Swelling Studies on Hydrogel Networks —A Review

S K Bajpai

Department of Chemistry, Government. Autonomous Science College, Jabalpur 482 001, India

The paper describes the wide spectra of studies that have been carried out in the recent past on the swelling behaviour of external stimuli responsive polymeric hydrogel networks, both naturally occurring as well as synthetic. It also highlights the condensed mathematical approach of Flory - Rehner theory describing the equilibrium-swollen state of hydrogels. A most widely accepted mechanism of swelling process of both ionic and non-ionic hydrogels has also been mentioned.

Introduction

Hydrogels are macromolecular networks which have ability to swell in water or aqueous solvent systems. The polymer network is able to retain the solvents, forming a gel phase and will not dissolve, if cross-linked, regardless of the solvent. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone and the difference in swelling osmotic pressure between gel phase and solvent phase which is created in the case of ionic hydrogels. The resistance to dissolution arises from crosslinks between network chains. Many materials, both naturally occurring and synthetic, are examples of hydrogels. Crosslinked guar gum and collagens are examples of natural polymers that are modified to produce hydrogels. Classes of synthetic hydrogels include poly (hydroxyalkyl methacrylates), poly (acrylamide), poly (N-vinyl pyrrolidone), poly (acrylic acid) etc.

Synthetic hydrogel networks are useful for applications that require a material with good compatibility with aqueous solvents, without getting dissolved into it. Some of the major applications include biomaterials, chromatographic packings, controlled-release devices and electrophoresis gels. Many properties of synthetic hydrogels make them suitable for biomedical applications that require contact with living tissue. Their ability to retain aqueous media gives them a strong superficial resemblance with living tissues and also makes them permeable to small molecules such as oxygen, nutrients and metabolites. The low interfacial tension between the hydrogel surface and the aqueous solution has been found to minimize protein adsorption and cell adhesion. Moreover, synthetic hydrogels can be fabricated in various shapes (e.g. cylindrical, disc, slab, nanoparticles) and can be easily washed to remove residual initiators and monomers or other undesirable byproducts.

The first polymer which gained acceptance for man-made plastics was poly (methyl methacrylate). It was observed that many pilots ended the war with PMMA splinters from their aircraft canopies embeded in their eyes, which was surprisingly tolerated by their eyes. But the first polymer of choice, precursor of the broad class of materials known today as hydrogels, was polyvinylalcohol (PVA) applied in surgery under the trade name Ivalon. It was crosslinked with formaldehyde, and could withstand autoclaving temperatures. Tissue reaction to the implanted Ivalon is very mild, but after prolonged periods shrinkage and calcification were observed. However, its application in plastics surgery or as bone and postenucleation implants have been reported.

In the 50s Wichterle and Lim synthesized a hydrophilic polymer based on hydroxyethyl methacrylate, and crosslinked with diesters of methacrylic acid and mono-, di-, and tri-ethylene glycols. Despite some technological problems in the beginning, poly HEMA was successfully used as a biotolerable material, primarily as a main component of contact lenses, but also in many other medical fields. HEMA and its various combinations with others, both hydrophilic and hydrophobic polymers, are till now the most often used hydrogelic materials for medical purposes.

The high solute permeability of hydrogels has led to their use in devices for controlled release of drugs or other active agents. The release of drugs from these hydrogels (initially dried) involves the absorption of
water into the matrix and simultaneous desorption of drugs via diffusion, as governed by Fick's law. The process can be modelled using a free-volume approach or a swelling-controlled release mechanism. Furthermore, controlled release of drugs from hydrogel nanoparticles and microspheres, allows the possibility of targeting the drug to the specific sites in the body where the drug is needed. This targeting may make optimum use of expensive drugs while minimizing system-wide toxic effects.

Besides their use in biomedical filed, hydrogels have also been used as extraction solvents, enzyme reactors, in the removal of metal ions from the solutions, in adsorption of proteins etc. In fact, several reviews have appeared from time to time, describing the applications of hydrogels in different fields. Shailaja and Yaseen have reviewed the applications of polymer monolithic systems for controlled release of agrochemicals, and Kazanski and Dubrovskii have reviewed the chemistry of hydrogels in agricultural applications. Davies and Tighe have reviewed the potential of hydrogels in sensor applications and Singh et al. and Corkhill et al. have reviewed the design of hydrogels for various medical applications.

**Synthesis of Hydrogels**

The synthesis of polymeric hydrogels is typically accomplished by one of two well-established schemes: (a) Polymerization of hydrophilic monomers and (b) Modification or functionalization of existing polymers. Various reviews have discussed in detail the synthetic methods of hydrogels. For example, a comprehensive review, describing the chemistry and various synthetic schemes have appeared in various chapters of a compilation edited by Peppas. More recently, Rosiak et al. and Mathur et al. have reviewed methods for synthesis of hydrogel networks. Table 1 describes the commonly used monomers for synthesis of hydrogels.

**Theory of Swelling Equilibrium**

The state of equilibrium swelling of a polymer network immersed in a solvent is obtained when the solvent inside the network is in thermodynamic equilibrium with the outside. This equilibrium state is described by the equality of the solvent chemical potential in both phases. Thus, at swelling equilibrium, we have:

\[ \Delta \mu^i = \Delta \mu^s, \]

where the subscripts g and s denote the gel and solution phases, respectively. In terms of the osmotic pressure \( \pi \), Eq.(1) can be written as:

\[ \pi = \frac{\mu^s - \mu^i}{V_f} = 0, \]

where \( V_f \) is the molar volume of solvent. Osmotic pressure \( \pi \) of a gel determines whether the gel tends to expand or shrink. When nonzero, \( \pi \) provides a driving force for the gel volume change. Within the framework of the Flory-Rehner theory, the osmotic pressure \( \pi \) of the gel is the sum of three contributions:

\[ \pi = \pi_{\text{mix}} + \pi_{\text{el}} + \pi_{\text{ion}}, \]

In above equation, \( \pi_{\text{mix}} \) represents the tendency of mixing of the polymer and solvent, while \( \pi_{\text{el}} \) accounts for the elastic response of the network due to crosslinking which opposes the dissolution. Moreover, \( \pi_{\text{ion}} \) denotes the osmotic pressure resulting from the difference in the ion concentrations between the swollen gel and the external solution.

According to the Flory-Huggins theory, \( \pi_{\text{mix}} \) is given as:

\[ \pi_{\text{mix}} = -\frac{RT}{V_1} \ln \left( 1 - u_2 \right) + u_2 + X_2 u_2^2, \]

where \( u_2 \) is the volume fraction of polymer in the hydrogel, \( X \) is the polymer - solvent interaction parameter, \( R \) is the gas constant, and \( T \) is the temperature. To describe the elastic contribution \( \pi_{\text{el}} \) to the swelling pressure, several theories are available. However, according to the simplest network model describing the behaviour of gels,

---

Dr S K Bajpai is Assistant Professor in Department of Chemistry, in the Government Autonomous Science College, Jabalpur, having 20 y teaching experience. He obtained his Ph.D in Chemistry from Jabalpur University in 1997 on 'Adsorption Behaviour of Polymers'. Presently, he is working on site specific drug delivery systems. He has published over 15 research papers in various journals of international repute.
Table 1—Commonly used synthetic monomers for hydrogel synthesis

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Abbreviation</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethyl methacrylate</td>
<td>HEMA</td>
<td>[ \text{CH}_2=\text{C}*(\text{CH}_3)\text{COOCH}_2\text{CH}_2\text{OH} ]</td>
</tr>
<tr>
<td>Methoxyethyl methacrylate</td>
<td>MEMA</td>
<td>[ \text{CH}_2=\text{C}*(\text{CH}_3)\text{COOCH}_2\text{CH}_2\text{OCH}_3 ]</td>
</tr>
<tr>
<td>Ethylene glycol dimethacrylate</td>
<td>EGDMA</td>
<td>[ \text{CH}_2=\text{C}*(\text{CH}_3)\text{COOCH}_2\text{CH}_2\text{OOC} ]</td>
</tr>
<tr>
<td>Acrylic acid</td>
<td>AA</td>
<td>[ \text{CH}_2=\text{CH} ]</td>
</tr>
<tr>
<td>Methacrylic acid</td>
<td>MA</td>
<td>[ \text{CH}_2=\text{C}*(\text{CH}_3)\text{COOH} ]</td>
</tr>
<tr>
<td>Methyl methacrylate</td>
<td>MMA</td>
<td>[ \text{CH}_2=\text{C}*(\text{CH}_3)\text{COOH}_3 ]</td>
</tr>
<tr>
<td>N-vinyl-2-pyrolidone</td>
<td>NVP</td>
<td>[ \text{CH}_2=\text{CH}\text{NCOCH}_2\text{CH}_2\text{CH}_2 ]</td>
</tr>
</tbody>
</table>
| Vinyl acetate                   | VAc          | \[ \text{CH}_2=\text{CH}***

The ionic contribution \( \pi_{\text{ion}} \) to the swelling pressure is caused by the concentration difference of counterions between the gel and the outer solution. To describe this effect completely, one should consider the ion-ion, ion-solvent and ion-polymer interactions. However, the ideal Donnan theory ignores these interactions and gives \( \pi_{\text{ion}} \) as the pressure difference of mobile ions inside and outside the gel:

\[
\pi_{\text{ion}} = RT \left( C_i^+ - C_i^- \right), \quad \ldots (6)
\]

where \( C_i \) is the mobile ion concentration of species \( i \). According to ideal Donnan equilibrium, the chemical potential of an ionic species \( i \) inside the hydrogel must be equal to that outside.

Thus, for aqueous solutions of univalent salts, we have:

\[
C_i^+ C_{\text{salt}}^e = C_i^- C_{\text{salt}}^e = C_{\text{salt}}^e. \quad \ldots (7)
\]

where \( C_{\text{salt}}^e \) represents the salt concentration in the external solution. On the other hand, the condition of electroneutrality inside the ionic hydrogel requires:

\[
C_{\text{salt}}^e = C_{\text{fix}}^e + C_{\text{fix}}^- \quad \ldots (8)
\]

and

\[
C_{\text{salt}}^e = C_{\text{fix}}^+ + C_{\text{fix}}^+ \quad \ldots (9)
\]

where \( C_{\text{fix}} \) is the concentration of the fix charges in the gel and Eq. (8) and (9) holds for anionic and cationic hydrogels, respectively.

Eqs (1-9) can be used to get expressions for equilibrium value of \( v_2 \) for the hydrogels and the distribution.
coefficient $K$ of the counter ions between the gel and solution phases.

In the case of swelling of hydrogels in water, free of ionic species ($C_{\text{salt}} = 0$), the above set of Eqs (1-9) may yield the following equation:

$$
\ln \left(1 - u_2\right) + u_2 + Xu_2
+ N^{-1}(u_2^{1.5} + \rho_2^{2/3} - u_2/2) - V_1 C_{\text{fix}} = 0 ,
$$

Moreover, for highly swollen gels, since $u_2 < 1$ the final equation can be written as:

$$
- (0.5 - \chi) u_2 + N^{-1} \rho_2^{2/3} u_2^{1/3}
- 2 V_1 C_{\text{salt}}^{(K-1)} - V_1 C_{\text{fix}} = 0 ,
$$

where $K = 0.5$

$$
\sqrt{\left[\frac{C_{\text{fix}}}{C_{\text{salt}}}\right]^2 + 4\left[\frac{C_{\text{fix}}}{C_{\text{salt}}}\right]} = 1
$$

Mechanism of Penetrant Uptake

Dynamic penetrant sorption into initially glassy non-ionic polymers generally involves a complex set of mass transport steps when the penetrant/polymer pair have compatibility. As the penetrant invades the polymer from the sample surface, a sharp boundary or moving front is commonly observed separating the unsolvated glassy polymer region ahead of the front from the swollen and rubbery get phase behind it\(^{18}\). Just ahead to the front the presence of solvent plasticizes the polymer and causes it to undergo a glass-to-rubber transition that initiates chain relaxation process and swelling\(^{19}\).

The time duration of overall penetrant uptake often deviates from classical Fickian diffusion behaviour when sorption is accompanied by a glass-to-rubber transition in the polymer\(^{20}\). In Fickian sorption the initial uptake in polymeric slabs is proportional to $r^{0.5}$ and is commonly observed in penetrant sorption into polymers well above $T_g$ (ref.21). In glassy polymer, however, sorption is often proportional to $r^n$, when the kinetic exponent $n$ can take on values between 0.5 and 1.0. This non-Fickian or anomalous sorption behaviour is generally associated with the concurrent process of inward diffusion of penetrant from the solution/gel interface and the process of polymer relaxation that occurs in response to penetrant invasion and plasticization at the moving front\(^{22}\).

This swelling process of gels in excess electrolyte solutions become more complex when sorption of water is accompanied by ionization of gel itself. For gels that contain weakly acidic or basic groups the ionization state of the gel will depend upon the electrolyte composition of the bulk solutions. During the process of dynamic water sorption in gels containing weakly basic groups, transport of mobile ions into the gel from the bulk solution is necessarily coupled to water sorption as the gel becomes hydrated and ionized. This coupling is required to maintain electroneutrality in the swollen gel phase. Furthermore, when the gel is initially glassy, polymer relaxation process will also contribute to the over all dynamics of water sorption as mentioned earlier.

Studies on Swelling Behaviour

In fact, several studies have been carried out in the past three decades, thus unfolding various aspects of swelling behavior of hydrogels. Here some of the most significant studies carried out in the recent past are critically presented so that a concrete base can be formed for those who wish to explore further possibilities of using swelling based properties of various types of polymeric systems in different technological, biomedical and other related fields in near future.

Studies With Chemical Signals - Responsive Gels

Some of the significant studies carried out with hydrogels sensitive to chemical signals in the swelling media are discussed. The Swelling behaviour of these polymer matrices depends upon factors like pH, ionic strength of the external solution.

However, most of the studies are based or pH- responsive gels which contain certain groups that undergo protonation/ionization with varying pH of the solution, thus causing a change in osmotic swelling pressure and hence swelling capacity.

The swelling response of these gels depends on size and shape of the hydrogels. A pioneering theory of gel swelling is developed of Tanoka-Fillmore\(^23\) (TF) according to which:

$$
t = \frac{R^2}{D} ,
$$

where $t$, $R$ and $D$ are characteristic time for the gel swelling, the size of the gel and cooperative diffusion coeffi-
cient respectively. As it is not easy to increase value of $D$ by a factor of 10$^2$ or more, the reduction of gel size is the only way to achieve quick response. For example, microgels (1-10 µm diam) show a faster response than the slab gels, 0.5 s vs h to d, to reach swelling equilibrium with their chemical surroundings.

The small-size and quick response of microsphere hydrogels have promoted their use in drug delivery and therapeutic applications$^{24}$ Moreover, they may be targeted to certain diseased tissues and even be taken up into the intracellular compartment of target cells. The micrometer sized (4-7 µm diam) poly (methylacrylic acid) (PMMA) hydrogel microspheres$^{25}$ exhibit a sharp volume change with pH-change in a very short period of 300 ms. This indicates that swelling rate is determined by the diffusion of the polymer matrix and not of ions into and out of the microsphere. Moreover, such quick pH-responsive volume change may have physiological importance as the time course of swelling for naturally occurring mast cell granules is also of the similar order.

Likewise, a pH-responsive hydrogel membrane, obtained by the copolymerization of N-isoproplacrylamide and acrylic acid$^{26}$ demonstrates pulsatile lengthwise swelling-deswelling similar to heart beat when placed in a continuous flow stirred tank reactor (CSTR) in which regular supply of the reactants hydrogen peroxide, hydrogen sulphite and hexacyanoferrate(II) is made. Such self-oscillating gel system may contribute to further understanding of biological phenomena. Similarly, a blend hydrogel, made of poly (allylguanidino-co-allylamine) and poly (vinyl alcohol)$^{37}$ shows pH dependent swelling behaviour. The membrane shrinks below pH 3 and above pH 10 while it is little affected in the range 3-10. Moreover, with the variation in ionic strength, the size of the membrane changes gradually. The multiple protonation states displayed by PAG and the shielding of electrostatic interaction among the charges on the polymer backbone by the added electrolyte play a key role in explaining above phenomena.

Polymer supports with complexing groups have been widely investigated by a number of workers$^{29,30}$ for the removal of metals in the homogeneous phase. A poly ($N,N'$- diethylacrylamide - co- acrylic acid) membrane hydrogel$^{30}$ shows a fair tendency to undergo complexation with metal ions like Co (II) Ni (II) etc., which form stable complexes with gels in the pH range 5-7. The complexation ability of the hydrophilic polymer depends upon pH and the filtration factor. The carboxylic acid moieties interact more strongly with the metal ions than do the tertiary amide moiety, particularly at pH 5 and 7. Similarly, the poly ($N$-vinylimidozole) hydrogels also bind with metal ions such as Cu(II), Co(II), Ni(II) etc as well as uranyl, vanadium, rhenium and molybdenum complexes$^{31}$. The binding ability of the hydrogels with metal ions depends upon the crosslinking degree of the gel, solution pH, concentration of the cation and the time of the cation-hydrogel equilibrium.

The crosslinked poly(acrylic acid) hydrogels$^{32}$ show a pH-dependent tendency to retain chromium. The chromium retention increases with pH in accordance with the two mechanisms. In the low pH range soluble chromium species are retained via ion-binding in the whole volume of the gel while at higher pH, the retention of insoluble chromium hydroxide is due to adsorption at the surface of the gel. The desorption of chromium species depends on the retention mechanism. When retention occurs via ion-binding, only partial desorption is achieved at very short aging time, while a fast desorption is achieved when retention occurs via adsorption at the surface.

When a polyelectrolyte gel is placed in a salt solution, the binding of coutherions with the polycations of the network influences the state of the hydrogel. The swelling of poly (sodium acrylate-acrylic acid) hydrogels$^{33}$ in dilute copper sulfate solution is associated with the presence of up to three coexisting phases: a dry phase, a swollen phase and a collapsed one due to the binding of metal ions to polycations. However, in the concentrated copper sulphate solution the hydrogel just absorbs a small amount of solvent.

The hydrogels, synthesized from natural proteins and polysaccharides also exhibit a fair swelling tendency depending upon various external conditions like pH, ionic strength etc. The interpenetrating network of gelatin and polyacrylamide$^{34}$ show a pH and temperature dependent swelling behaviour. At low pH, maximum swelling is observed due to larger presence of carboxylic groups which increases the diffusional flux of the carrier species into the hydrogel. With further increase of pH, the swelling decreases and finally it attains constant value in the alkaline range. Moreover, the swelling in creases with the temperature upto 50°C and than attains constant value. This may possibly be due to the formation of a complex structure between the amide and carboxylic groups produced due to the partial hydrolysis of polyacrylamide. Similarly, the hemoglobin-
crosslinked polyacrylamide hydrogels also exhibit maximum swelling at pH 7.0 while it decreases on either sides along the pH scale. Here also the possible hydrolysis of polyacrylamide seems to be responsible for pH-dependent swelling. The gels also undergo a number of swelling-drying cycles without undergoing any structural deformation.

The gelatin-sodium carboxymethyl cellulose (NaCMC) hydrogels also exhibit pH and temperature dependent swelling behaviour. The increase in the swelling capacity with pH is due to the ionization of carboxylic groups in NaCMC, whereas the swelling increases with temperature up to 50°C and then starts decreasing, possibly due to degradative process in the protein chain. The energy of activation for the swelling process is found to be on higher side as it involves the entire process of solvent entry, stretching of the network segments and consequent large scale dimensional change in the network.

The hydrogels containing carboxylic groups are suitable for the oral drug delivery of peptides as they can protect the encapsulated drug from the acidic environment of stomach by minimum swelling. The hydrogels composed of poly (methacrylic acid) (PMAA) grafted with poly (ethylene glycol) (PEG) can be used as drug delivery carriers for the oral administration of the polypeptide hormone salmon calcitonin (CST). The gels release the polypeptide hormone at pH 7.0 at 37°C with the ionic strength 0.1 M. The release behaviour is not much affected by the amount of diluent used during the polymer preparation. The devices follow relaxation controlled transport mechanism.

Amphiphilic hydrogel networks, are random assemblages of hydrophobic and hydrophilic chains and they swell in water as well as in non-polar solvent. The urethane acrylate hydrogels containing ionic groups (dimethylol propionic acid DMPA) with varying molecular weight of hydrophobic segment (poly ether type, PTMG) show amphiphilic properties. They also show pH-responsive swelling due to the presences of carboxylic groups in the polymer matrix. Owing to their amphiphilic nature, they can release the hydrophilic drugs (e.g. riboflavin) as well as hydrophobic drug (e.g. indomethacin) loaded into the gel matrix.

It is a well known fact that low molecular weight compounds (M.W.< 2900) can pass through membranes derived from chitosan. The release of ampicillin from the chitosan-amine oxide follows a pH-dependent release pattern due to the protonization of amino groups and dissociation of hydrogen bonding within the network with change in solution pH. The size of the polymer matrix decreases with time and finally the matrix disintegrates into pieces. This suggest that erosion takes place from the surface as well as from the bulk of the matrix. Therefore, the drug releases from the device by a combination of diffusion and erosion.

One of the ways to immobilize proteins and retain their biological activity is based on the complex formation between the oppositely charged protein and the polymer carrier. The polyelectrolyte hydrogels containing pendant phosphate groups are the suitable device for the loading and release of cationic protein drugs. The anionic hydrogels, synthesized by copolymerizing 2-methacyryloxyethyl dihydrogen phosphate and N, N, methylenebisacrylamide form complexes with the cationic protein lysozyme. The lysozyme loaded hydrogel releases the protein when placed in KCl solution of varying concentrations. This confirms that lysozyme is loaded in the hydrogel through electrostatic interactions. The ionic strength-dependence of release rate suggests that the ionic interactions of phosphate groups with the cationic charge of lysozyme are replaced with small electrolytes.

The structure-dependent swelling of hydrophilic polymers has been exploited for the release of perfumes, deodorants, essential oils. The glassy hydrophilic copolymers of 2-hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) demonstrate swelling controlled release of essential oils like carvone, limonene and eugenol. The zero-order release can be achieved by changing the degree of crosslinking. The minimum difference between the solubility parameter of hydrogel and that limonenc clearly indicates that maximum compatibility is achieved in the case of limonene-polymer pair.

The polymer matrices may provide an attractive alternative for the spray of pesticides to plants/soil to control the pests. The less toxic pesticide, such as neem seed oil (NSO) may be released from granular hydrogels containing crosslinked starch and guar gum. In order to have release for shorter time with higher concentrations of NSO, crosslinked starch matrix is more effective in soil applications especially at low moisture contents, while for higher moisture containing soil applications, guar gum is more effective as it swells less as compared to starch. The FTIR results of NSO loaded devices indi-
cate the absence of chemical interaction between NSO and polymer materials.

The studies involving absorption of multivalent cations in the negatively charged polyelectrolyte gels have mostly concentrated on their macroscopic swelling behaviour and their correlation with the distribution of multivalent ions between the gel and the exterior solution. The data on the molecular mechanism of the binding of ions to the network counter charges remain rather scare. However, a study of such possible interaction of polyamionic hydrogels composed of poly(acrylic acid) and (poly methacrylic acid) with multivalent cations in the aqueous medium, as examined by using europium ions as fluorescence probes, indicates a strong and asymmetric binding of carboxylate group of Eu ions, leading to the expulsion of up to five water molecules from the solvation shell of the ion. The relaxation studies of the non-radiative energy transfer from europium to neodymium ions inside the gel reveals the formation of aggregates consisting of ca. seven rare earth ions (together with the corresponding counter charges of the network chains). The aggregates are stabilized by high level of polarization of the quadruplets (RE$_{7}^{3+} + 3$ COO$^{-}$).

Natural fibres like cellulose, possessing fair mechanical strength due to high degree of orientation can be provided with fair swelling tendency through graft-polymerization with some hydrophilic monomers. For example, the ozon-induced graft polymerization of acrylic acid using cotton linters and wood pulp fibre substrates results in the formation of cellulose-fibre supported pH-sensitive hydrogels, with fair swelling tendency and good mechanical properties. At low pH the hydrogel shows minimum swelling which increases with the pH of the solution and finally becomes constant. Moreover, exposure of the hydrogel to alkali and subsequent drying results in an irreversible deformation of the hydrogel which, may be made reversible by addition of a bifunctional monomer, ethyleneglycol dimethacrylate into the monomer mixture at the time of grafting.

The pH-dependent swelling property of polybasic hydrogels has been exploited by a number of workers to develop glucose sensitive insulin release devices which contain immobilized enzyme glucose oxidase in a the matrix enclosing saturated solution of insulin. When the glucose, present in the swelling medium diffuses into the hydrogel, glucose oxidase catalyses its conversion to gluconic acid thereby lowering the pH of the gel micro environment, and resulting in the protonation of basic groups to cause the gel to swell with the subsequent release of entrapped insulin. A mathematical model describing these glucose-responsive hydrogels demonstrates two important points: (1) Progressive response to glucose concentration over a range of glucose concentration can be achieved only with a sufficiently low loading of glucose oxidase, otherwise, depletion of the oxygen causes the system to become insensitive to glucose and (2) a significant pH decrease in the hydrogel can be achieved only if the amine concentration is sufficiently low.

Recently, attention has been focused on employing natural polymers such as cellulose, starch, chitosan etc. to compose hydrogels with specific response to biological environment. The graft-copolymerization of chitosan (CS) and D, L-lactic acid (LA) results in the formation of pH-sensitive and biodegradable polymeric hydrogel. These hydrogels show maximum swelling in enzyme - free simulated gastric fluid (SGF, pH 2.2) due to the protonation of amino groups which finally increase the osmotic pressure and chain relaxation process. However the gels demonstrate minimum swelling in simulated intestinal fluid (SIF, pH 7.4) due to deprotonization of the protonated amino groups. In this way the gels possess different structures in acid and basic medium. FTIR studies also confirm the hypothesis.

Studies with Physical Signals - Responsive Hydrogels

Some of the most significant studies based on hydrogels responding to physical signals such as temperature, electric field, magnetic field, etc. are discussed. Out of these, temperature-sensitive gels have been studied most widely because of their special characteristic of undergoing drastic volume change at a definite temperature called lower critical solution temperature (LCST). Such hydrogels have a variety of applications in medical, pharmaceutical, industrial and technological fields.

In most of the applications, such hydrogels, a fast swelling-shrinking is required. Although microgels or thin gel membranes exhibit this property but they possess a poor mechanical strength. On the other hand hydrogels with porous structure swell or shrink very fast as compared with non porous gels of the same size. The free radical polymerization of N-isopropylacrylamide (NIPAAm) or N,N diethylacrylamide (DEAAm) results in the formation of hydrogels consisting of aggregated microgel particles, namely a porous structure. The gels
both pH and temperature sensitive properties may be temperature sensitive polymeric materials. The interpenetrating polymer network, (IPN) composed of temperature sensitive poly (N-isopropylacrylamide) and pH sensitive poly (methacrylic acid) exhibits a combined pH and temperature sensitivity at the temperature range of 31-32°C and pH value of approx 5.5, thus suggesting the independent response of each network in these IPNs, which is also verified by differential scanning calorimetry (DSC) measurements. The permeation study results indicate a significant size exclusion behaviour while model drugs with different sizes permeate through the IPN membranes.

The condition of synthesis of a hydrogel effects its properties significantly. The poly (N-isopropylacrylamide) (PNIPA) gels, prepared in the form of rods and slabs by solution and inverse polymerization techniques exhibit different swelling properties. The solution polymerization technique at temperatures as high as 35°C leads to the formation of heterogeneous PNIPA gels with high water retaining capacity. The swelling capacity further increases for the gels prepared in the form of beads using inversion suspension polymerization method. The PNIPA gels, synthesized by solution suspension polymerization demonstrate greater extraction efficiency in concentrating dilute solutions bovine serum albumin (BSA) as compared to the gels prepared by suspension polymerization.

The sharp volume phase transition, exhibited by thermoresponsive gels is often used for the removal of metal ions from the aqueous solutions. The microgel dispersions of poly (N-isopropylacrylamide) with cationic or anionic surface charge groups absorb significant amount of ions from aqueous solutions at 25°C. Under these conditions the microgel particles can be envisaged as porous-like materials with spherical conformation consisting of numerous interstitial spaces. At 50°C a reversible contraction of microgel takes place thus causing a large amount of the retained material to be released from within the closed interstitial spaces of the structures. The nature of ionic initiator used in the polymerization of microgel particles shows a considerable influence on the affinity of each ionic species.

The thermosensitive gels, having promising potential for being used as a molecular device for self regulating drug delivery suffer from the disadvantage of poor mechanical strength, which however may be increased by the attachment of gel to some ceramic surface. The composite crosslinked poly (N-isopropylacrylamide) (PNIPAAm) gel layer, after being attached covalently to the glass plate possess a good mechanical strength.
The glass plate as a substrate increases not only the strength of composite gels, especially with a lower crosslinking density, but also keeps the size of the composite gels unchanged in the horizontal direction. The composite gels exhibit hydrophilic property below 25°C and change to hydrophobic above 40°C.

The poly (N-isopropylacrylamide) (NIPAAm) and poly (NIPPAAm-co-acrylic acid) hydrogels exhibit the property to be used as injectable scaffolds for tissue engineering62. At room temperature they are transparent and extremely pliable, while at 37°C the matrices become opaque and significantly more rigid. The P(NIPAAm-co-AAc) hydrogels demonstrate significantly less volume change between the room temperature and 37°C and possess lower critical solution temperature (LCST). The hydrogels support bovine articular chondrocyte viability for at least 28 days in vitro culture, and cartilage-like tissue are formed in the matrices. These hydrogels can be injected through a small diameter aperture.

The addition of hydrophilic, hydrophobic and amphiphilic comonomers into the thermosensitive homopolymer can cause a great change in its volume phase transition behaviour. For example, the addition of small amount of anionic or cationic comonomers (sodium acrylate and methacrylamidopropyl trimethylylammonium chloride) to the hydrogel of N-isopropylacrylamide (NIPAAm) affects their thermosensitive and collapsing behaviour during discontinuous volume transitions occurring at their critical points63. Swelling ratios in the swollen gel states below the critical points are significantly greater than those of pure NIPAAm gels and collapsed state becomes much more condensed. This behaviour is explained by a gel structural model that considers the effect of hydrophilic constituents on the water transport in transition state network undergoing critical phenomena.

The addition of ionic surfactants also causes a change in the volume phase transition temperature of poly (N-isopropylacrylamide) (PNIPA) gels64 which depends on the chemical structure of the surfactants i.e. hydrophobic chain length and hydrophilic head group65. Similarly to the interaction between surfactants and water soluble linear polymers66, the effectiveness of the hydrophilic groups on the elevation of phase-transition temperature is roughly in the order of anionic > cationic > non-Ionic. Even among the anionic surfactant, sulphate-type surfactant elevates more than 60°C whereas phosphate-type surfactant elevates by 2 to 3°C. This elevation is due to the ionization of polymer chains of PNIPA gel by absorption of ionic surfactant molecules64. However, this may not be the sufficient cause to explain the appreciable elevation in temperature. The study of binding isotherms of surfactants onto the polymer gel of poly (N-isopropylacrylamide) (PNIPA) reveals67 that the amount of surfactant binding onto the PNIPA gel changes reversibly and discontinuously through the volume phase transition of the gel. The hysteresis in the binding isotherm is also observed. These results mean that the affinity of surfactant to the polymer chain alters by the conformational change of the polymer just like the functions of haemoglobin, enzyme etc.

The isotropic swelling behaviour of hydrogels may be changed by an external constraint such as stretching, and surface bonding68. Such anisotropic gels have been obtained by incorporating liquid crystals into gel networks69. A recent approach to get anisotropic hydrogels is to anisotropically constrain one of the network components before the gelation of the other network takes place. For example, the interpenetrated network of N-isopropylacrylamide and polyacrylamide with the former component prestressed during the gelation of the other one results in the formation of anisotropic gels70. The swelling properties of these gels along the prestressed direction is different from that along other directions. The change in ratio of gel length (non pre-stressed) to its diameter (pre-stressed) on heating the sample from below to above the volume phase transition temperature is proportional to the degree of initial stress.

There is not much information about the restriction on movement of counterions in a collapsing hydrogel. Some information about the degree of this restriction is provided by the measurement of dielectric spectra for the polymer gel of N-isopropylacrylamide (NIPA) and sodium styrenesulfonate (NIPAAm) in the swollen and collapsed states71 in the frequency range from 100 kHz to 2MHz. The characteristics of dispersions in the collapsing gels are different from those in the swollen gels, while former characteristic are very similar in NIPA and NIPAAm gels, thus suggesting that counterions of NIPA-SS gels bind tightly to the ionized groups. The dispersion analysis confirms the presence of electrically disconnected clusters, of water molecules.

In the hydrogels, sensitive to the electric current the mechanical energy is triggered by an electric signal72. Electrically controlled drug delivery system73 offer
unique advantage for providing on-demand release of drug molecules. For example the interpenetrating network (IPN) composed of poly (vinyl alcohol) (PVA) and poly (acrylic acid) (PAAc), loaded with ionic drugs (i.e. cefazoline) and nonionic drug (i.e. theophylline) demonstrate electric field responsive release behaviour [74]. The amount of loaded drug increases significantly with the contents of PAAc in IPN. As an electric stimulus is turned on and off, the release of drug molecules loaded within the IPN is switched on and off in a pulsatile pattern. The released amount and the release rate of drug are influenced significantly by the applied voltage, ionic group contents in IPN, ionic properties of the drug solute and ionic strength of the release medium.

The small-angle X-ray scattering (SAXS) techniques are often used to understand the structure of the fully ionized gels at the point of volume transition in a salt solution. The poly (allylamine hydrochloride) (PAAMHCL) gels collapse when equilibrated with sodium salts of various organic acids [75], and a less precipitous volume change is observed with NaCl and NaI. The SAXS studies, carried out with collapsing gels show a single broad peak for the collapsed gels with the sodium salts of organic acids, whereas no peak is observed for inorganic salts. The strong maximum in the SAXS pattern is attributed to the ordered structure in the collapsed gels due to electrostatic and hydrophobic interactions.

The mechanical strength and degradation time of hydrogels may be utilized to use them as cell-delivery vehicles for replacement of damaged tissues. One typically desires to time the rate of hydrogel degradation to the rate of new tissue formation. The mechanical strength enables these hydrogels to create and maintain a space for new tissue formation. For example, the poly (aldehyde guluronate) (PAG) gels, crosslinked with adipic acid dihydrazide (AAD) exhibit degradative behaviour [76] due to the hydrolysis of hydrazone bonds formed between the aldehyde of PAG and the hydrazide of AAD. The mechanical properties and degradation time of hydrogels vary with the degree of crosslinking. Moreover, hydrogels with many dangling single-end molecules show a retarded degradation behaviour.

It may be interesting to investigate the behaviour of charged rigid rods embedded in the flexible hydrogel network and their influence on the hydrogel properties. The incorporation of stiff-chain polyelectrolyte rods composed of poly (4,4'-disodium 2,5-dimethyl-1',1' ,4',4'-terphenyl-1'-3',2''-disulfonate) into the flexible network of polyacrylamide results in the improvement of mechanical strength and water absorbing capacity of the hydrogel [77] due to enhanced osmotic swelling pressure. The study of the release kinetics of polyelectrolyte rods shows that the rods, though not covalently attached, are effectively retained by the gel due to formation of aggregates with the network chains.

The swelling tendency of hydrogels is used in extracting water from the aqueous solutions of proteins. The polymer matrix, composed of poly (N-vinyl-2-pyrroldone-acrylamide) concentrates protein solutions like bovine serum albumin, hemoglobin, etc. [78]. The protein molecules, being larger in size, can not penetrate into the gel matrix. The swollen gel, after drying in vacuum oven at 40°C, returns to its original state and hence can be reused. In this way, using the same sample a number of times, the protein solution can be concentrated. The extraction efficiency varies with the degree of crosslinking and the concentration of protein solutions.

The synthesis of a gel sensitive to some molecular species has been a challenge before the researchers. Even the glucose-responsive gels function by responding to gluconic acid formed in gel's microenvironment by the enzymatic reaction of glucose oxidase. Tanaka [79] suggested that swelling behaviour of hydrogels is also governed by the crosslink density. Using this concept, Okano et al. [80] synthesized IPN of poly (acrylamide-co-butyl acrylate) and poly (acrylic acid) which showed temperature sensitivity due to reversible complex formation between acrylamide and acrylic acid. Similarly, the complex formation between polysaccharides and lectin at cross-linking points resulted in the formation glucose-responsive of hydrogel [81]. The Antigen-sensitive hydrogel has also been prepared [82] by the application of antigen-antibody complex formation at the crosslinking points. Here Rabbit immunoglobulin G (Rabbit IgG) and Goat anti-Rabbit IgG has been selected as antigen and antibody respectively. The Rabbit IgG-sensitive swelling of the antigen-antibody hydrogel is attributed to the decrease in the crosslink density due to the dissociation of the antigen-antibody bonding in the presence of a free antigen on the basis of the complex exchange between the polymerized antigen and free antigen. However, the complex does not dissociate due to addition of Goat IgG and hence the swelling ratio of hydrogel remains constant.
Conclusions

Owing to their wide range of applications in biomedical, agricultural and biotechnological fields, hydrogels have proved to be good friends of mankind. Some of the major applications include contact lenses, wound dressings, monolithic drug delivery systems, membrane materials, chromatographic packing materials, water-blocking tapes, sealing composites, artificial snow, gel actuators, immobilization of enzymes, phase transition catalysis etc. In fact, all such applications have emerged from a large number of swelling studies which were carried out under different experimental conditions.

However, it is still required to investigate more aspects of swelling behaviour of hydrogels so that the may be used as site-specific drug delivery systems, for releasing the drug in the desired amount and for the desired time at a particular site in human body. Similarly, it is suggested to fabricate such plant nutrients-loaded release devices which can be put inside the "sprinkler-systems" to release the contents at the time of irrigation so that crops can be provided with the desired nutrients with minimum cost and maximum protection of environment from toxic effects. The unique swelling property of hydrogels can be successfully utilized for the preparation of new commercial products with designed functions which satisfy expectations of mankind.

References