DESIGNING OF NEW ACRYLIC BASED MACROPOROUS SUPERABSORBENT POLYMER HYDROGEL AND ITS SUITABILITY FOR DRUG DELIVERY

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ABSTRACT

A novel biopolymer-based semi interpenetratin network (IPN) superabsorbent polymer (SAP) hydrogel was synthesized through chemical crosslinking by graft copolymerization of 2-hydroxy ethyl methacrylate (HEMA) and acrylic acid on to starch in presence of gum arabic, N,N'-methylene-bis-acrylamide (MBA) as crosslinker and benzoyl peroxide (BPO) as initiator. The structures of the copolymers were confirmed by FTIR. Morphological examination of SAP by SEM confirms the macro porous nature of the copolymer. The high char yield, up to 12.5wt%, at 600 ºC observed in thermogram indicates the thermal stability of the SAP. Because of its super absorbency, pH sensitivity, good swelling and re swelling ability, it can be concluded that the prepared polymer system may be useful in extending the delivery of entrapped drug in the form of formulations for predetermined period of time, in future.

Keywords: Superabsorbent polymer, Free radical polymerization, pH sensitivity, Re swelling ability.

INTRODUCTION

Superabsorbent polymer hydrogels are lightly cross linked hydrophilic polymers that can absorb, swell and retain aqueous solutions up to hundreds of times their own weight[1]. The super-swelling characteristics of SAPs make them ideal for use in water absorbing applications such as disposable diapers, famine napkins, agriculture, cosmetic and absorbent pads[2]. Because of their exceptional properties, polysaccharides and proteins are the main part of the natural-based super-absorbent hydrogels. The unique physical, chemical and biological properties of hydrogels like gel strength, equilibrium swelling, non-toxicity, biocompatibility, biodegradability, renewability, have sparked particular interest in their use in controlled drug delivery applications[3,4].Hydrogels made from synthetic polymers, such as polyacrylate possess excellent water-absorbing properties. Despite the advantages of these hydrogels, there are also severe limitations to this type of material which are worth noting. In fact their toxicity and non biodegradability might pose long-term environmental problems and limit their use in drug delivery systems and consumer products. Because of these shortcomings, natural product based SAPs which are mostly made from polysaccharides and proteins have attracted much attention in recent years. Polymers of natural and synthetic origin find extensive application as biomaterials on account of the flexibility to modified for specific applications. Starch based blends find wide applicability in biomedical and allied areas owing to their biodegradability; renew ability, nontoxicity and almost an unfailing source of raw material. Recently they are being viewed as having great potential for application in biomedical field as implant materials, drug delivery systems, and tissue engineering scaffolds. Most starches consist of two polysaccharides, amylose and amylopectin. Amylose is an essentially linear molecule

consisting of α-(1-4)-linked D-glucan chains. Amylopectin is a highly branched molecule containing short chains of α-(1-4)-linked D-glucan chains with α-(1-6)-linked branches. Both fractions are readily hydrolysed at the acetal link by enzymes. The-(1-4)-link in both components of starch is attacked by amylase; the-(1-6)-link in amylopectin is attacked by glycosidase[5, 6].

Gum arabic (GA) is a plant hydrocolloid and known to be a potent antioxidant [7-10]. It is most commonly used as a food additive. Its popularity is due to its physical properties including high solubility, pH stability, nontoxicity and gelling characteristics. It is a highly branched, branch-on-branch, complex acidic hetero-polysaccharide with main chain of (1−>3)-β-D-galactopyranosyl units and side chains containing L-arabinofuranosyl, L-rhamnopyranosyl, D-galactopyranosyl, and D-glucopyranosyl uronic acid units .This hydrocolloid is the most widely used natural gum in industry and extensively used in a wide range of application such as confectionery, beverage or liquid flavor emulsions, pharmaceuticals, cosmetic products, inks, etc. GA is classified E 414 in the European List of Permitted Food Additives. According to JECFA (Joint WHO/FAO Expert Committee on Food Additives) it has the status of ADI-non specified (Acceptable Daily Intake), i.e. no quantitative limitation is stated, and, as such Acacia gum (Gum arabic) is recognized as a nontoxic additive for human consumption. According to the US FDA, Acacia gum enjoys the GRAS (Generally Recognized as Safe) status [11].

2-Hydroxyethyl methacrylate (HEMA) is a commercially important monomer that has been widely used in the manufacture of soft contact lenses and intraocular lenses. HEMA is a favorable biomaterial because of its excellent biocompatibility, good blood compatibility and physicochemical properties (EWC of 40%) similar to those of living tissues [12, 13]. It also exhibits good chemical and hydrolytic stability and good tolerance for entrapped cells. Other biomedical applications for poly(HEMA) based materials include an embedding substrate for the examination of cells using light microscopy, and inert matrices for the slow release of drugs [14,15].

Poly acrylic acid (pAA) is a typical pH responsive polyelectrolyte polymer able to form ions when subjected to an aqueous environment causing considerable volume swelling due to hydrogen bridge or covalent bond formation. It has been widely used in the area of site -specific delivery to specific regions of the gastro-intestinal tract .However high water solubility has limited their use as a drug carrier to a certain extent; because of dissolution before the drug can be delivered. In order to overcome the above drawback, acrylic acid (AA) is polymerized with either hydrophilic or hydrophobic monomers in presence of organic crosslinkers to form copolymers of tunable physicochemical properties.

The aim of this study is to investigate the swelling behavior of the SAP hydrogel Starch-g-p[HEMA-co-AA]/GA prepared via free radical polymerization, using benzoyl peroxide as initiator. FTIR, SEM and TGA analysis were also carried out to characterize the bulk structure, morphologies and thermal stability of the SAP hydrogel.

MATERIALS AND METHODS

Starch and gum arabic were supplied by Himedia Laboratories Pvt.Ltd, Mumbai, India. HEMA and AA were purchased from E.Merck, Germany and were used after distillation under reduced pressure. Benzoyl peroxide (E.Merck) was recrystallized from benzene and a stock solution was prepared in acetone. *N, N'*-methylene bis acrylamide (MBA; E.Merck, Germany) was used as purchased. All other chemicals used in this study were of analytical grade quality. Milli-Q grade deionized water was used for preparing the solutions.

Synthesis of hydrogel

According to the basic knowledge of SAP hydrogels, the concentration of crosslinker (MBA), initiator (BPO), monomers (HEMA and AA) and starch/GA weight ratio are the key synthetic factors influencing the final swelling properties of the hydrogels (Scheme 1). These parameters were varied at different levels as shown in Table-1. The hydrogels were prepared through the free-radical copolymerization method. Briefly, starch and GA were mixed with $25cm^3$ of distilled water in a $500cm^3$ four-necked round bottom flask. The system was mechanically stirred at 250 rpm under heating within the temperature range of 80± 2ºC for 30 min under nitrogen atmosphere. To this, a known concentration of HEMA, AA and MBA were added (Table 1). The solution was stirred at 400-500 rpm while maintaining the temperature and inert atmosphere. The initiator BPO in acetone was carefully injected in to the reaction mixture. After the required time interval, the reaction was stopped by keeping the flask in ice-cold water and adding hydroquinone. The product was precipitated by pouring alcohol in to the reaction mixture. The precipitated polymer was filtered and purified by washing repeatedly with ethanol/water mixture (1:1) for several times under high-speed stirring and then soaked with the ethanol/water mixture (1:1) for 24h.The product was collected by centrifugation and dried in the oven under vacuum at 45ºC for 24 h.The dried superabsorbent polymer (1.0g) of 80 mesh size was added to 300 cm^3 deionized water. It was allowed to swell during agitation in a water bath at the constant temperature of 25 ºC for 24 h. Then it was extracted with ethanol in a soxhlet for 6 h followed by water. The precipitate was filtered and dried under vacuum at 45ºC.

Characterization

FTIR spectra of individual and crosslinked polymers were recorded in the range 400-4000 cm^{-1} on a Perkin Elmer Paragon 500 FTIR spectrophotometer using KBr pellets.

The Scanning electron microscopy of gold-coated samples were obtained using JSM - 6390LV scanning electron microscope (Jeol Ltd, Japan) at a magnification of x 5 to 300,000 (Resolution-HV 3.0nm).The thermo gravimetric analysis data were recorded with a shimadzu DTG-50 thermal analyzer. The samples were heated from room temperature to 600°C at a heating rate of 10°C per min.

Swelling behavior of hydrogel

Swelling behavior of the prepared hydrogel was performed by tea bag[16] method. About 0.1 g of sample was added to a small bag made of nylon (50 mm x 90 mm; 200 mesh). Then the bag was completely immersed in the swelling medium (200ml) at room temperature for 24 hr to reach the swelling equilibrium. It was removed from the swelling medium and hung up for 15 min to remove the excess fluid and weighed.

The equilibrium swelling (ES) was defined as follows:

$$ES\,(\%) = \frac{(Ws - Wd)}{Wd} \times 100$$

Where W_S and W_d are the weights of the swollen sample and the weight of dried gel, respectively.

RESULTS AND DISCUSSION
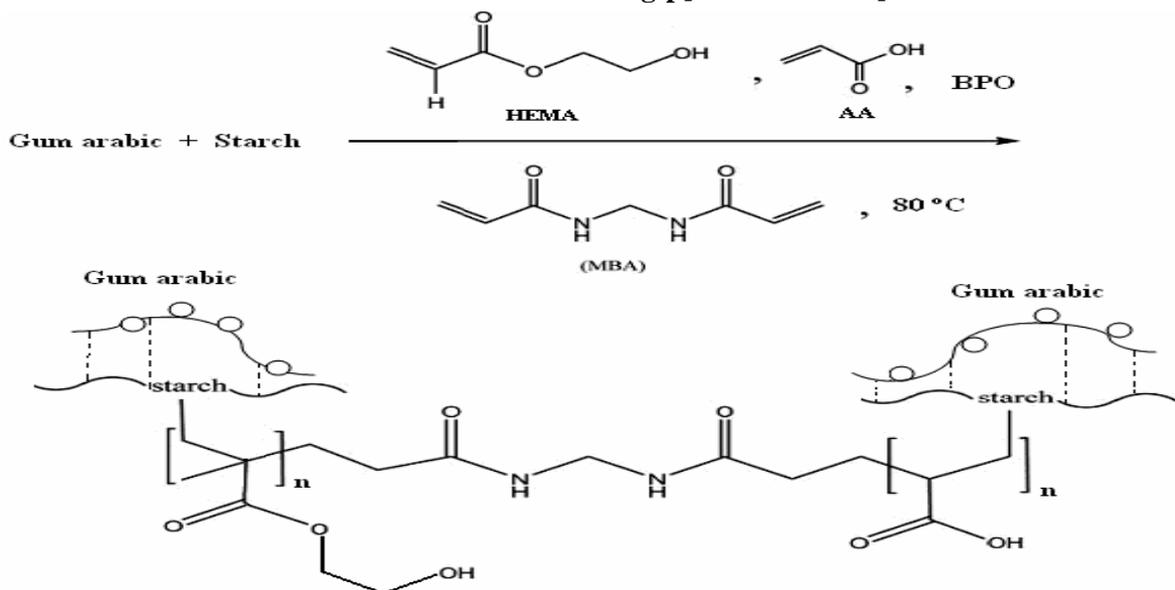
Scheme 1. Formation of Starch-g-p[HEMA-co-AA]/GA

Table 1 : Water absorbency with respect to variation of [starch/ gum arabic], [monomer], [initiator], [MBA] at 80^{0}C.

Polymer code	Starch/ Gum arabic (gm)	[HEMA] mol dm^{-3}	[AA] mol dm^{-3}	[BPO] mol dm^{-3}	[MBA] mol dm^{-3}	Swelling (%)
M1	1.36:0.34	0.3	0.3	0.02	0.02	946
M2	1.02:0.68	0.3	0.3	0.02	0.02	955
M3	0.66:1.02	0.3	0.3	0.02	0.02	830
M4	0.34:1.36	0.3	0.3	0.02	0.02	702
M5	1.02:0.68	0.1	0.3	0.02	0.02	971
M6	1.02:0.68	0.2	0.3	0.02	0.02	996
M7	1.02:0.68	0.4	0.3	0.02	0.02	901
M8	1.02:0.68	0.5	0.3	0.02	0.02	863
M9	1.02:0.68	0.2	0.1	0.02	0.02	971
M10	1.02:0.68	0.2	0.2	0.02	0.02	983
M11	1.02:0.68	0.2	0.4	0.02	0.02	1005
M12	1.02:0.68	0.2	0.5	0.02	0.02	1019
M13	1.02:0.68	0.2	0.6	0.02	0.02	1013
M14	1.02:0.68	0.2	0.5	0.005	0.02	1001
M15	1.02:0.68	0.2	0.5	0.01	0.02	1032
M16	1.02:0.68	0.2	0.5	0.015	0.02	1021
M17	1.02:0.68	0.2	0.5	0.025	0.02	1009
M18	1.02:0.68	0.2	0.5	0.03	0.02	998
M19	1.02:0.68	0.2	0.5	0.01	0.005	1041
M20	**1.02:0.68**	**0.2**	**0.5**	**0.01**	**0.01**	**1050**
M21	1.02:0.68	0.2	0.5	0.01	0.015	1037
M22	1.02:0.68	0.2	0.5	0.01	0.025	1024
M23	1.02:0.68	0.2	0.5	0.01	0.03	1001

FT-IR spectra

The FT-IR spectra of the SAP along with Starch, GA, Starch/GA blend, pHEMA and p[HEMA-co-AA] are shown in Fig 1. The sharp peak at 1724 cm^{-1} corresponds to the ester group present in pHEMA, p[HEMA-co-AA], Starch-g-p[HEMA-co-AA]/GA (Fig 1.d, f, g). The peaks at 1162 and 1080 cm^{-1} corresponding to C-O-C stretching also indicate the presence of the ester group. The peaks at 1568 (C=O asymmetric stretching) and 1406 cm^{-1} (C=O symmetric stretching) are due to the carboxylate anion[17] of pAA and p[HEMA-co-AA] (Fig 1. e, f). The broad absorption peak at 3438 cm^{-1}, which is in correspondence with the stretching vibration of O-H, is the characteristic peak of glucosidic ring of starch (Fig 1.a). The strong absorption peaks (a triplet peak) at 1025-1152 cm^{-1} correspond to C-O-C stretching. The main characteristic peaks of gum arabic are those at 1049 and 1413 cm^{-1} (C-Ostretch), 1612 cm^{-1} (C=O stretch and N-H bending), 2914 and 2995 cm^{-1} (C-H stretch) and 3000-3600 cm^{-1} (O-H stretch). The peak at 1612 cm^{-1} in GA and (starch/GA) blend overlapping with a new peak at 1572 cm^{-1} (Fig.1.g) indicates formation of semi IPN.

Fig. 1: FTIR spectra of (a) Starch, (b) Gum arabic, (c) Starch/ Gum arabic blend, (d) pHEMA, (e) pAA, (f) p[HEMA-co-AA], (g) Starch-g-p[HEMA-co-AA]/GA.
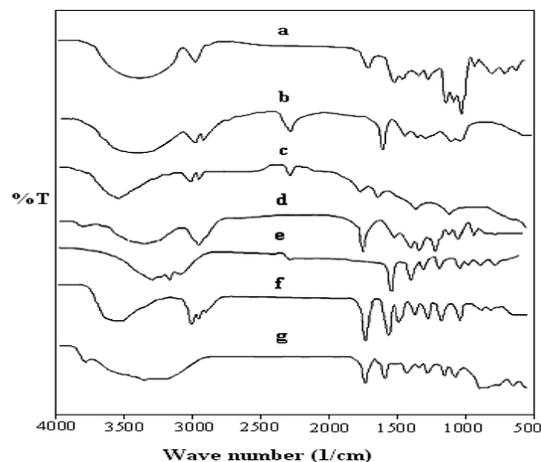
Scanning electron microscopy

The surface appearance of graft copolymer under different magnifications viewed by scanning electron microscope is depicted in Fig 2. The diameter of the pore was found to be in between 75-150μm. The visible macro pores are observed at higher magnifications indicates that water molecules can be accommodated and easily diffused in and out. Therefore, the swelling ratio of M20 and its response rate could be greatly enhanced which can be reflected in swelling or de swelling kinetics experiments.

Fig. 2 : Scanning electron microscopy images of superabsorbent polymer (M20) at different magnifications.
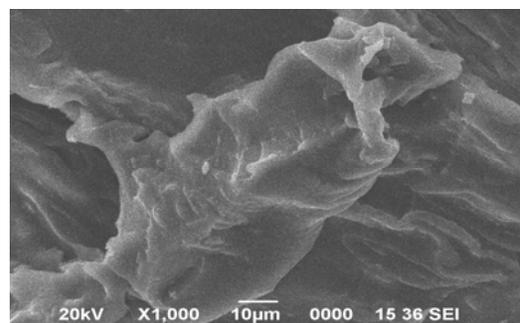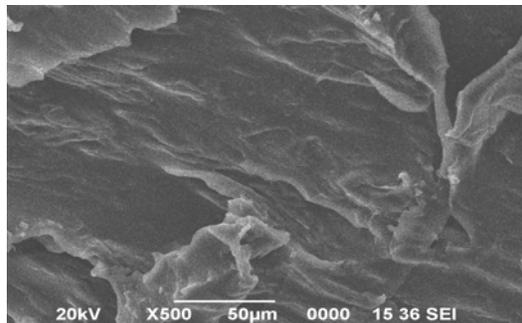
Thermo gravimetric analysis

The thermal behaviors of Starch, GA, pAA, pHEMA and Starch-g-p[HEMA-co-AA]/GA were studied at room temperature 28±2°C by comparing their thermogram curves as shown in figure 3. For GA and Starch, the first weight loss step occurring over the range 40-150°C may be attributed to the loss of residual water. For pure GA, the main decomposition occurs from 270 to 340 °C [18]. In the case of starch, major weight loss occurs over the range 273-383 °C. The thermograms of pAA (Fig 3. c) show three decomposition stages. The first decomposition stage in the range of 50-180 °C is attributed to the loss of bound water. The second one in the interval of 215-300 °C has been described to the dehydration and decarboxylation of the polymer which leads to the formation of inter- and intra-molecular anhydride. The third decomposition stage in the range of 365-470 °C was a result of the degradation of the residual polymer. For pHEMA, decomposition range was found to be in between 337 and 480°C. For graft copolymer, weight loss occurs slowly and gradually with temperature. The high residue content, up to 12.5wt%, at 600 °C observed in thermogram (Fig 3. e) suggested the presence of a rigid structure which indicates the thermal stability of the SAP.

Fig. 3 : TGA of (a) Gum arabic, (b) Starch, (c) pAA ,(d) pHEMA, (e) Starch-g-p[HEMA-co-AA]/GA.
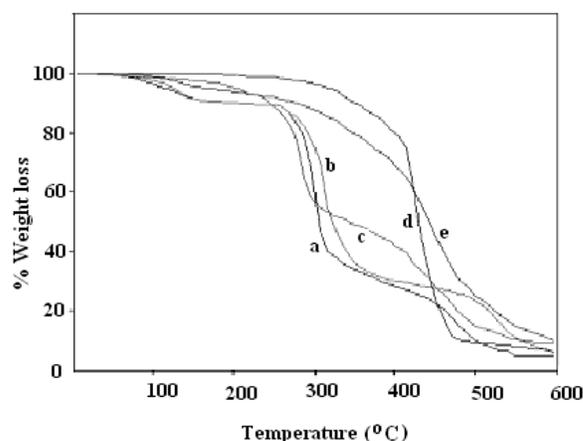
Effect of variables on swelling behavior

When a superabsorbent (SAP) hydrogel is immersed in an aqueous medium, the water molecules diffuse into the hydrogel through the pores and interact with functional ionic groups in the polymer networks. Upon contact with water, the functional ionic groups are converted to fixed-charged groups, which cause electrostatic repulsions among the polymer chains, increases the dimensions of gel networks.

Effect of weight ratio of (Starch/Gum Arabic) on swelling behavior

When the weight fraction of starch was varied over the range of 0.34 to 1.02g in the feed mixture of the blend, the swelling ratio was found to be increased. The result may be attributed to the fact that starch is a hydrophilic biopolymer, and its increasing amount in the blend will obviously increase the hydrophilicity of the blend and thus an increase in the swelling ratio was expected. However, beyond 1.02g of starch, it will produce stronger interactions with other

macromolecular chains, when present in increasing amounts in the blend. This will consequently result in an increased compactness and reduced mesh sizes of the blend. In this way, a smaller number of penetrant water molecules will be allowed to enter and swell the blend, thus, bringing about a fall in the swelling ratio[19].

When the weight fraction of GA was increased in the blend from 0.34 to 0.68g, the swelling ratio was found to be increased. The observed results may be explained by the fact that an increased GA content in the blend renders the network more hydrophilic due to the presence of hydroxyl and carboxyl groups in GA and hence forth, the degree of water sorption increases, which in turn increases the swelling ratio.

Another plausible explanation rest upon the possibility that as the content of GA increases in the blend matrix, there may be an increase in mutual repulsion between carboxylate groups of GA molecules and –COOH group of acrylic acid located at the backbone, which relaxes the network chains of the blend and widens the mesh size of the blend. This ultimately results in enhanced swelling of the blend. However, beyond 0.68g of GA, the amonunt of this biopolymer is so high in the blend that the water molecules have to travel a longer path to cause swelling of the blend, which obviously results in lower swelling.

Effect of initiator on swelling behavior

The effect of initiator concentration on water absorbency was studied. The swelling amount increases as BPO concentration rises from 0.005 mol dm^{-3} to 0.01 mol dm^{-3} (Table 1) and then, it is decreased considerably with a further increase in the amount of initiator.

Subsequent decrease in the water absorbency can be attributed to the increased number of radicals produced which lead to terminating step via bimolecular collision and to the decreasing molecular weight of the grafted hydrogel ,which both, results in shortening the macromolecular chains and reducing the available free volumes within the hydrogel.

Effect of crosslinker on swelling behavior

The relation between crosslinker and water absorbency for the samples are shown in the Table 1 .The water absorbency increases as the MBA concentration increases from 0.005×10^{-3} to 0.01×10^{-3} mol.dm^{-3}, then decreases considerably with higher MBA concentration. The results can be explained by the fact that MBA itself is a bifunctional and hydrophilic monomer, and its incorporation into this particular hydrogel results in an increased hydrophilicity, which, in turn, leads to an enhanced swelling ratio. Further increase in the amount of the crosslinker makes the hydrogel more and more compact, i.e the porous nature of the graft polymer decreases due to increase in crosslinking density and as a result, the water penetration becomes increasingly difficult.

Effect of HEMA and AA on swelling behavior

The absorbancy of the synthesized hydrogel in deionized water was found to be increased upto 0.2 mol.dm^{-3} of HEMA in the gel, afterwords absorbancy was found to be decreased (Table 1). This can be explained on the basis of Flory's ionic swelling theory [20]. According to this theory, the hydroxyl group of HEMA does not dissociate and the amount of dissociated ions inside the

polymeric gel decreases with increasing concentration of HEMA. This occurrence causes the decrease of the osmotic pressure difference between the polymeric gel and the external solution. In addition, the hydroxyl group is a weakly hydrophilic group and may subsequently produce a hydrogen bond between two neighboring chains that ultimately causes the network to shrink.

The effect of AA concentration on the swelling capacity of the hydrogel was studied by varying the AA concentration from 0.10 to 0.6mol.dm^{-3} (Table 1). Maximum swelling was obtained at 0.5 mol.dm^{-3} of AA concentration. This can be explained on the basis that a high concentration of charged ionic groups (COO$^-$) in the hydrogel increases the swelling due to osmosis and charge repulsion. In other words, the presence of more ionic groups in the polymer chains results in increased swelling, because the ionic groups are more strongly solvated than non-ionic groups in aqueous medium. The slight decrease in swelling after the maximum may be attributed to (a) preferential homopolymerization over graft copolymerization, (b) increase in viscosity of the medium which hinders the movement of free radicals and monomer molecules, (c) the enhanced chance of chain transfer to monomer molecules.

**Effect of pH on swelling behavior**

Equilibrium swelling studies indicated that the hydrogels were sensitive to environmental pH. So, the swelling behavior of the superabsorbent hydrogel was studied at various pH values between 1.0 and 13.0, at room temperature (Fig.4a). To clearly observe the net effect of pH, buffer solutions containing lots of ionic species, were not used as swelling media, because the swelling of a SAP is strongly decreased by ionic strength. Therefore a stock of concentrated NaOH and HCl solutions were diluted with distilled water to reach desired basic and acidic pH, respectively. The hydrophilic nature of starch and GA (mainly due to D-glucopyranosuronic acid [21] moieties) along with the ionic groups (COO$^-$) located on the acrylic polymer chain are the major reason for the super absorbency. At higher pH values (4.5–9.2), some of the carboxylate groups are ionized and the electrostatic repulsion between COO$^-$ groups causes an enhancement of the swelling capacity. Again, a charge screening effects of the counterions (cations) limits the swelling at higher basic pH Starch-g-p[HEMA-co-AA]/GA values (pH>9.2). The hydrogels are contracted at lower pH due to absence of electrostatic repulsive forces in the network.

Swelling in chloride salt solutions

The absorbency in 0.9% wt univalent cationic solutions such as LiCl, NaCl, and KCl were determined. The results indicated that the swelling amount was equal for all three solutions (Fig.4, b). This results corresponds to what reported by Buchanan et al.[22] that all univalent cationic species of the same concentration have a similar effect on the water absorbency of the poly (sodium acrylate) gel, that is independent of the radius of the cation or the nature of the anion. Further more it was observed that the swelling amount was very much decreased in case of chloride salt solutions compared to deionized water. This result is primarily due to the decrease in the osmotic pressure (ionic pressure) difference between the polymeric gel and the external solution.

Fig. 4 : (a) Influence of pH values on equilibrium swelling of SAP at 25^{0}c, (b) Swelling of SAP in 0.9% chloride salt solution.
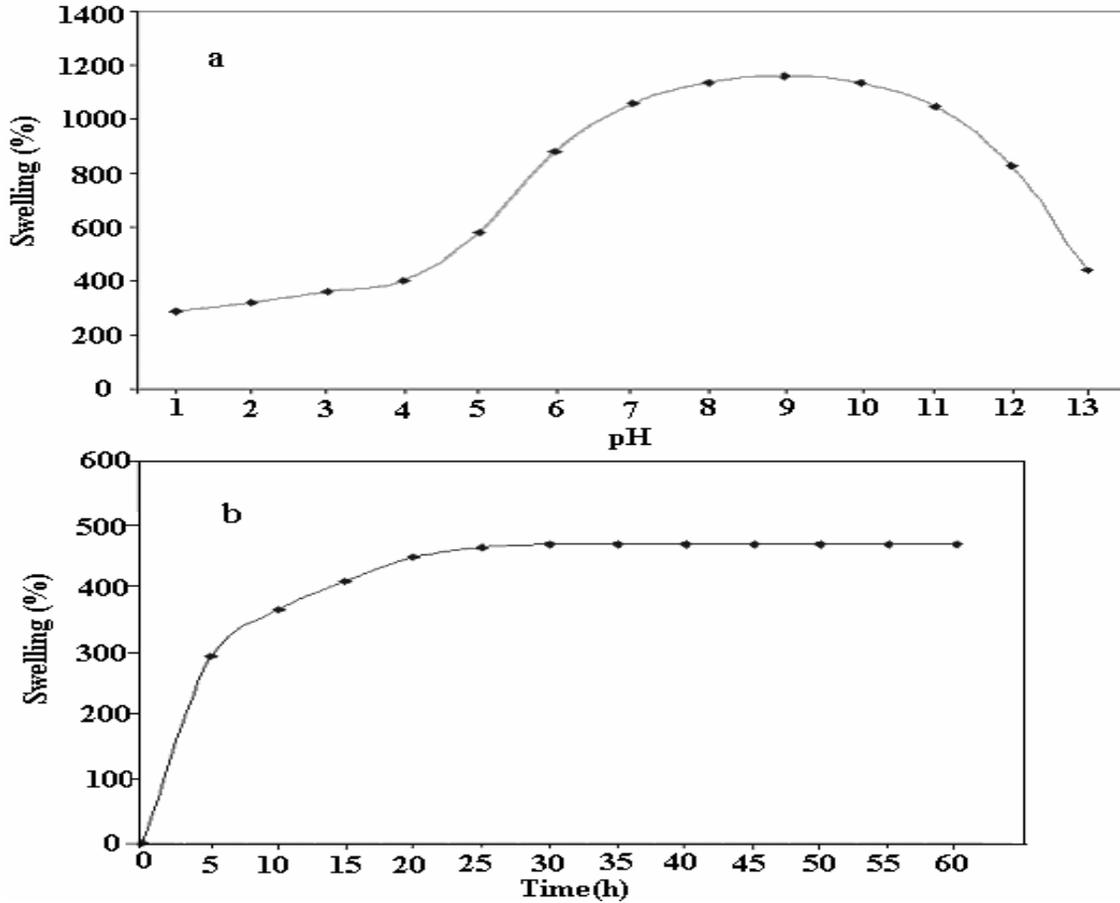

Re-swelling ability

To evaluate the re-swelling ability and the pH sensitivity of the hydrogels, the gel samples were put in pH 7.4 buffer solutions, then transferred to pH 1.0 solution. This operation was done in four cycles .We can see from Fig.5, that swelling ratio values almost remained unchanged in pH 7.4 solution and pH 1.0 solution. It is clear from the figure that the gel took almost 26 h to swell to maximum (i.e., 1105 %) while it required almost 18 h to deswell completely (i.e., 290 %) (Fig.5). The deswollen gel was again allowed to undergo further swelling-deswelling cycles. The initial deswelling rate is very fast i.e., in the first four hour, the equilibrium mass swelling decreases from 1105 % to 520 %. In other words, the equilibrium swelling decreases by nearly 52.94 % in the first four hour when the swollen gel is placed in the medium of pH 1.0. The above experimental findings may be explained as below: When the completely dried hydrogel sample is placed in the swelling medium of pH 7.4, the solvent diffuses into the outer surface of the gel through the micropores, resulting in the plasticization of macromolecular chains. At the same time, the carboxylic groups, attached along the polymer backbone, undergo ionization to yield –COO$^-$groups

(since the pH of the swelling medium is more than the pKa value of acrylic acid inside the gel matrix). This results in the formation of a charged hydrated layer through which the counter ions along with the solvent molecules embed into the interior dry core region and allow the gel to swell. In this way, the dry core slowly disappears and the gel matrix continuous to swell. The swelling is further enhanced due to relaxation (or unfolding) of macromolecular chains owing to the repulsion among similarly charged $-COO^-$ groups which also promotes the swelling process. When the fully hydrated gel is placed in the medium of pH 1.0, H^+ ions present in the external solution, diffuse into the gel matrix through water filled macrospores which have been existing in the fully hydrated gel. These H+ ions protonate the -COO^- groups to yield uncharged -COOH groups which ultimately results in folding of the macromolecular chains as the repulsive forces no longer exist, thus letting the solvent molecules to come out of the polymer matrix. The above results show that the hydrogel has good ability and maintain its sharp response to pH variation. This sharp swelling and deswelling behaviour of the hydrogels make them suitable candidates for controlled drug delivery systems. Such on-off switching behavior as a reversible swelling and deswelling has been reported for other ionic hydrogels.

Fig. 5 : Equilibrium re-swelling behavior of the SAP hydrogel transferred from a solution of pH 1.0 to 7.0 for four cycles at 37ºC.
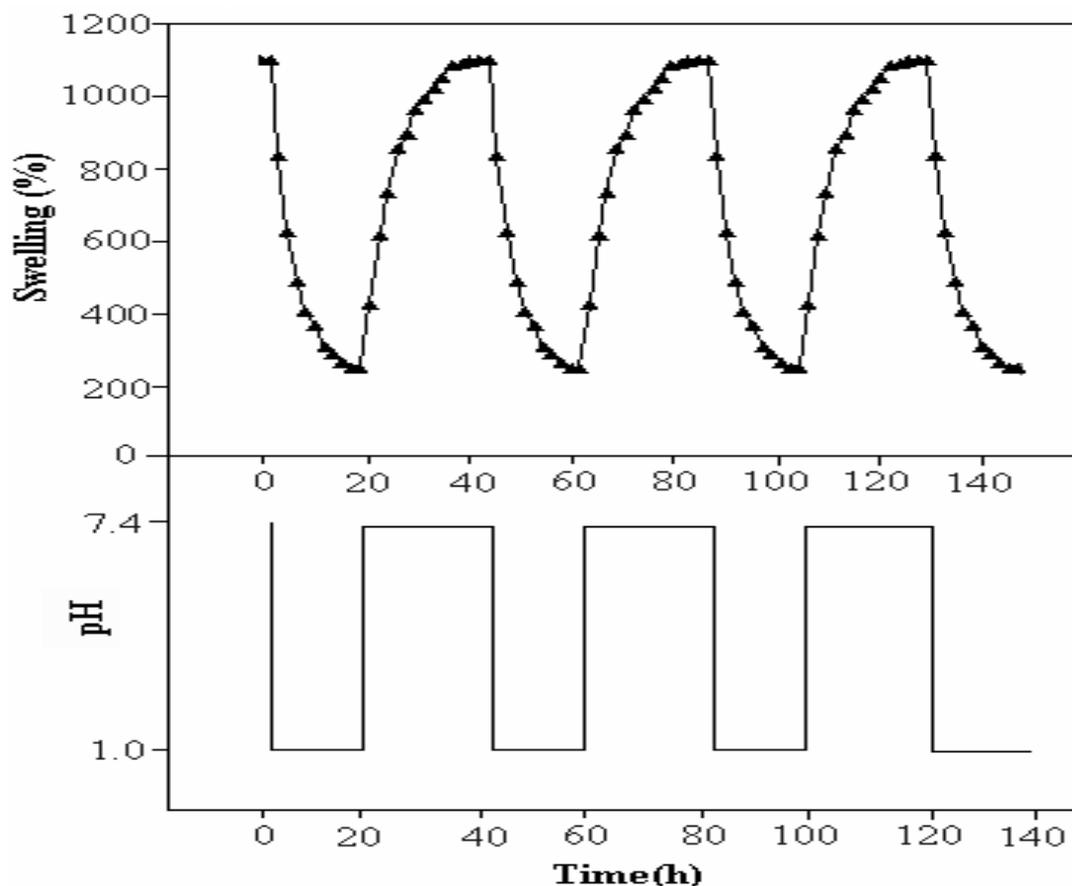
CONCLUSION

In summary, a new series of pH sensitive Starch-g-p[HEMA-co-AA]/GA superabsorbent hydrogels have been synthesized via free-radical polymerization, using benzoyl peroxide as initiator. The structures of the copolymers were confirmed by FTIR. Morphological examination of SAP by SEM indicates the macroporous nature of the copolymer. The high char yield, up to 12.5 wt % at 600ºC observed in thermogram indicates the thermal stability of the SAP. The SAP hydrogel prepared through above method was suitable for controlled drug delivery because of its high water absorption capability, pH sensitivity, good swelling and deswelling ability. The antioxidant nature of gum arabic makes it an ideal candidate for biomedical uses.

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