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Synthesis and characterization of novel pH-, ionic strength and temperature- sensitive hydrogel for insulin delivery

Nadia Rasool [a,b,c], Tariq Yasin [b,*], Jerry Y.Y. Heng [c], Zareen Akhter [a]

[a] Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan
[b] Department of Chemical and Materials Engineering, Pakistan Institute of Engineering and Applied Sciences, Nilore, Islamabad, Pakistan
[c] Surfaces and Particle Engineering Laboratory, Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom

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ABSTRACT

A series of novel silane crosslinked hydrogel was prepared from kappa carrageenan (KC), acrylic acid (AA) using vinyltriethoxysilane (VTESi). Potassium persulphate initiated the grafting and copolymerization reactions between reactants. In addition, the condensation of the hydroxyl groups of KC and VTESi resulted into crosslinking. Novelty of this work is the use of VTESi as crosslinker for such a composition of hydrogel. The structure of prepared hydrogels was characterized by Fourier transform infrared spectroscopy. The analysis of spectra confirmed the presence of feed components in the prepared hydrogels. Thermogravimetric analysis showed an increase in the stability of the hydrogels either having high AA contents or crosslinker amount. The effect of feed components, pH (buffer, non-buffer), electrolytic media and temperature on the swelling behaviour of the hydrogels is reported here.

Most promising results with high swelling ratio were observed in hydrogel having low monomeric ratio (KC:AA = 1:7). pH response of this hydrogel in acidic and neutral pH makes it suitable for drug delivery application. Insulin, a protein based drug was selected as a model drug. It requires its delivery in small intestine for proper action; therefore its release behaviour was studied in-vitro in simulated stomach and intestinal fluids. The release profile of insulin showed negligible release in simulated gastric fluid (SGF) and sustained release in simulated intestinal fluid (SIF). The obtained results are in good agreement with the swelling response of this hydrogel. The weak structure of this hydrogel makes it preferable for drug delivery, as it is able to get crumbled after releasing the drug for 6 h at neutral pH.

1. Introduction

Biomaterials based on natural polymers have gained considerable interest for practical application due to its biocompatibility and biodegradability. Natural polymers such as cellulose, starch, chitosan, carrageenan, and alginates can be modified by chemical means to impart certain physical and/or functional properties. Recently, natural polymer based hydrogels have been investigated by many researchers for different applications. The hydogels based on natural polymers, especially polysaccharides have many inherent advantages such as non-toxicity, biocompatibility and biodegradability [1–3].

Hydrogels are three-dimensional, crosslinked hydrophilic polymer networks, and are capable of holding a large amount of water due to physical and/or chemical interactions [4,5]. The water contents of hydrogel ranging from 30 wt% to 90 wt%, depends upon the nature of polymer used during synthesis. Due to their high swollen nature and permeability to hydrophilic agents, hydrogels have also been proposed as controlled drug delivery system. Those with good biocompatibility can be used to deliver a number of therapeutics such as enzymes, antibacterial, antibodies, vaccines, contraceptives and hormones [6]. They can be applied as inserts or implants or can be administered orally, subcutaneously or intramuscularly. They maintain a sustained level of drug in blood stream and also protect drugs against enzymatic degradation and have good patient compliance. On the contrary, parenteral drugs have low patient compliance because they require frequent administration and show varying drug levels in blood stream [6,7].

Hydrogels for oral drug delivery are made pH sensitive to respond against the pH change in the gastrointestinal tract. Hydrogel can provide non-invasive delivery system to some intravenous drugs such as insulin [5]. The oral drug delivery of insulin by various means is a challenge because it is a protein in nature and can be digested in the stomach and the gut. Generally, diabetic patients prefer oral intake in the form of pill having mostly hypoglycemic agents to avoid injection of insulin. In this regard, carrageenan based hydrogel is developed for insulin delivery.

* Corresponding author. Tel.: +92 51 2207381 2 (Work); fax: +92 51 2208070.
E-mail address: yasintariq@yahoo.com (T. Yasin).

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Carrageenan is a linear polyanion biopolymer, composed of D-galactose and 3,6 anhydrogalactose units having half-ester-sulphate moieties. The chemical structure of kappa carrageenan is shown in Fig. 1. Different types of carrageenan are available but only kappa and iota types are capable of forming hydrogels [8]. This polymer has good mucoadhesive and biocompatible properties and is commercially used in pharmaceutical formulations and food products [9,10].

Acrylic acid is also widely used in pharmaceutics as a gel forming agent for drug delivery and also for tumor treatment [11]. It has good mucoadhesive property, which is the main requirement for oral delivery of protein based drugs [12,13]. A variety of chemical crosslinker were used to crosslink polysaccharide and acrylic acid [14]. But for drug delivery applications, the toxicity of the chemical crosslinker should be low. Our group has successfully used vinyltriethoxysilane as crosslinker for carboxymethyl chitosan and acrylic acid [3].

In the present work, hydrogel with different ratios of kappa carrageenan and acrylic acid were prepared and characterized. Furthermore, the influence of its chemical composition on swelling behaviour in different media had also been carried out. The incorporation of KC made these hydrogels partially biodegradable. The most suitable hydrogel was loaded with insulin. The in-vitro release study of insulin will give a better understanding of prepared hydrogels towards its biomedical applications.

2. Experimental section

2.1. Materials

Kappa carrageenan (KC) was purchased from Quest International, Philippines. Acrylic acid (AA), potassium persulphate (KPS), vinyltriethoxysilane (VTESi), buffers and insulin were purchased from Sigma–Aldrich, Germany and used as received. Acrylic acid was used after vacuum distillation. All other chemicals were of analytical grade.

2.2. Preparation of hydrogel

Carrageenan (250 mg) was dissolved in water (25 mL), in a beaker fitted with magnetic stirrer. The solution was transferred into a glass reactor and 75% neutralized acrylic acid were added into this solution, followed by the slow addition of VTESi. Afterwards, KPS was added to this mixture and allowed to stir for 4 h at 60 °C. The resultant solution was transferred into plastic dishes and air dried at room temperature. After drying, the films were washed with deionized distilled water (DDW), dried under vacuum at 50 °C and stored in desiccators. The compositions of different hydrogel synthesized are specified in Table 1.

2.3. Infrared analysis

Infrared spectra were recorded using ATR technique on Fourier transform infrared spectroscopy (FT-IR, Nicolet 6700,) from Thermo Electron Corporation, USA. The samples were dried under vacuum before measurements. Spectra were scanned from 4000 to 500 cm^{-1} with a resolution of 4 cm^{-1} and were averaged over 120 scans. The crystal type used in ATR was diamond.

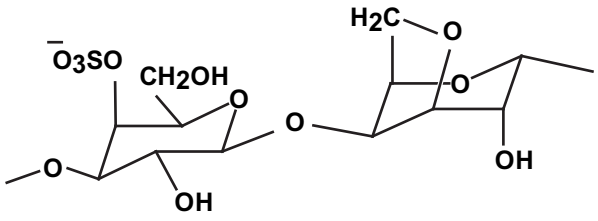

Fig. 1. Chemical structure of kappa carrageenan.

Table 1
Composition of the prepared hydrogels.

Sample code	Mass ratio (KC:AA)	KPS (g)	Crosslinker (%)
KC1	1:07	0.3	1.00
KC2	1:15	0.3	1.00
KC3	1:30	0.3	1.00
KC4	1:15	0.3	1.50
KC5	1:15	0.3	2.00

2.4. Thermogravimetric analysis

A Mettler Toledo thermogravimetric analyzer (Model-TGA/SDTA851^e), Switzerland, was used to measure the weight loss of hydrogels. Thermogravimetric analysis was performed with samples (~10 mg) in an alumina pan under nitrogen atmosphere with a gas flow rate of 40 mL/min. Experiments were carried out with heating rate of 20 °C/min, from 50 °C up to maximum of 500 °C.

2.5. Gel content

Known amount of samples were extracted by boiling in DDW for 8 h. After extraction, the samples were vacuum dried at 60 °C to constant weight. Gel fraction was measured gravimetrically by weighing the insoluble part of hydrogels obtained after the extraction. Gel fraction was calculated using following equation:

$$\text{Gel fraction}(\%) = W_g/W_o \times 100 \quad (1)$$

here W_g is the weight of dry hydrogel after extraction and W_o is the initial dry weight of the hydrogel.

2.6. Swelling measurements

In all swelling experiments, the following procedure was used for measurements. Dried hydrogels (~50.0 mg) were immersed in vials filled with solutions (100 mL) and the vials were set in a temperature controlled bath at desired temperature. After a certain time (t), they are weighed by removing the excess surface solution and again placed in the same solution. The swelling ratio of the hydrogel was determined gravimetrically by the following equation:

$$\text{Swelling ratio}(g/g) = (W_s - W_d)/W_d \quad (2)$$

here W_d is the dry weight and W_s is the swollen weight at time, t.

2.7. Swelling in buffer, non-buffer, salt solutions and at varied temperature

pH response of the hydrogel was studied in buffer and non-buffer solutions. Buffer solutions of pH 1.0–13.0 were purchased from Sigma–Aldrich. Non-buffer solutions of pH 1.0–13.0 were prepared from the dilution of stock solutions of HCl (pH 1.0) and NaOH (pH 13.0) using DDW. The pH values were confirmed by a pH-meter.

The dried samples were immersed in 100 mL of the media. Swelling of the hydrogel samples in sodium chloride and calcium chloride solutions (in the range of 0.05 M–1.0 M) was also evaluated. The effect of temperature on hydrogel swelling was done in

temperature controlled bath (±0.1 °C) at 20 °C, 35 °C and 45 °C. The swelling data obtained after 8 h are presented in all these cases.

2.8. Preparation of insulin solution

Solvent used in this study was 19.8 mL of 50% (v/v) ethanol and water, acidified with 0.1 mL of HCl (0.1 N) and neutralized with 0.1 mL of NH_4OH (0.1 N). The insulin solution was prepared by keeping the amount of insulin up to 0.5 mg/mL of solvent.

Simulated gastric fluid (SGF, pH = 1.2) was prepared by adding 3.5 mL of 37% HCl and 1.0 g of NaCl in 500 mL of water. Whereas, simulated intestinal fluid (SIF, pH = 6.8) was prepared by combining 250 mL of 0.2 M potassium dihydrogen phosphate and 118 mL of 0.2 N NaOH [4].

2.9. Insulin loading and release studies

The dried hydrogel (20 mg) was equilibrated in insulin solution of 10 mg/20 mL of solvent system for one day. Then the hydrogel was removed from insulin solution and washed with 100 mL of the 0.1 N HCl solution to remove excess insulin from surface of the hydrogel and dried under vacuum. The insulin release experiments were carried out by transferring drug loaded hydrogels in a vessel containing 30 mL of SGF at 37 °C and after 2 h the hydrogel was transferred to SIF where it was kept for more 6 h. At various times, aliquots of 3 mL were drawn from vessel to follow insulin release and then deposited back into the vessel so that the liquid volume was kept constant.

Insulin release was determined spectrophotometrically using a Perkin Elmer Lambda 40 UV–vis spectrophotometer at 276.0 nm and corresponding solution media (SGF and SIF) were used as reference. Calibration line was drawn using insulin solutions ranging from 0.0 to 5.0 mg/20 mL of solvent. The amount of insulin from the hydrogels was calculated using calibration line.

3. Results and discussion

3.1. Synthesis of KC/AA hydrogel

A novel approach has been designed to synthesize KC/AA hydrogel. The chemical active functional group (OH) present in KC can be used to prepare graft copolymer [15]. The copolymerization of carrageenan with acrylic acid and crosslinking with VTESi resulted into a network structure having hydrogel properties. Major factors that influence the degree of swelling of ionic polymers include the properties of the polymer as well as of the swelling medium [7,16]. Swelling behaviour of prepared hydrogels in different media and at different temperature has been studied. The gel content, structural and thermogravimetric analysis of the synthesized hydrogels have also been performed.

3.2. Structural analysis

Structural analysis of samples has been carried out using FTIR spectroscopy. The FTIR spectra of KC and KC2 are shown in Fig. 2. The spectra of the hydrogel films obtained at other compositions are qualitatively similar to that of KC2 and are not shown for the sake of clarity. Some characteristic peaks such as sulphate ester, 3,6 anhydro-D-galactose, D-galactose-4-sulphate and glycosidal linkage are given in Table 2. By comparing the spectrum of KC2 with KC, some new absorption bands are observed in addition to characteristic KC absorption bands. From spectrum of KC/AA hydrogel, it is clearly indicated that it contains functional groups of both, carrageenan and acrylic acid.

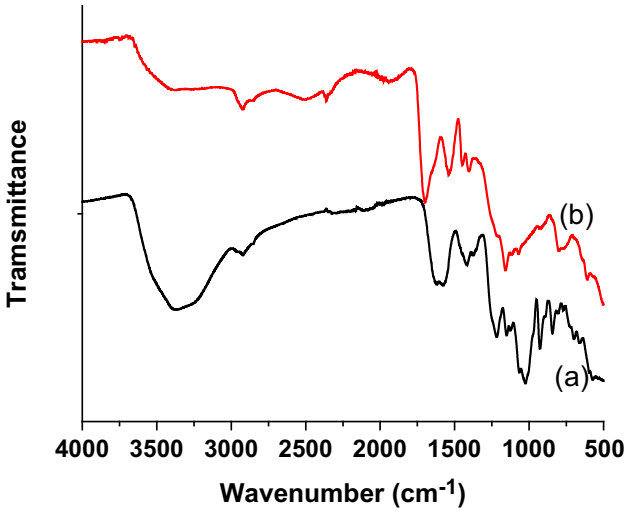

Fig. 2. FTIR spectra of kappa carrageenan (a) and KC2 hydrogel (b).

The new bands in KC2 at 1694 cm^{-1}, 1538 cm^{-1} and 1402 cm^{-1} are due to carbonyl stretching, asymmetrical and symmetrical deformation mode of COO^- confirming the presence of AA in KC2. Peaks for siloxane linkage (1100–1020 cm^{-1}) are overlapped with glycosidal linkage of carrageenan.

3.3. Thermogravimetric analysis

The thermogram of KC, KC1, KC2 and KC5 are shown in Fig. 3 and the thermal decomposition data at various percentage weight losses is given in Table 3. Fig. 3 suggests that KC/AA hydrogel was more thermally stable than carrageenan. All KC/AA hydrogel thermograms have three decomposition stages showing similar degradation behaviour between 280 °C and 500 °C. The first decomposition stage in the range of 50 °C–200 °C is attributed to the loss of bound water. The second stage (in the range of 200 °C–350 °C) is a result of dehydration, decarboxylation and desulphonization of the hydrogel. The third decomposition stage from 350 °C to 500 °C has been described to the degradation of the residual polymer. The addition of acrylic acid in KC/AA hydrogel increases the stability of the hydrogel. It can be seen from Fig. 3 that KC1 show 10% weight loss at 238 °C which is 108 °C higher than the carrageenan powder.

Increase in the crosslinker (VETSi) concentration showed increase in thermal stability upto 250 °C due to condensation reactions between the OH group of carrageenan and silanol which results into a crosslinked product. This behaviour can also be seen in Fig. 3, by comparing KC2 (1% crosslinker) with KC5 (2% crosslinker) which shows less weight loss up to 250 °C due to dehydration. Similar behaviour is reported previously for cm-chitosan/acrylic acid hydrogel [3].

Table 2
Characteristic IR peaks present in the samples.

Functional groups	Absorption (cm^{-1})[a]	Absorption (cm^{-1})[b]
Carboxylic acid	1675–1725	1694
Sulphate ester	1210–1260	1215
Glycosidic linkage	1010–1080	1023, 1064
3,6 anhydro-D-galactose	928–933	924
D-galactose-4-sulphate	840–850	842

[a] Literature values.
[b] Observed values.

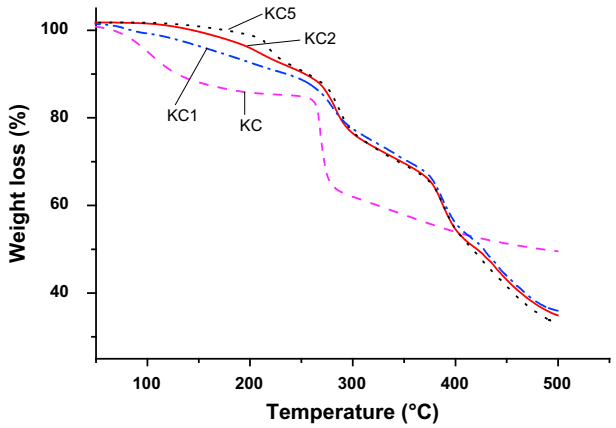

Fig. 3. Thermogram of carrageenan and crosslinked KC/AA hydrogels (– – –KC, —●—●—KC1, ——KC2, ▪ ▪ ▪ ▪KC5).

3.4. Gel content

Gel content is a parameter which describes the hydrogel strength. Table 4 shows the gel content percentage with varying crosslinker amount in KC/AA hydrogel. Table 4 shows that gel content increases from 15% to 24% as the amount of crosslinker is increased from 1% to 2%. The increased stability of the hydrogel resulted by increasing crosslinking is also confirmed by TGA as discussed earlier.

3.5. Effect of crosslinker concentration on swelling ratio

The swelling behaviour of hydrogel samples, obtained by different percent crosslinking (KC2, KC4 and KC5) in water was studied and the results are shown in Fig. 4. All the reported results are the average of three readings with a relative standard deviation of ±4.5%. An increase in crosslinker amount from 1% (KC2) to 2% (KC5) results in a decrease in swelling ratio of obtained hydrogels, whilst keeping all other variables constant. As the crosslinker concentration is increased, it increases the ability of polymer chain to get crosslinked. Highly crosslinked structure results a marked decrease in the swelling ratio of the hydrogel due to decrease in size of pores in the hydrogel network. Similar behaviour was observed in hydrogel obtained from poly(acrylic acid-co-acrylamide) grafted chitosan [17].

3.6. Effect of monomer ratio on swelling ratio

The influence of the feed ratio of KC:AA on the swelling ratio of KC/AA hydrogel is shown in Fig. 5. Increasing acrylic acid ratio in KC/AA hydrogel from 7 (KC1) to 30 (KC3), results in a decrease in the swelling ratio. The hydrogel structure obtained as a result of this reaction is so complex that it lowers the swelling ratio as well as the swelling rate. Acrylic acid is more prone to crosslinking in

Table 3
Thermal decomposition data of hydrogel samples at various percentage weight loss.

Samples	$T_{5\%}$[a](°C)	$T_{10\%}$ (°C)	$T_{25\%}$ (°C)	$T_{50\%}$ (°C)
KC	101	130	268	488
KC1	162	238	320	428
KC2	210	252	310	420
KC5	220	260	310	418

[a] Temperature at given percent weight loss.

Table 4
Gel content data of hydrogel samples.

Samples	KC:AA	Crosslinker (%)	Gel content (%)
KC2	1:15	1.0	15.4
KC4	1:15	1.5	17.2
KC5	1:15	2.0	24.1

aqueous medium and causes a decrease in swelling. Such behaviour has been reported earlier [9].

Diffusion behaviour of hydrogels was also analysed by using following equation:

$$F = kt^n$$

here F is fractional uptake at time t and k is characteristic constant of hydrogel and n is characteristic exponent of the mode of transport of the penetrating molecule [9]. The n and k values obtained from Fig. 5 are given in Table 5.

The value of n is responsible to show rate determining step of swelling mechanism.

Three steps are considered to direct hydrogel swelling in water. First is the penetration of water into the hydrogel structure. Second is the loosening up of hydrated polymer chains and third is expansion of hydrogel structure into the surrounding water. The hydrophilic polymer's response towards water is depicted in three models. Depending on the value of n, it is known as Fickian (Case I where $n = 0.5$ or Case II where $n = 1.0$) and non−Fickian or anomalous diffusion ($0.5 < n < 1.0$). In Fickian diffusion the rate of diffusion is lower than the rate chain relaxation within a hydrophilic polymer structure and vice versa for Case II transport. In non−Fickian diffusion Case I and Case II have comparable rates of diffusion [18]. It is seen that the transport model shift from non−Fickian to Fickian as the acrylic acid amount is increased in KC/AA hydrogel as shown in Fig. 5.

3.7. Effect of buffer media on swelling ratio

The effect of media conditions on hydrogel swelling is very important and is reported here. This includes the effect of pH, electrolytic media and temperature. Ions in the swelling media do have a certain impact on the swelling ratio of the hydrogels depending on the type of ions and charge and also on the nature of hydrogel composition. The swelling behaviour of these hydrogels is extremely pH dependent and therefore known as a pH sensitive hydrogel. The presence of sulphate and hydroxyl groups of carrageenan and carboxylic group of acrylic acid makes these hydrogels pH sensitive.

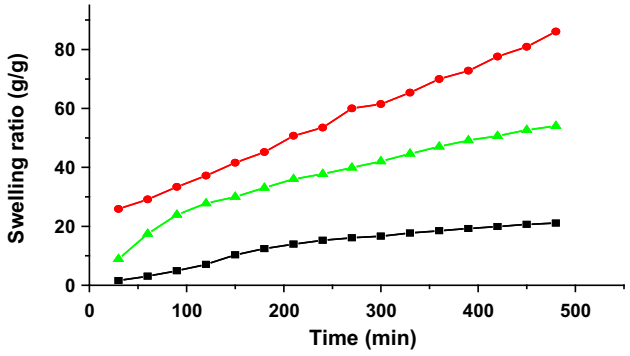

Fig. 4. Swelling ratio in water with varying percent crosslinker (– ● –KC2, – ▲ –KC4, – ■ –KC5).

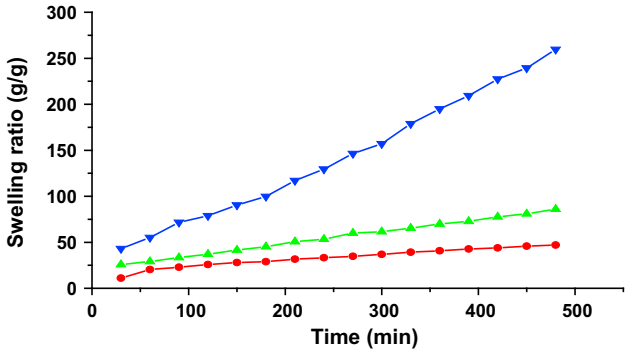

Fig. 5. Swelling ratio of hydrogel at various monomer feed ratio (-▼-KC1, -▲-KC2, -●-KC3).

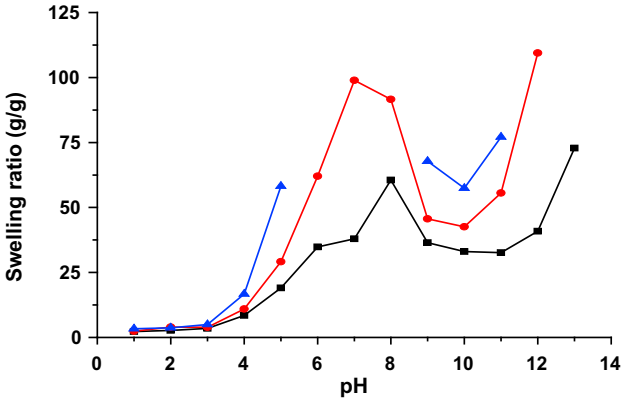

Fig. 6. Swelling ratio of hydrogels in buffer media (pH = 1.0–13.0), (-▲-KC1, -●-KC2, -■-KC3).

Swelling trends of KC1, KC2 and KC3 having varying acrylic acid concentration, is shown in Fig. 6 against pH. All hydrogels show lowest swelling ratio in an acidic medium and it increases with increasing pH of the solution in Fig. 6. At lower pH (1.0–3.0) the carboxylic and sulphate groups are protonated. As a result, more hydrogen bonds are formed between hydroxyl and $-OSO_3H$ group of KC and $-COOH$ groups of AA. Consequently, a compact network structure is formed which restrict the movement and relaxation of the chains within the hydrogel.

At and above pH 4.0, ionization of these groups started and resulted in an increase in swelling ratio. Due to the presence of the ionic groups $-COO^-$ and $-OSO_3^-$, the charge density on the hydrogel network changes. These charged groups are repelled by each other and also by solvent molecules which gives high swelling. In KC2, maximum swelling is observed at pH 7.0 whereas KC3 shows it at pH 8.0. At high pH, complete removal of proton from $-OSO_3H$ and $-COOH$ groups occurs, resulting in maximum ionization of these groups within the hydrogel structure results in high swelling ratio [14,19,20].

The swelling of KC1 after 8 h at pH 6.0–8.0 and at pH 13.0 could not be measured because the hydrogel structure crumbled. As the swelling data was measured after every 60 min, the swelling ratio of KC1 was increased rapidly with the increase in the swelling time. After 8 h the highly swelled weak structure of KC1 could not withstand and collapsed resulting in an immeasurable swelling data at this pH.

3.8. Effect of non-buffer media on swelling ratio

The effect of non-buffer media having varying pH, on swelling ratio of KC1, KC2 and KC3 is presented in Fig. 7. The swelling response of the hydrogel towards the pH obtained by the buffer and non-buffer method is different. This is due to the reason that less number of ions are present in non-buffer as compared to buffer media. As a result, more swelling is observed for non-buffer media as compared to buffer media. The trend in swelling index of KC/AA hydrogel is similar with previously studied hydrogel [3].

Table 5
Diffusion parameters of KC/AA hydrogel at varying acrylic acid ratio.

>Samples	n	$k \times 10^2$
KC1	0.6778	1.326
KC2	0.4653	5.196
KC3	0.4690	5.537

Fig. 7 shows that swelling ratio is higher in non-buffer media, as there are fewer ions present as compared to buffer media. Swelling behaviour is similar to buffer results in low swelling till pH 3.0 due to the protonation of anionic groups that suppress ionization. After this point screening effect of ions in media directs the hydrogel swelling. While swelling loss at high pH values is due to the screening effect of the excess cations (i.e. Na^+) which shield the anions and lowers the repulsion between them and result in loss of swelling ratio [21].

The swelling ratio of the hydrogel increases with increasing pH of the external solution up to a maximum when ionization of the charged network is complete. Since the swelling is determined to a large extent by osmotic pressure, a further increase of pH will increase the osmotic pressure of the external solution, hence decreasing the ionic pressure within the hydrogel, reducing the swelling ratio. At a higher pH, the half-ester-sulphate moieties of carrageenan and carboxylate groups of acrylic acid are facilitated for ionization so an increase in osmotic pressure would result within the hydrogel; hence the swelling ratio of the hydrogel also increases [9]. This swelling is related to the intense repulsive forces between the negatives charges of carboxylate and sulphate groups and the negative ions in the media.

3.9. Effect of electrolytes on swelling ratio

Fig. 8 reveals two trends for KC1, KC2 and KC3 in varying concentration of NaCl and $CaCl_2$ solutions. Firstly, as the

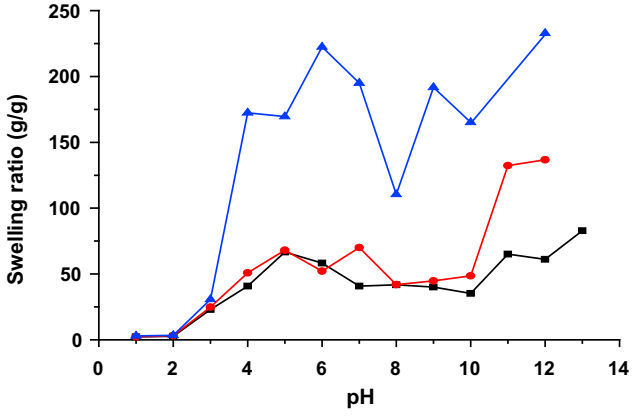

Fig. 7. Swelling ratio of hydrogels in non-buffer media (pH = 1.0–13.0), (-▲-KC1, -●-KC2, -■-KC3).

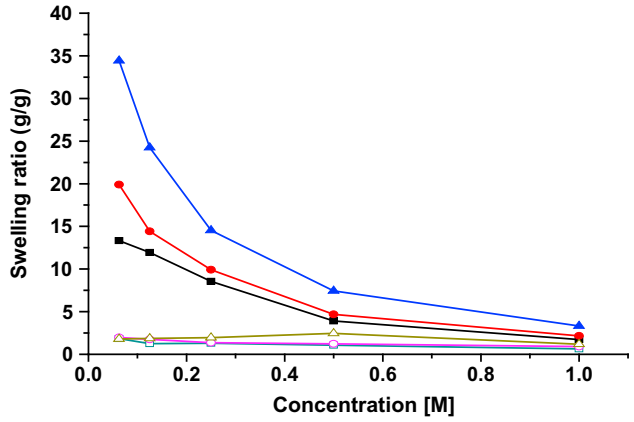

Fig. 8. Swelling ratio of hydrogels in NaCl solutions (-▲-KC1, -●-KC2, -■-KC3) and in $CaCl_2$ solutions, (-△-KC1, -○-KC2,-□-KC3).

concentration of the salt is increased the swelling ratio is decreased. Secondly, as the valency of the salt is changed from mono- (Na^+) to divalent (Ca^{2+}), a marked decrease in the swelling ratio is observed.

In the former case an increase in the salt concentration causes the cations attracted by anionic groups of the hydrogel. This restricts the relaxation of chains in hydrogel network. Therefore, the swelling is drastically reduced [9].

In later case, the swelling is decreased with an increase in charge of metal cation. It is explained by complexation ability arising from the coordination of the multivalent cations with $-COO^-$ and $-OSO_3^-$ groups and results in interchain complexation. This increases compactness of hydrogel structure which in turn lowers the swelling ratio [22].

3.10. Effect of temperature on swelling ratio

Fig. 9 shows, for increasing temperature from 20 °C to 35 °C and further to 45 °C, an enhancement in the swelling ratios of all hydrogel samples. All hydrogels show high swelling at high temperature which is attributed to an increase in the porosity of the hydrogel creating more space for water penetration. Swelling data for KC1 at 45 °C, show similar behaviour of high swelling and could not be measured due to disintegration of the hydrogel structure. At high energy input, both the entanglement and intermolecular forces which help the molecular chain associated together become less strong between the molecules and subsequently swelling increased. Such a temperature response of these hydrogels can be

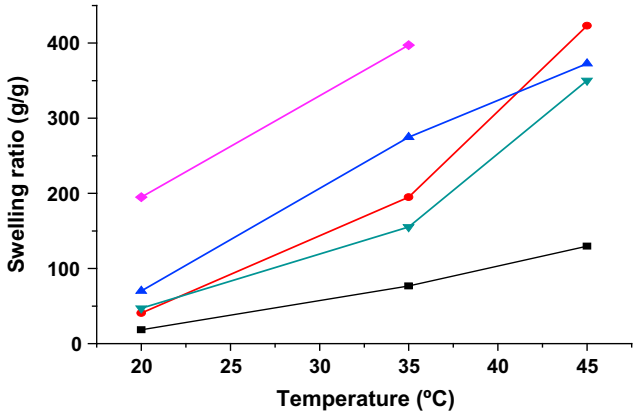

Fig. 9. Temperature dependent swelling of hydrogel (-◆-KC1, -▲-KC2, -●-KC3, -▼-KC4, -■-KC5).

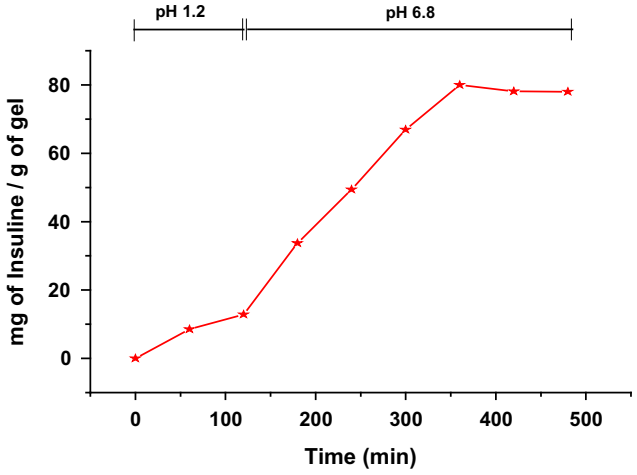

Fig. 10. Insulin release profile of KC1 in SGF and SIF.

exploited in terms of medical and environmental applications. Study of hydrogel swelling behaviour at 37 °C is beneficial especially if it is aiming for drug delivery applications [7].

3.11. Insulin release

The insulin was loaded in KC1 hydrogel and its release was studied as a function of time. The in-vitro release profile of insulin from this loaded hydrogel in SGF and SIF is shown in Fig. 10. This figure shows a negligible release of insulin from loaded hydrogel for first 2 h in SGF at pH = 1.2. The insulin remains within the hydrogel due to its shrunken structure in acidic media. After 2 h, this insulin loaded hydrogel is transferred into SIF (pH = 6.8). In SIF, the hydrogel swell and showed higher release rate of insulin as compared to SGF. A sustained release of insulin is observed for 6 h in SIF and this release is not influenced by the amount of insulin retained within the hydrogel. The release behaviour of insulin at different pH is in good agreement with the swelling response of KC1 at different pH as previously discussed. Similar release behaviour has also been observed for insulin delivery using different pH sensitive hydrogels [23,24]. Wood et al. observed 10% insulin release at pH 1.2 and 75% at pH 6.8 from pH sensitive lectin functionalized complexation hydrogels.

Similarly, Nho et al. prepared hydrogel using polyvinyl alcohol grafted with acrylic acid/methacrylic acid using gamma radiation. In-vitro release of insulin from this hydrogel was observed in SIF but not in SGF [4]. Similarly, Kim et al. found a negligible release of insulin in SGF and a high release in SIF from poly(methacrylic acid-co-methacryloxyethyl glucoside) and poly(methacrylic acid-g-ethylene glycol) hydrogels [25].

The adsorption of drug in small intestine mainly depends on the mucoadhesive property of the polymer used in hydrogel synthesis. Polyacrylic acid and carrageenan are found to be highly mucoadhesive, which increase the area available between the cells, allowing the movement of molecules across the layers [26]. KC1 was found crumbled into small fragments after 6 h at neutral pH which can be easily removed along with other indigestible food, when these hydrogels will be used in-vivo.

4. Conclusions

KC based hydrogel are prepared by incorporating various amounts of AA and VTESi. The structural analysis of the hydrogel confirmed the presence of the feed components in the hydrogel.

Thermal stability of the hydrogel is increased by increasing the amount of AA or crosslinker content in KC/AA hydrogel. The low swelling ratio is observed in the hydrogel having high AA content and high crosslinker amount. The response of the prepared hydrogels against pH, ionic strength and temperature revealed that these hydrogel can be classified as acid–base hydrogel, ionic hydrogel and thermoresponsive hydrogel respectively. Most promising results with high swelling ratio are observed in hydrogel having low monomer ratio (KC:AA = 1:7). This makes this hydrogel to be used for in-vitro release of insulin. A sustained release of insulin is observed in SIF with negligible release of insulin in SGF.

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