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Synthesis and Characterization of Biomedical Hydrogels by using Chemically Modified Biopolymers for Drug Delivery Application

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Abstract

The aim of this research work was to develop a chemically cross-linked polymer-based hydrogel that is environmentally benign, economic, and pH sensitive. PVA mixed with Alginate and cross-linked with tetraethyl orthosilicate (TEOS). Alginate / PVA based hydrogel was synthesized for controlled drug delivery systems. The characterization of hydrogel was done by different techniques FTIR, SEM, TGA, and UV-VIS Spectroscopy. Surface morphology of hydrogel was checked by scanning electron microscopy (SEM), and thermal stability of hydrogel was checked by thermogravimetric Analysis (TGA). A linkage between polymers of hydrogel was detected by Fourier transform infrared spectroscopy (FT-IR). It was found that hydrogel was porous which played a key role in swelling. The swelling of hydrogel was checked in diverse solutions such as aqueous, electrolytes and different pH solutions. The swelling of hydrogel was maximum at low pH and minimum at high pH. The hydrogel was loaded with two different drugs: sitagliptin and ciprofloxacin HCl. For In-vitro release study, both the drugs were selected as modal drug and studied in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). In SIF, sitagliptin release was 99% in 180 minutes. The ciprofloxacin HCl showed 98.8% release in SIF for 5 hours. So, ciprofloxacin HCl and sitagliptin both the drugs were compatible with Alginate/PVA hydrogel which was determined from drug release study of drugs.

Key words: Alginate, Polyvinyl alcohol, Sitagliptin, Ciprofloxacin HCl

1. Introduction

The term “hydrogel” originally arose around 1900 and was used to describe a colloidal gel of inorganic salts. The first report on hydrogels was made in 1960 by Wichterle and Lim [1]. Hydrogels are hydrophilic viscoelastic substances made of a polymeric network with physical and chemical cross-links that soak up and hold a lot of water and swell while retaining their three-dimensional structure, mechanical strength, and elasticity. Recently, hydrogels have numerous utilization in biomedical field [2]. Hydrogel exhibit pores with well-defined diameters that can be regulated by the cross-linking density and that can be responsive to outside stimuli like pH, temperature, light, pressure, ionic strength and magnetic field and they are easily changed with functional groups. Due to the diversity of its composition, processing, and subsequent physical properties, hydrogels have gained significant interest across many fields. Hydrogels are highly relevant for biomedical, environmental, and other applications due to their soft mechanical system, ability to diffuse solvent molecules quickly inside the body, controllable bond attraction for specific molecules, and tendency to undergo physiochemical variations that are responsive to environmental influences [3]. The majority of hydrogel applications depend on the hydrogel’s porosity, which directly control the hydrogel’s transport capabilities [4]. Hydrogels show response towards physical and chemical stimuli.

Hydrogels are further classified as natural and synthetic based on their origin. Natural polymers are used to make natural hydrogel while that of synthetic origin are synthesized

by chemically polymerizing man-made monomers. By mixing synthetic and natural polymers another class of hydrogels are formed which is known as hybrid hydrogels. Based on their composition; homopolymer, copolymer and multipolymer hydrogels are formed. They can also be classified based on charge as neutral hydrogel having no charge on their polymer chain. Ionic hydrogels carry either positive or negative charges, but amphoteric hydrogels carry both positive as well as negative charges. Based on pore size, they may be non-porous, microporous, and super porous. Hydrogels may be matrix, film or microsphere based on their physical appearance. Physical and chemical hydrogels are two another type of hydrogels based on their cross-linkage property [5]. The primary components employed in the production and manufacturing of hydrogels are monomers, naturally occurring polymers, or synthetic polymers. There are many polymerization methods that are used to prepare hydrogels. Three main methods are suspension polymerization, solution polymerization and polymerization by irradiation. These methods allow for the formation or reformation of hydrogel products into small particles, powder, fibers and membranes [6].

Hydrogels with biocompatibility, degradability, and adjustable mechanical qualities offer many advantages in biological disciplines like 3D cell culture, cell therapy, drug/gene delivery, stem cell, cancer research, and regenerative medicine. The use of biodegradable polymers for controlled drug delivery is growing exponentially. There are two mechanisms: diffusion and erosion which control the release kinetics of drugs from drug delivery system [7]. The diffusion mechanism controls the drug elution kinetics for non-erodible polymers, providing a burst release of the drug that should occasionally be unavoidable. The drug elution response for biodegradable polymers is influenced by both diffusion and degradation [8]. Therefore, biodegradable polymers are preferred over non-erodible polymers in drug delivery system [9]. Ordinarily, pills, ocular drops, ointments, and intravenous solutions are used in traditional drug administration methods [10].

Alginates are derived from several types of brown seaweed that abundant at shores of the North Atlantic, South America, and Asia [11]. Alginate, in brown algae is the earlier prevalent polysaccharide that accounts for up to 40% of the dry content. It is a gel that contains Ca^{+2}, Na^{+1}, Ba^{+2}, and Sr^{+2} ions that is found in the intercellular matrix. It is frequently employed in manufacturing because having capacity to hold onto water as well as its gelling, viscosifying, and stabilizing qualities [12]. Additionally, alginate is a safe matrix due to its biodegradability, low toxicity, and immunogenicity [13].

PVA, a significant polymer that has been around for more than 90 years [14]. A linear synthetic polymer called PVA is created by partially or fully hydroxylating polyvinyl acetate. The extent of hydrolysis determines the qualities of polyvinyl acetate. Which categorize into two classes partially hydrolyzed or fully hydrolyzed. The degree of hydroxylation affects the PAV's mechanical, chemical and physical properties. It is soluble in water but in most organic solvents it is insoluble. PVA's intrinsic qualities prevent complete disintegration in water below 100 °C without a holding period of more than 30 minutes [15]. PVA has a high level of chemical and thermal stability and a low cost of production, making it useful in a variety of industries including paper ,textile, and food packing [16]. TEOS is a fragrance-free and transparent liquid. It is extensively used as fabricator [17]. TEOS has many studies in literature especially in sol gel process. Strong silica structures formed by TEOS are resistant to thermal expansion and tension. As compared to other cross-linkers like glutaraldehyde, epichlorohydrin, borate and tripolyphosphate, TEOS is a non-toxic and biocompatible cross-linker [18]. It has the ability to create covalent connections between amorphous polymer chains and inorganic areas [19].

Naturally ciprofloxacin is a white powder that is bitter in taste, is useful for bacterial infections. Ciprofloxacin has high activity against aerobic organisms and extremely low activity against the majority of anaerobic organisms [20]. The pharmaco-kinetic profile of ciprofloxacin exhibits greater absorbing property when compared to other drugs in its class, as seen by the bigger volume of distribution [21].

Sitagliptin is the first antidiabetic drug from the class of dipeptidyl peptidase-4 enzyme inhibitors. It raises the levels of incretins in the blood, which promote insulin secretion and prevents the synthesis of glucose. It can be taken alone or in combination with metformin or thiazolidinedione [22].

We investigated the swelling response in aqueous, salt solutions (NaCl, $CaCl_2$), and pH mediums. The procedure of releasing drugs is greatly influenced by the degree of swelling. The hydrogel made of Alginate, PVA and cross-linker loaded with ciprofloxacin and sitagliptin drugs. The drugs which are compatible with hydrogel were selected and their release profile was studied in stomach at low pH and in gut at high pH with help of UV-Visible spectrophotometer.

2. Experimental

2.1. Materials

Alginate powder (viscosity = 20 mPas), poly vinyl alcohol hydrolyzed 98-99% pure, 146,000-186,000 (average molecular weight), TEOS (tetraethyl Orthosilicate) molecular weight = 208.33 g/mol, Hydrochloric acid (HCl), Calcium chloride ($CaCl_2$), sodium chloride (NaCl), sodium hydroxide (NaOH), Ethanol (C_2H_5OH) molecular weight=40.069 g/mol with 99.8% purity were bought from sigma-Aldrich, Milwaukee, WI were used. All additional compounds, which are of analytical grade, were bought from Sigma Aldrich.

2.2. Synthesis of hydrogels

2.2.1. Preparation of solutions

A chemical cross-linking method was used to prepare hydrogels. In this method, crosslinker TEOS and ethanol were used. Weighed 0.8 g alginate and dissolved into 50mL of deionized water with constant magnetic stirring and maintained at 50 ℃. Weighed 1.95 g PVA and dissolved into 40 mL of deionized water with constant magnetic stirring and maintained the temperature at 80 ℃ until it completely dissolved. 20 uL of TEOS was dissolved into 5 mL of ethanol.

2.2.2. Synthesis of Alginate/PVA hydrogel

After preparing the solutions of alginate and PVA, the alginate solution was kept on stirring for some time and maintained the temperature at 50 ℃ and then added PVA solution into the alginate solution kept on stirring at the temperature 50 ℃ for 1 hour. After 1 hour, a TEOS solution was added drop wise into alginate solution with constant stirring at 50 ℃ for 5 hours. When the time completes, the blend was transferred into the petri dish and allowed it to dry in the clean and favorable surroundings at room temperature for 5 to 6 days. Possible crosslinking mechanisms between alginate, PVA, and TEOS have been shown in Figure 1.

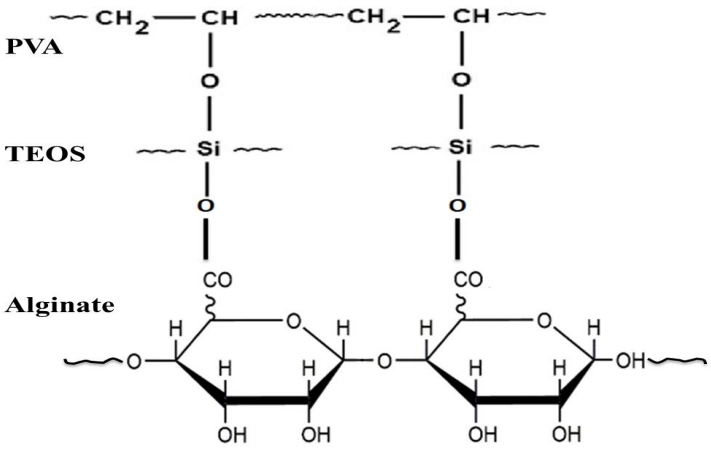

Figure 1: Possible interactions between alginate, PVA, and TEOS crosslinker.

2.3. Swelling studies of hydrogels

The various phases have an impact on how well biopolymers swell i.e., acidic, basic, and ionic phases. The swelling property of the biopolymeric hydrogels is impacted by all these phases. The immersion approach was used for experiments on swelling.

2.3.1. Swelling studies in deionized water

The following method was used for calculations in all swelling experiments. The ability of synthetic hydrogels to swell was evaluated in deionized water at room temperature (25 ℃). Dehydrated samples and petri dishes were required for this purpose. The dehydrated sample and petri dish was weighed before dipping the sample into the 10 mL of deionized water for 20 minutes. Then, with the help of syringe, the deionized water was removed from the petri dish. To monitor the hydrogel's swelling response, extra water was removed with the help of filter paper at intervals of 20 minutes. This process was repeated and again until the constant value of the weight was achieved. The swelling proportion of each sample was estimated gravimetrically by using equation 1.

$$\text{Swelling (g/g)} = W_s - W_d / W_d \quad (1)$$

Where, W_S is the weight of sample (g) at given time and W_d is the initial weight of the sample (g).

2.3.2. Swelling study against pH

Using the above equation of swelling, the behavior of hydrogel against pH was measured. The solutions were made by using 0.1 M NaOH and 0.1 M HCl, ranging from 2-12 pH. The pH meter was used to precisely measure the pH (2, 4, 7, 9, 10 and 12) of the standard solutions.

2.3.3. Swelling studies in salt solutions

The behavior of hydrogels in comparison to various molar concentration of sodium chloride (NaCl) and calcium chloride ($CaCl_2$) salts in the electrolyte, ranging from 0.1 to 1 M, was examined, and the gravimetric equation was used to calculate the swelling of the hydrogels.

2.3.4. Gel content

The measured value samples were put into a stainless-steel cloth, which was then used in a Soxhlet extractor to extract the samples after 8 hours of boiling in distilled water. At 60 ℃ samples that had been withdrawn were put in a vacuum for 1 hour, weighed, and then measured the weight of sample again after 20 minutes, and so on, until the weight of the sample became constant. The gel content of a hydrogel sample that had been extracted and contained an insoluble part was calculated. The gel fraction was calculated using equation 2.

$$\text{Gel fraction (\%)} = W_S/W_0 * 100 \quad (2)$$

In the above equation, W_S is the weight of the removed sample in grams (g) and W_0 is the initial weight of the sample in grams (g).

2.4. In-vitro drug release study

2.4.1. Preparation of buffer solutions

For the preparation of simulated intestinal fluid (SIF, pH =6.8), added 250 mL of 0.2 M KH_2PO_4 into the 118 mL of 0.2 M NaOH.

For the preparation of simulated gastric fluid (SGF, pH =1.2), added 3.5 mL HCL into 1 g of NaCl.

2.4.2. Drug loading process for ciprofloxacin

The commercially available drug ciprofloxacin was taken and put into an alginate/PVA hydrogel. The process of loading was performed by dissolving 0.05 g of ciprofloxacin drug into 10 mL of deionized water water and then it was mixed to the alginate/PVA solution after 1 hour of the addition of cross-linker TEOS. For 5 hours, it was allowed to mix with the solution at 50 ℃ with continuous stirring. After that, it was placed onto the petri dish and dried for 5 to 6 days. The drug loading process on the alginate/PVA/TEOS hydrogel is shown in Figure 2.

2.4.3. Study of drug release for ciprofloxacin

Drug loaded hydrogel was placed in a beaker containing 100 mL of simulated gastric fluid (SGF) (pH =1.2) and left in this buffer solution for 3 hours at 37 ℃. The same experiment was repeated for simulated intestinal fluid (SIF) solution. 5 mL of aliquant was removed from the vessel after every 15 minutes, and 5 mL of additional solution was added to the beaker to keep volume of liquid constant. The amount of drug released was measured using a UV spectrophotometer set to 264 nm. In SIF and SGF solutions, a drug reference solution (CMO) was produced. An absorbance-concentration calibration curve was used to plot the released profiles and determine how much ciprofloxacin drug was released.

2.4.4. Drug loading process for sitagliptin

The commercially available drug sitagliptin was taken and put into an Alginate /PVA hydrogel. The process of loading was performed by dissolving 0.05 g of sitagliptin drug into 10 mL of deionized water and then it was mixed to the alginate / PVA solution after 1 hour of the addition of cross-linker TEOS. For 5 hours, it is allowed to mix with the solution at 50 ℃ with continuous stirring. After that, it was placed onto the petri dish and dried for 5 to 6 days.

2.4.5. Study of drug release for sitagliptin

Drug loaded hydrogel was placed in beaker with 100 mL of simulated gastric fluid (SGF) and left in the buffer solution (1.2) for 3 hours at 37 ℃. Some experiments are repeated for simulated intestinal fluid (SIF) solution. 5 mL of aliquant was taken from the beaker to keep volume of liquid constant. The drug released was found using a UV spectrophotometer set to 264 nm. In SIF and SGF solutions, a drug reference solution (CMO) was produced. An absorbance-concentration calibration curve was used to plot the released profiles and determine how much sitagliptin drug was released.

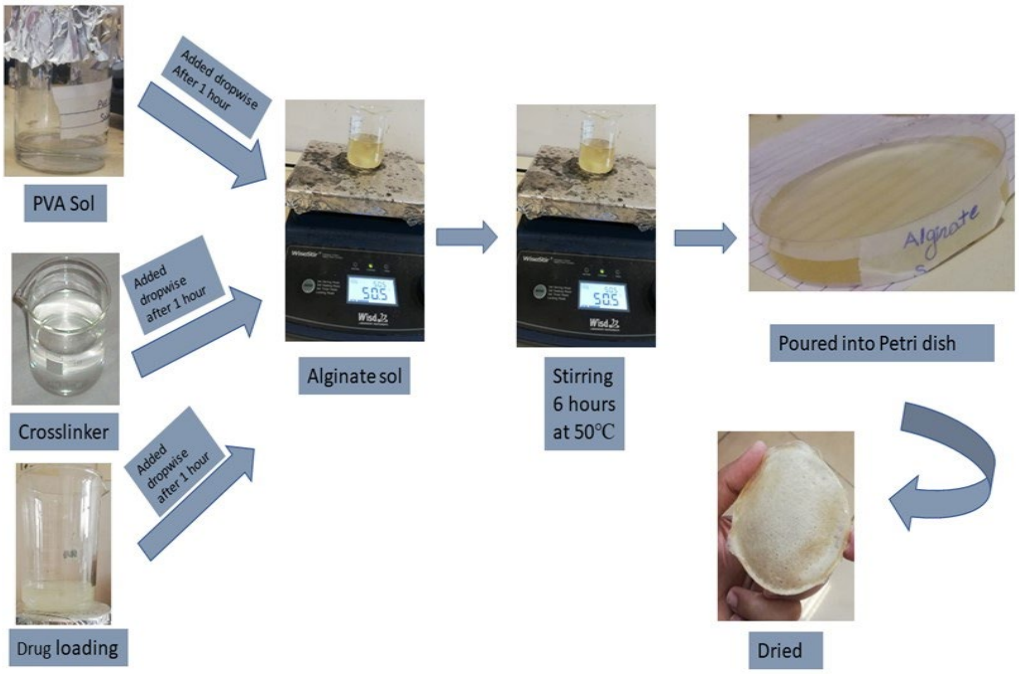

Figure 2: Images of drug loading process on Alginate/PVA/TEOS hydrogel.

2.5. UV-visible spectroscopy

UV–VIS spectrophotometer UV-2600 (Shimadzu) was applied for the determination of ciprofloxacin and sitagliptin concentration during the sorption and release process. Ciprofloxacin and sitagliptin measurements were made in the range of 240–300 nm (λ_{max} = 264 nm). In each case, blank runs were done to ensure that nothing besides drug absorbed in the wavelength of interest [23].

2.6. Scanning electron microscopy and energy dispersive X-ray

The morphology of the hydrogel was analyzed using SEM equipment (MIRA3 XMU, TESCAN) while elemental analysis was conducted using energy dispersive X-Ray analysis (EDX) [24]. SEM used in the study of pharmaceuticals, such as in the investigation of drug distribution, where it is a crucial tool for detecting nanoparticles [25]. Topography describes an object's surface characteristics, or "how it looks", including its texture, smoothness, and roughness, while morphology describes an object's size and shape [26].

2.7. FT-IR spectroscopy

To confirm the complexation and compatibility of ingredients in the hydrogel network, FTIR analysis was conducted. Over a scanning range of (4000–500 cm^{-1}), the samples were scanned through FTIR spectrophotometer (Nicolet iS10 spectrometer). The absorption peaks in an IR spectrum, related to the frequency of vibration [27].

2.8. Thermogravimetric analysis

To check the thermal stability of the hydrogel, thermogravimetric analysis was carried out using Mettler Toledo (TGA / SDTA851e) machine. The sample was placed in a sealed aluminum pan and heated from ambient temperature to 600 °C at 10 °C/min in nitrogen environment [28].

3. Results and Discussion

3.1. FT-IR analysis

The FT-IR spectrum of the synthesized hydrogel sample is shown in Figure 3. The characteristic broad absorption band at 3400 cm^{-1} is due to the O−H stretching vibrations

of inter and intramolecular hydrogen bonding. The band near 2900 cm^{-1} is attributed to the C−H stretching vibration. The absorption band at 1600 cm^{-1} is endorsed to the symmetric and asymmetric -COO stretching vibration and indicated the hydrogen bonding between the constituent of the hydrogel. A notable stretching band of -CH_2 groups is found at 1500 cm^{-1}. The absorption peak at 1100 cm^{-1} confirmed PVA. The absorption band confirmed the Si-O-Si linkages of TEOS at 599 cm^{-1}. The sharp band near 1049 cm^{-1} is corresponded to the C–O stretching, O–H bending, and C–H deformation of PVA–alginate hydrogel.

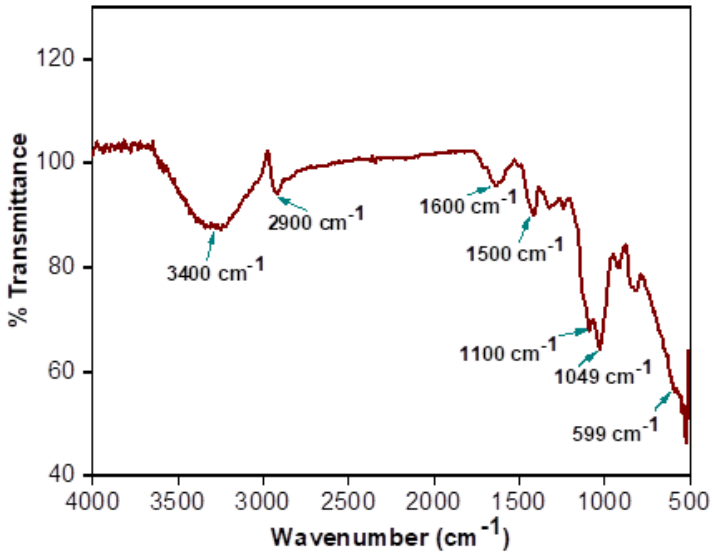

Figure 3: FT-IR analysis of PVA-Alginate hydrogel.

3.2. Scanning electron microscopy

Scanning electron microscopy was used to investigate the shape, size, and surface morphology of Alginate-PVA hydrogel. SEM images of prepared hydrogel are shown in Figure 4. The micropores and crosslinked networks in the Alginate/PVA hydrogel are evenly dispersed across the surface, indicating the smoothness of surface. The image of Alginate/PVA shows that the hydrogel is porous this is due the presence of alginate in the hydrogel. The pore size ranges from 236.49 nm to 298.72 nm. PVA is a hydrophilic polymer. The proportion of alginate added is less as compared to PVA, so the pore size is smaller. Porosity causes swelling which is very useful in biomedical and other applications.

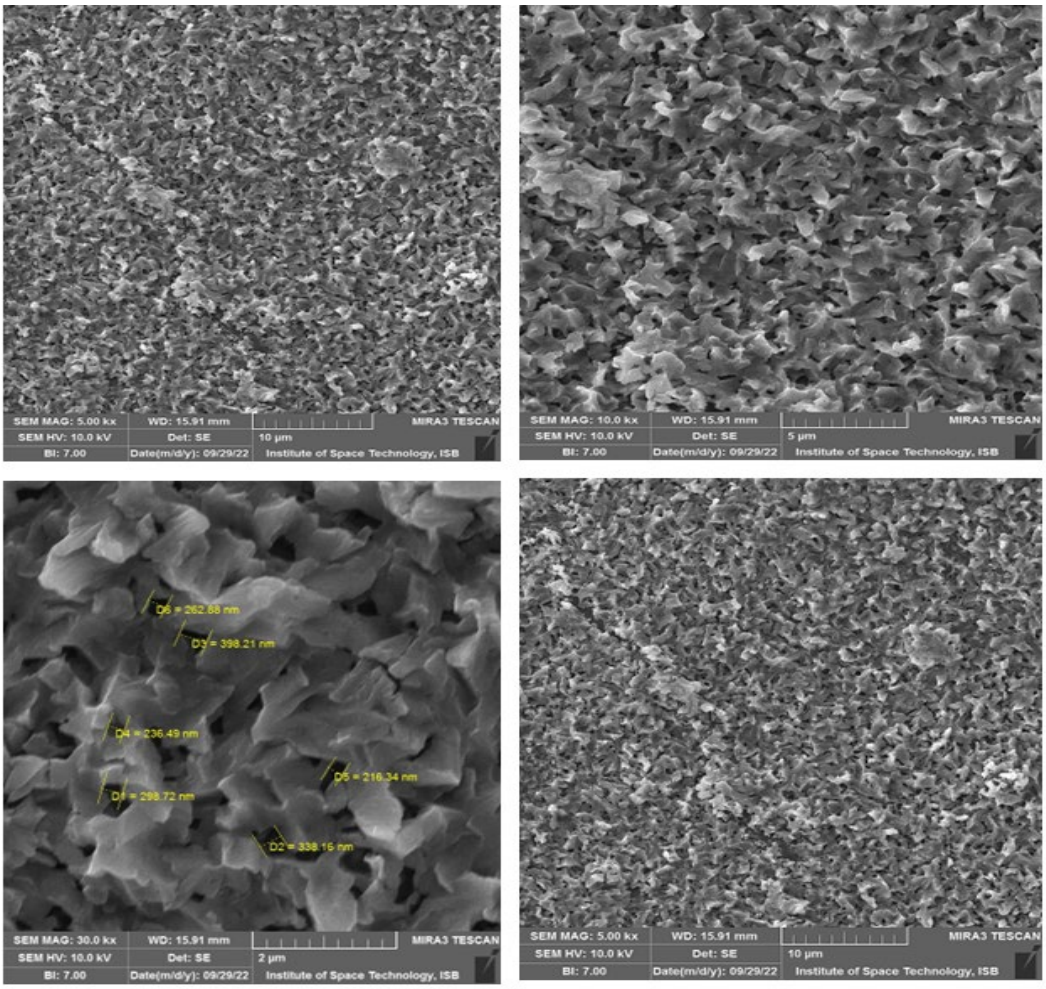

Figure 4: Scanning electron microscopic images of Alginate/PVA hydrogel.

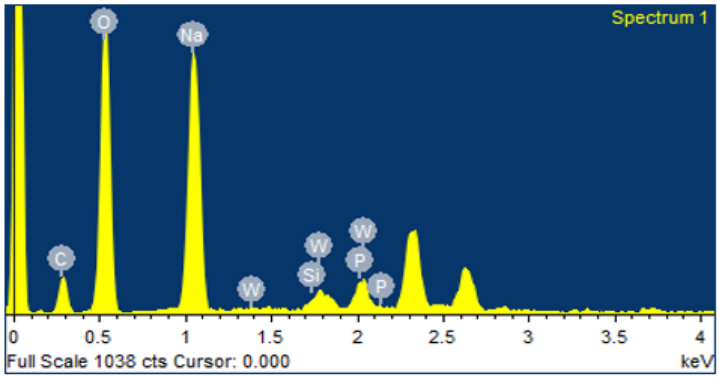

Figure 5: Composition chart of Alginate/PVA hydrogel.

3.2.1. Composition analysis

Energy dispersive X-ray spectroscopy is a popular method for determining and assessing the elemental composition of a very small sample of material. Carbon, oxygen, sodium, silicon, tungsten and phosphorous (Table 1) are found in the hydrogel which is shown by EDX report of Alginate/PVA hydrogel. Figure 5 shows that oxygen and sodium are present in higher percentages as compared to carbon and other elements. Tungsten is present as impurities. One element is missing in the chart, which is not detected by EDX, that is hydrogen.

Table 1. Percentage of different elements in Alginate/PVA hydrogel.

Element	Weight%
Carbon	16.91
Oxygen	52.27
Sodium	24.72
Silicon	0.28
Phosphorous	2.65
Tungsten	3.17

3.3. Thermogravimetric analysis

TGA was used to characterize how the stabilizing method affected the degradation behavior of the PVA/Alginate hydrogel. Figure 6 shows the TGA analysis of Alginate/PVA hydrogel and Table 2 shows the percentage weight losses at different temperatures. The hydrogel sample showed three decomposition stages. The first decomposition stage for Alginate/PVA hydrogel is from ambient temperature to 120 ℃ with 6% of their weight loss. This event is usually due to the removal of water which is present in the hydroxyl group form in the polymer chain. The second decomposition stage is from temperature 250 ℃ to 350 ℃ at which a 55% weight loss of hydrogel has been seen. This happened due to the loss of ester bonds. The third decomposition stage is seen from 350 ℃ to 550 ℃ with 25% weight loss which is due to the breakdown of main polymer chain.

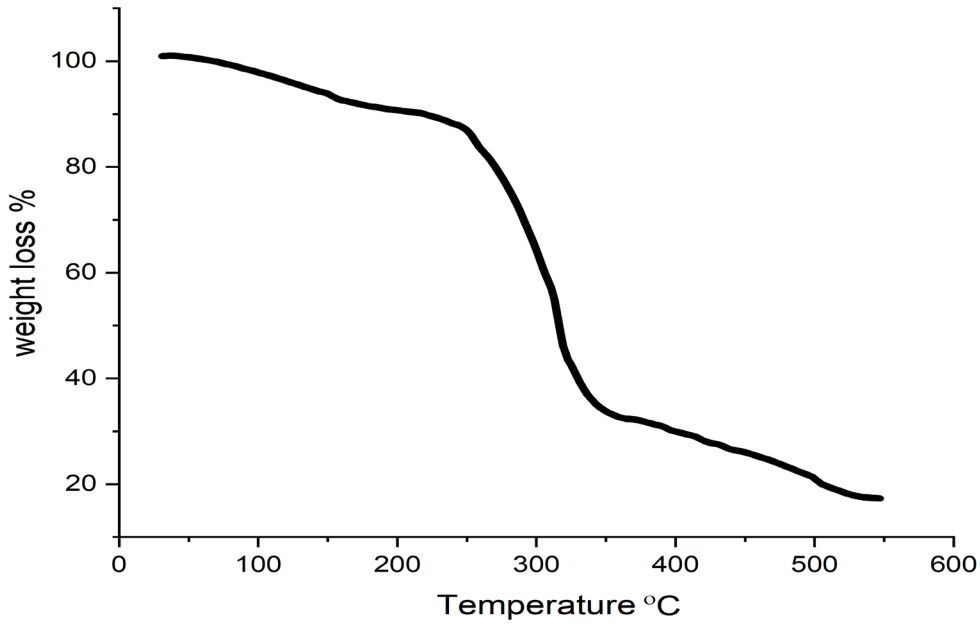

Figure 6: TGA analysis of PVA/Alginate hydrogel.

Table 2. Percentage weight losses at different temperature in Alginate/PVA hydrogel.

S. NO.	Temperature	Weight loss %	Composition loss
1	Ambient temp. to 120 ℃	6	water
2	250 to 350 ℃	55	Ester bonds

3	350 to 550 ℃	25	Polymer chain

3.4. Swelling response in deionized water

The process of swelling is a continual change from un-solvated glassy or slightly flexible condition to a relaxed rubbery region. Hydrogels could swell, when in contact with a water-based solution. The hydrogel surface is attacked by the water, which then enters the polymeric structure. The meshes of the network will frequently begin to open during the rubbery phase, allowing additional solvent molecules to enter the hydrogel network cause swelling. Consequently, a moving front is used to separate the un-solvated glassy phase from the rubbery hydrogel area. The swelling of hydrogels depends upon osmotic pressure forces, viscoelastic restorative forces, and electrostatic forces. The key factors that regulate equilibrium swelling are the hydrophobic/hydrophilic balance of the hydrogels, the extent of ionization and its interaction with counterions. Swelling is not a continuous process. An opposing elasticity force is present which balances the stretching of the network and avoids its distortion in opposition to the beneficial osmotic force [29].

At room temperature, the cross-linked hydrogel's swelling behavior is observed over time and results are shown in Figure 7. According to the graph, water absorbed linearly and became stable in 3 hours. After 3 hours, the equilibrium is reached, and further swelling did not take place which is due to the reduction in the hydrophilicity of the polymers as the complete combination of the hydroxyl groups of the polymers in the structure of the hydrogel. These groups are primarily in charge of the cross-linking of polymers, and when they are blocked, the size of the pores in hydrogels is reduced, which also limits the swelling of deionized water into the hydrogels. The maximum swelling observed in 3 hours is 0.080 (g/g). The diffusion mechanism of water is measured by the following equation:

$F = kt^n$

Where "F" represents the fractional swelling at time t and the "k" represents the swelling rate constant. Whereas "n" is the diffusional exponent that shows the transport mechanism. The values of diffusional parameters ("k" and "n") are calculated by applying the swelling data of hydrogel. A graph is plotted between the ln t and ln F as shown in Figure 8. The value of 'n' in hydrogels is less than 0.5 according to Fick's law as shown in Table 3. Hence the mechanism of Fickian diffusion is observed in the swelling process of hydrogel.

3.5. Gel content analysis

The proportion of cross-linking between the polymer chains that make up the hydrogel's structure is measured gravimetrically for the gel fraction using the Soxhlet device. For the percentage of cross-linking contained in the sample hydrogel, the crosslinked portion of the manufactured hydrogels is removed with water. The equation is used to measure the cross-linking of removed hydrogel. The gel content of cross-linked hydrogels is shown in Table 3. The calculated gel content is 82.82%.

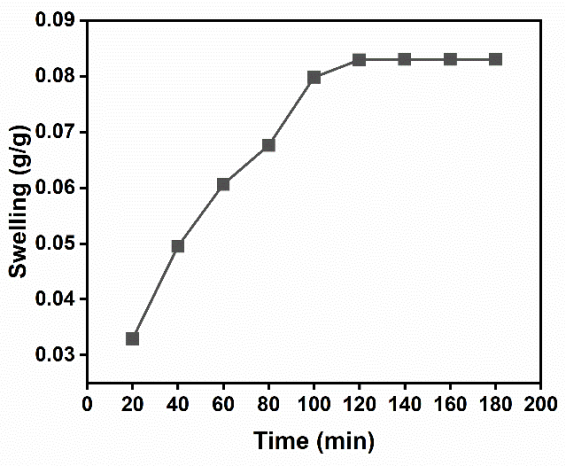

Figure 7: Swelling response in deionized water.

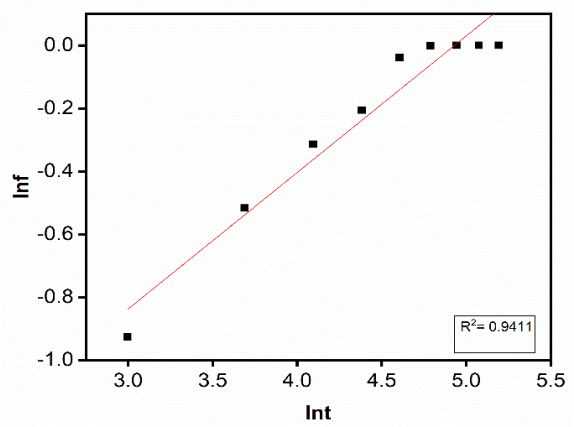

Figure 8: Graph between ln t and ln F.

Table 3. Diffusion parameters of cross-linked hydrogel.

Parameter	Alginate/PVA hydrogel
n	0.14699
Intercept	-2.13836± 0.17072
Regression (R^2)	0.94849
Gel content (%)	82.8%

3.6. Swelling response against pH

The pH of the medium has an impact on the hydrogel's swelling behavior. Hydrogels are stimuli-sensitive, and they endure significant changes in the swelling behavior with relatively little changes in the surrounding environment, such as pH. For the creation of novel drug delivery systems, pH-sensitive hydrogels that alter their characteristics in response to pH variations have been properly studied [30]. Ionizable groups are present in the hydrogel, and they allow the movement of solvent molecules into the hydrogel's matrix. Cationic and ionic hydrogels are present, and they swell at lower and higher pH. There are some factors upon which swelling of pH-sensitive hydrogels depend are: pH of medium, hydrophilicity, ionic charge and the pKa or pKb values of ionizable groups.

3.6.1. Swelling response

The swelling behavior of hydrogel depends upon polymer bonding type, surrounding solvents characteristics and chemical structure. Figure 9 shows the swelling of hydrogel in pH 2, 4, 7, 9, 10 and 12 solutions. pH 2 to 12 are used to measure the hydrogel's swelling.

The ability to swell at acidic pH is high due to strong repulsion of anion-anion COO- groups. The swelling is low at basic pH due to the nonionic hydrophilic -OH and -COOH groups of PVA and alginate backbone, also due to the protonation of carboxylate groups. As the pH rises higher (to pH 12 or pH >7), the swelling capability declined. The counter ions, specifically Na^+ which protect the charge of the carboxylate anions and stop affective anion-anion repulsion are also responsible for slow swelling. PVA and alginate have more extended negatively charged ionic backbones due to the negatively charged protonation of COO- groups. This expanded form allowed more water molecules to enter the hydrogel. However, at pH 7, -OH groups exhibited small polar behavior. At higher pH, polymers have lower affinity to water and hydrogels are less expended [31].

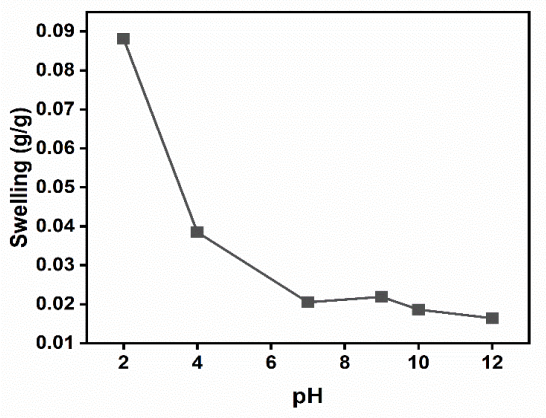

Figure 9: Swelling response in different pH solutions.

3.7. Swelling response in salt solutions

Due to the ex-osmosis phenomena and the imbalance of hydrophilic-hydrophobic ions in the network, hydrogels do not swell significantly in electrolyte solutions as compared to deionized water. Figure 10 depicts the hydrogel swelling in NaCl and $CaCl_2$ at various concentrations. It is shown that as the salt concentration increased, the hydrogels swelling ratios dropped. It is possible to predict the contracting and expanding behavior of hydrogels in salt solution by ion interaction between static charges and moveable ions, which create osmotic pressure between the hydrogel and the external solutions. When the concentration of NaCl solution is increased, the hydrogels swelling will be decreased due to high osmotic pressure of solution ions.

Similarly, for $CaCl_2$ salt solution when salt concentration is larger, the hydrogels' equilibrium swelling is smaller than NaCl. This effect is explained by the reduction in the osmotic pressure difference between the external solvent and the hydrogel. Another factor that influences swelling in salt solutions is the charge shielding effect of cation.
In $CaCl_2$, the charge +2 is present on the cation while in NaCl, +1 charge is present, so $CaCl_2$ has tightly packed structure with the hydrogels of ionic nature. This effect the further condensation which decreased the swelling in $CaCl_2$ solution as compared to NaCl salt solution.

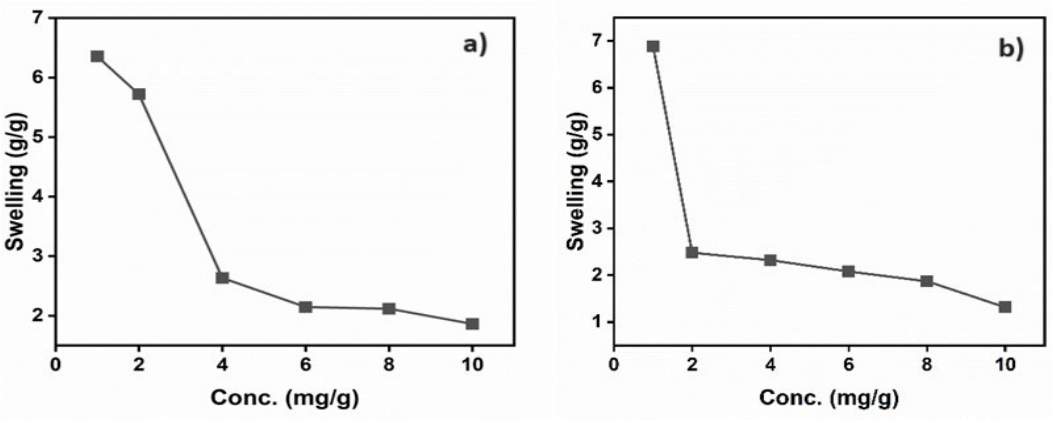

Figure 10: Swelling response in NaCl (a) and $CaCl_2$ (b) salt solutions.

3.8 Release analysis of sitagliptin

In SGF and SIF buffer solutions, the release rate of sitagliptin drug is studied as a function of time. By using UV-VIS spectroscopy at 266 nm wavelength, the study of the sitagliptin is detected. The swelling of hydrogel at various pH levels caused the release of the sitagliptin. The release of drug is directly related with time. As shown in Figure 11, the release rate of sitagliptin drug increased linearly with the increasing of time at body temperature. The diffusion process is responsible for it. The release of the drug is examined in SIF and displayed a release of 99% in 180 minutes.

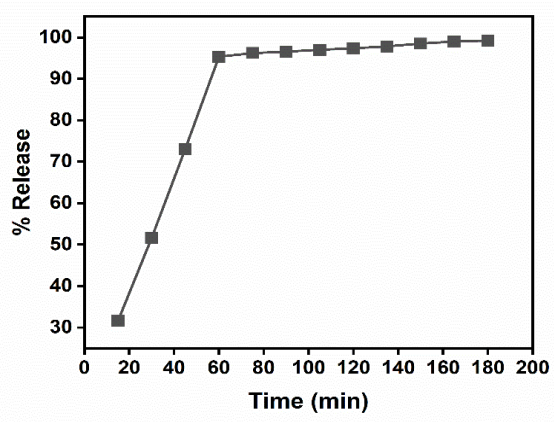

Figure 11: Sitagliptin drug release profile in SIF.

3.9 Release analysis of ciprofloxacin HCl

In SIF buffer solution, the release rate of ciprofloxacin HCl drug is studied as a function of time. By using UV-VIS spectroscopy at 278 nm wavelength, the release of ciprofloxacin is detected. The swelling of hydrogel at various pH levels caused the release of ciprofloxacin. The release of drug is directly related with time. Figure 12 shows the release rate of sitagliptin drug increased steadily with the increasing of time at body temperature. Diffusion process and hydrophilicity are responsible for the release of drug. The graph shows that the enteric-coated hydrogel is transferred to SIF and showed a release of 98.85% in 280 minutes.

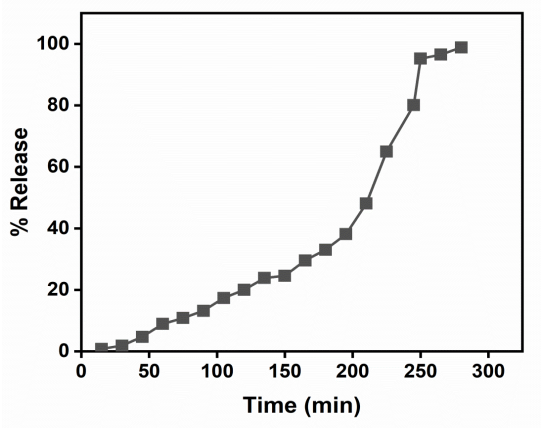

Figure 12: Release analysis of Ciprofloxacin HCl in SIF.

3.10 Comparison with literature

Table 4. Drug release percentages with literature.

Sr. NO.	Membrane Composition	Drug	Percentage Release	Duration	References
1	Chitosan/polyeth-ylene glycol	Ciprofloxacin	16% in SGF and 38% in SIF	24 hours	[32]
2	Alginate/gelatin	Ciprofloxacin	52% in SIF	24 hours	[33]
3	NRL membrane	Ciprofloxacin	59.08%	312 hours	[34]
4	Gel/PGS fibrous membrane	Ciprofloxacin	40%	5 days	[35]
5	Dextrin and poly (2-hydroxyethyl methyl acrylate) membrane c-Dxt/pHEMA	Ciprofloxacin	33.75%	18 hours	[36]
6	HPMC AND PLGA Based nanoparticles	Sitagliptin	98.9%	24 hours	[37]
7	Chitosan Nanoparticles	Sitagliptin	73.77%	24 hours	[38]

3.11 Present Work

Table 5. Drug release percentage of present work.

Sr. No	Composition	Drug	Release percentage	Duration
1	Alginate/PVA	Sitagliptin	99% in SIF	180 minutes
2	Alginate/PVA	Ciprofloxacin	98.85% in SIF	280 minutes

4. Conclusions

A novel pH sensitive alginate/PVA based hydrogel was prepared by blending with hydrophilic polymer PVA and crosslinked with TEOS. FT-IR was used to check the functional group and inter-linked linkages among the constituents. Surface morphology and porosity were confirmed by SEM. The percentages of weight loss and decomposition stages were analyzed by TGA. The highest degree of swelling was at acidic pH and lowest at basic pH. When the concentration of electrolytic solution (NaCl and $CaCl_2$) increased, the swelling of was also decreased. In deionized water, 0.083 g/g swelling of hydrogel was observed. The swelling behavior is due to the process of diffusion. By comparing the swelling behavior in different solutions, the maximum was at pH<2 and then decreased in neutral and at pH>7. The pH-sensitive hydrogels have been shown to be effective for drug delivery applications. The sitagliptin drug loaded hydrogel showed 99% *in-vitro* release in SIF in 180 minutes which also confirmed the compatibility with the hydrogel. Another antibacterial drug ciprofloxacin HCl was loaded which showed 1.7% release in SGF for 2 hours and the remaining 98.8% was released in SIF for 5 hours. This drug also showed good compatibility. The release study of both the drugs showed that they are compatible with the hydrogel and are suitable for oral and other drug delivery administration.

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