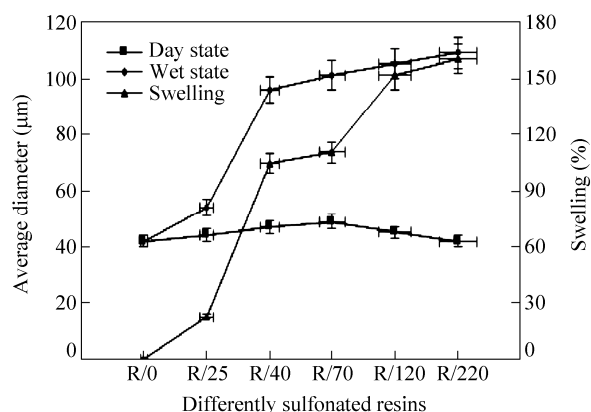


Fig. 5 Average diameter in dry (square), wet (diamond) states and swelling (triangle) of differently sulfonated resins

Particle size analysis

The success and reproducibility of sulfonation and hence the polymerization process was determined by measuring the average particle size distribution of the resin beads^[24, 25]. The particle size distribution of the sulfonated AAP-MMA resin (R/40) was determined using a Malvern particle size analyzer. The average particle

size of the resin is $1.967\ \mu\text{m}$ and the distribution curve is relatively broad. The specific surface area of the resin is $3.84\ \text{m}^2/\text{g}$. The particle size distribution curve is shown in Fig. 6.

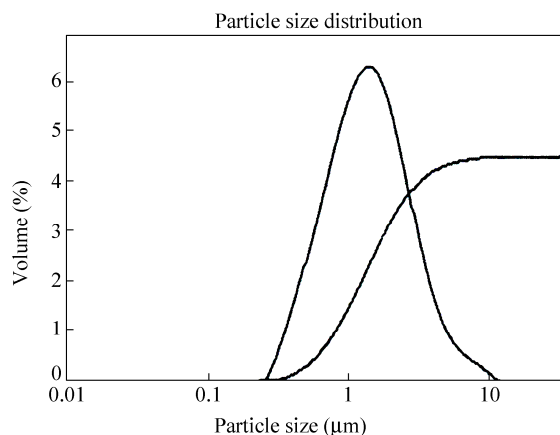


Fig. 6 Particle size distribution curve of the sulfonated AAP-MMA resin (R/40)

Thermal analysis

Figure 7 shows the TGA and DTA curves of AAP-MMA copolymer (R/0) and its sulfonated resin (R/40) under N_2 atmosphere over a temperature range $30\text{--}500\ ^\circ\text{C}$ with a heating rate of $20\ \text{K}/\text{min}$. The TGA curve of R/0 shows only one decomposition stage. It appears to begin around $345\ ^\circ\text{C}$ and stops at around $432\ ^\circ\text{C}$ with maximum rate at $365\ ^\circ\text{C}$. The DTA curve of AAP-MMA copolymers also shows a single endo-peak which indicates degradation in one stage. The degradation of R/40 starts at $180\ ^\circ\text{C}$ with the probable loss of sulfonic groups and a sudden weight loss between $340\ ^\circ\text{C}$ and $432\ ^\circ\text{C}$ indicating the degradation of copolymer matrix. The DTA curve of R/40 also shows weak exo effects around $127\text{--}163\ ^\circ\text{C}$ which might be related to “physical aging” of hydrogen bonded copolymers accompanied by the breaking of inter and intra molecular hydrogen bonds of the polymer structure^[26].

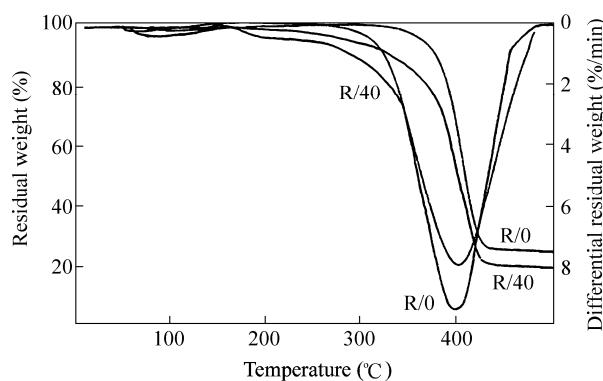


Fig. 7 Thermo gravimetric and differential thermal analysis curves of AAP-MMA copolymer (R/0) and sulfonated AAP-MMA resin (R/40)

Purity and toxicity

It is necessary to establish the safety/toxicity of the ion exchange resins because of very high fraction of the resin in drug-resin complexes ($> 60\%$). Most commercial products cannot be used in such cases because they contain impurities that cause severe toxicity besides some pharmaceutical grade resins (Amberlite IRP series from Rohm & Haas). Therefore, a thorough purification of the resin is required to eliminate the impurities for the pharmaceutical application. Purified ion exchange resins are insoluble and nontoxic. However, administration of large enough quantities of ion-exchange resin may disturb the ion strength in the gastrointestinal fluids and cause harmful side effects^[27, 28]. Hence, a comprehensive study is needed before the resins are put in the market.

Advantages of Sulfonated Resins in Controlled Drug Delivery

The use of IER into drug delivery systems have been encouraged because of their physicochemical stability, inert nature, uniform size, spherical shape, assisting coating and equilibrium driven reproducible drug release in ionic environment^[29]. The physical and chemical properties of the IER will release the drug more uniformly than that of simple matrix formulations^[30]. Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins.

IER have been used as drug carriers in pharmaceutical dosage forms for controlled release formulation^[3, 4, 31]. The prolonged release of the active drug is accomplished by providing a semi-permeable coating around discrete, minute, ion exchange resin particles with which the drug component has been complexed to form an insoluble drug resin complex. The semipermeable coating creates a diffusion barrier and the thickness of which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time^[5]. Several preparations involving strong resonates of sulphuric acid (cation exchange resins) provided more moderate release than the weak resins of carboxylic acid^[32]. Hence, resins of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles.

Behavior of Differently Sulfonated Resins as Drug Carriers

After the resin was placed in the drug solution, ATL dissociated into a cationic molecule would exchange with the resin counterion (H^+) and then form the resinate. The ATL loadings (wt%) in the resins prepared from the differently sulfonated resins are presented in Table 2. As expected, the drug loading was greater in the resins treated with the longer sulfonation times and hence the higher contents of sulfonic groups. 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 resins 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 ATL (25 mg), greater amounts of resins were necessary, thus requiring higher amounts of resinate formulations than the resins with the full ion-exchange capacity. This point could be considered as 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 reduce the use of fillers when the resinate is further prepared in certain dosage forms, e.g., capsules.

The *in vitro* release of ATL from various resins in SGF and SIF is illustrated (Fig. 8 and Fig. 9). In both media, a similar pattern of the drug release was observed being slower from the resins with the higher content 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. Therefore, the resins with the higher amount of sulfonic groups would have a wider diffusive path depth for drug passage. It should be noted that the wet size of the resins with the higher sulfonic group content was larger because of the greater swelling, 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^[12], 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 2, the resins with the higher sulfonic group content were correspondingly employed in lower amounts than those with the smaller sulfonic group content, 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.

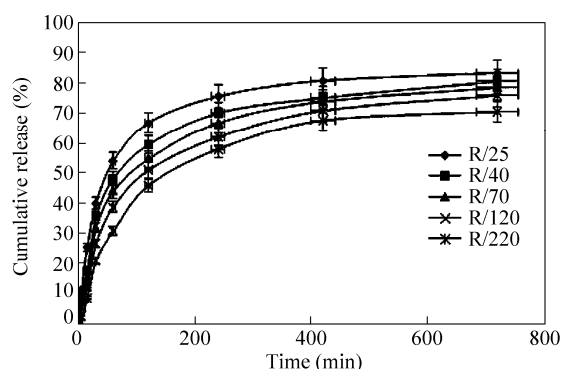


Fig. 8 ATL release from the resins in stimulated gastric fluid
(Each value is the mean of three determinations.)

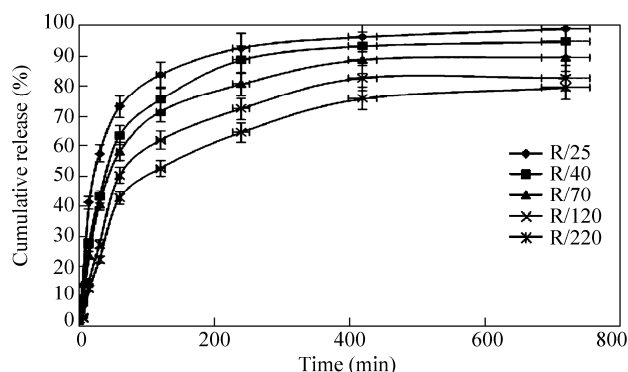


Fig. 9 ATL release from the resins in stimulated intestinal fluid
(Each value is the mean of three determinations.)

Table 2. ATL loading and resinate formulation obtained from differently sulfonated resins

Resin	ATL loaded in resinate (wt%) ^a	Amount of resinate formulation (mg) ^b	Amount of employed resin (mg) ^c
R/0	0	0	0
R/25	12.65 ± 0.002	210.4	185.4
R/40	34.02 ± 0.003	74.3	49.3
R/70	51.15 ± 0.005	52.8	27.8
R/120	56.85 ± 0.002	47.1	22.1
R/220	60.38 ± 0.001	45.8	20.8

^a Mean ± SD from triplicate measurement

^b Containing equivalently 25 mg ATL

^c The amount of resinate formulation minus 25 mg ATL

The ATL release in both SGF and SIF was incomplete (Fig. 8 and Fig. 9) because it was driven by the ion-exchange process toward equilibrium^[33]. From a survey of the 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^[11, 12, 33], the amount of loaded drug^[34], the type of release medium^[33] and the sampling procedure of release testing^[35]. Nevertheless, the effect of the degree of resin sulfonation on equilibrium release has not been mentioned. As seen in Fig. 8 and Fig. 9, the equilibrium release from the resins seemed to decrease with increasing content 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.*^[12] 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 sulfonation had both larger diffusive path depth and larger wet size. 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 sulfonation, thus providing the lower equilibrium release.

In existing literature, the type of release medium always affects the drug release from resins. In the present case, the ATL release determined in SGF (Fig. 8) was little lower than that in SIF (Fig. 9), although the total cation concentration in SGF was higher than that in SIF, which was similar to the previous work^[33]. 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). In SIF (pH 7.5) ionization was less than 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. The secondary amino group of the drug seems to be ionized only a little greater extent in SGF (pH 1.2) than that in SIF (pH

7.5), thus allowing a little smaller amount of the drug to be available for release. This is further substantiated by the fact that the exchange capacity of strong acid resins is independent of the solution pH^[36]. The results obtained in the present study are further substantiated by the reports made in the literature^[17] on the controlled release characteristics of chlorpheniramine from differently sulfonated styrene-divinylbenzene resins in stimulated gastric (SGF) and intestinal fluids (SIF).

CONCLUSIONS

In this study, the differently sulfonated 2-acryloxyacetophenone-methylmethacrylate copolymer resins were successfully prepared. The resin characteristics, atenolol loading and its *in vitro* release were found to be clearly affected by the degree of sulfonation in the prepared resins. In addition, atenolol release was also depended on the ionization of the drug in the release medium. In stimulated gastric fluid, the drug ionized and preferred to bind with the resin to a greater extent than in the stimulated intestinal fluid. Hence, a smaller amount of the drug was found to be available for release in stimulated gastric fluid. Therefore 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.

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