RECENT EXPANSIONS IN AN EMERGENT NOVEL DRUG DELIVERY TECHNOLOGY: HYDROGEL


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ABSTRACT

With the arrival of medical science large numbers of new therapeutic moieties are discovered and demands specialized carrier for their delivery into specific sites of the body. Hydrogels which are three-dimensional cross-linked polymer network that can respond to the fluctuations of the ecological stimuli. These biomaterials can incorporate large quantum of biological fluids and swell. When swelled, they are soft & rubbery and resemble the living tissue, exhibiting excellent biocompatibility. Today, drug delivery incident several challenges where hydrogel could be one potential answer to those. The specific requirements of advanced drug delivery could easily be met by hydrogels. Wide range of methods for the synthesis of these novel biomaterials has extended its application from drug delivery system to tissue engineering scaffolds, wound dressing material, gene delivery device and biosensors. Further explore into the fundamentals of multi-polymer based hydrogel and their properties, may give raise a novel approach for implementing the biomaterials in the biomedical field in a better way. In this review article an attempt has been made to describe the advancement in hydrogel for novel drug delivery as well as use of it in various applications.

KEYWORDS: Hydrogels, Drug Delivery, Novel, Biomaterials.
1. INTRODUCTION

Natural polymers are derived from renewable resources widely distributed in nature.[1] These materials exhibit a large diversity of structures, different physiological functions and, may offer a variety of potential applications in the field of tissue engineering due to their various properties, such as pseudo plastic behavior, gelation ability, water binding capacity and biodegradability. Many of these polymers form hydrogels that can respond to external stimuli. Hydrogels resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content and soft consistency which is similar to natural tissue.[2] Furthermore, the high water content of these materials contribute to their biocompatibility and can be used as contact lenses, linings for artificial hearts, materials for artificial skin, membranes for biosensors and drug delivery devices[2-10]

Hydrogels are polymeric materials that do not dissolve in water at physiological conditions. However, they swell considerably in aqueous medium[3] and reveal extraordinary capacity (>20%) for imbibe water into their network structure. Gels that exhibit a phase transition in response to change in external conditions such as pH, ionic strength, temperature and, electric currents are known as “stimuli-responsive” or “smart” gels.[4] As these are three-dimensional hydrophilic networks they can retain a large amount of water that contributes to their good blood compatibility and maintains a certain degree of structural integrity and elasticity.[5]

This phenomenon can be explained by the presence of hydrophilic functional groups in their structure, such as -OH, -COOH, -CONH2, and -SO3H, capable of absorbing water without undergoing dissolution. In spite of these many advantageous properties, hydrogels also have several limitations. The low tensile strength of many hydrogels limits their use in load bearing applications and can outcome in the premature dissolution or flow away of the hydrogel from a targeted local site.[6] However, this restriction may not be important in some typical drug delivery applications (e.g. subcutaneous injection). In the case of hydrophobic drugs, the quantity and homogeneity of drug loading into the hydrogel may be limited. On the other hand, the high water content and large pore sizes of the most hydrogels often result in relatively rapid drug release, over a few hours to a few days.

The present review addresses recent developments, which have focused in hydrogel systems. The literature is comprehensive on general aspects about hydrogels. However, the article intends to focus on the hydrogel applications and emphasis on the drug delivery.
2. Network Structure and Classification

Hydrogels can be deliberate to have some specifications, such as swelling and mechanical characteristics, justifying their variety of biomedical applications, from contact lenses to controlled release drug delivery and tissue engineering\textsuperscript{[7,8]}. They can be prepared from natural and synthetic polymer materials\textsuperscript{[9]} and classified using various criteria depending on their preparation method and physicochemical properties Table 1. Natural polymers, such as proteins\textsuperscript{[10]}, polysaccharides\textsuperscript{[11]}, and deoxyribonucleic acids (DNAs) are cross-linked by either physical or chemical bonds, and synthetic hydrogels can be easily prepared by cross-linking polymerization of synthetic monomers\textsuperscript{[12]}. In addition, natural polymers can be combined with synthetic polymers to obtain special properties in the same hydrogel\textsuperscript{[13]}. For example, the biodegradable property of natural polymers has been combined with several functionalities of synthetic polymers to give new functional hydrogels\textsuperscript{[14, 15]}. Various monomers and cross-linking agents have been used for the synthesis of hydrogels with wide range of chemical compositions\textsuperscript{[16]}

Hydrogels, particularly, those intended for application in drug delivery and biomedical purposes are required to have acceptable biodegradability and biocompatibility, relevant requisites on the development of novel synthesis and cross-linking methods to design the desired products.

Table 1. Classification of Hydrogel.\textsuperscript{[9, 18-33]}

<table>
<thead>
<tr>
<th>Classification</th>
<th>Content</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Natural</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>Synthetic</td>
<td></td>
</tr>
<tr>
<td>Ionic charge (based on the nature</td>
<td>Neutral</td>
<td>[18-20]</td>
</tr>
<tr>
<td>of the pendent groups)</td>
<td>Anionic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cationic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampholytic</td>
<td></td>
</tr>
<tr>
<td>Water content or degree of</td>
<td>Low swelling</td>
<td>[21]</td>
</tr>
<tr>
<td>swelling</td>
<td>Medium swelling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High swelling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Superabsorbent</td>
<td></td>
</tr>
<tr>
<td>Network Structure (Porosity)</td>
<td>Nonporous</td>
<td>[22-23]</td>
</tr>
<tr>
<td></td>
<td>Microporous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macroporous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Superporous</td>
<td></td>
</tr>
<tr>
<td>Network morphology</td>
<td>Amorphous</td>
<td>[24-25]</td>
</tr>
<tr>
<td></td>
<td>Semicrystalline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrogen bonded structures</td>
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</tr>
</tbody>
</table>
Thus, a great variety of cross-linking approaches have been developed to prepare hydrogels for each particular application.\[17\] A great variety of chemical and physical methods to establish cross-linking have been used to prepare hydrogels.\[17\] In chemically cross-linked gels, covalent bonds are present between different polymer chains. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer chains. The network structure of a hydrogel will determine its properties as a drug delivery device.


Some of the important methods to prepare and measure hydrogels and some vital characterization parameters are highlights in Table 2.\[34-37\]

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Characterization Parameter</th>
<th>Techniques of measurement</th>
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<tr>
<td>Isostatic ultra high pressure (IUHP)</td>
<td>Morphology/Network pore size</td>
<td>Quasi-elastic laser-light scattering; Electron microscopy; Mercury morosimetry; Rubber elasticity measurements;</td>
</tr>
<tr>
<td>Use of cross linkers</td>
<td>Degree of swelling</td>
<td>Dimensional changes with time; Aqueous medium or medium specific pH; Volume or mass degree of</td>
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</tr>
</tbody>
</table>
Use of water and critical conditions of drying

Use of gelling agents

Use of nucleophilic substitutio reaction

Use of irradiation and freeze thawing

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Swelling:
Equilibrium water content

Cross-linking and mechanical strength

Ultimate compressive strength, change in polymer solubility

Drug diffusion

Membrane permeability, Controlled strength experiments, Nuclear magnetic resonance (NMR), Fourier transform infrared (FTIR) spectroscopy, Scanning electron microscopy (SEM), Quasi-elastic laser light scattering.

Drug distribution

FTIR microscopy, SEM

4. Responsive Hydrogels

Over the last few years, researches have devoted much attention to “stimuli-responsive” or “environment-sensitive” polymers. This kind of polymers are the ability to answer concerning to small physical or chemical stimuli. Hydrogels can exhibit vivid changes in their swelling behavior, network structure, permeability or mechanical strength in response to different internal or external stimuli.\(^{[38]}\) Fig 1 shows various stimuli that have been explored for modulating drug delivery.

![Fig 1. Representation of hydrogels stimuli responsive swelling.](image)

External stimuli are produced with the help of different stimuli-generating devices, whereas internal stimuli are produced within the body to control the structural changes in the polymer network and to exhibit the desired drug release.\(^{[39]}\) Versatile stimuli sensitive controlled release systems can be fabricated, provided that the hydrogels are well designed to change
their configuration in response to these stimuli based on almost infinitely available mechanisms.[40]

The responsive hydrogels are highly sensitive to changes in the environment and have been used in several applications, such as biosensors,[42-44], superabsorbent polymers,[44-46], site specific drug delivery systems,[41, 42,43-53], emerging nanoscale technologies[54-61] and tissue engineering. Other important area for the use of polyelectrolytic hydrogels is bio and mucoadhesive drug delivery systems.[62-64] Responsive hydrogels are unique concerning many different mechanisms for drug release and a lot of many different types of release systems based on these materials are formulated. For occurrence, in most cases drug release occurs when the gel is highly swollen or swelling and is typically controlled by the rate of swelling, the drug diffusion, or a coupling of swelling and diffusion. Other interesting characteristic of many responsive hydrogels is that the mechanism causing the network structural changes can be entirely reversible. This behavior is depicted in Fig 2 for a pH or temperature responsive hydrogels.

![Image](image_url)

**Fig 2.** Swollen temperature- and pH-sensitive hydrogels may exhibit an abrupt change from the expanded (left) to the collapsed (syneresed) state (center) and then back to the expanded state (right), adapted from.[65]

The ability of these systems to exhibits rapid changes in their swelling behavior and pore structure in response to changes in environmental conditions lend to these materials favorable characteristics as carriers for delivery of bioactive agents, including peptides and proteins. Typical examples of environmental sensitive hydrogels are listed in (Table 3).
Table 3. Various environmental stimuli used for triggering drug release from responsive hydrogels.\(^{[66-101]}\)

<table>
<thead>
<tr>
<th>Environmental stimuli</th>
<th>Mechanism</th>
<th>Applications</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>Competition between hydrophobic interaction and hydrogen bonding.</td>
<td>On/off drug release, squeezing device.</td>
<td>PNIPAAm; PDEAAm</td>
</tr>
<tr>
<td>Electrical signal</td>
<td>Reversible swelling or deswelling in the presence of electrical field.</td>
<td>Actuator, artificial muscle, on/ off drug release.</td>
<td>Polyelectrolytes PHEMA</td>
</tr>
<tr>
<td>Light</td>
<td>Temperature change via incorporated photosensitive molecules; dissociation into ion pairs by UV irradiation.</td>
<td>Optical switches, ophthalmic drug delivery.</td>
<td>Copolymer of PNIPAAm</td>
</tr>
<tr>
<td>Magnetic fields</td>
<td>Applied magnetic field causes pore in gel and swelling followed by drug release.</td>
<td>Controlled drug delivery while the magnetic particles, used for medical therapy.</td>
<td>EVAc, Copolymer of PNIPAAm</td>
</tr>
<tr>
<td>Ultrasonic irradiation</td>
<td>Temperature increase causes release of drug.</td>
<td>Drug delivery.</td>
<td>EVAh</td>
</tr>
<tr>
<td>Ionic strength</td>
<td>Change in concentration of ions inside the gel causes swelling and release of drug.</td>
<td>Biosensor for glucose, used for medical therapy.</td>
<td>Nonionic PNIPAAm</td>
</tr>
<tr>
<td>pH</td>
<td>Ionization of polymer chain upon pH change; pH change causes swelling and release of drug.</td>
<td>pH-dependent oral drug delivery.</td>
<td>PAA, PDEAEM,</td>
</tr>
<tr>
<td>Chemical agents</td>
<td>Formation of charge-transfer complex causes swelling and release of drug.</td>
<td>Controlled drug delivery.</td>
<td>Chitosan - PEO, polyelectrolytes</td>
</tr>
<tr>
<td>Glucose</td>
<td>pH change causes by glucose oxidase; reversible interaction between glucose containing polymers</td>
<td>Self-regulated insulin delivery.</td>
<td>EVAc; pH-sensitive hydrogels; Concanavalin A-grafted polymers,</td>
</tr>
<tr>
<td>Antigen</td>
<td>Competition between polymer-grafted antigen and free antigen.</td>
<td>Modulated drug release in the presence of a specific antigen; sensor for immunoassay and antigen.</td>
<td>Semi-IPN with grafted antibodies or antigens.</td>
</tr>
</tbody>
</table>

Note: PNIPAAm = poly(N-isopropylacrylamide); PDEAAm = poly(N,N’-diethylacrylamide); PHEMA = poly(2-hydroxyethyl methacrylate); EVAc = ethyl-ene-co-vinyl acetate; EVAh = ethylene-co-vinyl alcohol; PEO = polyethylene oxide; IPN = interpenetrating network.
4. DRUG DELIVERY AND APPLICATIONS OF HYDROGELS

4.1. Drug Delivery of Hydrogels

Controlled-release or controlled-delivery systems are intended to provide the drug at a predetermined temporal and/or spatial way within the body to accomplish the specific therapeutic needs. Hydrogels, among the different controlled release systems exploited so far, have particular properties which make them to be potentially considered as one of the ultimate future controlled release systems. There are two major categories of hydrogel based delivery systems: 1) time-controlled systems and 2) stimuli induced release systems.\[^{40,138}\]

Sensitive hydrogel systems are developed to deliver their content(s) in response to a fluctuating condition in a way that desirably coincides with the physiological requirements at the right time and proper place.\[^{101}\] The most considerable drawback of stimuli sensitive hydrogels is their significantly slow response time, with the easiest way to achieve fast acting responsiveness being to develop thinner and smaller hydrogels which, in turn, bring about fragility and loss of mechanical strength in the polymer network and the hydrogel device itself.\[^{102}\]

In all routes of drug administration, oral administration has been considered to be most convenient, and hence the majority of dosage forms are designed for oral drug delivery. Different types of hydrogels can be used for delivery of drugs to certain areas in the gastrointestinal tract ranging from the oral cavity to the colon, as shown in Fig 3.

![Fig 3. Tissue localization of hydrogel-based drug delivery systems.\[^{12}\]](image-url)
Controlled drug delivery can be used to achieve some objectives. That is:

- Sustained constant concentration of therapeutically active compounds in the blood with minimum fluctuations;
- Predictable and reproducible release rates over a long period of time;
- Protection of bioactive compounds having a very short half-time;
- Elimination of side-effects, waste of drug and frequent dosing;
- Optimized therapy and better patient compliance;
- Solution for drug stability problems.

Hydrogels have a unique characteristics combination that makes them useful in drug delivery applications. Due to their hydrophilicity, it can absorb large amounts of water (>90%, w/v). Therefore, the molecular release mechanisms from hydrogels are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of a drug from a hydrogel device as a function of time. These models are based on the rate limiting step for controlled release and are therefore categorized as follows [103]:

1) Diffusion-controlled systems:
   a. Matrix (monolithic systems)
   b. Reservoir (membrane systems)
2) Swelling-controlled systems:
   a. Solvent-activated systems
   b. Osmotically controlled systems
3) Chemically controlled systems:
   a. Bioerodible and biodegradable systems
   b. Pendent chain systems

4.2. Applications of Hydrogels: [104-107]

4.2.1. Wound Healing – Modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatin and polyvinyl alcohol (PVA) together with blood coagulants are formulated.

4.2.2. Soft Contact Lenses (silicon hydrogels and polyacrylamides) – The first commercially available silicon hydrogels adopted two different approaches. First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced
compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units.

4.2.3. Industrial Applicability - Hydrogels are used as absorbents for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.

4.2.4. Tissue Engineering – Micronized hydrogels are used to deliver macromolecules (phagosomes) into cytoplasm of antigen-presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel materials used for tissue engineering include agarose, methylcellulose and other naturally derived products.

4.2.5. Drug Delivery in GI Tract – Hydrogel deliver drugs to specific sites in the GIT. Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs. They are designed to be highly swollen or degraded in the presence of micro flora.

4.2.6. Ocular Delivery – Chitoni et al. reported silicon rubber hydrogel composite ophthalmic inserts. Cohen et al. developed in-situ forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.

4.2.7. Transdermal Delivery – Swollen hydrogels can be used as controlled release devices in the field of wound dressing. Hydrogel based formulations are being explored for transdermal iontophoresis to obtain enhanced permeation of products viz. hormones and nicotine.

4.2.8. Subcutaneous Delivery – Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. crosslinked PHEMA was applied to cytarabine (Ara-c). Implantable hydrogels are now leading towards the development of biodegradable systems which don’t require surgical removal once the drug has been administered 5,6.

4.2.9. Tropical Drug Delivery – Instead of conventional creams, hydrogel formulation are employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti – inflammatory for better patient compliance.
4.2.10. **Protein Drug Delivery** – Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.

4.3. **Hydrogels as Scaffold Materials**

Hydrogels are an attractive scaffolding material because their mechanical properties can be tailored to mimic those of natural tissues. As scaffolds, hydrogels are used to provide bulk & mechanical constitution to a tissue construct whether cells are adhered to or suspended within the 30 gel framework. The fundamental obligation of a tissue scaffold is to maintain cellular proliferation and desired cellular distribution throughout the expected service life of the construct. Therefore a critical design consideration for hydrogels in regenerative medicine is the transition in functional dependence between the scaffold and the emergent tissue during scaffold biodegradation and the healing process.[108]

4.4. **Hydrogels with drug delivery capabilities:** Hydrogels are often used as localized drug depots because they are hydrophilic, biocompatible, and their drug release can be controlled and triggered intelligently by interactions with biomolecular stimuli. Macromolecular drugs such as proteins or oligonucleotides that are hydrophilic are inherently compatible with hydrogels. By controlling the degree of swelling, crosslinking density, and degradation rate, delivery kinetics can be engineered according to the desired drug release schedule.[109]

4.5. **Hydrogels for cell encapsulation:** Cell transplantations can be achieved with hydrogels because they can provide immunoisolation while still allowing oxygen, nutrients, and metabolic products to diffuse easily into the hydrogel. The development of a bio-artificial endocrine pancreas, photopolymerized PEG diacrylate (PEGDA) hydrogels have been fabricated to transplant islets of Langerhans.[110]

5. **CHALLENGES OF HYDROGEL DEVICES**

There are still many challenges associated with the modeling of drug delivery phenomena and release profile related to complex hydrogel systems.

Fundamental understanding of drug transport processes helps in developing a suitable mathematical model. Mass transport governs the translocation of drug from the interior to the surrounding environment of hydrogel devices. Factors affecting mass transport of encapsulated molecules are as follows.
• Network cross linking density
• Extent of swelling
• Gel degradation
• Size and charge of the encapsulated molecules
• Physical interactions between the encapsulated molecules and the polymer matrix
• Drug ligand binding present within hydrogel devices.

5.1. Dynamic Hydrogel Delivery Devices

a. Degradable hydrogels - Rate of matrix swelling and degradation mechanism govern the diffusion of encapsulated molecules. With the help of appropriate design of polymer chemistries and network structure, degradable hydrogel matrices are enabled with proper degradation profiles. Mathematical modeling has enriched us with sufficient information to facilitate the design of degradable hydrogels and identify critical parameters dictating molecule release profiles.

b. Stimuli sensitive hydrogels - This advanced hydrogel system detects changes in complex in vivo environments and utilize such triggers to modify drug release rates. As the swelling or deswelling of such hydrogels is mediated by external stimuli, it is critical to model the dynamic swelling response in order to predict solute release.\(^{[111-113]}\)

5.2. Composite Hydrogel Delivery Devices

It has been exhausted for delivering multiple protein therapeutics for tissue engineering applications where temporal and spatial control over drug delivery is desirable. It is of two types which are listed below

• Multilayer
• Multiphase

Examples of in-vivo simultaneous delivery of multiple proteins is angiogenesis, bone remodeling and nerve regeneration.

a. Multilayer hydrogel devices - The system comprises of a basal polymer layer, followed by lamination of subsequent layer. Different proteins are encapsulated into each layer while fabrication and tunable multiple protein release or unique single-protein release approach are made possible by independently adjusting the cross-linking density of each layer. Various
models have been developed for predicting drug release from multilayer hydrogel devices.\[114\] It employs Fick’s second law of diffusion to predict drug release profiles\[115\]

**b. Multi-phase hydrogel delivery devices**- Prefabricated microspheres possessing one or more proteins are uniformly embedded within a hydrogel having a second protein.\[116-118\] The release of the protein encapsulated in microsphere is delayed due to the combined diffusion resistances of the microsphere polymer and surrounding gel. Richardson and colleagues have prepared a composite polymeric scaffold containing. It was the first heterogeneous polymeric system for delivering two proteins with distinct release profiles which can be adjusted by varying the protein loaded in each polymer phase.\[119\]

**5.3. Micro/ nanoscaled hydrogel devices:** Mathematical approaches proposed to predict molecule release from hydrogel microspheres are of two types viz.

- Macroscopic diffusion models
- Microscopic Monte carlo simulations

For macroscopic modeling, models used are based on Fick’s second law of diffusion. Particle size, geometry and surface area are important parameters in this type of modeling. Further molecule diffusivities must be considered and accurately determined.\[119\]

Monte carlo simulation is useful for describing the transport behavior of molecules with in degradable microsphere system and has been widely applied to hydrophobic polymer networks viz. PLGA61.\[120\]

**a. In- Situ Hydrogels**- Recent advancement in hydrogel engineering has led to the development of in-situ hydrogel formation for drug delivery applications. The in-situ sol-gel transition enables the surgery or implantation procedure to be performed in a minimally invasive manner. Various physical and/or chemical cross linking mechanisms have been used for in-situ network formation. Physical phenomenon involved in the formation of in-situ hydrogels are as follows

- Hydrogen bonding
- Hydrophobic – hydrophobic interactions.
- Electrostatic interactions.
For example, sodium alginate hydrogels are formed physically by cross-linking due to addition of calcium ions but are unstable and disintegrate rapidly and unpredictably.\textsuperscript{[121]}

b. Chemical cross linking mechanism – Covalent cross linking methods performed under physiological conditions produce relatively stable hydrogel networks with predictable degradation behavior. For example, photo polymerization of multivinyl macromere. It is a fast process and can be conducted at room temperature without organic solvents.\textsuperscript{[122]} Photo polymerization of degradable hydrogels may be applied to protein and gene delivery.\textsuperscript{[123]}

Finally, it is possible to conclude that many significant recent advances in biomaterials occur at the interface of clinical medicine, materials science and engineering. This aspect creates opportunities and training programs for individual cross disciplinary research and the engaged in these areas can significant accelerate the advance of biomaterials and create new applications for these materials in medicine.

6. FUTURE PERSPECTIVE AND CONCLUSION
Significant progress has been made in improving the properties of hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be achieved using a hydrogel based delivery vehicle. However, several challenges remain to improve the clinical applicability of hydrogels for drug delivery. One set of major challenges relates to improving the ease of clinical usage. Designing physical gelators which gel at lower polymer concentrations and at more precise gelation temperatures would reduce the risk of premature gelation inside the needle upon injection. Similarly, for covalently cross-linked hydrogels, the further development of strategies to release cross-linker in a triggered manner inside the body would minimize the risk of syringe clogging, improve the localization of cross-linker release to minimize in vivo toxicity, and enable mixing of the chemically reactive gel precursors in a single syringe, eliminating the need for double-barreled syringes. The development of hydrogel based systems where the rate of drug delivery could be easily modulated one off over time could also be of benefit for applications requiring varying doses of a drug over time (e.g. delivery of insulin or analgesics). Hydrogels with different degradation profiles and/or environmentally responsive segments may help to address these kinetic issues. There is a need for continued improvement in the delivery of not only hydrophobic molecules, but also the delivery of more sensitive molecules such as proteins, antibodies, or nucleic acids which can readily be deactivated or unfolded by interactions with the hydrogel delivery vehicle. This is a particular issue with in situ cross-linking hydrogels, in which the hydrophobic
domains formed in thermal, physically gelling polymers or the functional group chemistry used to form covalently gelling hydrogels can significantly affect the biological activity of the entrapped bimolecular. Progress on any or all of these challenges would greatly expand the potential of hydrogel-based drug delivery to successfully deliver the next generation of designed drugs at the desired rate and location in the body.

7. REFERENCES


