Abstract

Synthesis and structural characterization of hydrogels composed of sodium alginate, polyethylene oxide and acrylic acid with cyclodextrin as the hydrocolloid prepared at different pH values is presented. The hydrogels synthesized show significant variations in rheological properties, drug encapsulation capability and release kinetics. The hydrogels prepared at lower pH (pH 1) are more elastic, have high tensile strength and remain almost unaffected by varying temperature or frequency. Further, their Ibuprofen encapsulation capacity is low and releases it slowly. The hydrogel prepared at neutral pH (pH 7) is viscoelastic, thermoreversible and also exhibits sol–gel transition on applying frequency and changing temperature. It shows highest Ibuprofen encapsulation capacity and also optimum drug release kinetics. The hydrogel prepared at higher pH (pH 12) is more viscous, has low tensile strength, is unstable to change in temperature and has fast drug release rate. The study highlights
the pH responsiveness of three composite alginate hydrogels prepared under different conditions to be employed in drug delivery applications.

**Key words:** Hydrogel; Swelling ratio; Shear stress, Encapsulation Capacity

### 4.1 Introduction

Hydrogels are three dimensional hydrophilic networks composed of homopolymers or copolymers absorbing large quantities of water or biological fluids without dissolving due to the presence of crosslinks. The high water content of hydrogels contributes to biocompatibility and their close resemblance to living tissues. The applicability of hydrogels is vast spread over fields like chemical engineering, medicine, pharmaceuticals, food science, and agriculture. Medical and pharmaceutical industries have shown an increased inclination toward the use of biopolymers and in particular alginate has large usage domain due to its unique biocompatibility, biodegradability, immunogenicity, and nontoxicity. Alginites are salts of alginic acid, a linear polysaccharide constituted of two uronic acids as repetitive units, mannuronic acid (M) and guluronic acid (G), in the form of homopolymeric (MM or GG blocks) and heteropolymeric sequences (MG or GM blocks). The β(1–4) linkages of mannuronic acid results in linear and flexible conformations of M-block segments while α(1–4) linkages of C5-epimer of guluronic acid leads to steric hindrance around the carboxyl groups with subsequent folded and rigid structural conformations of G block segments responsible for pronounced stiffness of the molecular chains. Alginate is regarded as an excellent polysaccharide for drug delivery due to its ease of chemical modification, controllable degradation and self-healing properties but at the same time it is prone to enzymatic degradation which limits its application in fabrication. Further, alginate hydrogels have poor mechanical properties and are very permeable so drug release cannot be controlled particularly in case of water soluble drugs. The processing of alginate hydrogels and preserving of its biological properties increases its production and recovery cost. Researchers have been able to circumvent these problems by mixing alginate with other polymers so that it can act as a natural polysaccharide backbone imparting biodegradability and non-toxicity to
the matrix. Composite gels and films of alginate and polyethylene oxide (PEO), overcome most of the above mentioned problems. These have been widely studied and used to reduce postsurgical adhesions in animal models\textsuperscript{13}. Acrylic acid (AA) on other hand is an electrolyte with proton donating carboxyl groups known to form interpolymer complexes stabilized by hydrogen bonding with H-accepting neutral polymers like Polyethylene oxide (PEO)\textsuperscript{14}. PEO polymers modified with AA have a wide range of medicinal applications as their components are considered pharmaceutically safe\textsuperscript{15}. Hydrogels based on AA and sodium alginate may produce combination of electrolyte properties based on the carboxyl groups of AA and the ionized carboxylate groups of alginate. A number of studies are reported in literature where the viscoelastic or drug delivery properties of alginate hydrogels are modified by its combination with AA\textsuperscript{16} but the composite hydrogels are reported to be non-porous which swell slowly, limiting their loading capacity and hence restricting their use in effective drug delivery\textsuperscript{17}. PEO, on the other hand, is a hydrophilic polymer and retains a significant amount of water. A composite hydrogel of the three polymers could prove much promising and a hydrocolloid like cyclodextrin (CD) can be added to improve its mechanical properties within the application domain\textsuperscript{18}. Hydrogels that undergo change in their structure and physical properties in response to small changes in environmental parameters like temperature, pH, and electric field, are very attractive materials for controlled drug delivery\textsuperscript{19}. The time interval and site of delivery is dictated by the reversible volume phase or sol–gel transitions of smart materials upon changes in the environmental conditions\textsuperscript{20}. pH sensitive hydrogels have been widely used in targeted drug delivery applications to various diseased body parts having wide range of pH. All pH-sensitive polymers contain pendant acidic (e.g., carboxylic and sulfonic acid) or basic (e.g., ammonium) groups that either accept or release protons in response to changes in environmental pH. The effect of pH of the release medium on the drug delivery by hydrogels has been widely studied\textsuperscript{19, 21}, but the effect of pH of the medium used for synthesis of hydrogels on their elementary structure is unmapped. In this work, we explored for the first time the structural diversity and hence the variation in properties of composite hydrogels of
alginate, PEO, AA and CD prepared at three different pH values by the free-radical copolymerization and semi-IPN technology. The structure and morphologies of the hydrogels were characterized by Fourier Transformation Infrared (FTIR) spectroscopy, Scanning Electron Microscopy (SEM) and Rheology. Further, the synthesized hydrogels were explored for their drug encapsulation capacity, and release behavior toward poorly water soluble drug Ibuprofen (IBU), an acidic, non-steroidal anti-inflammatory drug and has been studied extensively with respect to its encapsulation and delivery.

4.2 Experimental

4.2.1 Materials

IBU was obtained from Himedia laboratories (India, >98%). Acrylic acid and PEO were obtained from Sigma–Aldrich. H₂O₂ used was of analytical grade. Phosphate buffer was used for preparing the solutions (resistivity of water used for preparing buffer solution was ∼18 MΩcm) and all chemicals were used as received. Sodium alginate (SA) was purchased from Sigma–Aldrich (Fluka, biochemika, 71238-Norway), and was characterized by NMR and viscometry. The details can be found in Chapter 2.

4.2.2 Methods

4.2.2.1 Preparation of hydrogel

For the preparation of hydrogel the procedure of Dar et al. was followed. Sodium alginate (5% wt) and PEO (5wt %) dissolved in 30 ml of phosphate buffer (pH 3) contained in a three necked flask (100 ml) fitted with a reflux condenser, a nitrogen line and a thermometer, were continuously stirred on a magnetic stirrer to form a sticky solution. The polymeric solution was heated to 60 °C on an oil bath and purged with N₂ for 30 min to remove the dissolved oxygen. For generation of radicals, 5 ml of H₂O₂ (50 mM) was added drop wise under continuous stirring keeping the solution at 60 °C for 10 min. The polymeric solution was cooled to 50 °C and then mixture of AA with a neutralization degree of 65% and 0.01% of CD was added under magnetic stirring. The temperature of reaction mixture was raised to 70 °C, maintained for 3h.
and continuously purged with nitrogen. The same procedure was repeated to prepare samples at pH 7 and pH 12.

4.2.2.2 Characterization of Hydrogels by IR Spectroscopy

The structural properties of the hydrogels were examined using a Perkin Elmer Spectrum Two FT-IR spectrophotometer fitted with a Perkin Elmer Universal ATR sampling accessory. Spectra were recorded in 4000–400 cm$^{-1}$ range using KBr pellets, acquiring 64 scans with a resolution of 1 cm$^{-1}$.

4.2.2.3 Scanning electron microscopy (SEM)

The morphology of synthesized gels was characterized with Hitachi S-3000H Scanning Electron Microscope equipped with a digital camera. Samples of the xerogels were prepared by placing small aliquots of hydrogel on carbon tape placed over sample stub, coated with gold in a Hitachi Fine Coat Ion Sputter.

4.2.2.4 Rheological measurements

Steady and dynamic rheological experiments were performed on Anton Paar MCR-102 Rheometer equipped with a Peltier temperature control system having an accuracy of ±0.01 °C. CP25-2(diameter = 25 cm, cone angle = 1.998°) was used for the measurements. A thin layer of silicone oil was placed on the periphery of the hydrogel held between the plates to prevent dehydration during rheological measurements. Oscillatory temperature, stress and frequency sweep tests were carried out to obtain flow curves for the three hydrogels. The stress sweep was performed at a constant frequency of 1 Hz to determine the linear viscoelastic region profiles by shearing them till the structural breakdown of the hydrogels. Frequency sweep in the linear viscoelastic region (stress of 35 Pa) were carried out to study the viscoelastic performance over a wide range of frequencies (0.01–100 Hz). The thermal behavior of hydrogel was investigated by temperature sweep [oscillation frequency (1 Hz), deformation (0.01)] where the hydrogels were subjected to a temperature ramp in the range of 0–100 °C with a heating rate of 2 °C/min, and to check thermo-reversibility cooled in the reverse cycle at the same rate.
4.2.2.5 Swelling studies

A completely dry weighed hydrogel sample of weight \( W_d \) was immersed in a 10 ml of 10 mM CaCl\(_2\) solution (pH 7.4) at room temperature (25 ± 0.5 °C). The surface of the swollen hydrogel was wiped dry with a filter paper and its weight (\( W_s \)) determined. The swelling ratio (SR) of polymer networks was then determined as the ratio:

\[
SR = \left[ \frac{W_s - W_d}{W_d} \right]
\]  (1)

4.2.2.6 Drug encapsulation and in vitro release

The encapsulation capacity (EC), loading capacity (LC) and release kinetics of hydrogels toward Ibuprofen was determined spectrophotometrically with a Schimadzu Spectrophotometer (model UV-1650PC) at a temperature of (25 ± 0.5) °C according to the procedure reported elsewhere.\(^{18}\)

4.2.2.7 Fluorescence measurements

The fluorescence spectra of IBU in the hydrogels were obtained on a Schimadzu Spectrofluorimeter (Model RF-5301) operating in the steady-state mode at 25 ± 0.1 °C with quartz cuvette using a 3-mm excitation/emission slit width with the procedure mentioned in our earlier work.\(^{18}\)

4.3 Results and discussion

4.3.1 Structural characterization

The IR spectra of sodium alginate, AA, CD, PEO, hydrogels at different pH’s and the drug loaded hydrogel at pH 7 are shown in Fig.4.1. Sodium alginate shows vibrational bands at 3438.5 cm\(^{-1}\) due to O-H stretch, at 2065 cm\(^{-1}\) due to C-H stretch and at 1633 cm\(^{-1}\) and 1417 cm\(^{-1}\) due to asymmetric and symmetric stretches of the carboxylate group. Further the band at 1025 cm\(^{-1}\) is due to C-O-C antisymmetric stretching.\(^{23}\) In case of CD, O-H stretching band is observed at 3391 cm\(^{-1}\) while C-H stretching band appears at 2926 cm\(^{-1}\). The band at 1640 cm\(^{-1}\) is due to O-H bending and the one at 1034 cm\(^{-1}\) due to C-O-C stretching.\(^{24}\) In acrylic acid (Fig.4.1) the IR bands at 3436,
Figure 4.1. FTIR spectra of AA, PEO, Sodium Alginate, CD, and Hydrogels prepared at different pHs and drug loaded hydrogel prepared at neutral pH.

1730 and 1633 cm\(^{-1}\) are due to O-H, C=O and C=C stretches respectively, while the one at 1417 cm\(^{-1}\) is due to CH\(_2\) bending.\(^{25}\) PEO shows bands at 3429 cm\(^{-1}\) due to O-H
stretching and at 2881 cm$^{-1}$ because of methylene stretching; the peaks at 1470.8, 1342 and 1097 cm$^{-1}$ are due to C-H deformation, CH$_2$ wagging and C-O-C stretching respectively$^{26}$. For the IR spectra of the three hydrogel samples prepared at acidic, neutral and basic pHs, the O-H stretching peak occurs at 3432, 3427 and 3422 cm$^{-1}$ respectively in the three samples indicating the strengthening of the bond at low pH and its easy dissociation at high pH. On the contrary, the carboxylic group peak at 1720 cm$^{-1}$ for the sample prepared at lower pH (pH 1), at1722 cm$^{-1}$ for the one at neutral pH (pH 7) and at 1718 cm$^{-1}$ for that at higher pH (pH 12) indicate weakening of C=O bond both at acidic as well as basic pH. This could be attributed to extensive H-bonding at pH 1 and to resonance at pH 12 when COOH groups exist as COO$^-$ ions. Further, the C=O stretching frequency is lower in all hydrogel samples when compared to the parent polymers indicating occurrence of interactions in the interpenetrating polymeric network. The peak due to C-O-C stretching shows similar type of variations. Comparison of the IR spectra of hydrogel sample prepared at neutral pH and that of the drug loaded one revealed only reshuffling of peaks with no new peak indicating that the drug is stabilized by non-covalent forces like dipole–dipole and vander Waals interactions.

4.3.2 Rheological observations

4.3.2.1 Flow curve

The flow curves of all the three hydrogels prepared at pH values 1, 7 and 12 given in Fig.4.2, shows typical gel like behavior with high viscosity at low shear rates which decreases with increase in shear rate. The hydrogel samples prepared at acidic (pH 1) as well as basic pHs (pH 12) exhibit higher viscosity at low shear rates compared to the sample prepared at neutral pH (pH 7). The probable reason could be the polarization of hydroxide, carboxylate bonds at higher and lower pHs respectively thereby increasing the magnitude of polar interactions between the constituent polymers and hence resulting in the formation of a stiffer hydrogel. Being stiff the decrease in viscosity as a function of shear rate is steeper for these samples while for the neutral hydrogel the decrease is slower resulting in its relative higher viscosity at high shear rates. To quantify the rheological response of hydrogel samples prepared at
different pHs different yield stress fluid models were applied. Bingham model shows least applicability (very low r² value) for the prepared hydrogels owing to the inherent inadequacy of the model being discontinuous and hence not valid at all deformation rates.\(^{27}\) Viscoelastic materials can be well approximated uniformly at all levels of stress as liquids that exhibit infinitely high viscosity in the limit of low shear rates followed by a continuous transition to a viscous liquid. This approximation could be made more and more accurate at even vanishingly small shear rates by means of a material parameter that controls the exponential growth of stress. Bingham model lacks an exponential stress-growth term which renders it a purely viscous one. According to Bingham model\(^{28}\)

\[
\sigma_B = \sigma_{B0} + \eta_B \gamma 
\]

Where \(\sigma_{B0}\) is the yield stress and \(\eta_B\) is the Bingham viscosity. Bingham viscosity is not a real viscosity value but describes the slope of the Newtonian portion of the curve. The values of \(\sigma_{B0}, \eta_B\) and \(r^2\) obtained for the hydrogel samples are listed in Table 4.1. Casson model \(^{29}\), an alternative to the Bingham model, has all components as in the Bingham equation raised to the power of 0.5. It consequently has a more gradual transition between the yield and Newtonian regions and tends to fit the materials better than the Bingham model but its applicability has also a narrow range and could not fit the data of this study.

Shear rate versus apparent viscosity data of the present study follows a power law \(^{27}\) with a good regression given in Table 1. According to the law

\[
\eta = K \gamma^{n-1} 
\]

K is the consistency index, a measure of average viscosity of the fluid, and n is the power law index, a measure of its deviation from Newtonian behavior. Hydrogels composed of large polymeric molecules tumble at random under low shear but gradually align themselves in the direction of increasing shear producing less resistance, thus exhibit pseudo-plastic behavior. Both K & n, included in Table 4.1, are important for a sample; once they are known the apparent viscosity can be calculated at any desired shear rate. Hydrogel prepared at acidic pH has higher average viscosity
(K) and is also significantly more shear thinning (lower n values) followed by the sample prepared at basic pH while the sample prepared at neutral pH has lower K but higher n values. Thus the model confirms the experimental observation that the hydrogel samples prepared at lower and higher pH are much harder to pour at low shear but offer much less resistance at higher shear rates when compared to hydrogel prepared at neutral pH. We also tried yield stress model of Herschel–Bulkley\textsuperscript{30}
defined by the equation:

\[ \sigma_{HB} = \sigma_{HB0} + K\gamma^n \]  

(4)

where $\sigma_{HB0}$ is Herschel–Bulkley yield stress. Unlike the Bingham equation, this model describes non-Newtonian behavior after yielding and is basically a power law model with a yield stress term. Hydrogels prepared at low and high pHs exhibit yield flow behavior, i.e., do not flow until the applied stress exceeds a certain critical value, known as the yield stress. Below the yield stress the hydrogel sample deforms elastically (like stretching a spring) and above the yield stress it flows like a liquid. The hydrogel prepared at neutral pH does not exhibit Herschel–Bulkley yield stress.

The results suggest that the hydrogels prepared at lower and higher pH have more tightly ordered packing of the dispersed phase exhibiting solid like behavior at low shear rate and thus showing a yield stress. The values of K and n as per this model (Table 4.1) show that for the yielded hydrogels the consistency exhibits the same trend as yield stress, i.e., highest for the sample with highest yield stress. The value of n is highest for hydrogel prepared at acidic pH quite different from the trend obtained for unyielded sample.
Figure 4.2. *Flow curves of three hydrogel samples prepared at different pH values.*

Table 4.1: Parameters and regression coefficient ($r^2$) of various flow models in shear rate-shear stress curve used in this study.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters</th>
<th>pH 1</th>
<th>pH 7</th>
<th>pH 12</th>
</tr>
</thead>
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<tr>
<td>Bingham</td>
<td>$\sigma_B$</td>
<td>35.05</td>
<td>5.56</td>
<td>26.31</td>
</tr>
<tr>
<td></td>
<td>$\eta_B$</td>
<td>0.11</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>$r^2$</td>
<td>0.61</td>
<td>0.46</td>
<td>0.28</td>
</tr>
<tr>
<td>Power law</td>
<td>$K$</td>
<td>45.54</td>
<td>21.99</td>
<td>36.47</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>0.24</td>
<td>0.41</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>$r^2$</td>
<td>0.87</td>
<td>0.93</td>
<td>0.88</td>
</tr>
<tr>
<td>Herschel-Bulkley</td>
<td>$\sigma_{HB}$</td>
<td>24.27</td>
<td>0</td>
<td>13.24</td>
</tr>
<tr>
<td></td>
<td>$K$</td>
<td>25.68</td>
<td>12.12</td>
<td>15.97</td>
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<tr>
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<td>$N$</td>
<td>0.44</td>
<td>0.38</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>$r^2$</td>
<td>0.97</td>
<td>0.97</td>
<td>0.85</td>
</tr>
</tbody>
</table>
4.3.2.2 Stress sweep

The stress sweep for all the three hydrogels was carried out at 25 °C and are presented in Fig.4.3. In the linear viscoelastic region (LVR) $G'$ is almost independent of the applied shear stress but at higher shear stress structural breakdown occurs. The applied stress and the resulting strain are in phase in the LVR region and beyond it the elastic modulus abruptly decreases due to the imposition of large deformations resulting in structural breakdown. $G'$ and critical shear stress (stress at which polymeric system begins to show nonlinear viscoelastic behavior) decreases with increase in pH. Since at very low pH the COO\(^{-}\) groups of alginate are completely protonated, the extent of H-bonding increases, increasing the proportion of effective intermolecular cross-links in the hydrogel network and consequently $G'$ increases. Also an increase in H-bonding increases the tensile strength of the hydrogel with consequent extension in LVR region. At neutral pH since the mole fraction of Alginic acid would be very small, the extent of H-bonding will consequently be lower compared to acidic hydrogels, resulting in decreased cross-linking density and lower value of $G'$. In the basic range the carboxylate groups would be completely dissociated, enhancing the repulsion between them and hence destabilizing the interpenetrating polymeric network. Thereby decreasing the LVR and $G'$ values.

4.3.2.3 Creep study

At constant stress we studied the strain as a function of time for the hydrogel samples prepared at different pH’s. A continuous increase of strain (creep) was observed for all the samples (Fig.4.4). The sample prepared at acidic pH behaved like a Maxwell’s body where Hooks and Stokes elements are connected in series so that the stress is equal to either of Hooks body or Stokes body but the strain is additive. Strain varied linearly with time in accordance with the behavior of Maxwell bodies\(^{31}\) as seen in the figure. The hydrogel prepared at basic pH shows creep like a Kelvin-Voigt body\(^ {31}\) where the increase in strain as a function of time is faster at the beginning and slows down later. Hydrogel prepared at neutral pH exhibited plastic flow\(^ {32}\) wherein the total strain of a body can be decomposed into a recoverable elastic strain which remains
almost constant with time and a plastic part which changes nonlinearly with time (Fig. 4.4). Thus, the hydrogels prepared at different pHs show different creep behavior.

**Figure 4.3.** Variation of $G'$ with applied stress the hydrogel samples prepared at different pH values.

**Figure 4.4.** Strain-time diagrams at a constant stress applied for the hydrogel samples.
4.3.2.4 Oscillatory frequency sweep

The variation of $G'$ and $G''$ with frequency is shown in Fig.4.5. The hydrogel prepared at pH 1 is in the gel form throughout the frequency sweep at stress 35 Pa indicating that the hydrogel is stable with respect to applied frequency without undergoing any sol–gel transition. Since strong polar interactions and H-bonding are expected at this pH\textsuperscript{33}, the hydrogel sustains the applied frequency. Both the moduli appear essentially independent over a wide range of frequency. The viscoelastic relaxation of the polymeric network seems to occur in the very low frequency region indicating that reorganization time required by network to reach equilibrium and form well defined network is quite large. When prepared at neutral pH, the hydrogel shows sol–gel transition and gellifies at moderate frequency (20.6 Hz) attributed to poor hydrogen bonding capability and poor dipole–dipole interactions. Therefore the hydrogel is in sol-phase at lower frequencies and in gel-phase at higher frequencies. The relaxation time is ideal, much longer for polymeric network systems with less significant viscoelasticity and much smaller for those with rigid solid-like behavior. Since at higher pH there occurs repulsion between the polymeric chains owing to deprotonated carboxylic ends. So the hydrogel formed is weakly viscoelastic, more liquid like with sol–gel transition at lower frequency (0.74 Hz). The results thus indicate that a more solid-like gel is formed at low pH, a weak hydrogel with more liquid like behavior is obtained at high pH while the neutral pH hydrogel exhibits ambient viscoelasticity. Elastic solid like hydrogel formed at low pH is undesirable for clinical use while as the basic hydrogel, having poor viscoelasticity is quite unstable to the applied frequency probably due to the repulsion between carboxylate anions. However, the hydrogel prepared at neutral pH is stable over a good range of frequency besides showing the sol–gel transition as the degree of H-bonding and electrostatic repulsion is intermediate to the systems prepared at higher and lower pH’s.

4.3.2.5 Oscillatory temperature sweep

The temperature sweep plots of the hydrogels are given in Fig.4.6. The behavior of the three hydrogels is significantly different indicating the difference in their structure
For the hydrogel prepared at acidic pH, it is observed that throughout the temperature sweep both during heating and cooling $G'$ is higher than $G''$ and also the values of both the moduli are large when compared to the hydrogels prepared at neutral and basic pHs. As already noted, at lower pH protonation of the COO$^-$ groups reduces the repulsion between polymeric chains with a consequent increase in H-bonding, as reported for polymers like PAA and PEO $^{34}$, so the number of effective crosslinks increases resulting in the formation of a harder gel with higher $G'$ and $G''$ values. Further, the cooling curves for both $G'$ and $G''$ display a dip probably due to precipitation of alginic acid within this temperature range under acidic conditions as reported in earlier studies$^{33}$. The neutral pH hydrogel exhibits thermoreversible nature, the gel breaks near 90 °C and remains in the sol-phase at higher temperatures. The hydrogel retains its sol form upon cooling upto a temperature of 55 °C. These results show that the crosslinks responsible for gellification break at higher
temperature for the hydrogel prepared at neutral pH and the hydrogel is stable only at low to moderate temperature. Since the degree of neutralization and extent of H-bonding is reduced with increase in pH, the resulting neutral hydrogel is more viscoelastic and suitable for pharmaceutical applications. For the hydrogels prepared at pH 12, we observed that the hydrogel remained in the gel phase almost throughout the heating sweep changing into the sol phase only toward the end of the sweep. However, it remains in the sol-phase throughout the cooling sweep. Thus, the breaking of hydrogel crosslinks for this pH is irreversible indicating that once the gel breaks the magnitude of electrostatic repulsion is too high to allow gellification even at very low temperatures.

**Figure 4.6.** Temperature sweep of the hydrogel samples during heating and cooling cycle between 0 and 100 °C.
4.3.3 Morphological analysis

The SEM micrographs of the hydrogels prepared at the three different pH’s are given in Fig. 4.7. Hydrogel prepared at low pH shows porous structure, rougher and denser morphology with some deep and interconnected pores. Such morphologies are frequently encountered in highly cross-linked gels. The morphology changes to a smoother sheet like structure with less porosity for the hydrogels prepared at neutral pH. The smoothness and experimentally observed enhanced swelling capacity of this hydrogel could be attributed to its relatively sparse H-bonding capability. The hydrogel prepared at pH-12 shows light cavities and less porosity relative to hydrogel prepared at pH-1. The rough and dense morphology of hydrogel prepared at basic pH when compared to hydrogel prepared at neutral pH may be a consequence of enhanced hydrophilicity owing to higher degree of dissociation of alginic acid at this pH.

(A-Series)

(B-Series)

(C-Series)

Figure 4.7. SEM micrographs of A series) Hydrogel prepared at pH1 B series) Hydrogel prepared at pH7 C series) Hydrogel prepared at pH12 under different magnifications.
4.3.4 Swelling capability

The swelling ratio is less for the hydrogel prepared at pH 1, increases sharply for the hydrogel prepared at neutral pH but again decreases sharply for the samples prepared at pH 12. At low pH, extensive H-bonding between OH, CO and COOH groups increases the crosslinking density and hence results in small swelling ratio. For the hydrogel prepared at neutral pH most of COOH groups are in the dissociated state and the hydrogen bonding among COOH, OH and CO groups is disrupted. The electrostatic repulsion between the polymer chains makes the hydrogel to swell dramatically. In the hydrogel prepared at basic pH, the polymeric chains disintegrate in the aqueous CaCl\(_2\) solution before the hydrogel swells, resulting in decreased swelling ratio.

4.3.5 Drug encapsulation capacity and release kinetics of hydrogels toward IBU

Ibuprofen encapsulation by the three hydrogels was investigated and it was observed that the hydrogels prepared at different pHs exhibit different drug encapsulation and loading capability toward Ibuprofen. The encapsulation capacity (EC = 45.76\%) and loading capability (LC = 0.176) is lowest for the hydrogel prepared at lower pH, it increases for the one prepared at neutral pH, (EC = 54.73\% & LC = 0.211) and then again decreases for the hydrogel prepared at higher pH (EC = 50.78\% & LC = 0.196). Ibuprofen is stabilized through H-bonding and polar interactions of the drug molecules with the ionized groups of the polymer chain and through hydrophobic interaction between the respective hydrophobic moieties of the drug and hydrogel. The pKa value of Ibuprofen being 4.5, so its solubization will be mainly governed by H-bonding with the hydrogel prepared at pH1. Besides the steric and electrostatic interactions, the hydrogel prepared at pH 1 is extensively cross-linked so that the unbalanced charges are satisfied. This results in the formation of more rigid solid-like structure having less appeal for the drug and consequently reducing its solubilization capability toward Ibuprofen compared to other systems. For the neutral pH hydrogel both the dipole–dipole and H-bonding interactions seems to be optimum for the solubilization of IBU. On the contrary though the crosslinking is least in the hydrogel prepared at higher pH, steric and electrostatic repulsive interaction seem to be
operative between the carboxylate anions of Ibuprofen and hydrogel sample which explains its relatively lesser solubilization capability than for the hydrogel prepared at neutral pH. The drug release profile for the hydrogels is presented in Fig.4.8. It was obtained by plotting a curve of $M_t/M$ against $t$, where $M_t$ is the amount of drug released in time $t$ and $M$ is the amount released once the equilibrium state is reached. The Higuchi model describes drug release as a diffusion process based on the Ficks law:

$$F_t = K_H t^{1/2}$$  \hspace{1cm} (5)

![Higuchi model fit of the experimental data for the hydrogel samples.](image)

**Fig.4.8.** (a) Ibuprofen release profiles of the hydrogel samples prepared at different pH values measured in methanol at 25°C, (b) Higuchi model fit of the experimental data for the hydrogel samples.
Where, $K_H$ is the Higuchi dissolution constant and $F_t$ is the amount of drug released in time $t$ per unit area. A good correlation was obtained between Higuchi model and experimental data for first 100 min given in Fig.4.8 with $r^2$ values 0.99, 0.96 & 0.99 and $K_H$ values of 0.0874, 0.0937 & 0.1016 mmol mm$^{-1}$min$^{-3/2}$ for the hydrogel prepared at pHs 1, 7 and 12 respectively (Table.4.2). The results reveal that the release rate of Ibuprofen is faster from the hydrogel sample prepared at basic pH the possible reason for which may be the electrostatic discomfort between the hydrogel and the drug molecule. The difference in release rates of the drug from neutral and acidic pH hydrogel can be attributed to its different solubilities. The saturation solubility of Ibuprofen in the hydrogel prepared at neutral pH is more, so the high concentration of Ibuprofen can lead to a large concentration gradient resulting in high osmotic pressure that favors the diffusion of Ibuprofen molecules out of the hydrogel.

**Table.4.2:** Data of release kinetics of drug and Higuchi model for the hydrogel samples.

<table>
<thead>
<tr>
<th>pH1</th>
<th>Time</th>
<th>$M/M$</th>
<th>$t^{1/2}$</th>
<th>$F_t$</th>
<th>pH7</th>
<th>Time</th>
<th>$M/M$</th>
<th>$t^{1/2}$</th>
<th>$F_t$</th>
<th>pH12</th>
<th>Time</th>
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4.3.6 Partitioning of IBU

IBU has emission maximum at around 280 nm in polar solvent water which shifts significantly to 380 nm in nonpolar solvent CCl₄, indicating high degree of sensitivity of the drug emission toward solvent polarity. Fig.4.9 reveals the change in emission spectrum of the drug at different concentrations of hydrogel prepared at neutral pH. Addition of hydrogel to the solution of drug in ethanol decreases the intensity of the peak at 289 nm and simultaneously a new peak appears at 370 nm. This indicates that the drug gets partitioned between ethanol represented by the peak at 289 nm and hydrophobic regions of the hydrogel represented by the appearance of peak at 370 nm. Successive additions of the hydrogel to the drug solution results in increase in peak intensity at 370 nm with simultaneous decrease at 289 nm indicating migration of higher fraction of IBU from polar to non-polar region of the medium.

Figure 4.9. Fluorescence spectra of IBU at different concentrations of hydrogel prepared at neutral pH.
4.4 Conclusions

The structure and hence properties and behavior of the composite alginate hydrogel (containing pH sensitive polymers) was found to be a function of pH of the synthetic medium. Interaction between polymers in a composite hydrogel changes with pH resulting in dramatic changes at the macroscopic level. The hydrogel prepared at pH 1 is more elastic, apparently independent of applied frequency and temperature. Further its drug encapsulation capacity is low and also releases the drug slowly. Hydrogel prepared at neutral pH has desirable viscoelasticity, higher encapsulation capacity and comparatively faster release rate. The hydrogel prepared at pH 12 was found to be more like a liquid and unstable to temperature and the applied frequency. Further its encapsulation capacity is lowest of all the studied hydrogels with fastest release rate.
References

1. Van, V.S.; Dubruel, P.; Schacht, E. Biomacromolecules. 2011, 12, 1387.


