A Review: Biocompatibility and Drug Delivery Applications of Mannan Nanogel

Hongrui Zhang*
School of The University of Manchester, Manchester, England, UK

Abstract: Drug delivery researches has drawn tons of attention to achieve the targeted therapies that work for many diseases. Nanogels, a type of polymeric hydrogels with a nanoscale size, are promising materials for drug delivery applications. However, many current polymers used for synthesizing nanogels are lack in biocompatibility, stability, and low biosafety. This review focuses on the mannan-based nanogels with high loading capacity, biocompatibility, and multifunctional stimuli-response properties due to their unique structure and biochemical properties. These characteristics make mannan nanogels very suitable for drug delivery applications.

1. Introduction

Nanogels (NGs) are a kind of polymeric hydrogels with three-dimensional cross-linking structures on a nanoscale size (20-200 nm), which can swell in water without breaking their 3D structure [1-5]. In comparison to other nanocarriers, NGs often possess excellent biocompatibility, high water dispersibility, high loading capacity, and a well-defined structure [6-8]. Nanogels can be synthesized even without the drug addition, and it is mainly because the loaded drug in nanogels can be accomplished obviously once the nanogels are swelled in biological or water fluid. In nanogels, drug loading happens spontaneously [9]. These promising properties make nanogel an ideal material for biomedical applications. However, many current polymers used for synthesizing nanogels have low biocompatibility, low stability, and low biosafety. Self-assembled mannan nanogels, which consist of mannan regarding as the major composition, which can take advantage of the bioactive characteristics of mannan to synthesize nanogels as bioactive agent carriers [10]. Mannan comprises an R-1,6-linked mannose backbone with a large proportion of various R-1,2 and R-1,3 side chains [11]. As a polysaccharide, mannan can improve the biochemical and physical stability of nanogel and its targeting ability to particular organs and cells [12].

2. Properties and discussions

Ferreira, et al [10], studied the biocompatibility of self-assembly prepared mannan nanogels by interacting them with plasma proteins. By taking use of intrinsic circular dichroism spectroscopy and tryptophan fluorescence, the human serum albumin (HSA) to mannan nanogels and time-dependent binding of human apolipoprotein A-I (apoA-I) were investigated. The results found that the protein corona evolves over time and is formed by a slow process; equilibrium is not attained until 24 hours. The effect of mannan nanogel on blood coagulation was evaluated using a thrombin generation assay. There is no any inhibition or thrombin production stimulation when mannan nanogel is loaded to the system, as shown in Figure 1. Using a continuous ThT binding test, the development of amyloid aggregates was examined in the absence and presence of mannan nanogel. The results show that the inclusion of mannan nanogel delays the aggregation of Aβ(M1-40) and β2m by a factor of two to three at the concentrations from 0.03 to 0.90 mg/mL due to the interaction of Aβ(M1-40) and β2m with the mannan nanogel. These findings indicate biocompatibility and biosafety, which are essential for biomedical use.

*Corresponding author: hongrui.zhang-3@postgrad.manchester.ac.uk

© The Authors, published by EDP Sciences. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).
Rabyk, et al, [13] prepared mannan-based conjugates and conducted in vitro and in vivo tests to prove the biocompatibility of mannan-based polymers. In vitro tests with four different cell lines were conducted and the results showed that after incubation with the mannan-based conjugates (mannan-graft-poly(2-methyl-2-oxazoline), and allylated mannan), there is no significant changes in the viability of any of the treated cells, as shown in Figure 2. Mannan-based conjugates were accessed into the calf muscle of the right hind leg of healthy C57/6J B6 mice for in vivo tests. Images of lymph nodes were taken by MRI during the tests. The results showed that the MN-based conjugates have better properties, including MR relaxivity and fluorescence imaging ability, compared to the commercially available contrast agent GM. The visualized accumulation of the drugs in the lymph nodes verified their immune system-targeting capabilities and potential diagnostic use for metastasis.

Table 1 summarizes the classical free radical polymerization and their advantages/disadvantages. Normally, the free radical crosslinking copolymerization of monomers can be combined in one reaction. Most of the current reported polymerization process are performed via free radical polymerization. Many key parameters such as the shear stress, power and surfactant can form the resulting nanodroplet dimensions, thus deciding different properties and corresponding applications [14-15]. Besides traditional methods, the controllable heterogeneous living radical polymerization techniques were also applied in nanogel synthesis. In this aspect, reversible addition fragmentation chain transfer (RAFT) and atom transfer radical polymerization (ATRP) are intensively explored.

<table>
<thead>
<tr>
<th>Method</th>
<th>Detailed description</th>
<th>Advantages and disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miniemulsion</td>
<td>The high shear stress (ultrasonication) enables the mixture of monomers and surfactants to form nanodroplets</td>
<td>The reaction can accurately control in a narrow size distribution (50-500 nm). The reactions require in situ encapsulation/surfactant and co-stabilizer. Meanwhile, the ultrasonic device is necessary.</td>
<td>[14]</td>
</tr>
<tr>
<td>Microemulsion</td>
<td>The monomer molecules are in</td>
<td>The reaction can produce usually</td>
<td>[14-15]</td>
</tr>
</tbody>
</table>
micelles if the high shear stress is absent and the critical concentration of surfactant is used. Meanwhile, no special shear stress is required while co-surfactants with high concentrations are needed.

Dispersion

The reaction ingredients are first soluble and then insoluble once the polymerization occurs, thus forming a stable dispersion with the help of enough colloidal stabilizers. The batch synthesis is simple. The particle sizes in the range of 0.1~15 nm can be easily adjusted by varying monomers and dispersant concentration.

Precipitation

The reaction occurs initially in homogeneous solution of the monomers and the resulting polymer is soluble in the reaction medium. The reaction does not need any surfactant. The particle sizes with the range from 100 to 600 nm can be obtained by adjusting the monomer concentrations. However, this method usually yields irregular shape and high polydispersity.

Table 2 summarizes the physical self-assembly crosslinked nanogels. In these resulting aggregations, the hydrophilic polymers are supposed to be interacted and bonded by electrostatic interaction, van der Waals forces of attractions and/or hydrogen bonding. The reaction systems are required as mild or aqueous medium. Comparing to the chemical crosslinked nanogels, the physical crosslinked nanogels exhibit less stability [16-19]. Frequently, the polysaccharides such as dextran, mannan, pullulan and polyaninoacids which are modified with cholesterol, derivative of chitosan with deoxycholic acid are the typical examples.

<table>
<thead>
<tr>
<th>Nanogels</th>
<th>Examples</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposome</td>
<td>Liposomes featuring succinylated polyglycidol usually undergo chain shrinking below 5.5 and deliver calcine to the cytoplasm. This type of physically crosslinked nanogels is frequently studied for transdermal drug delivery.</td>
<td>[16]</td>
</tr>
<tr>
<td>Micellar</td>
<td>Micellar nanogels are normally obtained by supramolecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions. The core of micelles creates enough space for drug/biomacromolecules encapsulations.</td>
<td>[17]</td>
</tr>
<tr>
<td>Hybrid</td>
<td>Hybrid nanogels are composite ones that are dispersed in inorganic or organic matrices. The hybrid hydrogel enables the system to form various complexed proteins, drugs and DNA.</td>
<td>[18-19]</td>
</tr>
</tbody>
</table>

3. Summary and outlook

Extensive literature has shown that Nanogel particles are an ideal platform for triggered drug delivery [6] [20-21]. As mentioned above, nanogel possesses great loading capacity, biocompatibility, and multifunctional stimuli-response properties, which make them very suitable for triggered drug delivery. Their nano-scale characteristic and flexibility allow them easily penetrate human skin without losing the bioactivity of drugs. The flexibility can also help them to avoid attacks by macrophages to expand the circulating lifetime. Meanwhile, the superior stability of nanogels can assure bioavailability and safety during use. The multifunctional stimuli-response properties of nanogels mean drug release can be stimulated by several intracellular environmental stimuli like temperature, PH, redox, and internal stimuli to trigger the drug release. With the appropriate chemical design, the control of drug release over time, regulation of drug release, and improvement of therapeutic effectiveness can be achieved. In summary, nanogel particles are believed to be an ideal platform for triggered drug delivery platform due to their unique and promising properties.

References


