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Polysaccharide-based micro/nanohydrogels for delivering macromolecular therapeutics

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ABSTRACT

Increased interest in developing novel micro/nanohydrogel based formulations for delivering macromolecular therapeutics has led to multiple choices of biodegradable and biocompatible natural polymers. This interest is largely due to the availability of large number of highly pure recombinant proteins and peptides with tunable properties as well as RNA interference technology that are used in treating some of the deadly diseases that were difficult to be treated by the conventional approaches. The majority of marketed drugs that are now available are in the form of injectables that pose limited patient compliance and convenience. On the other hand, micro/nanotechnology based macromolecular delivery formulations offer many alternative routes of administration and advantages with improved patient compliance and efficient or targeted delivery of intracellular therapeutics to the site of action. This review outlines and critically evaluates the research findings on micro and nano-carrier polymeric hydrogels for the delivery of macromolecular therapeutics.

1. Introduction

The development of recombinant macromolecular therapeutics has grown quite rapidly over the past decade due to the advent of peptide and protein drugs [1]. In recent years, macromolecular therapeutics such as proteins, peptides, small interfering RNA (siRNA), vaccines and hormones have emerged as a significant class of medicine used in the treatment of various deadly diseases. With more than 130 FDA approved products available today in the market and many more in the pipeline, such drugs are gaining a significant importance in almost every discipline, such as cancer therapy, inflammatory disease, vaccines, and as diagnostics. These drugs have numerous advantages over the small-molecule generic drugs, since they are highly specific and exhibit a complex set of functions such as biochemical reactions, protein-based membrane receptors and channels, cellular or organ transport of molecules and transcellular scaffolding support for which small synthetic molecules can hardly mimic [2].

Macromolecular drugs do not easily cross the mucosal surfaces and biological membranes, since these are susceptible to loss of native structure through cleavage of peptide bonds and destruction of amino acid residues (e.g., proteolysis, oxidation, deamination, and elimination) and conformational changes due to the disruption of non-covalent interactions such as aggregation, precipitation, and adsorption. Specialized uptake mechanisms like transmucosal M-cell uptake in Peyer's patches and other lymphoid tissues may be necessary to transport such water-soluble macromolecules through mucosal surface to systemic circulation, since these are prone to rapid clearance in liver as well as other body tissues and may require accurate dosing [3]. Polymeric (especially those of polysaccharide-based)-based delivery systems will diminish the inherent instability of these drugs to improve their bioavailability after administering through oral, nasal, pulmonary and other routes [4].

Presently, protein drugs and antigens are administered parenterally i.e., by subcutaneous (sc) or intramuscular injections as well as intravenous (iv) infusions, but these pose problems of oscillating drug concentrations [5]. Drugs like growth hormone, insulin, oxytocin, parathyroid hormone, and vasopressin have short half-lives of <25 min [6], which necessitate multiple injections per week causing the compliance issues, especially when long-term treatment is required as in the treatment of diabetes mellitus by insulin. These drawbacks impose immense challenges and opportunities for developing delivery vehicles using biopolymeric hydrogels.

Among the various approaches, researchers have developed needle-free administration routes with high bioavailability such as pulmonary, oral, and nasal delivery [7–9]. Other approaches include extending circulation time and masking immunogenicity of protein drugs through conjugation with other biopolymers as well as developing injectable or transmucosal controlled release (CR) systems including liposomes, polymeric micro/nanoparticles, and hydrogels [4]. Therefore, development of efficient micro/nanocarrier-based delivery systems provides tremendous opportunities for improving the patient compliance and pharmaco-economic benefits. This review compiles the literature on such materials since 2000 until now. The current status and future

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prospects of this emerging field of micro/nanotechnology will be the focus of our discussion that surrounds the delivery of macromolecular therapeutics, with a special emphasis on biopolymeric hydrogels.

2. Hydrogels

Hydrogels are the cross-linked 3D network structures prepared from hydrophilic polymers that are capable of retaining a large amount of water and remain insoluble due to their physical and/or chemical cross-linking. Since their early development in the 1960s [10], innumerable hydrogels are available for a wide range of pharmaceutical applications [11]. These hydrogels can be prepared from both natural and synthetic polymers composing homopolymers, copolymers, and interpenetrating polymer networks (IPNs) by selecting proper building blocks as well as using relevant cross-linking approaches [12–14].

Hydrogels possess high water content and are soft networks, resembling those of natural extracellular matrices that minimize the tissue irritation or cell adherence [15]. The high loads of water-soluble therapeutically active proteins, peptides, siRNA, DNA, vaccines, etc., can be encapsulated into their 3D networks, due to their porous structure along with retaining high water content. Unlike other delivery systems (microparticles, emulsions, etc.), where preparation conditions are sometimes detrimental to proteins (i.e., use of organic solvents and protein denaturing processes like homogenization, exposure to interfaces, and shear forces), hydrogel preparation procedures are beneficial to preserve the protein stability as mild conditions such as aqueous environment and room temperature are commonly employed. Their unique properties have created increasing interest in developing the CR systems for proteins/peptides to maintain therapeutic plasma concentrations in the surrounding tissues or in circulation for longer time.

Hydrogels can be prepared from natural as well as synthetic polymers. Chemically cross-linked networks have permanent junctions, while physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, H-bonds or hydrophobic interactions. The physical appearance as matrix, film or microsphere depends on the polymerization method used to prepare hydrogels. Hydrogel networks are also based on the network electrical charge, called nonionic (neutral), ionic (including anionic or cationic), and amphoteric electrolyte (ampholytic) containing both acidic and basic groups. Hydrogel-forming natural polymers include proteins such as collagen, gelatin and polysaccharides like starch, sodium alginate (NaAlg), chitosan (CS), and agarose.

Hydrogels based on homopolymers consists of a single monomer with a cross-linked skeletal structure, while copolymer-based hydrogels are formed from two or more different types of monomers with at least one hydrophilic component arranged in a random, block or alternating configuration along the polymer backbone [16]. On the other hand, IPNs are made from two independently cross-linked synthetic and/or natural polymers in a network, while in a semi-IPN hydrogel, one polymer component is cross-linked, and the other is not. Various such structures are depicted in Fig. 1.

The stimuli-responsive hydrogels that can undergo volume transitions in response to various physical stimuli such as temperature, electric or magnetic field, light, pressure, and sound, as well as chemical stimuli like pH, solvent composition, ionic strength, and molecular species, are widely employed in drug delivery area [12,17]. Upon removing the external stimuli, swollen hydrogel contracts to the unswollen state. Stimuli-responsive hydrogels offer remarkable prospects for the delivery of macromolecules and genes as the carriers are active contributors to optimize the therapy instead of a passive delivery vehicle.

Recent interest in cell mechanics and effects of substrate elasticity on cell structure as well as its function together with the ability of synthesizing the novel polymers that approximate the material property of biological tissues has motivated research on different materials for use in wound healing and tissue engineering [18]. Synthetic gels prepared from polyisocyanopeptides grafted with oligo(ethylene glycol) side chains reportedly mimic gels prepared from intermediate filaments in almost all aspects. These responsive polymers have a stiff and helical architecture with a tunable thermal transition where the chains bundle together to generate transparent gels at extremely low concentrations. These materials show a very fast sol–gel phase transition that can be completely reversible. However, the ease of modification of these materials provides avenues for the preparation of functional biomimetic materials required in biomedical applications [19].

3. Polysaccharide-based hydrogels

Naturally occurring polysaccharides are frequently used in the delivery of macromolecular therapeutics as these are highly biodegradable and biocompatible, and can be prepared as conjugates or complexes with proteins, peptides and other biomacromolecules. Among the widely investigated polysaccharides, NaAlg, chondroitin sulfate, CS, and hyaluronic acid (HA) are the prime candidates. Specifically, these polysaccharides in combination with other polymers offer the desired chemical and/or biological advantages. Some representative members of this class are discussed briefly here, but details can be found elsewhere [20].

3.1. Chitosan

CS, a copolymer of glucosamine and *N*-acetylglucosamine, has been widely used in drug delivery area [21]; it is a nontoxic, mucoadhesive, biodegradable, non-allergic and easily absorbable polymer, whose properties can be tailored to suit to specific applications in the form micro and nanoparticles or hydrogels [2,8,22–25]. Innumerable studies have been reported on colon specificity of CS [26,27], but its intestinal delivery to colon is insufficient because of its deswelling nature in alkaline media. In this pursuit, polyelectrolyte complex of CS (such as CS-pectin and CS-NaAlg) with water-soluble polyionic species that are swollen in neutral pH was developed [28–30]. High insulin association efficiency of 81% was reported for CS-NaAlg NPs (size, 850 nm)

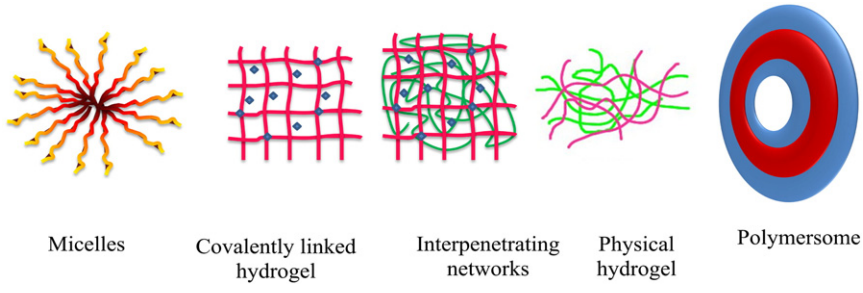

Fig. 1. Types of hydrogel network structures used in macromolecular drug delivery.