Mechanism of Cross-Linking, Self-Assembly, Controlled Release, and Applications of Nanogels in Drug Delivery System

Fengqian Jiao *

Beijing Huijia Private School, Beijing, China

* Corresponding author: 15030340413@xs.hnit.edu.cn

Abstract. Drug delivery system has been very important for achieving the last goal of precision medicine, also, among various drug carrier materials, nanogel is considered a promising one. Nanogels are a kind of material that have been proven very effective and specialized on targeted controlled release of drugs in medical therapies. Many researches and applications have used nanogels as an efficient drug carrier through its properties of loading and high capacity, and very high future expectations has been given to this material as a future idealized material in nano medical areas. This paper mainly discusses the key features of the nanogels including degradability and high drug capacity, as well as the mechanism of cross- linking mechanism and self assembly of nanogels in both physical and chemical ways. In addition, this paper explains how nanogels can carry different drugs and control-release the drug under different stimuli to aim the goal at targeted drugs delivery. Finally current research situations and future expectations of this topic are also proposed.

Keywords: Nanogels, self-assembly mechanism, controlled release, drug delivery.

1. Introduction

Nanogels, defined as nanoscale sized particles composed with different polymer networks, have been now widely discussed as an ideal material for targeted drug delivery. Due to its characteristics of sensitivity, high loading capacity and small size that can be easily transferred in the body, it became the container of drugs that are highly toxic as it can release the drug under only certain conditions. Hydrogel, a kind of colloid with strong water absorption ability, which is composed of weak and chemical bonds due to its hydrophilicity. While nanogel is a bifunctional system composed of polyionic and nonionic polymers, containing both properties of hydrogel and nanoparticles [1]. Hydrogels are constructed of water-soluble or expandable chains. As they are stimulated or triggered by the targeted part of body, the chains dissolve or change in shape to release the drug.

There are several key features that make nanogles a very ideal material for the targeted drug delivery function. Because the nanogels are composed of mainly biocompatible and biodegradable materials like polysaccharides, they will decompose and will not leave any burden to the organs with unconsumable remains or wastes. Most nanogels are designed to have very specific functional groups that combines with either drugs or antibiotics, providing the material higher loading capacity of the drug. Some of the functional groups provide with the nanogel particles hydrogen bonds, making it a better 3-dimensional structure with larger capacity spaces. Moreover, functional groups that binds with certain proteins only make it effective on targeted release. The particle size range of nanogel is usually 20-200nm, which can ensure that it is not absorbed by the reticuloendothelial system to avoid burden to the kidney. In addition, such a small size also brings easy permeability to nanogel molecules, which have been proved that it is able to go across through the blood brain barrier (BBB) [2].

There are different past researches based on nanogels done by scientists. Because nanogel has infinite potential features, scientists have studied its practicability in the field of nano medicine in past experiments. Researchers discovered that nanogels' significantly increased surface areas, being functionalized, biological coupling, and encapsulation of bioactive chemicals make them ideal carriers of genetic material, proteins, and vaccines [3]. For example, doxorubicin-loaded composite nanogels for cancer treatment has been widely studied. As a very toxic drug that is widely used on panther therapy, doxorubicin may damage the patients' body though killing normal cells while being

very effective on killing cancer cells [4]. The nanogels, in this case, are used as a protective layer that cover the drug particles, preventing them from attacking normal, healthy cells before they reach the cancer cells' region. As it reaches the region, the shape and structure of the nanogel changes and decomposes according to the trigger of either pH, temperature, magnetic field or other stimulus.

With researches and applications like this, nanogel technologies have been very well expected to be used in such medical applications. Now more types of nanogels are being developed for different diseases and drugs. Because this material is very specialized, that one very specific type of nanogel only applies to certain drugs, polymers and parts of body. For example, some are listed below in Table 1 [2].

Table 1. Polymers, targeted drugs, and applications for different nanogels

Types of Nanogel	Polymer	Targeted Drug/Apply
Nanogels for self-organizing	chondroitin sulfate materials that has been acetylated	Doxorubicin loaded
Biodegradable nanogel	Polyethyleneimine, PEG, pluronic, that are cross-linked	5'-triphosphorylated ribavirin reduced toxicity
pH-responsive	3-Diethylaminopropyl groups were grafted onto glycol chitosan.	The rate of doxorubicin's uptake increased
Polysaccharide-based nanogels that self-quenchs	Pullulan/folate-pheophorbide	Pheophorbide's phototoxicity is minimized to a very low quantity
Polyplex nanogel	Polyethyleneimine and PEG crosslinked into a branching network	Fludarabine had improved activity and decreased cytotoxicity
PEGylated amine nanogels	Cross-linked polymethacrylate core/PEG	Being able to efficiently deliver siRNA
Magnetic nanogels with novel core shell	Polyacrylamide	radiopharmaceutical delivery system for radiotherapy for cancer.
Reducible nanogel	Reducible heparin with disulfide linkage	Heparin internalization causes melanoma cells to apoptose
Nanogel quantum dot hybrid	Cholesterol bearing pullulan with modified amino group	Probe for bioimaging

2. Mechanism of Cross-Linking and Self Assembly

The mechanism of cross-linking and self-assembly of nanogels are based mainly on synthetic or natural polymers according to different structures. Many of the properties of nanogels, like sensitivity and loading capacity, are due to the cross-linking and self-assembly ability of nanogels. The most important thing for a nanogel to be ideal in self-assembly has four perspectives: cost effective, multi-functional, small in size and stable. There are mainly two ways for the nanogel to cross link and self-assemble, either through physical ways or chemical ways.

2.1. Physical ways of cross-linking and self assembly

In physical ways, nanogels self-assemble through weak connection of non-covalent bonds including either inter-molecular forces between molecules or intra-molecular forces in molecules.

Physical crosslinking usually occurs between polymer precursors with special properties. For example, when the functional group on a nanogels molecule and a functional group on the drug molecule it carries form the intermolecular force of non-covalent bond. Due to the difference in polarity, a force between the two molecules, such as a hydrogen bond or van der Waals force, will

cause the nanogels to adhere to the medicine and improve its accessibility, efficacy, and protection [5]. However, even though the way of using physical approach to form nanogels often uses mild water medium, so the nanogels with small molecular volume can fully wrap biological macromolecules, the strength of non-covalent bond is still weak. The strength of intermolecular forces like hydrogen bonds changes depending on the concentration of the functional groups. When contacting with high concentration of water, just like when the nanogels are formed, in the body, the nanogel can easily be diluted and break down, causing the instability of releasing the drug too early [6].

2.2. Chemical ways of cross-linking and self assembly

A chemical self-assembly ability is more stable in carrying certain drugs. Chemical cross-linking and self-assembly is based on the covalent bonds in molecules formed, connecting the structure together and form a whole structure containing drugs inside. This method does not require any surfactants or solvents, as a stable way of manufacturing biodegradable stimulus responsive nanogels. However, this method is relatively less productive [7].

Click chemistry is a recently developed, important part of chemical cross-linking. Copper-free click chemistry has been an excellent example. In this part of research, reactions including the tetrazole-alkene click chemistry, strain-promoted azide-alkyne cycloaddition, radical-mediated thiolene chemistry, Dielse Alder reaction, and oxime reaction can make the creation of nanogels safer and prevent the usage of dangerous ingredients [8]. Also, the click chemistry has biorthogonal feature, which means that the produced nanogels through this method will not affect living organisms. This means that neither human cells nor enzymes nor drugs will be affected by the nanogel itself. The nanogel will become a harmless, controllable material that is very ideal for drugs carrying.

3. Controlled Release

The most crucial characteristic of nanogels as a substance for targeted medication administration is its ability to be controlled. s, so that designers can determine where they will stop and release the drug they carry and for other times, they will carry the drug properly without leaking any of the toxic drugs that may damage healthy cells. There are multiple triggers of nanogels, that can change their shape and open the coverage of the package and release drug. When the nonagels are exposed to these controllable triggers, they release drugs. These triggers include: pH as most commonly seen, temperature in body, certain enzymes, cells, conditions in parts of the body, magnetic fields, etc.

3.1. pH controlled release

One method that is commonly used in composing nanogels that are triggered by pH to complete controlled release reaction is to use the characteristics of constructions of certain polymers. Some polymers ionize and react at certain pH. For example, amines ionize at low pH, and when there is difference in pH values in between cytosol and vesicles, polymers with pKa values between 5.0-8.0 reacts. During the process, physical or chemical properties of the polymers change [9]. Protonation of the functional groups that has been triggered by controlled variables may be disassembled, leading to the release of drugs.

Another example is on NVCL nanogels, which can be synthesized through free radical emulsion polymerization of NVCL and AGA [10]. Through emulsion polymerisation, poly-NVCL-co-AGA nanogels are developed so that is sensitive to certain pH and temperature. As in the Figure 1, it indicated that in high pH surroundings, the poly-NVCL-co-AGA nanogels would release drug molecules rather than in low pH surroundings. A the nanogel material is stimulated by the surroundings, it would result in release of drug.

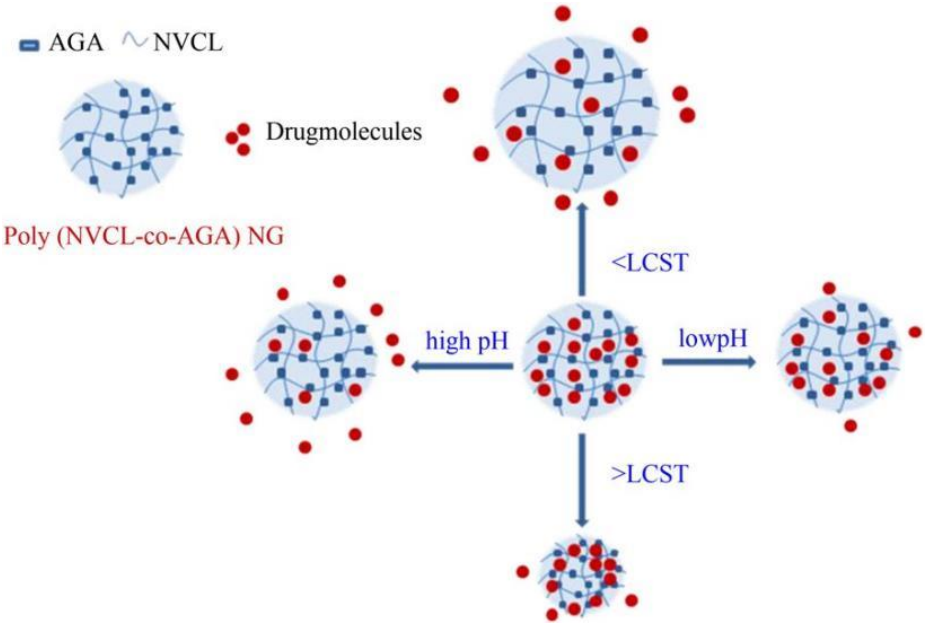

Figure 1. pH and temperature responsive nature for AGA and NVCL nanogels [10].

3.2. Temperature controlled release

Some nanogels are also extremely temperature-sensitive. Poly N-isopropyl acrylamide is usually considered the most well-known and widely researched thermoresponsive polymers (PNIPAM). This nanogel exhibits a sharp phase separation in water at the lower critical solution temperature (LCST), which is around 32°C [10]. The dissolution of polymer chains occurs below the LCST as a result of favorable reactions and affections of hydrogen bonding between the amide groups in the polymers and water molecules. The hydrogen bond ruptures above the LCST, releasing water molecules. Drugs are frequently transported with PNIPAM because its LCST is so near to body temperature.

However, compared to another type of nanogel, Poly vinyl caprolactam (PVCL), which is also sensitive to temperature, PNIPAM is more toxic and dangerous. In water surroundings, PVCL would be precipitate from an LCST of 32-34°C, which is suitable for biomedical applications because it does not release small amide particles in the reaction [10]. However, compared to the number of researches in PNIPAM, the number of researches on PVCL is still in smaller quantity. More researches are needed to be conducted on this topic.

3.3. The control release system of other stimulus

Except for the trigger of pH and temperature, many other stimuli may work on the nanogel to control release drugs. Most commonly seen are magnetic responsive nanogels. As an illustration, the delivery of the medication cisplatin (CDDP) uses NIPAm, a type of magnetic field, NIR, and thermal responsive unit, primarily as a switch to regulate the release of the drug by magnetic field or NIR irradiation heating [11].

Another type of nanogels composed of MnFe2O4 nanoparticles, chitosan and carbon nanotube (CNT) [1]. This type of material responds to either pH and magnetic fields. Also, for nanogels that are responsive to certain enzymes, because there are specific enzymes located in specific areas in the body, it is very specialized that the nanogel will only release when they approach the location with certain enzymes, which means that it is very accurate, reliable and specialized for targeted drugs delivery. In the structures of these nanogels, there are functional groups that can combine, block, or react with certain enzymes only. For example, a type of metal oxide-based nano-composite hydrogel, researched by Mauro et al., has been proven that it can be triggered by enzymes [12].

4. Applications

Nowadays, many specific researches have been developed and some are even already applied in realistic biomedical clinical trials applications [13]. Brain is a very specific and complex structure in human body, and the treatment of brain diseases without harming any other healthy brain cells has long been a problem for medical researchers and doctors. However, as an excellent material, nanogels provide protection to the drug or antibiotics and prevent them from contacting healthy brain cells. Many diseases can now be treated using nanogel techniques, including cancer, which drugs are often toxic, immune disease, ophthalmic, diabetes, anti-inflammatory action and even bleeding [2]. Table 2 lists some applications for some nanogels that are developed for certain diseases and are tested to be very successful [5].

Table 2. Applications of nanogels

Name of nanogel	Drugs carried	Disease specified	Mechanism
PAMA-DMMA nanogels	Doxorubicin	Cancer	Release drug in acidic surrounding
HPMC and Carbopol gel	Spantide II	Allergic contact dermatitis and other skin inflammatory disorders	percutaneous delivery
pH-sensitive polyvinyl pyrrolidone-poly (acrylic acid) (PVP/PAAc) nanogels	Pilocarpine	-	to make the concentration of pilocarpine at the targeted spot in high concentration and prevent it from reacing other sites.
PCEC nanoparticles in Pluronic hydrogels	Lidocaine	Local anesthesia	Produced long-lasting infiltration anaesthesia
Chitosan-based nanogels decorated with hyaluronate	Photosensitizers	Rheumatic disorders	Sensitive to macrophages and attracted by cytoplasm and organelles
Cross-linked poly (ethylene glycol) and polyethylenimine	Oligonucleotides	Neurodegenerative diseases	Can be transported across BBB

5. Conclusion

Nanogels is a breakthrough platform, which plays a vital role in the development of high-tech. A significant aspect influencing the toxicity, pharmacokinetics, bioavailability, and therapeutic indicators of pharmaceuticals that are encapsulated is the drug release method of nanogels. Depending on their polymer networks and methods of synthesis, nanogels exhibit a variety of physical and chemical properties. Hydrophilic and hydrophobic molecules can both be encapsulated by these systems without undergoing structural change. They offer a wonderful possibility to develop a fresh and effective controlled release system since they have the ability to co-encapsulate molecules with various physical and chemical properties.

Nanogels are currently being used more frequently in clinical practice, with positive outcomes. Few nanogel-based medications, nevertheless, have advanced to the point of clinical trials. The industry for nanogels has great potential, nevertheless, as seen by the growing number of studies, papers, products, and patents available today. Growing numbers of nanogels with improved controllability, drug capacity, and innovation potential have been created, offering crucial support for the application of hazardous medicines.

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