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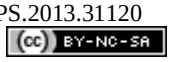
ISSN 2231-3354 

Controlled drug release studies of valsartan using differently sulfonated methacryloxyacetophenone and methyl methacrylate co-polymer resins as drug carriers

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ABSTRACT

2-methacryloxyacetophenone (MAP) was prepared and subjected to suspension polymerization with methyl methacrylate (MMA) using benzoylperoxide (BPO) as free radical initiator. The differently sulfonated MAP-MMA cross-linked copolymer cationic exchange resins were prepared by sulfonation with concentrated sulphuric acid at 70^{o}C. Several characteristics of the prepared resins were evaluated, i.e. FT-IR, the Ion-exchange capacity (IEC), Swelling studies, 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 valsartan (VLN) 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 sulfonic group and hence the drug binding site in resin employed. The drug release was lower from the resins with higher degree 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 stimulated intestinal fluids (SIF). The basic group, 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.

INTRODUCTION

There are many reports in the literature referring to the utilization of drug bound to ion-exchange resin (drug–resinate), especially in the drug delivery area. Ion-exchange resin complexes, which can be prepared from both acidic and basic drugs, have been widely studied and marketed. Salts of cationic and anionic exchange resins are insoluble complexes in which drug release results from exchange of bound drug ions by ions normally present in body fluids. Controlled drug delivery systems are gaining momentum in the recent two decades as these results in reduced frequency of dosing and patient compliance. Intensity and duration of action has been the subject of increasing multidisciplinary research. One of the attractive methods for modified drug delivery systems is the use of ion exchange resins (IER) as carriers for such systems (Chaudhary and Saunders, 1956). Complexes between IER and drugs are known as ion exchange resinates, which have been used in pharmaceutical formulations for several decades. IER are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is exhibited like small bead with a diameter between 1-2 mm. It is usually white or yellowish and it is fabricated from an organic polymer substrate backbone (Kasture *et al*., 2002). Ion exchange is a reversible process in which ions of like sign are exchanged between liquid and solid when in contact with a highly insoluble body (Borodkin, 1993). The drug is released from the resinate by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion (Notari, 1987). Due to the presence of high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. IER have specific properties like available capacity, acid base strength, particle size, porosity and swelling, on which the release characteristics of drug resinates are dependent (Guo *et al*., 2009). Drug resinates are generally prepared with purified resins and appropriate drugs. However, the above application employs only the commercial resins with the ion-exchangeable site fully filled. But the characteristics and behavior of different partially sulfonated MAP-MMA resins in delivering a drug has not been reported.

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As a novel approach, this work was aimed at preparing, characterizing the differently sulfonated resins and to study their effectiveness as cation exchange resins. Valsartan is a pharmaceutical drug used in the treatment of high blood pressure. The behavior of the obtained resins in terms of drug, valsartan (VLN), loading and *in vitro* release were evaluated and discussed. The different partially sulfonated resins had lower ion exchange than the usual resins with the full ion-exchange capacity. Thus, they are feasible for use in delivering the low dose drug.

EXPERIMENTAL SECTION

Materials

2-methacryloxyacetophenone (our previous work) (Doraswamy and Venkata Ramana, 2013), methylmethacrylate (Merck), polyvinyl alcohol (MW 85,000–1,24,000, 87–89% hydrolyzed, Merck), benzoyl peroxide (Merck), valsartan (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. Milli pour water prepared by a water purifier (Milli Q Gradient Century) was used entirely in this work.

Preparation of MAP-MMA cross-linked copolymer

The cross-linked copolymer bead was 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 added to the flask, and the temperature was raised to around 65°C. Under a fixed stirring (400 rpm), the monomer mixture containing MAP (35g), MMA (3.99 g), and BPO (0.5g) was gradually added to the aqueous phase. Then, the temperature was raised around 80°C and maintained at that temperature until the polymerization was terminated (12 h). Thereafter, the bead was washed several times with deionized water, petroleum ether, butan-2-one, acetone and methanol and then sieved. The fraction in the range of 72–150μm (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 (15.3g) approximately corresponded to 56.8% of the whole beads (26.9g) and 39.2% of the employed monomers respectively.

Preparation of differently sulfonated resins

Prior to sulfonation, the dried copolymer beads (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 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 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 50 °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 (Harland, 1994). 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 IEC (meq/g) of the resins was calculated from:

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

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 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 50°C for overnight were suspended in deionized water for 3h. 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 resin was calculated using the following equation (Halder and Sa, 2005).

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

Behavior of Differently Sulfonated Resins as Drug Carriers

VLN Loading

VLN loading into the differently sulfonated resins was carried out by the double batch method. In this process, 0.5 g of resin was placed into a 1.0% (w/v) VLN 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 N KCl solution (200 ml) and then calculated in % w/w as the (amount of drug/amount of resinate) x100 (Cuna *et al*., 2000). The eluted drug was assayed by a UV spectrophotometer (LABINDIA, 3000^{+}) at 254 nm.

VLN Release

In vitro VLN release was investigated in the USP simulated gastric and intestinal fluids (600 ml) by a USP release testing apparatus (LABINDIA) (Rockville, 2006). Each resinate prepared from the differently sulfonated resins was weighed to obtain an equivalent of 25 mg VLN 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 (5ml) 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 Co-polymer (MAP-MMA)

Elemental Analysis

The MAP-MMA co-polymer was characterized by elemental analysis. The found values of C & H are consistent with calculated values. Anal. Calcd: C, 65.97; H, 6.52. Found: C, 64.86; H, 5.92.

IR Spectral studies

The IR spectrum of the MAP-MMA co-polymer (Figure. 1, R/0) shows absorption around 2955cm^{-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 1734 cm^{-1}. The C-O-C stretching vibrations in the compound are confirmed by absorption at 1183 cm^{-1}. The keto carbonyl functionality is identified by a sharp absorption band at 1696 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 ion-exchange capacity of the obtained resins were determined. The IR spectra of the differently sulfonated resins are shown in Figure. 1.

There are significant new absorption bands around 1241-1166 and 3430-3415 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 (–SO_3H), respectively (Oliveira *et al*., 2005). 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 MAP-MMA 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 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 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 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 bead increased as the sulfonation time was increased (Table 1). 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 scanning electron micrographs of the resins show that the surfaces and shapes of the different partially sulfonated resins were smooth and spherical in shape. The scanning electron micrographs show fractures on the hollow surface of moderately sulfonated resin, i.e., R/40 (Figure. 2). No sulfonation (R/20) and the fully (R/220) 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. 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 (Coutinho *et al*., 2004). 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.

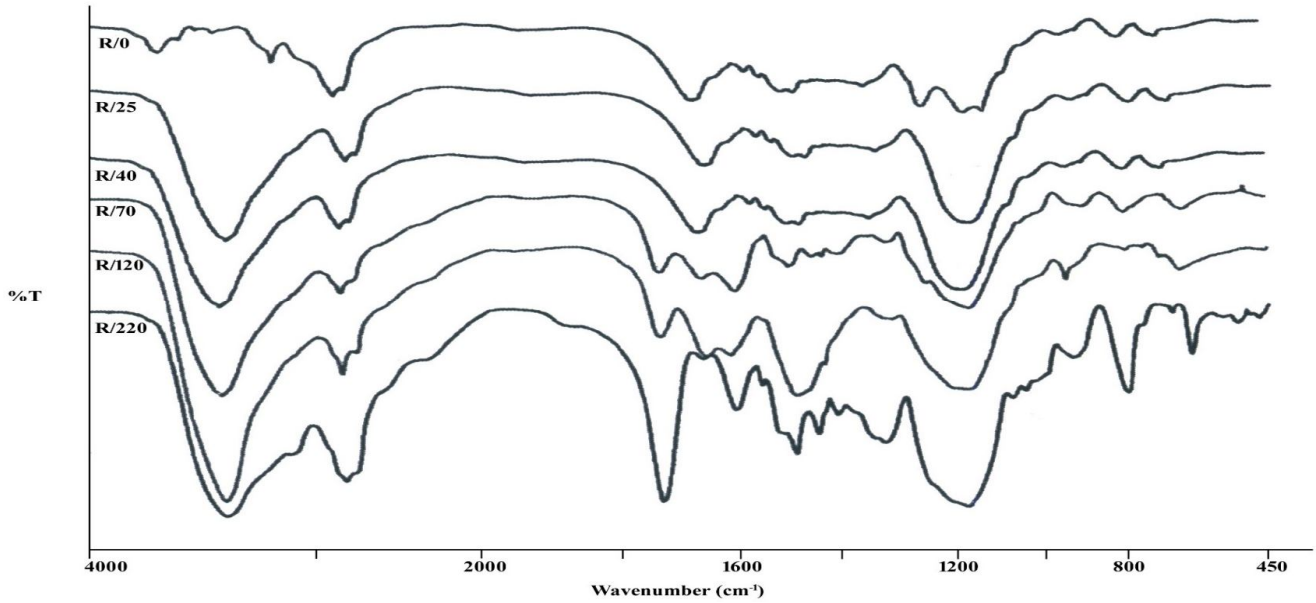

Fig. 1: Fourier Transform infrared spectra of MAP-MMA copolymer(R/0) and its differently sulfonated resins.

Table. 1: Assignment, resin weight, % weight increase and IEC of differently sulfonated resins of MAP-MMA.

Sulfonation Time (min)	Assigned code	ResinWeight (gm)[a]	% weight increase[b]	IEC (meq/g)[c]
0	R/0	3.000	0.000	0.000 ± 0.000
25	R/25	3.153	5.100	0.616 ± 0.002
40	R/40	3.496	16.530	2.436 ± 0.002
70	R/70	4.704	56.800	4.268 ± 0.009
120	R/120	5.850	95.000	5.624 ± 0.006
220	R/220	6.647	121.566	5.873 ± 0.008

[a]After drying at 50°C for 6 h
[b]100 x (resin wt-bead wt)/bead wt, where bead wt =3.000g
[c]Mean ± SD from triplicate measurement

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

Resin	VLN loaded in resinate (%w/w)[a]	Amount of resinate formulation (mg)[b]	Amount of employed resin (mg)[c]
R/0	0	0	0
R/25	13.26±0.001	206.56	181.56
R/40	36.93±0.007	76.08	57.08
R/70	52.42±0.003	63.92	38.92
R/120	57.63±0.002	58.52	33.52
R/220	61.86±0.005	56.23	31.23

[a]Mean ± SD from triplicate measurement
[b]Containing equivalently 25mg VLN
[c]The amount of resinate formulation minus 25mg VLN

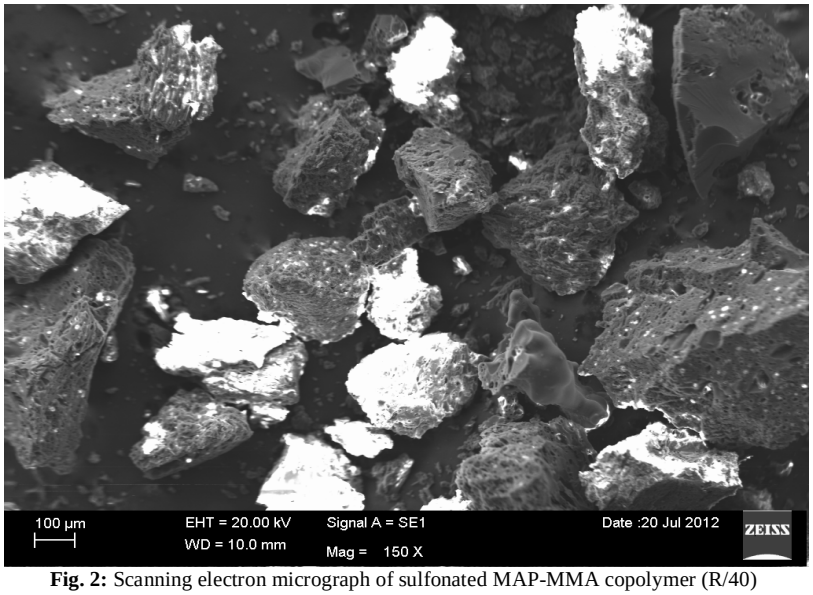

Fig. 2: Scanning electron micrograph of sulfonated MAP-MMA copolymer (R/40)

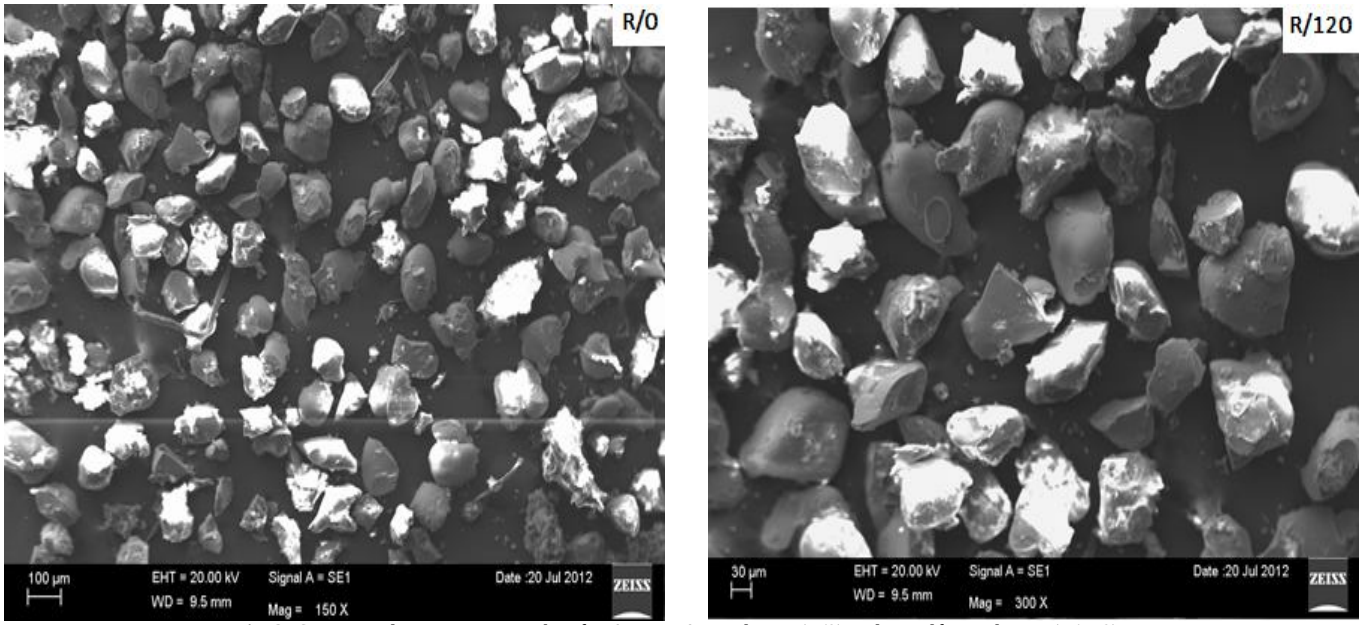

Fig. 3: Scanning electron micrographs of MAP-MMA copolymer (R/0) and its sulfonated resin (R/120).

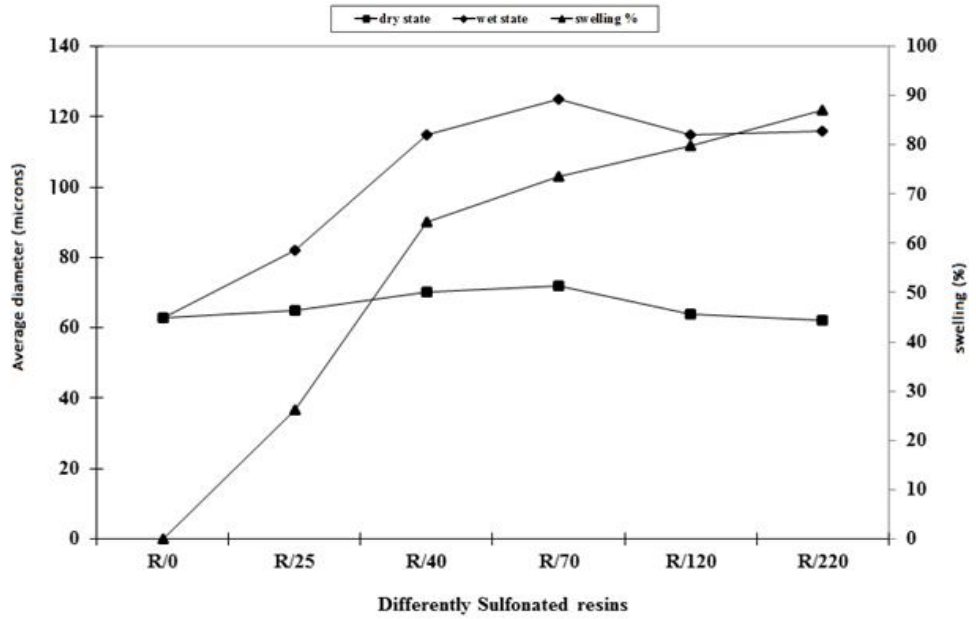

Fig. 4: Average diameter in dry (square), wet (diamond) and swelling (triangle) states of differently sulfonated resins.

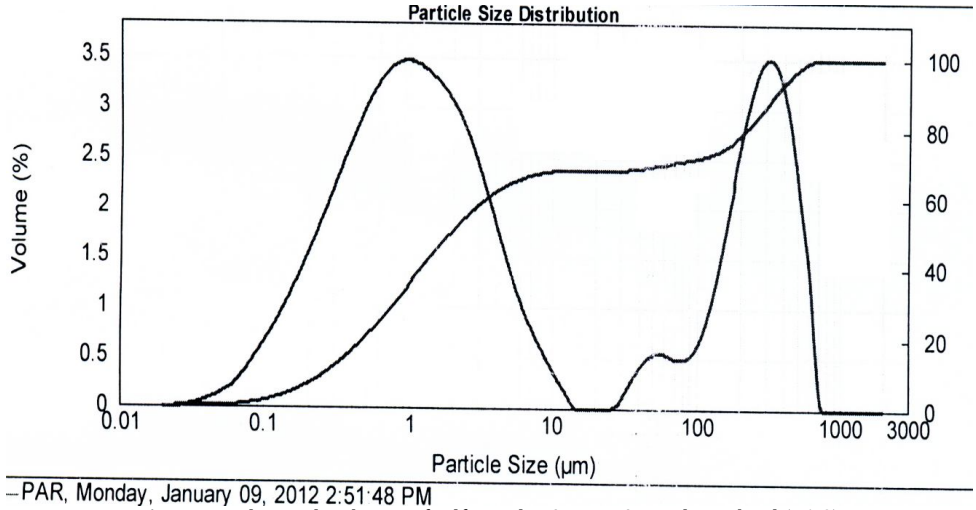

Fig. 5: Particle size distribution of sulfonated MAP-MMA copolymer bead (R/40)

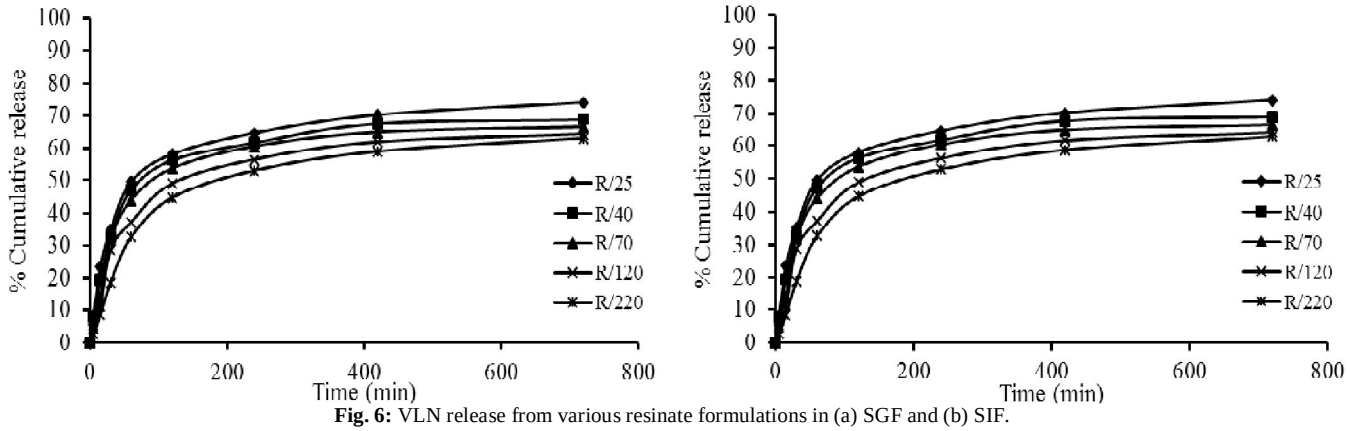

Fig. 6: VLN release from various resinate formulations in (a) SGF and (b) SIF.

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. The scanning electron micrographs of R/0, R/120 are shown in Figure. 3.

Average diameters in the dry and wet states as well as the swelling of the resins are shown in the Figure. 4. In the dry state, the average diameters of the differently sulfonated resins were comparable (63 to 72 µm), where as those in the wet state progressively increased from (82 to 125 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. The swelling occurrence help to confirm the successful introduction of sulfonic group in to the 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 (Allen, 1981; Barth, 1984). The particle size distribution of the sulfonated MAP-MMA resin (R/40) was determined using a Malvern Particle size analyzer. The average particle size of the resin is 0.27 µm and distribution curve is relatively broad. The specific surface area of the resin is 8.44 m^2/g. The particle size distribution curve is shown in Figure. 5.

Behavior of Differently Sulfonated Resins as Drug Carriers

After the resin was placed in the drug solution, VLN dissociated into a cationic molecule would exchange with the resin counterion (H^+) and then form the resinate. The VLN loading (% w/w) in the resinates 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 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. It was observed that, the different partially sulfonated resins have the lower ion exchange and hence the drug loading than the resins with the full ion exchange capacity. Hence, to deliver the same amount of VLN (25 mg), greater amounts of resins were necessary, thus requiring higher amounts of resinate formulations than the resins with the full ion-exchange capacity.

The *in vitro* release of VLN from various resinates in SGF and SIF is illustrated in Figure. 6. In both media, a similar pattern of the drug release was observed being slower from the resins with the higher degree of sulfonic group. This behavior may result 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 group would have a wider diffusive path depth for drug passage. The drug located at the deeper site near the resin center would require more time to diffuse out.

Therefore, the resins with the higher degree of sulfonation provide a slower rate of drug release. Moreover, the resins with the higher sulfonic groups were employed in lower amounts than those with the lower sulfonic group. 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 VLN release in both SGF and SIF was incomplete (Figure. 6) because it was driven by the ion-exchange process towards equilibrium (Pongjanyakul *et al*., 2005). 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 can be explained by the heterogeneous nature of the cross-linked copolymer matrix. Irwin *et al*., 1987 reported that all ion exchangeable sites (sulfonic group) were not 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. Hence there was 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. In the present case, the resins with the higher degree of sulfonic group 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 sulfonic group, thus providing the lower equilibrium release. Literature survey reveals that, the type of release medium always affects the drug release from resinates. In the present case, the VLN release determined in

SGF was little lower than that in SIF (Figure. 6), although the total cation concentration in SGF was higher than that in SIF, which was similar to the previous work (Pongjanyakul *et al*., 2005). 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 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 (Bhalekar *et al*., 2004).

CONCLUSION

In this study, the differently sulfonated 2-methacryloxyacetophenone-methylmethacrylate copolymer resins were successfully prepared. The resin characteristics, valsartan loading and its *in vitro* release were found to be clearly affected by the degree of sulfonic group in the prepared resins. In addition, VLN 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.

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