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Formulation and Development of Hydrogel for Poly Acrylamide-Co-acrylic acid

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ABSTRACT:

Controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research work is going on in obtaining better drug product effectiveness, reliability and safety. In this regard, many polymers are very useful with majority of hydrogels, which undergo reversible volume and/or sol-gel phase transitions in response to physiological or other external stimuli. The first use of gels for medical applications was presented by Wichterle and Lim in 1960 and involved the manufacturing of soft contact lenses. Poly (Acrylamide-co-acrylic acid) hydrogels, poly(AAm-co-AAc), were synthesized by free radical crosslinking copolymerization in solution using N,N'-methylenebisacrylamide (MBAAm) as the crosslinker. The swelling behaviour of the hydrogels thus obtained was analyzed in buffer solutions at various pH. The pH sensitive hydrogel were characterized by Fourier transform infrared analysis, differential scanning calorimetry and evaluated for swelling properties, SEM, and in vitro drug release. The use of hydrogels for drug release was investigated with Rabepazole sodium as the model drug. The release data shows that, as the concentration of acrylic acid was increased, swelling increased resulting in increased release of the drug.

Keywords: Hydrogel; Poly (Acrylamide-co-acrylic acid); N, N'-methylenebisacrylamide; pH sensitive.

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INTRODUCTION:

Hydrogels are three dimensional hydrophilic polymer networks that can swell in water and hold a large amount of water while maintaining the structure¹. A three dimensional network is formed by crosslinking polymer chains. Crosslinking can be provided by covalent bonds, hydrogen bonding, Vander Waals interactions or physical entanglements. They experience reversible volume changes in response to external stimulus such as pH, temperature and ionic concentration; they are therefore called as "SMART" hydrogels². Many physical and chemical stimuli have been applied to induce various responses of the smart hydrogel systems. Physical stimuli include temperature, electric fields, solvent composition, light, pressure, sound and magnetic fields while chemical or biochemical stimuli include pH, ions and specific molecular recognition events.

Because of their unique properties of high water content, elastic properties, good biocompatibility and ability to control and tailor these properties, hydrogels are useful for numerous applications including controlled drug delivery system, contact lens, wound dressing and in making artificial muscles, chemical valves etc. It has been increasingly studied as matrices for tissue engineering. It is designed for use as tissue engineering scaffolds, may contain pores large enough to accommodate living cells, or they may be designed to dissolve or degrade away, releasing growth factors and creating pores into which living cells may penetrate and proliferate.

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The properties of a hydrogel depend strongly on the interaction of water and the polymer. The former prevents the polymer aggregating to form a compact mass while the polymer prevents water flowing out^{3,4}.

Hydrogels have been developed as stimuli-responsive materials, which can undergo abrupt volume change in response to small changes in environmental parameters: temperature, pH, ionic strength, etc. These unique characteristics of hydrogels are of great interest in drug delivery, cell encapsulation and tissue engineering. Stimuli-responsive polymers play an important role in the development of novel smart hydrogels. Stimuli-responsive sensitive polymer gels offer potential economic alternatives to conventional separation processes for industrial application⁵. Controlled permeability variations of responsive gels have also been used to achieve a variety of size- or charge-selective separations. In addition to pH and temperature, other stimuli-responsive hydrogels have been produced that exhibit dramatic changes in their swelling behaviour, network structure, permeability and mechanical strength in response to a number of external stimuli, including the presence of specific solutes and applied electrical or magnetic fields.

pH sensitive polymers are normally produced by adding pendant acidic or basic functional groups to the polymer backbone; these either accept or release protons in response to appropriate pH and ionic strength changes in aqueous media⁶. The network porosity of these hydrogels changes with electrostatic repulsion. Ionic hydrogels containing carboxylic or sulfonic acid groups show either sudden or gradual changes in their dynamic or equilibrium swelling behaviour as a result of changing the external pH. The degree of ionization of these hydrogels depends on the number of pendant acidic groups in the hydrogel, which results in increased electrostatic repulsions between negatively charged carboxyl groups on different chains. This, in turn, results in increased hydrophilicity of the network and greater swelling ratio at high pH. Conversely, hydrogels containing basic pendant groups, such as amines, ionize and show electrostatic repulsion at low pH⁷. Various drugs delivered through pH responsive hydrogels for drug delivery are given in Table 1

Poly (Acrylamide-co-acrylic acid) is a copolymer, which has non-ionic acrylamide and anionic acrylic acid units. The hydrophilic amide and carboxylic acid moieties in its backbone, impart sufficient polarity, charge and hydrogen bonding ability for hydration. Poly (Acrylamide-co-acrylic acid) is a classical copolymer the comonomer reactivity ratio of which is very sensitive to pH. Acrylic acid is anionic in nature

Table 1 Various drugs delivered through pH responsive hydrogels for drug delivery

Therapeutic moieties	Polymers
Insulin	Tri polymer of N-vinyl 2-pyrrolidone methacrylamide and itaconic acid ⁸
Caffeine	Polydimethylaminoethyl methacrylate ⁹
Camptothecin	Polyethylene glycol ¹⁰
Ketoprofen	Copolymer of cationic guar gum and acrylic acid monomer ¹¹

and this prepared pH sensitive hydrogel shows varying swelling behaviour in response to change in pH. It gives low swelling activity in acidic medium and high swelling activity in basic medium¹². Thus when a drug is loaded in the hydrogel, release of the drug will be only in alkaline pH and the drug is sustained in the acidic environment i.e. the stomach.

The present study focuses on the synthesis of poly(Acrylamide-co-acrylic acid) hydrogels having a range of acrylamide contents and subsequent attention to effects of cross linker. To prepare pH sensitive hydrogels Acrylic acid and acrylamide monomers were chosen because Acrylic acid swells in water and is a typical pH sensitive hydrogel that exhibits a typical volume phase transition in response to pH changes at around pH 7.4. On the other hand, acrylamide is a versatile hydrophilic monomer but its homopolymer does not show volume phase transition pH in water. Introduction of acrylamide component improves mechanical strength of hydrogels as in this case poly(Acrylamide-co-acrylic acid) hydrogels should have both good mechanical strength and pH sensitivity.

MATERIALS AND METHOD

Reagents and Chemicals

Poly(Acrylamide-co-acrylic acid) hydrogel was synthesized by cross linking polymerization mechanism. Thus, the synthesis requires the use of a cross linker namely N, N-Methylene bisacrylamide (BIS). The monomers Acrylic acid and acrylamide were cross linked and polymeric chains were synthesized. The copolymerization reaction was initiated with the help of the initiator Ammonium persulphate. Also, the reaction was accelerated using the accelerator such as N, N, N', N'- Tetramethylethylenediamine (TEMED).

The drug sample of proton pump inhibitor Rabeprazole sodium was obtained from Naprod Life Sciences. The monomers cross linker and other reagents were obtained

from SD Fine Chemicals Ltd. The hydrogels synthesized with different monomer ratios as mentioned in Table 2.

Table 2.Hydrogels synthesized with different monomer ratios.

Sr. No	Sample	Acrylic acid :Acrylamide
1	HG1	1:3
2	HG2	1:6
3	HG3	1:9
4	HG4	1:12
5	HG5	1:24

Method of Preparation of Poly (Acrylamide-co-acrylic acid) hydrogel

The monomers (Acrylamide, acrylic acid) and crosslinking agent (methylene bis acrylamide) were dissolved in solvent (distilled water).The solution of initiators in distilled water were added and the polymerisation reaction was conducted in a thermostated water bath at 22^oC with continuous stirring in a 3 necked round bottom flask. The reaction was allowed to take place by maintaining the temperature to 50^oC. The obtained poly (Acrylamide-co-acrylic acid) hydrogel was immersed in distilled water for 15 days and the water was refreshed every day in order to remove any possible unreacted materials. The purified hydrogels were dried in oven at 50^oC for 24hrs. The products were dried till a constant weight was achieved. The dried gels were crushed using mortar and pestle and sieved through 22# sieve to obtain uniform particles of the product.This dried hydrogels were kept in air tight bags before use for further studies.

Drug loading into hydrogel

Drug loading into hydrogels is one of the important parameters for characterization of the hydrogels for its use as an efficient drug delivery tool. The presynthesized dry hydrogels were loaded by swelling to equilibrium in a suitable drug solution. For drug loading into the synthesized hydrogel a simple and convenient swelling loading technique was used. Hydrogels were dried to a constant weight .100mg as well as 200mg of the hydrogel was soaked in the drug solution. Drug being potent 1mg/ 5ml of drug solution was used for drug loading. The weighed hydrogel was soaked into the drug solution. The hydrogels were allowed to swell into the drug solution for about 10 hrs. The drug loaded hydrogels were then filtered on a vacuum pump. The products were then dried in an oven at 50^oC until constant weight was obtained. The drug concentration in the solution was determined by UV spectroscopy at λ_{max} 284nm.71% Drug loading was achieved

with 200 mg of polymer and hence 200mg of the polymer was used for the drug loading procedure.

The entrapment efficiency was determined using the formula The Entrapment efficiency is calculated as,

$$E.E\% = \frac{\text{Total amount of drug- free drug}}{\text{Total drug}} * 100$$

Estimation of Rabeprazole Sodium content of the hydrogels:

Rabeprazole Sodium content in the hydrogels was estimated by an UV spectrophotometric method based on the measurement of absorbance at 284 nm in pH 7.4 phosphate buffer. The method was validated for linearity, accuracy and precision. The method obeyed Beer's Lambert's law. When a standard drug solution was assayed repeatedly (n=6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6% and 0.8% respectively.

CHARACTERIZATION:

Fourier transforms infrared (FT-IR) analysis: The spectral characterisation of the synthesized hydrogel was carried out by Fourier Transformer Infrared spectroscopy. The functional groups present had a profound effect on the water holding capacity of the hydrogel. The adopted procedure was as follows: KBr pellet method was used. Well dried sample of the hydrogel was crushed in an agate mortar with pestle. Crushed sample was then mixed with potassium bromide in the proportion of 1:100 and then compressed to obtain a semi-transparent disc. The spectrum was recorded in the range of 4000cm⁻¹- 400 cm⁻¹

Dynamic swelling studies:

The dynamic swelling experiment was conducted by measuring the humid weight of the hydrogels immersed in aqueous buffer solution with different pH value (pH 1.2, 2.5, 4, 7.4, 8) at R.T. The dried hydrogels about 0.1gm were immersed in buffer solution for 60,120,180,240,300,360,420,480 min respectively. The hydrogel were withdrawn from the buffer solutions and the surplus surface water was removed by filter paper and then the humid weight was measured carefully. The weight gain as a function of time was taken as a swelling measurement. The percent swelling is expressed as the percent weight ratio of water held in hydrogel to dry hydrogel at any instant during swelling.

$$\text{Swelling ratio (SR)} = \frac{W_t - W_0}{W_0} * 100$$

Equilibrium degrees of swelling values are the maximum swelling values of the samples

$$EDS = \frac{W_t - W_o}{W_o}$$

Where W_o , being the initial dry weight and W_t the weight of swollen hydrogel at time t , respectively

In vitro drug release studies from hydrogels:

The drug release properties of the gel were evaluated under the normal physiological pH conditions of the gastrointestinal tract as the method used should simulate the environment to which the hydrogels will be exposed in the gastrointestinal tract. Thus sequential drug release method was used by continuously changing the pH of the dissolution media.

Drug loaded hydrogel with known amount of drug was placed in the muslin cloth. The cloth was tied with the help of a thread. The dissolution studies were carried out in USP dissolution apparatus. The muslin cloth filled with drug loaded hydrogel was tied to the paddle. The hydrogel was stirred in acidic buffer pH 1.2 placed in dissolution flask for 2 hrs with temperature maintained at 37°C at 100rpm and aliquots were drawn at an interval of 30 min. The dissolution studies were carried in phosphate buffer pH 7.4 with temperature maintained at 37°C and 100rpm. 5ml of aliquots were withdrawn at an interval of 60 minutes and replaced by a 5ml of the phosphate buffer pH 7.4. The drug released in each 5ml aliquots were analyzed by UV spectroscopy at wavelength of maximum absorption 284nm. The drug release studies in phosphate buffer pH 7.4 were carried out for 8 hours.

Differential scanning calorimetry (DSC)

The DSC studies were carried out to confirm synthesis of the product as well as the drug loading into the synthesized hydrogel. The DSC thermograms for the monomers acrylamide and acrylic acid for the drug synthesized hydrogel and drug loaded hydrogel was recorded using differential scanning calorimeter (Universal TA Model Q 200).

About 10mg of sample was placed in 50µL perforated aluminium pans and sealed. The sample was purged with pure dry nitrogen at a flow rate of 50 ml/min. DSC scan was carried from 0-300 °C at a heating rate of 10°C/min

Morphological characterization

Scanning Electron Microscopy (SEM) was employed to investigate morphology of the synthesized hydrogel. The hydrogels were immersed in pH 1.2 (acidic) and pH 7.4 (basic) respectively and then the hydrogels were sputtered with carbon before observation. In this study, morphology of prepared particles was examined on JEOL SEM (JSM-7600F, Japan

RESULTS AND DISCUSSION

1. Fourier transforms infrared (FT-IR) analysis

The structures of the compounds were characterized by recording their infrared (IR) spectra. The FTIR spectra of the sample given in Figure 1 the spectra show characteristic peaks for acrylic acid-acrylamide copolymer. Table 3 gives the Characteristic frequencies in the IR spectra of the synthesized hydrogel. FT-IR Analysis confirms the co- polymerization of acrylamide and acrylic acid.

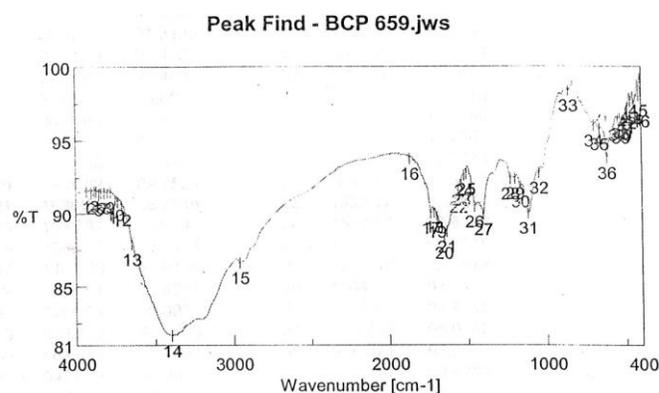


Figure 1: FT-IR Spectra of synthesized hydrogel

Table 3. Characteristic frequencies in the IR spectra of the synthesized hydrogel

Wave frequencies (cm-1)	Inference
3648,3396	O-H (s), N-H (s)
2961	C-H (s)
1636	C=O (s)
1400	C-N
1260	C-O

2. Dynamic swelling studies

Environment pH value is a key factor to determine the swelling in the poly (Acrylamide-co-acrylic acid) hydrogels. To evaluate the pH sensitivity of hydrogels, dynamic swelling behaviour of the hydrogels were studied. Swelling profiles and Equilibrium degree of swelling (EDS) of the samples are given in Figure 2. At the initial stage of hydrating, a gradual increase in swelling ratios from pH 1.2 to pH 8 at a determined interval of time is illustrated from figures 2. The main reason for this was the free carboxylic acid groups of hydrogel which loses the proton and tends to dissociate at a pH 4.0 results in swelling. In low pH value, most carboxylic acid groups were in the form of COOH and large amounts of hydrogen bonds

formed by acrylamide and acrylic acid chain. As shown in the figure, the hydrogen bond breaks as the environmental pH value rises to 7.4 and carboxylic acid groups began to ionize. Meanwhile, the osmotic pressure inside the hydrogels increases and electrostatic repulsion causes the network to expand.

So, higher EDS values are obtained for the copolymeric hydrogel samples at higher pH values. These data showed that the synthesized hydrogels have high sensitivity to pH.

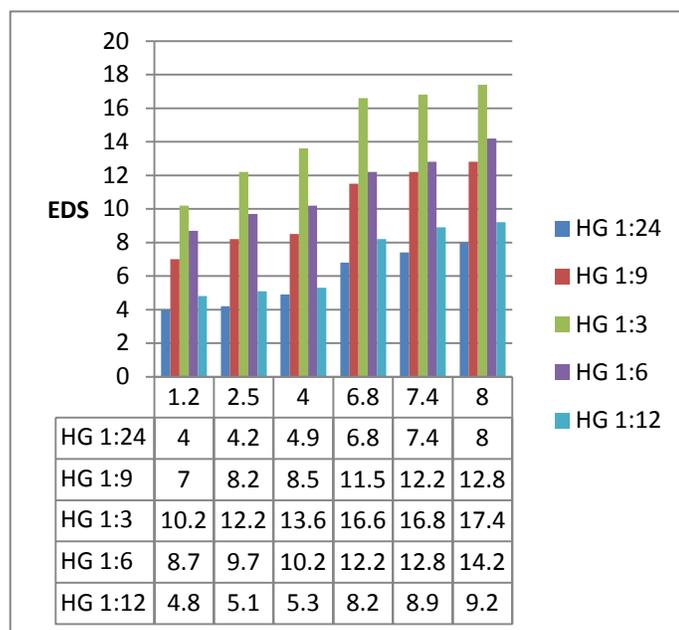


Figure 2: Graph of Equilibrium degree of swelling (EDS) Vs. pH of hydrogels with different monomer ratio.

It was observed from the graph in Figure 2 that EDS of HG 1:3 is more than other samples and that of HG1:24 is less. This was because the concentration of Acrylic acid goes on decreasing and Acrylamide concentration goes on increasing starting from 1:3 ratios to 1:24. This was mainly attributed to the carboxyl group of Acrylic acid in the hydrogel. As Acrylic acid content increases, an electrostatic repulsive force operating between the charged carboxyl groups of acrylic acid increases the hydration of the hydrogels, causing swelling and on increasing the Acrylamide content, the charges on the polymeric chains decrease, which leads to decrease in swelling capacity.

3. Drug Release studies

Drug release from rabeprazole sodium loaded hydrogel was carried out using paddle type dissolution apparatus in acid phosphate pH 1.2 and phosphate buffer pH 7.4. The rabeprazole hydrogels were checked for drug release kinetics by plotting the % drug release as a function of time and shown in Figure 3.

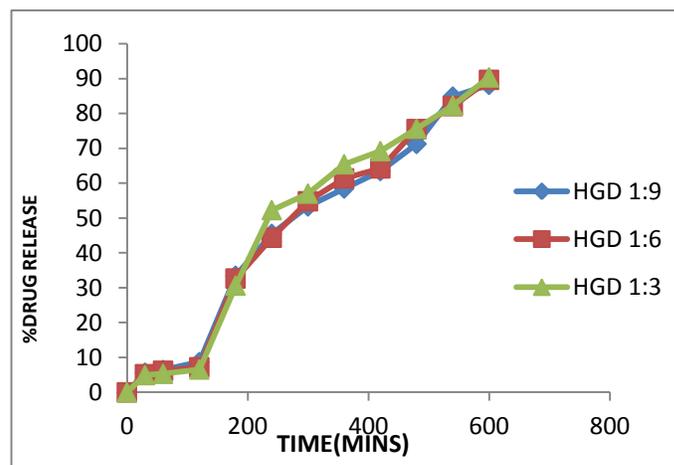


Figure 3: Graph of % Drug (Rabeprazole Sodium) release Vs. Time

The drug release study shows that the drug release from all three hydrogels is comparable. The amount of drug release in the acidic pH is less than 20% for all the three hydrogels. Around 80% of the drug is available for release into the intestine. Around 90% of the total drug release was obtained at the end of the tenth hour. The drug release occurs slowly for a period of 8 hours in the alkaline pH.

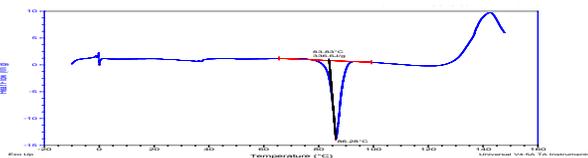
Swelling of the polymer in response to the external pH plays a major role in the drug release kinetics. Swelling of the hydrogel polymer was more in the alkaline pH due to the ionization of the ionizable groups and action of electrorepulsive forces. In alkaline medium hydration of the hydrogels increased due to the electrostatic repulsive forces between the charged groups of the acrylic acid and leads to swelling and in acidic environment, electrostatic forces vanish between uncharged carboxyl group and causes the decrease in the hydration thus low swelling and in turn restrict the release of the Rabeprazole sodium in the medium.

4. Differential scanning calorimetry (DSC)

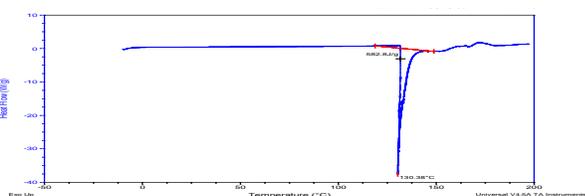
DSC study was done to check drug-excipients interaction. Any abrupt or drastic change with thermal behavior of either the drug or excipients may indicate a possible interaction. The characterized well recognizable thermal profile of the drug showed a sharp endothermic peak at 216.83°C. Also, the DSC thermograms of monomer Acrylic acid, Acrylamide and hydrogel show sharp endothermic peak corresponding to their melting point at different temperature indicating that the hydrogel has been formed. The DSC thermograms show that the endothermic peak found in the monomer AAm at 86.28°C was not found in the synthesized hydrogel. Similarly the endothermic peak found in the DSC thermogram of Acrylic acid at 130.38°C did not appear in the DSC thermogram of the

synthesized hydrogel. This indicates that a new product was being synthesized. Figure 4 gives the DSC thermograms of Acrylamide, Acrylic acid, Rabeprazole sodium, Plain hydrogel and Drug loaded hydrogel.

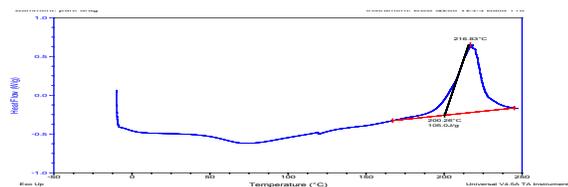
The peak obtained in the DSC thermogram of drug rabeprazole sodium at 216.83°C had diminished in the DSC thermogram of the drug loaded hydrogel indicating that the drug had been successfully loaded in the hydrogel.



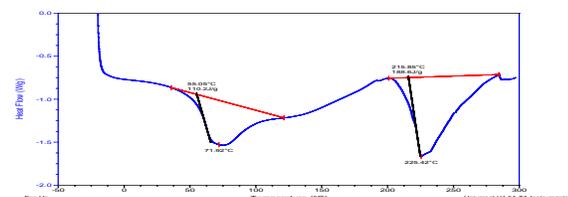
a) Melting temperature: 86.28°C



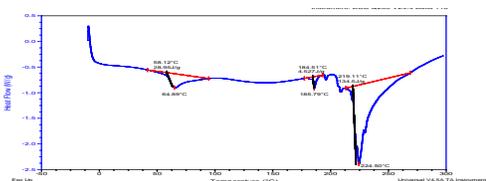
b) Melting temperature: 130.38°C



c) Melting temperature: 216.83°C



d) Melting temperature: 71.92 °C, 225.42°C



e) Melting temperature: 64.89°C, 185.79°C, 224.5°C

Figure 4. DSC thermograms of a) Acrylamide; b) Acrylic acid; c) Rabeprazole sodium; d) Plain hydrogel; e) Drug loaded hydrogel with their melting temperature.

5. Scanning Electron Microscopy

The synthesized product was characterised for its surface morphology and pH sensitivity by SEM analysis. SEM analysis monitored the pore sizes. The appearance of the pores in the hydrogels when the hydrogels were allowed to swell at two different pH values, pH 1.2 and pH 7.4. The SEM microphotographs of the hydrogels in pH 1.2 and pH 7.4 are presented in Figure 5A and 5B

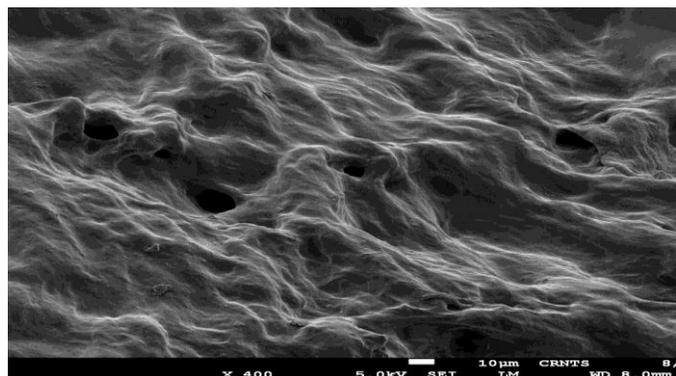


Fig 5A: SEM observation of poly (acrylamide-co-acrylic acid) hydrogel in pH 1.2

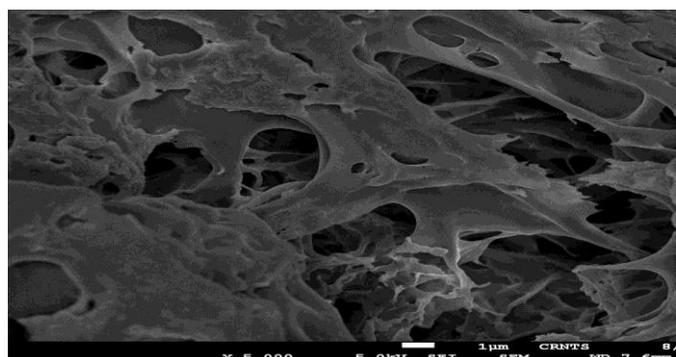


Fig 5B: SEM observation of poly (acrylamide-co-acrylic acid) hydrogel in pH 7.4

The SEM microphotographs show the presence of pores in the synthesized hydrogel. The size of pores in hydrogel in pH 1.2 is less than that in pH 7.4. This shows that the pore size is affected by the pH to which the hydrogel is exposed.

In all, these figures implied the pH-sensitive characterization of the prepared hydrogel and indicated that the hydrogels have a good pH-responsibility.

CONCLUSION:

A polymeric hydrogel was successfully synthesized by free radical crosslinking polymerisation method using ammonium persulphate as initiator and BIS as cross linking agent in different monomer ratio (AA: AM)-1:3,1:6,1:9,1:12,1:24. By

modifying their physical and chemical properties to optimize their properties, such as permeability, enviro-responsive nature, biodegradability and surface bio recognition sites, they can be widely applied as intelligent carriers in controlled drug-delivery applications. The design and synthesis of smart hydrophilic polymers and hydrogels has significant potential in future biomedical and nanotechnology applications. A hydrogel has been synthesized satisfactorily with highly pH sensitivity for oral drug delivery using Rabepazole sodium as a model drug and can be used for site-specific controlled drug delivery.

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