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Review

Injectable hydrogels for delivering biotherapeutic molecules

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ABSTRACT

To date, numerous delivery systems based on either organic or inorganic material have been developed to achieve efficient and sustained delivery of therapeutics. Hydrogels, which are three dimensional networks of crosslinked hydrophilic polymers, have a significant role in solving the clinical and pharmacological limitations of present systems because of their biocompatibility, ease of preparation and unique physical properties such as a tunable porous nature and affinity for biological fluids. Development of an *in situ* forming injectable hydrogel system has allowed excellent spatial and temporal control, unlike systemically administered therapeutics. Injectable hydrogel systems can offset difficulties with conventional hydrogel-based drug delivery systems in the clinic by forming a drug/gene delivery or cell-growing depot in the body with a single injection, thereby enabling patient compliance and comfort. Carbohydrate polymers are widely used for the synthesis of injectable *in situ*-forming hydrogels because of ready availability, presence of modifiable functional groups, biocompatibility and other physiochemical properties. In this review, we discuss different aspects of injectable hydrogels, such as bulk hydrogels/macrogels, microgels, and nanogels derived from natural polymers, and their importance in the delivery of therapeutics such as genes, drugs, cells or other biomolecules and how these revolutionary systems can complement existing therapeutic delivery systems.

Contents

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1. Introduction

A gel is a crosslinked system formed by a three dimensional network of crosslinked polymers in an extending fluid. When the extender or dispersion medium of a gel is water, it is termed a hydrogel. The hydrogel concept came to the attention of the biomedical field in the early 1960s, when Wichterle et al. [1] established a synthetic hydrogel for biomedical application. Over the long term, hydrogels have been greatly modified and improved, leading to the present day hydrogels that have received special consideration in the last few decades because of their many biomedical and pharmaceutical applications [2–10].

A hydrogel is defined as a three dimensional hydrophilic polymeric network with a very high affinity for water and other body fluids such as serum or plasma, equal to thousands of times the dry weight of the gel, but is insoluble in these fluids. The polymeric backbone of the hydrogel has many hydrophilic functional groups, such as hydroxyl (−OH), carboxylic (−COOH), amine ($-NH_2$), and sulfate ($-SO_3H$) groups, which allow the hydrogel to absorb water. The hydrogels are capable of reversible swelling and de-swelling, and retains large amount of water in it. The crosslinks between the network chains make the hydrogel water insoluble and give it proper geometrical dimensions. The swelling property of hydrogel largely depends on the external environments such as temperature, pH, ionic concentration etc. which in turn can assist the volume transition (collapse or phase transition) of the hydrogel. Thus the swelling of hydrogel mainly depends on the external environment [11–14]. Hydrogels mimic natural living tissues due to their high water imbibition rate (up to 99.9% water), their soft and rubbery nature and very low adsorption of proteins because of their low interfacial tension, which allow the diffusion of molecules of various sizes in and out of the system, thus making them suitable for use as a delivery system [7]. Hydrogels can also potentially endure changes in their three-dimensional (3D) structure and volume as a result of their exposure to external environmental conditions, such as pH, ionic concentration and temperature, and show relatively little toxicity, good injectability, good biodegradability and mucoadhesive and bioadhesive properties that make them an extremely attractive material for therapeutic delivery and tissue regeneration. A hydrogel causes negligible inflammatory response, tissue damage and thrombosis, is easily molded into a precise shape and can be used for an extended period of time since it is inert [15–18].

Since the dawn of nanotechnology, many nanoscale materials that can revolutionize medical procedures have been developed. Nanomaterials have enhanced properties compared to their specific bulk counterparts and are important due to their behavior, which has led to the development of particles of smaller size ranges such as microgels (hydrogels on a microscopic scale) and nanogels (hydrogels on a submicron scale) [19,20]. Many recent studies have demonstrated the importance of a nanoscale size range for drug delivery. Microscale and nanoscale hydrogels have a faster response to their surroundings and have a high exchange rate because of their high interfacial area per unit mass [21–23]. Nanogels can encapsulate many therapeutics, such as proteins, genes, drugs and contrast agents, show superior colloidal stability and inertness [24–26] and can effectively circulate in the blood to reach target sites after injection into the body. Other than drug delivery, another rapidly developing application is hydrogel-mediated gene therapy. DNA, siRNA or oligonucleotides, which are negatively charged nucleic acids, can be easily incorporated into a weakly crosslinked polyelectrolyte hydrogel or easily loaded into another nanoscale delivery vehicle such as liposomes or stable polyplexes, which in turn can be loaded into bulk or macroscale hydrogels for localized and long-term delivery of therapeutic nucleotides.

Recently, research has been more focused on hydrogels responsive to physiological conditions or that are formed *de novo* under particular physiological conditions and that can reduce the risks involved in the surgical implantation of a conventional hydrogel such as pain, scarring and infection. An injectable hydrogel is a subclass of hydrogels prepared by extruding the various hydrogel components through a syringe to a specific site *in vivo*. These self-healing gels are injected in a liquid form into the body and instantly get converted into a solid hydrogel *in situ* via physical or chemical crosslinking without the aid of a potentially toxic or denaturizing crosslinking agent. Cells, nanoparticles, drugs, proteins, or other biomolecules can be mixed with the precursor polymer solution prior to injection and later become entrapped in the hydrogel network. The injectable hydrogels can bypass first-pass metabolism and is a major advantage. First-pass effect/first-pass metabolism/presystemic metabolism occurs when the administered drug enters the portal circulation before entering the systemic circulation thus decreasing the concentration of drug rapidly before it reaches its target. This happens mainly when the drug is administered orally. Route of drug administration such as intramuscular (IM), intravenous (IV), subcutaneous (SC), sublingual, rectal, transdermal and pulmonary routes are better in avoiding or minimizing the first-pass effect. Since the injectable hydrogel mainly utilizes parenteral routes such as subcutaneous, rectal or transdermal, it can avoid first pass metabolism [27,28]. The gelation chemistry underlying hydrogel formation should be bioorthogonal to maintain the functionality of the encapsulated material. A lack of bioorthogonality is a disadvantage of some conventional hydrogel preparations that are incompatible with fragile pharmaceutical proteins [29–31].

To date, a variety of *in situ*-forming injectable hydrogels have been developed for biomedical applications such as drug delivery, gene delivery, regenerative medicine and cell therapy. An injectable gelling system can undergo sol-gel transformation in the body and be utilized for the sustained and controlled release of therapeutics, thus reducing the dosing frequency and side effects [32,33]. A deformable hydrogel can adopt the shape of any surface that it encounters, and the therapeutics that are loaded inside will slowly elute into the surrounding tissues for an extended period from several days to months. The use of biodegradable polymeric materials, such as carbohydrate polymers, allows a hydrogel to undergo controlled degradation in the body with the concomitant controlled release of therapeutics, and the degraded polymers will be easily excreted from the human body. This circumvents the need for further surgery to remove the injectable hydrogel after the therapeutics have been completely released, unlike with a conventional hydrogel, which must be surgically removed [31,34]. Fig. 1 depicts an *in situ*-forming injectable hydrogel system.

An injectable hydrogel-based drug delivery system facilitates the injection of a viscous polymer formulation along with cells or biologics incorporated into a localized site, where the viscous polymer converts into a semi-solid gel system that maintains a constant

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