Biodegradable hydrogels in drug delivery
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Contents
Summary................................................................................................................. 60
I. Introduction.................................................................................................... 60
1. Requirements of biodegradable hydrogel systems ............................................... 61
   (a) Biocompatibility ..................................................................................... 61
   (b) Balance between mechanical and degradation properties .................................. 61
   (c) Adaptability to commonly used sterilization procedures................................. 61
II. Mechanisms of biodegradation ............................................................................ 61
   1. Solubilization ............................................................................................. 62
   2. Chemical hydrolysis ..................................................................................... 62
   3. Enzymatic hydrolysis ................................................................................... 62
   4. Ionization or ion-exchange resulting in solubilization .......................................... 63
III. Chemical gels and physical gels ........................................................................... 64
IV. Chemical gels .................................................................................................... 65
   1. Hydrogels with degradable polymer backbone ................................................... 65
   2. Hydrogels with degradable crosslinking agent .................................................... 65
   3. Hydrogels with degradable pendant groups ....................................................... 65
V. Physical gels.................................................................................................... 72
   1. Polymer blends or block co-polymers .............................................................. 72
   2. Simple entanglement systems ......................................................................... 72
   3. Ion-mediated networks ................................................................................. 76
   4. Thermally-induced networks .......................................................................... 78
   5. Systems formed by specific interactions ............................................................ 78
VI. Conclusion...................................................................................................... 78
References................................................................................................................ 80
Summary

Biodegradable hydrogels have been exploited in the controlled drug delivery area due to various advantages. This review describes different types of biodegradable hydrogel systems, mechanisms and factors affecting their degradation, and their applications in drug delivery. Biodegradable hydrogels were classified according to their method of preparation, degradable moiety in the systems, and the mode of biodegradation. In addition, this review describes the advantages and limitations of these systems pertaining to their potential for future applications.

I. Introduction

The preparation of biodegradable polymers has been of great interest in pharmaceutical, veterinary, agricultural, and environmental applications. Webster's Dictionary defines a biodegradable system as one capable of being broken down especially into innocuous products by the action of living things (such as microorganisms). For biomedical and pharmaceutical applications, however, the definition of biodegradation has to be broad enough to include all types of degradation occurring in vivo whether it is due to simple hydrolysis or by metabolic processes. Thus, biodegradation can be defined as conversion of materials into less complex intermediate or end-products by solubilization, simple hydrolysis or the action of biologically formed entities. The biodegradation process leads to the decrease in the integrity of the material. The polymer molecules may, but not necessarily, break down into smaller fragments. Other terms, such as “biodesorption”, “bioabsorption” or “bioerosion”, have been used to describe not only degradation but also elimination of the degraded polymers from the body [1–3].

Recently, biodegradable hydrogels have been used quite extensively in the controlled release drug delivery area. The use of biodegradable systems eliminates the need for the removal of the “ghost” drug delivery system after all the drug is released. The biodegradable hydrogel systems present unique advantages in drug delivery, such as improved biocompatibility and improved flexibility in controlling the stability and diffusion properties of the protein drugs. In addition, drug targeting to a selected region of the body can be achieved using the biodegradable hydrogel systems. For example, hydrogels which can be degradable by microbial enzymes in the colon can be used for colon-specific drug delivery [4]. The biodegradable hydrogels can also be fabricated as microparticles suitable for injection [5]. Biodegradable hydrogels can be prepared from both synthetic and natural polymers. The use of natural polymers in the preparation of biodegradable hydrogels would be beneficial, since many natural polymers are inherently biodegradable and possess special properties, such as self-assembly, specific recognition of other molecules, and the formation of reversible bonds [6].
I.1. Requirements of biodegradable hydrogel systems

For biomedical and pharmaceutical applications biodegradable hydrogels need to have the following few properties.

I.1(a). Biocompatibility

Ideally, the degradation processes leading to the formation of subspecies should take place without any side effects [6]. The concept of biocompatibility should be an important issue not only for the “parent” system but also for the degradation products originating from them. The removal of the anticipated by-products from the body should be given consideration before the actual formulation of these systems. A review by Drobnik and Rypacek [7] describes the fate of water-soluble polymers and/or their degradation products in body. This factor may be of importance for implantable systems, especially if the degradation products cannot be removed by excretory pathways.

I.1(b). Balance between mechanical and degradation properties

Since a biodegradable material is expected to remain functional for its desired life-span, an appropriate balance between mechanical and degradation properties is necessary. The degradation process may lead to the loss in mechanical properties. Hence, maintenance of mechanical integrity, not only in the undegraded form, but also during degradation, is required. Tensile strength, elastic modulus, and matrix integrity can be used for the determination of mechanical properties [8]. In case of biodegradable hydrogels, the swelling property needs to be considered, since it may have a significant influence on the rate of degradation. Various approaches have been used to obtain hydrogels with desired mechanical, swelling and degradation properties. One of the most common approaches is to form a two-component system from a hydrophilic, swellable component and a biodegradable, hydrophobic component. The former would ensure swelling of the system while the presence of the latter would impart the degradability and mechanical strength to the system. Ratios of the individual components could be varied to modify the system properties. In addition to biodegradable properties, other properties such as cell adhesion property can be added by using the two-component system [9,10]. Variations of this approach range from simple physical blends of polymers [11] to the synthesis of co-polymers having segments with necessary properties [12]. The physicochemical properties of the polymer itself can be varied. The crystallinity, stereoregularity and the chemical structure of the polymer can be modified to change its integrity or its degradation property [13].

I.1(c). Adaptability to commonly used sterilization procedures

This property will be of particular importance for implantable systems. The practical application of biodegradable hydrogels as implants would require their sterility. The processing of the system should allow ease of sterilization. Additionally, the sterilization procedures should not have an undesirable effect on the functional properties of the system [8].

II. Mechanisms of biodegradation

Understanding different mechanisms of biodegradation is important in the
development of biodegradable systems. It not only provides a background for the design of particular systems, but also gives an idea about the degradation products, factors affecting degradation, and possible modifications of these factors to achieve the desired effect. The degradation of hydrogels can be classified into four mechanisms: solubilization, chemical hydrolysis, enzyme-induced degradation, and other mechanisms such as ion-exchange leading to soluble or bioabsorbable moieties.

II.1. Solubilization
Various water-soluble polymers, such as poly(ethylene oxide), polyvinyl alcohol, and dextrans, can be categorized as biodegradable simply due to their ability to absorb water and dissolve. The degradation process involves diffusion of water into the hydrophilic polymers leading to the formation of a swollen system which ultimately dissolves on further uptake of water [13]. The extent of swelling and dissolution may vary depending on the hydrophilicity of the polymer, polymer–polymer interaction as opposed to the polymer–water interaction, and molecular weight of the polymer. The environmental variations in pH, ionic strength, or temperature may also influence the solubilization processes.

II.2. Chemical hydrolysis
A vast amount of literature is available regarding the polymers undergoing chemically induced hydrolysis. The list comprises mainly of poly(lactic acid) and poly(glycolic acid), polylactones, polydioxanones, polyhydroxybutyrates and polyhydroxyvalerates, polycarbonates, polyphosphates, polyorthoesters, and polyanhydrides. Even though all of these polymers do not form hydrogels, combinations of any of these with gel-forming hydrophilic polymers can be used to obtain desired biodegradable systems. Biodegradation of the above-mentioned polymers takes place by the hydrolysis of the ester linkages leading to the formation of a carboxylic acid and an alcohol. Factors that affect the hydrolytic susceptibility include the crystallinity, molecular weight, and the hydrophilicity of the polymer. Various examples of the possible contribution of the enzymes to the otherwise non-enzymatic hydrolysis of the polymers have been cited by Holland and Tighe [8].

II.3. Enzymatic hydrolysis
Hydrolases are a group of enzymes which catalyze the hydrolysis of C–O, C–N, and C–C bonds. Thus, they are of particular importance to the degradation of proteins and polysaccharides. Synthetic polypeptides or poly(α-amino acids) also degrade by enzymes and for this reason they have been used as building blocks of enzyme-degradable drug delivery matrices and biomaterials [14]. Hydrolases that act on proteins are divided into peptidases (or exopeptidases) and proteinases (or endopeptidases). Exopeptidases are divided into aminopeptidases and carboxypeptidases which hydrolyze the N-terminal and the C-terminal ends of the polypeptide chain, respectively [15]. Gelatin, collagen, albumin, and fibrin gels have been used most widely in the preparation of enzyme-degradable protein hydrogels.

Of the many polysaccharides, starch and dextran have been used extensively in the preparation of biodegradable polysaccharide hydrogels [16–18]. They are hydrolyzed by enzymes known as “glycosidases”. The presence of a specific
glycosidase in certain regions in the body can be used to develop site-specific drug delivery hydrogels [5,19,20]. Drugs will be released upon degradation of the hydrogels by the specific enzymes. Various chemical modifications of polysaccharides have been made to impart the desired degree of biodegradability and drug release profile [21]. Natural and synthetic derivatives of agarose have also been prepared for use in biochemical separations [22].

Since the formation of enzyme-substrate complex is highly specific, enzyme-induced digestion is sensitive to changes that may affect the conformation of substrates or the active site of enzymes. These factors may include pH, ionic strength or temperature. Diffusion of the enzymes in the hydrogel network could be of importance, since it is the contact between the active site on the enzyme and the substrate that decides the degradation of the system. This may be particularly important for highly crosslinked networks which could pose steric hindrance to the enzyme penetration, thus making the system more resistant to the enzymatic attack. The mode of degradation (i.e., heterogeneous versus homogeneous) would also be decided by the rate and extent of enzyme penetration into the system. Parameters such as the crosslinking density of the hydrogel and/or the substrate conformation could be modified to obtain the system with desirable degradation profiles. In addition to proteins and polysaccharides, many synthetic polymers, such as polydiols [23] and polyvinyl alcohol [24], are also known to undergo degradation by bacterial enzymes.

II.4. Ionization or ion-exchange resulting in solubilization

The pH-dependent water-solubility of some polymers has been exploited in the development of pH-sensitive drug delivery systems. Polyacids or polybases can be used for this purpose depending on the pH at the site of action. Ionization of the otherwise water-insoluble polymers leads to their solubilization [25]. This concept has been used for preparing enteric coating materials, such as hydroxypropylmethylcellulose phthalate, poly(vinyl acetate phthalate), and cellulose acetate phthalate.

Partial ester co-polymers of alkyl vinyl ether and maleic anhydride have been used in the development of a chemically self-regulated drug delivery device [26]. The dissolution of partially esterified co-polymers is highly sensitive to the pH of the surrounding medium. They undergo either surface erosion or bulk erosion depending on the type of the alkyl group in the co-polymer.

Some water-insoluble polymers form soluble macromolecules by ion-exchange process. These comprise mainly of insoluble divalent metal salts of polyanions such as calcium salt of alginic acid and pectic acid. When in contact with fluids containing monovalent ions, ion-exchange takes place leading to the formation of water-soluble counterparts [27]. These systems can be highly sensitive to pH and the type and concentration of ions in the surrounding media.

The pH-sensitive properties of polyelectrolyte complexes were manifested by microgels of methyl-methacrylate-acrylic acid co-polymer mixed with poly(L-lysine) (PLL). At lower pH where PLL is ionized, the microgels became flocculated due to bridging by PLL. An increase in pH induced PLL to transform from ionized coil to α-helix conformation and that resulted in the desorption of the PLL from microgel surface assisted by electrostatic repulsion between negative charges on the microgels [28].
Fig. 1. Schematic description of a chemical gel with point crosslinks (A) and physical gels with multiple junction zones (B).

III. Chemical gels and physical gels

The biodegradable hydrogels can be classified into covalently crosslinked networks (i.e., chemical gels) and networks obtained without covalent crosslinking (i.e., physical gels). The schematic description of the chemical and physical gels is shown in Fig. 1. The biodegradable chemical gels can be further classified based on

A. Biodegradable polymer backbone

B. Biodegradable crosslinking agent

C. Biodegradable pendant group

Fig. 2. Degradation of hydrogels by cleavage of polymer backbone (I), crosslinking agent (II), and pendant group (III).
the degradation site in the network. The three subclasses include those with [1] degradable polymer backbones, (2) degradable crosslinking agents, and (3) pendant chains that can be cleaved from the polymer backbone. A schematic representation of these three modes of degradation is shown in Fig. 2. Chemical gels are commonly prepared by polymerization of monomers or by chemical crosslinking of watersoluble polymers. Unlike chemical gels, physical gels are formed by linking polymer chains through non-covalent bonds, such as entanglements, ion-mediation, hydrophobic interactions, or specific ligand-receptor type interactions. The physical gels are reversible due to their non-covalent interaction among polymer chains.

The design of a biodegradable system depends on the mechanism of degradation at the target site. The following sections deal with the preparation of different classes of biodegradable hydrogel systems and description of specific systems with emphasis on their intended use and potential applications.

IV. Chemical gels

IV.1. Hydrogels with degradable polymer backbone

The polymer backbone chains of hydrogels are cleaved by either chemical hydrolysis or enzymatic degradation. The resultant degradation products are low-molecular-weight water-soluble fragments. As shown in Tables I and II, various types of polymers have been used. Proteins and polysaccharides offer the advantage of enzymatic degradation. Albumin, gelatin, and dextran have been used most widely for the preparation of biodegradable drug delivery systems. Interpenetrating networks (IPN's) and semi-IPN’s are also included in this class. The IPN represents a system which contains two crosslinked polymer networks independent of each other. In semi-IPN’s, only one of the polymer networks is covalently crosslinked. These hybrid systems offer a unique way of obtaining a biodegradable system with other necessary properties.

IV.2. Hydrogels with degradable crosslinking agent

Unlike the polymers with degradable polymer backbone, these systems may form high-molecular-weight degradation products. The crosslinkers may vary widely in size, progressing from small-molecular-weight moieties such as N,N'-methylenebis-acrylamide [53] to oligopeptides [54] and then to macromolecules such as proteins [55,56]. The macromolecular crosslinkers offer lesser steric restrictions for the formation of the enzyme-substrate complexes and hence easier degradation of the system. Table III lists hydrogels prepared with degradable crosslinking agent.

IV.3. Hydrogels with degradable pendant groups

The degradation products of these gels may or may not result in complete solubilization of the gel. This approach has been used mainly for attaching drug molecules to the polymer backbone via the spacer groups. Kopecek used this approach to develop targetable polymeric prodrugs. Drug molecules were attached to N-(2-hydroxypropyl)methacrylamide co-polymers through oligopeptide side chains [59]. The drug release rate is determined by the degradation rate of the spacer. Examples are listed in Table IV.
### TABLE I
Covalently crosslinked, synthetic and semisynthetic hydrogels with degradable polymer backbone

<table>
<thead>
<tr>
<th>System components and preparation</th>
<th>Mode of degradation</th>
<th>Other information</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PEG fumarate backbone crosslinked by co-polymerization with N-vinyl pyrrolidone. Other PEG esters, such as combinations of fumaric acid with ketomalonic, ketoglutaric and diglycolic acids, were also used as prepolymers.</td>
<td>Chemical hydrolysis. In vitro degradation studies at pH 7.4 and 37°C</td>
<td>The hydrolysis rate was dependent on the type of electron-withdrawing ester structure and the number of PVP crosslinks. Non-degradable PVP derivative was one of the hydrolysis by-products</td>
<td>29</td>
</tr>
<tr>
<td>2. Esters of PEG with itaconic and allylmalonic acid as prepolymers. Polymerization by free radical initiation</td>
<td>Chemical hydrolysis at pH 7.4 and 37°C</td>
<td>Completely degradable systems. BSA release was affected by the type and concentration of ester prepolymers</td>
<td>29</td>
</tr>
<tr>
<td>3. Crosslinked PHEG. Prepared from treatment of PBLG with mixture of ethanolamine and 1,12-diaminododecane.</td>
<td>Bulk degradation after subcutaneous implantation. In vitro proteolysis by pronase or papain. No effect of trypsin and collagenase. In vivo subcutaneous degradation by proteolytic enzymes</td>
<td>Rate of oligomer formation by papain digestion in vitro increased with increasing crosslinking density. Increase in swelling ratio after 2 weeks of implantation in vivo due to chain degradation by proteolytic enzymes released during acute and chronic stages of normal inflammatory response</td>
<td>30,31</td>
</tr>
<tr>
<td>4. PHEG homo-polymers and co-polymers</td>
<td></td>
<td>Degradation by papain, pepsin, pronase and cathepsin B. Degradation by chymotrypsin or elastase if co-polymerized with hydrophobic amino acid</td>
<td>32</td>
</tr>
<tr>
<td>5. Poly(sucrose adipamide) derivatives. Chemoenzymatic synthesis using Proleather, an alkaline protease from <em>Bacillus</em> species</td>
<td></td>
<td>Proleather-catalyzed synthesis of sucrose 1',6-bis(trifluoroethyl adipate). Polymerization by addition of ethylene diamine and N-methyl pyrrolidone</td>
<td>33</td>
</tr>
<tr>
<td>6. Dextran or hydroxyethylcellulose mixed with PVP and PVAc. Crosslinking with epichlorohydrin to form beads containing herbicides</td>
<td>Release of herbicides was investigated at different pH values</td>
<td>Release of herbicides ranging from 10-25% after 4 months under neutral and acidic conditions</td>
<td>34</td>
</tr>
</tbody>
</table>
7. Random co-polypeptides of N-hydroxyalkyl L-glutamine and γ-methyl L-glutamate. Prepared by amino-alcoholysis of poly(γ-methyl-L-glutamate) with octamethylenediamine as crosslinker. Surface hydrolysis by pronase E. In vitro degradation studies by incubation of polymer fibers in pronase-containing PBS at 37°C and pH 7.4. First-order hydrolysis by pronase. Tensile properties and degradation rate were dependent on the type of the alkyl moiety in the glutamine side chain.

8. Poly(DTH iminocarbonate) films. Chemical hydrolysis at pH 7.4 and 37°C. Biocompatible polymer with high tensile strength. Low processing temperature of polymers useful for thermolabile drugs.

9. Semi-IPN’s of PHEMA and linear PCL. Prepared by polymerization of HEMA in the presence of PCL. No degradation studies conducted. Expected degradation of PCL after implantation of the system. Higher tensile strength of hydrogel with increased PCL content due to interfacial adhesion between the two components in the swollen network. Improvement of mechanical properties of PHEMA without affecting biocompatibility.

10. IPN’s of PHEMA and PCL. Prepared by swelling of PCL-depleted semi-IPN in vinyl-derivatized PCL. Crosslinking of incorporated PCL to form network of PCL in PHEMA network. PCL as a degradable component. Improved thermal stability and mechanical properties of the IPN.

11. Graft hydrogels of collagen-PHEMA. Prepared by polymerization of HEMA in the presence of collagen. Incorporation of 5-fluorouracil during polymerization. Drug release studies in pH 7.4 phosphate buffer at 37°C. Proposed implantable delivery system for anticancer drugs for its biocompatibility and degradability of collagen. Characterization of the system by IR, TGA, SEM and swelling studies in water. Swelling trend was inversely proportional to the percent of collagen in the hydrogels. In vitro zero-order drug release lasted for 10 days.

12. Copolymerization of acrylamide with BIS in the presence of gelatin. Crosslinking of gelatin with glutaraldehyde to form IPN. Gelatin as a proteolytically digestible component. Characterization of the system by IR, TGA, SEM and swelling studies in water. Swelling trend was inversely proportional to the percent of collagen in the hydrogels. In vitro zero-order drug release lasted for 10 days.

PEG = poly (ethylene glycol); PVP = poly(vinylpyrrolidone); BSA = bovine serum albumin; PHEG = poly(2-hydroxyethyl L-glutamine); PBLG = poly(γ-benzyl-L-glutamate); PVAc = poly(vinyl acetate); DTH = desaminotyrosyl-tyrosine hexyl ester; IPN = interpenetrating network; PHEMA = poly(hydroxyethyl methacrylate); PCL = polycaprolactone; HEMA = hydroxyethyl methacrylate; IR = infra red; TGA = thermogravimetric analysis; SEM = scanning electron microscopy; BIS = N,N-methylenebisacrylamide.
### TABLE II

Covalently crosslinked hydrogels made of natural polymers

<table>
<thead>
<tr>
<th>System components and preparation</th>
<th>Mode of degradation</th>
<th>Other information</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Albumin microbeads containing progesterone. Prepared by crosslinking with 1% glutaraldehyde</td>
<td>Susceptible to chymotrypsin digestion</td>
<td>Enzyme degradation if glutaraldehyde concentration was lower than 1%. Complete disappearance of microbeads 2 months after subcutaneous implantation in rabbits</td>
<td>41</td>
</tr>
<tr>
<td>2. Albumin microbeads containing insulin. Crosslinked using 1% glutaraldehyde</td>
<td>Proposed chymotrypsin digestion on subcutaneous implantation in diabetic rats</td>
<td>Complete degradation of microspheres after implantation required more than 5 months. Formation of fibrous capsules retarded insulin release in rats</td>
<td>42</td>
</tr>
<tr>
<td>3. Albumin microcapsules prepared by high-intensity ultrasound</td>
<td></td>
<td>Superoxide produced by acoustic cavitation was responsible for forming disulfide bonds necessary for formation of microcapsules. Encapsulation of non-aqueous liquids during microcapsule formation</td>
<td>43, 44</td>
</tr>
<tr>
<td>4. Albumin gels by heat denaturation</td>
<td></td>
<td>Gelation of albumin due to aggregation to form strands followed by interaction of these strands to form gels</td>
<td>45</td>
</tr>
<tr>
<td>5. Albumin gels. Comparison of gelation on exposure to heat and guanidine hydrochloride at pH 2.5</td>
<td></td>
<td>Rate of denaturation and aggregation increases with increasing temperatures. Hardness of the gels obtained by chemical denaturation was higher than those obtained by heat-induced denaturation</td>
<td>46</td>
</tr>
<tr>
<td>6. Gelatin hydrogels containing α-interferon. Prepared by sonication of aqueous solution of drug and gelatin in toluene/CHCl₃ containing span 80 followed by crosslinking with glutaraldehyde</td>
<td>Degradation by collagenase in vitro</td>
<td>Rate of degradation affected by crosslinking density. Phagocytosis by macrophages was independent of crosslinking density</td>
<td>47</td>
</tr>
<tr>
<td>7. Gelatin hydrogels prepared by gamma-irradiation. Gelatin was functionalized with glycidyl acrylate</td>
<td>Pepsin-induced digestion. In vitro incubation with pepsin-containing simulated gastric fluid</td>
<td>Dynamic swelling and enzyme-induced digestion was affected by the gamma-irradiation dose and gelatin concentration</td>
<td>48</td>
</tr>
<tr>
<td>Component</td>
<td>Description</td>
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<tr>
<td>Mixed gelatin-egg white gel.</td>
<td>Prepared by mixing the two proteins in NaCl and NaH₂PO₄ buffer (pH 6) and heating the mixture at 80°C followed by cooling at 5°C. Fixing of gels was done with 3% glutaraldehyde.</td>
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<tr>
<td>Polyacryldextran microspheres containing HSA, catalase, immunoglobulin G, or carbonic anhydrase</td>
<td>Expected degradation by proteolytic enzymes. Proposed formation of interpenetrating networks. Formulation of macroscopic single phase was dependent on the ratio of gelatin and egg-white protein.</td>
<td></td>
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<tr>
<td>Dextran gels. Crosslinked by gamma-irradiation. Dextran was functionalized with glycidyl acrylate.</td>
<td>Degradation by dextranase. Treatment of dextran with acrylic acid glycidyl ester to obtain 3-acryloyl-2-hydroxypropyl dextran ester. Crosslinking of acryldextran with BIS to form microspheres. Heat stability of carbonic anhydrase was improved.</td>
<td></td>
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<tr>
<td>Dextran gels. Crosslinked by gamma-irradiation. Dextran was functionalized with glycidyl acrylate.</td>
<td>In vitro digestion by dextranase in pH 6 phosphate buffer.</td>
<td></td>
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</tr>
<tr>
<td>Polyacryl starch. Prepared by free radical polymerization of glycidyl methacrylate grafted starch</td>
<td>In vitro enzyme degradation at 37°C and pH 7.2 buffer containing α-amylase. The hydrogels were made acidic by addition of AA, MAA, MA, IA to starch solution before polymerization. Proposed for the triggered delivery of naltrexone.</td>
<td></td>
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<tr>
<td>Polyacryl starch microspheres containing lysozyme, carbonic anhydrase, HSA, and immunoglobulin G</td>
<td>In vitro incubation with amyloglucosidase at pH 4.5 or α-amylase at pH 5.5. Treatment of starch with acrylic acid glycidyl ester to obtain 3-acryloyl-2-hydroxypropyl starch ester. Crosslinking of acrylstarch with BIS to form microspheres. Microspheres prepared with low acryloyl starch content were completely degraded by amyloglucosidase.</td>
<td></td>
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<tr>
<td>Starch crosslinked with phosphate or adipate.</td>
<td>Used as a binding agent in a conventional wet granulation process.</td>
<td></td>
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<tr>
<td>Partially deacetylated chitin crosslinked with glutaraldehyde.</td>
<td>In vitro incubation with pH 5 buffer containing lysozyme. Digestion of hydrogels by lysozyme was dependent on the lysozyme concentration.</td>
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</table>

AA = human serum albumin; AA = acrylic acid; MAA = methacrylic acid; MA = maleic acid; IA = itaconic acid.
<table>
<thead>
<tr>
<th>TABLE III</th>
<th>Covalently crosslinked hydrogels with degradable crosslinking agent</th>
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</thead>
<tbody>
<tr>
<td><strong>System components and preparation</strong></td>
<td><strong>Mode of degradation</strong></td>
</tr>
<tr>
<td>Hydrogels prepared from acrylamide or N-vinylpyrrolidone with BIS as crosslinker. Prepared by emulsion polymerization</td>
<td>Hydrolysis of BIS at pH 7. Formaldehyde was formed as a by-product of degradation</td>
</tr>
<tr>
<td>N-2-HPMA co-polymers containing oligopeptide sequence in the crosslinks</td>
<td>Digestion by bovine spleen cathepsin B. Incubation of the gels with cathepsin B in phosphate buffer at pH 6 for degradation studies</td>
</tr>
<tr>
<td>PAM and PAA hydrogels with functionalized albumin as crosslinker</td>
<td>Digestion by either trypsin or pepsin. In vitro degradation studies at 37°C in PBS with trypsin or in SGF with pepsin</td>
</tr>
<tr>
<td>PVP hydrogels with functionalized albumin as crosslinker. Prepared by free radical polymerization</td>
<td>Degradation by pepsin. In vitro enzyme-digestion studies in pepsin-containing simulated gastric fluid</td>
</tr>
</tbody>
</table>
7. Polyacrylate hydrogels crosslinked by allyl ethers of polysaccharides

<table>
<thead>
<tr>
<th>System components and preparation</th>
<th>Mode of degradation</th>
<th>Other information</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Poly(sucrose 1'-acrylate) hydrogels. Chemoenzymatic synthesis</td>
<td>Probable digestion of the pendant sucrose moieties</td>
<td>Proleather, the alkaline protease from <em>Bacillus</em> species was used for the synthesis of sucrose acrylate. Polymerization of the sucrose acrylate using H₂O₂ and potassium persulfate</td>
<td>33</td>
</tr>
</tbody>
</table>
Physical gels differ from chemical gels in the type of crosslinks, randomness of the network formation, and the effects of these parameters on the rigidity and elastic moduli of the formed networks. As opposed to the covalent crosslinking points in chemical networks, physical gels are formed through extended junction zones of several laterally associated polymer chains [63]. A large number of natural polymers form physical networks. Physical gels can be viewed as viscoelastic solids and can be classified according to the method of preparation [64,65].

V.1. Polymer blends or block co-polymers

Blending of two different polymers and synthesizing block co-polymers are useful in obtaining hydrogels with necessary biodegradable, mechanical, swelling and biocompatible properties. Polymer blends may be classified as incompatible, semicompatible, or compatible depending on whether two immiscible phases are formed, partial mixing takes place at the molecular level, or a single thermodynamically stable phase is formed [49]. The properties of the blends can be varied by altering the ratio of each component. The properties of the block co-polymers can also be varied by changing the ratio of the hydrophilic and hydrophobic components. Examples of polymer blends and block co-polymers are listed in Table V.

V.2. Simple entanglement systems

Many water-soluble polymers tend to entangle with each other and form gels at concentrations higher than a certain critical concentration. This type of gel behaves as a solid as long as the shear stress applied to the gel is below the yield stress, but as a viscous liquid above the yield stress [68]. The properties of such gels are qualitatively explained by assuming the existence of non-covalent crosslinks between different polymer molecules which form a network extending throughout the solution. Examples of this type of system are gels formed from bio-polymers, such as hyaluronic acid, mucin, and carboxymethylcellulose [68].

Hyaluronic acid is a muco-polysaccharide present in the connective tissue and in cartilage of higher animals. In dilute solutions at neutral pH and physiological strength, hyaluronate molecules exist as random coils with their own solvent shells. An increase in the concentration causes interpenetration of the chains and entangled network. The interpenetrating chains can hold water molecules like a molecular sponge. Hydration characteristics have been found to be affected by the pH and ionic strength [69–71]. Hyaluronic acid is degraded by the action of lysosomal hyaluronidase which hydrolyzes the N-acetyl glucosaminic bonds. Due to its polyanionic nature hyaluronic acid can form interpolymer complexes with cationic polymers [71]. Benedetti et al. prepared hyaluronic acid ester microspheres as a prodrug vehicle for hydrocortisone. The in vitro drug release was thought to be primarily controlled by hydrolysis of the ester bond [72].

Isolated gastric mucus glycoprotein forms a gel above a threshold concentration of about 40–50 mg/ml. A proposed model for the mucus gel suggests that the glycoprotein molecules of mucin are highly hydrated and expanded to the extent that they influence the whole solution volume at a concentration of about 20 mg/ml. As
<table>
<thead>
<tr>
<th>System components and preparation</th>
<th>Mode of degradation</th>
<th>Other information</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blends of PVA and PGLA. Films were cast from hexafluororisopropanol solutions containing different proportions of the two polymers. Incorporation of naltrexone, naltrexone HCl, cytochrome c, myoglobin, somatotropin, and albumin</td>
<td>Chemical hydrolysis was reflected by decrease in molecular weight. In vitro studies in deionized water at 37°C</td>
<td>Combination of biodegradable PGLA and non-degradable PVA. Miscibility of components when PVA content greater than 70%. Increased hydrolysis as increase in PVA content. First-order release of myoglobin and cytochrome c over 48 h from the PVA/PGLA (80:20) system. Lower permeability coefficients as molecular weights of the proteins increased</td>
<td>9</td>
</tr>
<tr>
<td>2. Block co-polymers of hydrophilic components, such as PVA, PEG or PVP, and hydrophobic degradable components, such as polylactide, polyglycolide or polyamides</td>
<td>Chemical hydrolysis</td>
<td>Incorporation of LHRH, EGF, ACTH and somatostatin. Initial release by diffusion through hydrophilic regions followed by enhanced release due to degradation. Adjustment of the ratio of ingredients to obtain hydrogels with suitable mechanical, swelling, and degradable properties</td>
<td>66</td>
</tr>
<tr>
<td>3. PEO/PET elastomer. Co-polymerization by polycondensation of PEG and diethylene glycol terephthalate at 290°C</td>
<td>Hydrolysis at pH 7 and 37°C</td>
<td>Ester functionality adjacent to PEO segment was most susceptible to hydrolysis. Deterioration of mechanical properties over 2-4 weeks. Minimal tissue reaction and toxic response of degradation products</td>
<td>13</td>
</tr>
<tr>
<td>4. PEO/PBT segmented co-polymer</td>
<td>Implantation in tibia and subcutaneous region as bone bonding polymer</td>
<td>Increased degradation rate with higher PEO content. Extensive calcification seen for materials with at least 40% PEO content</td>
<td>67</td>
</tr>
<tr>
<td>5. Block co-polymers of PEO/PLA. Prepared by polyesterification of lactic acid in the presence of PEO chains</td>
<td>PLA as the biodegradable component</td>
<td>Increase in water uptake with higher PEO content. Insignificant effect of PEO chain length on water uptake</td>
<td>10</td>
</tr>
</tbody>
</table>

PVA = polyvinyl alcohol; PGLA = polyglycolic acid-co-lactic acid; LHRH = leutinizing hormone releasing hormone; EGF = epidermal growth factor; ACTH = adrenocorticotropic hormone; PEO = poly(ethylene oxide); PET = poly(ethylene terephthalate); PBT = poly(butylene terephthalate); PLA = polylactic acid.
<table>
<thead>
<tr>
<th>System components</th>
<th>Applications</th>
<th>Other information</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ca-alginate beads</td>
<td>Incorporation of sulfamethoxazole during formation of beads</td>
<td>In vitro release was affected by pH, hydration, compression, and CaCl₂ concentration</td>
<td>80</td>
</tr>
<tr>
<td>2. Ca-alginate beads</td>
<td>Proposed for the delivery of acid-sensitive drugs.</td>
<td>No swelling of beads in pH 1.6 KCl-HCl buffer.</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Use of appropriately sized xerogels to avoid local build-up of released drug</td>
<td>In pH 7 phosphate buffer, swelling of beads to original size in 1 h, followed by gradual disintegration</td>
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</tr>
<tr>
<td>3. Ca-alginate beads</td>
<td>Incorporation of herbicides</td>
<td>Higher release rates were obtained for more water-soluble compounds</td>
<td>82</td>
</tr>
<tr>
<td>4. Ca-alginate spheres</td>
<td>Encapsulation of hybridoma cells for large-scale antibody production</td>
<td>Control of the membrane permeability determined by the polycations, their molecular weight, the charge density and the reaction time of the coating process. Formation of a rigid, semi-permeable membrane by exposure of the formed spheres to polycationic polyamino acid</td>
<td>83</td>
</tr>
<tr>
<td>5. Ca-alginate beads with polylysine membrane</td>
<td>Useful for mammalian cell culture engineering</td>
<td>Enhanced encapsulation efficiency due to positively charged polylysine. Membrane molecular weight cut-off can be controlled by changing viscosity average molecular weight of polylysine or by changing the alginate-polylysine reaction time</td>
<td>84,85</td>
</tr>
<tr>
<td>6. Ca-alginate/polylysine/polyethylene imine</td>
<td>Entrapment of islet of Langerhans for intraperitoneal delivery</td>
<td>Inflammatory response due to polyethylene imine</td>
<td>86</td>
</tr>
<tr>
<td>7. Ca-alginate/polylysine/ Ca-alginate.</td>
<td>Immobilization of islets cells and hepatocytes</td>
<td>Entrapped islets as long-term insulin delivery system which reversed diabetes in rats for up to 650 days. Encapsulated hepatocytes increased survival rates of rats with liver failure</td>
<td>87,88</td>
</tr>
<tr>
<td>8. Polyelectrolyte complexes of Na-alginate with chitosan</td>
<td>Proposed encapsulation of islets of Langerhans, pituitary cells, and thyroid hormone adrenocortical cells</td>
<td>Spherical capsules of 300 μm were formed using jet propulsion technique. High production rate and uniform controllable sizes could be obtained</td>
<td>89</td>
</tr>
<tr>
<td>9. Eudragit-RL-coated alginate microcapsules</td>
<td>Encapsulation of human erythrocytes</td>
<td>Alginate immobilized erythrocytes coated with Eudragit RL. Probable involvement of ionic interaction during coating. Increase in the critical compressive strength of alginate capsules after Eudragit coating. Viability of encapsulated cells was not affected</td>
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<tr>
<td>10. Ca-pectinate gels</td>
<td>Ca-induced formation of gels if the degree of esterification in pectin was lower than 40%</td>
<td>Complex composition affected by solution pH but not by ionic strength</td>
<td></td>
</tr>
<tr>
<td>11. Chitosan-polyacrylic acid</td>
<td>Proposed coagulation of proteins from food-processing waste</td>
<td>Capsules formed by dropwise addition of chitosan solution in alginate solution. Addition of CaCl₂ to chitosan and glucose to alginate increased capsule strength</td>
<td></td>
</tr>
<tr>
<td>12. Chitosan-alginate complex coacervate capsules</td>
<td>Capsules consisting of liquid chitosan core with a hard alginate coating. Candidates for plant biotechnology applications</td>
<td>Membranes prepared by exposure of the Ca-alginate microcapsules to 0.1% (w/w) solution of chitosan or its amine derivatives at pH 6.5. Molecular weight of chitosan was found to affect membrane formation</td>
<td></td>
</tr>
<tr>
<td>13. Chitosan-alginate microcapsule membranes</td>
<td>Potential applications in cell culture engineering, agrochemical delivery, and oral delivery of vaccines, nutrients and growth hormones in fish farming</td>
<td>Even dispersion of heparin in the complex as indicated by the colorimetric reaction</td>
<td></td>
</tr>
<tr>
<td>14. Chitosan-heparin</td>
<td>In vitro thrombus formation tests indicated antithrombogenic properties</td>
<td>No complex formation between pH 2 and pH 6.5. The complex is insoluble in most organic solvents but partially soluble in hot formic acid</td>
<td></td>
</tr>
<tr>
<td>15. Chitosan-Na-CMC</td>
<td>Proposed antithrombogenic potential of the polyelectrolyte complex formed</td>
<td>Formation of gel microbeads when PCPP was exposed to CaCl₂ or A1-acetate at pH 4.5. Coating of the microbeads with polylysine of different molecular weights to improve retention of the cell-secreted antibodies inside the beads</td>
<td></td>
</tr>
<tr>
<td>16. Ca-PCPP or A1-PCPP microbeads coated with polylysine</td>
<td>Encapsulation of hybridoma cells in the microbeads</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ca = calcium; Na = sodium; Na-CMC = sodium carboxymethylcellulose; A1 = aluminium; PCPP = poly[bis(carboxylatophenoxy)phosphazene].
the concentration of glycoprotein increases, overlapping and interpenetration of the molecules takes place. The intermolecular interactions ultimately lead to gel matrix formation. Pepsin and other proteolytic enzymes, such as pronase, papain and trypsin, degrade mucin by acting on the non-glycosylated protein component [73,74].

V.3. Ion-mediated networks

Many polysaccharides in solution form gels upon introduction of counterions. The degree of crosslinking is dependent upon various factors such as pH, ionic strength, type of counterion, and the functional charge density of these polymers. Alginites and pectins have been studied extensively for their ability to form gels on introduction of divalent cations.

Alginate is a binary linear hetero-polymer containing 1,4-linked α-L-guluronic acid (G) and β-D-mannuronic acid (M). Algic acid forms water-soluble salts with monovalent cations, low-molecular-weight amines and quaternary ammonium compounds. But algic acid becomes water-insoluble in the presence of polyvalent cations such as Ca$^{2+}$, Hg$^{2+}$, Be$^{2+}$, Cu$^{2+}$, Co$^{2+}$, Al$^{3+}$ and Fe$^{3+}$ [75]. The Mg$^{2+}$-salt of algic acid is water-soluble because of the absence of strong intermolecular linkages [76]. The primary mode of interchain association in calcium alginate gels is the dimerization of poly(L-guluronate) chains in a regular, buckle-shaped conformation, with interchain chelation of cations on specific binding sites along each chain in much the same way as an “egg-box” [75,77,78].

The alginate gels have been used widely in controlled release drug delivery. Examples are listed in Table VI. The in situ formation of a net-like lattice of Ca$^{2+}$-alginate gel was also used for controlled-release drug delivery. This spongy matrix was responsible for the slow release of the embedded drugs [100]. Alginites have also been used to encapsulate various herbicides, micro-organisms and cells. The process eliminates exposure of these biologicals to harsh conditions such as heat or organic solvents used for other encapsulation procedures. This has been shown to enhance the viability and integrity of the encapsulated cells [87].

Since the basic poly-D-galacturonate structure of pectin is an exact mirror image of the poly-L-guluronate chain in the alginites except at the carbon-3 position, their similarity in cation binding behavior is expected [77]. The selectivity of the counterions also follows the same order as in alginites (i.e., Ba$^{2+} >$ Sr$^{2+} >$ Ca$^{2+}$), while Mg$^{2+}$ does not induce chain association. The distribution pattern of free and esterified carboxyl groups in pectins affects their calcium binding and gel-forming ability [91].

Due to the batch-to-batch variation that may be present in the natural polymers, use of synthetic polymers such as polyphosphazenes, was proposed for the encapsulation of drugs and cells [97]. The claimed advantage of these polymers over the conventional synthetic polymers was that the encapsulation could be achieved under mild conditions which would maintain the viability of the encapsulated biomolecules [98,99].

Chitosan is water-soluble in dilute acid, but precipitates at pH above 6. Chitosan forms a gel in the presence of anions such as phosphate. Chitosan, due to its cationic nature, forms polyelectrolyte complexes with anionic proteins and polysaccharides. The chitosan polyelectrolyte complexes can be used for controlled drug delivery (Table VI).
<table>
<thead>
<tr>
<th>System components</th>
<th>Gel formation and applications</th>
<th>Other information</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C_{10}-alkyl glycoside branched chitosan</td>
<td>Undecenyl β-D-glycosides of glucose, galactose and lactose ozonolyzed to give formyl-nonyl glycosides, which were reductively N-alkylated to chitosan</td>
<td>Aqueous acetic acid (1%) solution of 5% (w/w) polymer gelled upon heating to 30°C when degree of substitution was greater than 1 (ds &gt; 1). Samples with ds &lt; 1 or those with disaccharide pendant group, i.e. lactose, did not gel</td>
<td>101</td>
</tr>
<tr>
<td>2. Pectins with high degree of methoxylation</td>
<td>Gel formation on cooling of pectin solution heated with sucrose at conc. &gt; 55% (w/w) below pH 3.6</td>
<td>Two crosslinking loci constituted a junction zone. Contribution of hydrophobic interaction to the free energy of gelation was half that from hydrogen bonding</td>
<td>102, 103</td>
</tr>
<tr>
<td>3. Gelatin</td>
<td>Gelation of aqueous solutions by lowering temperature of solutions initially heated at 45°C or above. The concentration of gelatin was larger than 1%</td>
<td>Random coil conformation of gelatin in hot water changes to partial helical arrangement below 35°C. Concentration-dependent formation of 3 left-handed helices wrapped into a super right-handed helical junction zone</td>
<td>103–106</td>
</tr>
<tr>
<td>4. Agar</td>
<td>Setting of 1% agar solution at 35–50°C to a firm gel which melts at 80–100°C</td>
<td>Double helix crosslinks in junction zones. Gelling property is attributed to the agarose component</td>
<td>67, 107, 108</td>
</tr>
<tr>
<td>5. Agarose microbeads</td>
<td>Bioartificial pancreas by encapsulation of islets in the microbeads by low temperature gelation</td>
<td>Normalization of plasma glucose levels in diabetic mouse 2 days after transplantation in peritoneal cavity</td>
<td>109</td>
</tr>
<tr>
<td>6. Maltodextrin gels</td>
<td>Gelation by cooling of the boiled maltodextrin solution. Use of small-angle X-ray scattering for the investigation of the gel structure</td>
<td>Weakly hydrated ordered regions were connected to each other by strongly hydrated disordered regions. Disintegration of weakly hydrated regions on heating</td>
<td>110</td>
</tr>
</tbody>
</table>
V.4. Thermally-induced networks

Some polymers, such as gelatin and agar, form gels by lowering the temperature of the solution (Table VII). Gelatin is known to undergo gelation by forming junction zones, each comprising a triple helix of gelatin molecules. The water molecules are incorporated into the triple helix structure in interstitial positions and form hydrogen bonds with the CO or NH groups. The gelation kinetics of gelatin based on crystallization theories suggest instantaneous primary nucleation followed by a unidirectional crystal growth [104]. Agar is composed of neutral, partially methylated polysaccharide (agarose) and sulfuric acid ester (agaropectin) of a linear galactan. The gelling properties of agar have been attributed to agarose while agaropectin provides the viscous component. Thus, the viscosity is varied based on the $\text{SO}_4^{2-}$ content [107]. Agarose obtained from agar by removing the charged groups also forms thermoreversible gels. The agarose molecules are considered to be present as double helices which aggregate during gelling [108].

Gel is formed by lowering the temperature in most cases, but not always. Some polymers form a gel upon heating above a certain temperature. Polymers, such as methylcellulose, hydroxymethylcellulose, or certain PEO/PPO/PEO triblock co-polymers, dissolve only in cold water forming a viscous solution. On raising the temperature these polymers thicken or gel. This thermogelation is mainly due to the enhanced hydrophobic interaction between polymer chains at elevated temperatures. Other examples of polymers which form thermally induced networks include pectins with a high degree of methoxylation, hydrophobically derivatized chitosan and maltodextrin (Table VII).

V.5. Systems formed by specific interactions

The specific interactions between certain biomolecules have been used in various areas such as immunology, biochemical separations, biological recognition processes, and protein modifications. Examples of specific interactions include antigen–antibody, lectin–carbohydrate, and avidin–biotin interactions (Table VIII). Due to their multivalent nature, antibody, lectin, and avidin are able to form viscoelastic gels [117,122]. Actins and fibrinogen are also able to form gels by specific interactions. These systems may have an advantage that the gel can be formed in the presence of other molecules due to their specific interactions.

VI. Conclusion

While many innovative biodegradable hydrogel systems have been prepared as discussed in this review, many more exciting systems are expected to be developed in the near future. The advantage of biodegradable hydrogels is that they can provide partial answers to the problems associated with drug delivery using non-biodegradable polymers or biodegradable but hydrophobic polymers. A large number of protein drugs can be easily loaded into the hydrogels. The use of physical gels or certain chemical gels avoids high temperature or organic solvents during gel formation. This is an advantage in the loading of labile drugs, especially protein drugs. Biodegradable hydrogels provide an alternative mechanism of drug release from the polymer matrix [128]. The release of the entrapped drugs can be controlled by adjusting the degradation rate of the hydrogel. By making the hydrogel...
<table>
<thead>
<tr>
<th>System components</th>
<th>Formation of network</th>
<th>Other Information</th>
<th>Applications</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fibrin network</td>
<td>Conversion of fibrinogen to fibrin by thrombin. Polymerization of fibrin by formation of half-staggered array stabilized by electrostatic interactions</td>
<td>Degradation of the fibrin gel by plasmin. Gel architecture was affected by pH, ionic strength, temperature, Ca-ion, and the concentration of thrombin and fibrinogen</td>
<td>Adhesive adjunct in surgical procedures. Incorporation of antibiotics in fibrin glue used for presealing of grafts in vascular surgery. Bio-adhesio-chemotherapy containing fibrinogen, thrombin, Factor XIII, gelatin, and cis-platinum, for the treatment of pleural effusion</td>
<td>111–114</td>
</tr>
<tr>
<td>2. Lectins (carbohydrate binding proteins)</td>
<td>Non-covalent binding to specific carbohydrates. Hydrogen bonds and van der Waals forces were involved in stabilization of the interaction</td>
<td>Tedious isolation of lectins from respective sources</td>
<td>Used for receptor purification. Used for site-specific bioadhesion and for self-regulated insulin delivery</td>
<td>115–121</td>
</tr>
<tr>
<td>3. Antigen-antibody complexes</td>
<td>Specific binding sites on antibody</td>
<td>Probable formation of extended lattice network due to crosslinking</td>
<td>Three-dimensional network may be formed if biopolymers with epitopes for particular antibody are used</td>
<td>122</td>
</tr>
<tr>
<td>4. Networks composed of actin</td>
<td>Homo- and co-polymer formation with other proteins in body</td>
<td>Crosslinking of actin by α-actinin, spectrin, filamin, and microtubule-associated proteins to form 3-dimensional gels</td>
<td>Gel-forming ability of the gelation proteins can be used for targeted drug delivery</td>
<td>123–124</td>
</tr>
<tr>
<td>5. Avidin–biotin systems</td>
<td>Binding of biotin and biotin analogues to avidin</td>
<td>pH-dependent binding of iminobiotin to avidin</td>
<td>Possible application as pH-dependent drug delivery system. Use of biotinylated biopolymers to form a 3-dimensional network</td>
<td>125–127</td>
</tr>
</tbody>
</table>
degradable only in the presence of certain enzymes, the biodegradable hydrogels can release drugs at a particular site in the body. In other words, drug targeting can be achieved using biodegradable hydrogels. Biodegradable hydrogels can also possess other properties, such as bioadhesive, pH-sensitive, temperature-sensitive, or other environment-sensitive properties. These properties can be used to design self-regulated drug delivery systems.

References


