REVIEW ARTICLE

Advance Nanogels of Drug Delivery System: A Review

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ABSTRACT

The term 'nanogels' defined as particles in nanosized made cross-linked polymers networks by chemically or physically which is a swell in a suitable solvent.

The nanogels are made up of various forms of synthetic or natural polymers that are bound together by physical non-covalent bonds such as H-bonds, electrostatic bonds, and hydrophobic bonds or by chemical covalent bond. A nanosize of nanogel is designed to reduce some of the disadvantages of micron size particles, which includ retention at targeting site, surface area, site specificity, swelling properties, loading efficiency of drug, and finally release behavior. It classifies based on responsive behavior and on the basis of linkages (physical and chemical). This review aims to provide general introduction on nanogels, their novel application in different approach and recent synthesis methodology.

Keywords: Cross-linked particles, Nanogel, Physical chemical properties, Polymers.

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INTRODUCTION

The term 'nanogels' defined as particles in nanosized made cross-linked polymers networks by chemically or physically which is a swell in a suitable solvent.

The origin word nanogel was first presented to explain of bi-functional networks with cross-linked of a nonionic and a multi-ion polymers to delivery of polynucleotides like poly ethylene glycol (PEG) and cross-linked poly ethyleneimine (PEI).[1]

The nanogels can be made from different of synthetic, natural polymers, or a mixture of physically cross-linked by non-covalent bonds like hydrophobic interactions, hydrogen bonds and electrostatic or by chemically (covalent) cross-linked. The most capacity of absorbing water is result to the presence of groups with hydrophilic properties, like –CONH–, –$CONH_2$–, –SO_3H and –OH, alongside the macromolecular chains in the structure of polymers.[2]

Nanogels are particles with less than 100 nm in dimension polymers network. The nanogels are biocomptable nanocarriers, which have been introduced in the biotechnology and biomedicine sciences to a day.[3]

Due to their size, it can avoid from renal clearance and lead to increase of serum half-life period. It has hydrophilic networks with three dimensional that have the ability to absorb physiological fluid or water in a high amount, without altering in internal structure of network. Changes of nanogels by chemical process can be made to aid introduction of ligands which can be used for drug as targeting delivery system, preparation of composite materials or stimulus responsive drug release.[4]

Nanogels may composed from amphiphilic molecules which are a charged or non-charged system.[5] The loading of drug in a nanogels requires physiochemical interaction between drug and polymeric compounds through functional groups.[6]

Nanogel nanosize regimens are designed to resolve some of the drawbacks of micron-sized particles, such as retention at the target site, site specificity, surface area, drug loading efficiency, swelling, and release behavior. Nanogels are ideal because they are biodegradable, biocompatible, leak-resistant, and flexible.[7]

Advantages of Nanogels Drug Delivery Approach[8]

- It produced good protection from biodegradation of drugs inside the body.
- Physical properties like size of nanogels can be easily adjusted and maintained according to the desired delivery molecule.
- Low doses of drug due to low amount drug is required .
- Enhance the bioavailability of the drug and reduce the drugs toxicity.
- Drugs loaded nanogels can be applied topically and can be delivered inside the body without side effects .
- These are able to pass through physiological barrier like skin and also can cross blood brain barrier.

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Disadvantages of Nanogels[9]

- The process of removal the surfactants and solvents at the end of preparation process are very expensive technique.
- The presents traces amount of monomer or surfactant can produce adverse effects.
- Due to the mean size and weight, scaling up is difficult.

Classification of Nanogels

Based on Responsive Behavior

Nanogels may be either stimuli-responsive or nonresponsive:

- Swelling or deswelling of nanogels in response to environmental stimulus like magnetic field, pH, temperature, and ionic strength.
- Non-responsive nanogels which swell when come in contact with water.[10]

Based on Linkages

A. Physically Cross-linked Nanogels

Hybrid Nanogels

These are the complex of nanogel particles dispersed in both organic or inorganic medium. A number of studies have verified the synthesis of nanogel through self-assembly or accumulation of polymer amphiphiles in an aqueous medium, like hydrophobized polysaccharides, pullulan-poly N-isopropylacrylamid (PNIPAM), and hydrophobized pullulan. Mostly, pullulan is employed in cosmetics, food and in pharmaceutical industries due to its easy chemical modification, as well as nonmutagenic, nontoxic, noncarcinogenic, and nonimmunogenic nature.[11]

This type of nanogels can form complexes with many proteins, DNA and drugs and it also have ability to coat particles, solid surface (cells), and liposomes. The hybrid nanogels are also ability of delivering anticancer drugs and insulin more efficiently. Cholesterin-producing pullulan is made up of a backbond and branches made up of cholesterol. It self-aggregates by lipophilic groups, resulting in stable nanogels as shown in Figure 1.

Liposome Modified Nanogels

These are vesiclar of lipid bilayer structure, where the lipid can form vesicles when present in aqueous medium. The main ingredients of liposome are phospholipid and cholesterol.[12] pH and thermo responsive liposome modified nanogel are being investigated for transdermal drug delivery. It is made by combining poly (N isopropylacrylamide) and succinylated poly (glycidol) and is used to deliver calcein to the cytoplasm by fusing the chain below pH 5.5.[13]

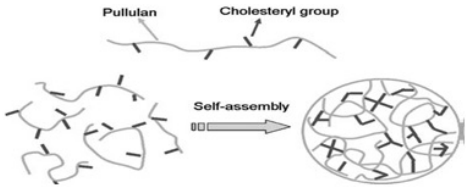

Figure 1: Schematic demonstration of cholesterol-bearing pullulan nanogel preparation by physical cross-linking (self-assembly)

Micellar Nanogels

Both hydrophilic and hydrophobic blocks are supramolecular self-assembly to produce micellar nanogls or by graft copolymers in an aqueous mediumIt is made up of a hydrophobic core and a hydrophilic shell that work together to keep the micelle stable.[14] The advantages from shape of micellar nanogels is to produce good space to carry biological macromolecules or drugs just by physical entrapment of these matreials within the shell, there by acting as a drug delivery system. Following micelle administration in the body, the aqueous media form hydrogen bonds with the hydrophilic shell to shield the drug inside the hydrophobic core, which transports it to the target area. By this process can protects the drug from hydrolysis or enzyme degradation.[15]

B. Chemically Cross-linked Gels

These are composed of chemical linkage of covalent bonds along entire the gel networks. The properties of these type depend on functional groups and the chemical linkages which present in the gel networks.[18] Chemically cross-linked gels are prepared through electron and gamma beam polymerization, chain growth polymerization and addition condensation polymerization. The polymerization lead to chain growth includes anionic and cationic polymerization, free radical polymerization and controlled free radical polymerization. It is completed through three procedures such as initiation, propagation and termination. The active site of free radical is produced after initiation, that accommodates monomers in a chain network-like style.[19]6

The crosslinking mediator is explained by using disulfide crosslinking exhaustion in nanogel preparation (20–200 nm), where the pendant thiol groups are obtained by 'environmentally friendly chemistry.

Synthesis of Nanogels

Inverse Microemulsion Method

In this method can synthesize nanogels with greater controlled morphology, composition, and size by radical polymerization. The inverse microemulsion prepared by dissolved the crosslinker and monomer molecules in aqueous phase and then added this mixture to surfactant solution in organic phase. The polymerization is initiate by irradiation and finally removal of surfactant molecules from contents, then washed and drying by freezing technique. Modifications on nanogels can be formed by series of chemical functionalities for electrostatic and hydrophobic interactions of various nanogels with drug. To solve problems with instability, this modifications can be created by co-polymerizing a nucleophillic group. the degree of substitution should be limited to 10%. Polyvinyl alcohol, polyethyleneimine, poly (acrylic acid), and polycrylamide nanogels have all been successfully synthesized using emulsion polymerization.[17]

Inverse (mini) Emulsion Method

In this method, the nanogel can prepared by mixing continuous oil phase with droplets of aqueous bipolymer by using either a homogenizer or a high-speed mechanical stirrer.

Due to the presence of appropriate crosslinking agents, the resulting biopolymers are crosslinked as aqueous droplets.

When crosslinked microgel particles are produced, they are dispersed in an organic solvent, then purified by centrifugation, precipitation, and finally washing with organic solvents such as isopropanol, followed by lyophilization. During the preparation of an inverse emulsion, the amount of surfactants, crosslinking agents, and stirring speed can all be used to monitor the size of the microgel particles.[18]

Dispersion Polymerization

In this technique, the continuous phase contain is organic solvent in which most of polymeric stabilizers,monomers and initiators are soluble in it. By homogeneous reaction mixture, the polymerization are obtained in which the obtained polymers become insoluble in the organic solvent, ultimately leading to the formation particles as polymeric dispersion in presence of colloidal stabilizers. By this technique can prepare hydrophilic monodisperse micron-sized particles from poly (2-hydroxyethyl methacrylate) in the presence a diblock copolymer stabilizer of poly (ethylene oxide) -b-poly (1,1,2,2-tetrahydroperfluorodecyl acrylate) in supercritical methacryloyl-terminated poly (methyl methacrylate) and carbon dioxide in a mixture of 2-butanol/tolune 55/45 (wt/wt).[19]

Physical Self-assembly of Interactive Polymers

In this technique, the principle forces are hydrogen bonds and van der Waals forces which responsible for interaction between solvent and drug moiety.[20] The macro- and micro molecules are captured inside them during the self-assembling process of nanogels. By using hydrophilic polymers, this method is used to deliver insulin nanogels.When prepared by this technique (self-assembling method) can obtain samm particles size of ananogel (less than 30 nm). However, it was based on the polymer concentration as well as various environmental factors such as temperature, ionic strength and pH. In a study, when the size of nanogels between 120 to 150 nm can enhanced stability by using of two types of polymer with different ratios. Furthermore, also can obtain the nanogels from amphiphilic block copolymers by the reversible addition–fragmentation chain transfer technique.[21]

Novel Pullulan Chemistry Modification

The reaction of cholesterol isocynate in pyridine and dimethyl sulfoxide produces this form of nanoge. The modification of pullulan was obtained when each 1.4 units cholesterol are substituted with 100 units of anhydrous glucoside. The freeze drying of this preparation resulted in the formation of nanogels in aqueous media, which were used to deliver the w-9 peptide-complexed for osteological disorders. Due to high loading capacity of pullulan, it act as good carrier for protein delivery.

Further chemical modification of cholesterol based pullulan nanogels by michael addition reaction in which thiol group and acrylate group are replacing through polyethylene glycol, this allowed for a mesh size reduction to 40 nm, encapsulating 96% of interleukin-12 (IL12).[22] Another modification of pullulan, in which 100 glucose units for 1.1 units of cholesteryl group showed important association with monomer and Aβ oligomer for treatment of alzhiemer's disease by improving cortical cell and microglia viability, was investigated.[23]

Mechanism of Drug Release from Nanogels

pH-responsive Mechanism

The pH-sensitive polymers responsible for shrinking-swelling behavior which related to the ionizing groups, which when change in pH lead to change by ionization or deionization in response.[24] Some scientific research has show that change of microenvironments of tumor cells (pH 5.0–6.5 in endosomes and pH 4.5–5.0 in lysosomes) and tumor tissues (pH 6.5–7.2) to acidic medium in compared with the physiological pH 7.4 in normal tissues and the blood circulation.[25] The monomers methacrylic acid and methyl ester are pH-sensitive which reported to polymerize as a nanogels, which at basic medium it will become more swollable with high permeability.

The deionization of methyl ester and methacrylic acid is accompanied by a decrease in pH values, which lead to entrapment of the hydrophilic drug doxorubicin and the hydrophobic fluorescent indicator oligothiophene and then shrinkage of nanogels. Moreover, due to the shrinkage of pH-sensitive nanogels and the protonation of doxorubicin, increased doxorubicin release was observed at pH 5.5.[26]

Thermo-sensitive and Volume Transition Mechanism

The volume phase transition temperature is defined as the temperature effect on the variations ability of nanogels. When the surrounding medium is below the volume phase transition temperature, polymers become hydrated and shrink. The swelling of shrunken and hydrated polymer lead to releases the loaded active ingredient. This type of nanogel when swell and increases in volume lead to degreded within cell and biological environment.

N-isopropyl acrylamide prepared as nanogels have thermo-responsive properties. These nanogels when maintain the heat of the solution less than the lower critical temperature, lead to indomethacin is released as a result of the rapid contraction of the gel volume. The 5-fluorouracil was prepared as gel from poly (N-isopropyl acrylamide-co-acrylamide) and ex vivo experiments on rats have been conducted. Since the 5-fluorouracil is loaded at lower temperatures and released from nanogels at body temperature, this method is suitable for drug delivery.[27]

Photochemical Internalization and Photo Isomerization

Excitation of photosensitizer-loaded nanogels produces reactive oxygen and singlet oxygen,which cause oxidation reaction at cellular compartment walls like endosomal barrier walls allowing drug release into the cytoplasm. Eventually, intracellular compartment walls prevent drug release into the cytoplasm.[28]

By using photo-regulation in the isomerization of azobenzene, the trans-cis can see with aspirin as model drug in which azo dextran loaded nanogel that exhibited azo group in Z–configuration of is less release in compare with E–configuration at 365 nm radiation.

Diffusion of the Drug from Nanogel

In this type of nanogel the diffusion mechanism is responsible for drug release in control manner.

The diffusion of drug can occur as macroscopic scale at molecular level by passing through pores presented within the matrix or between the chains of polymers. A process diffusion as normal level is given in Figure 2. A homogeneous system is obtain by mixing of polymer with active agent which called to as a matrix system. In this type of system (homogeneous system) upon administered into biological environment, permit for drug release by diffusion mechanism through the macromolecules or pores of the polymer structure without any changes in it structure. Two important factor responsible for drug release by diffusion mechanism from the delivery system: (a) the binding force of the drug in the micelle core, which is depended on the partitioning of drug between the external environment and micelle, and (b) binding chain of the polymer to each other in micelles structure.[29]

The doxorubicin released from polymer through diffusion mechanis is regulated for a longer time by the addition of anionic and cationic polyelectrolytes, where the drug begins to release layer by layer rather than releasing rapidly at first.[30]

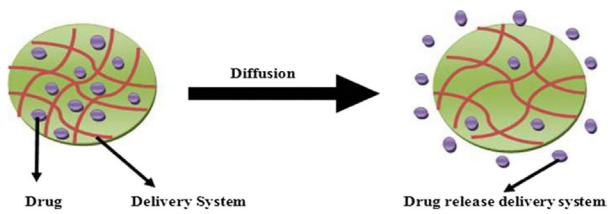

Figure 2: Drug release from nanogel by diffusion mechanism

The Application of Nanogels

Transdermal Application of an Analgesic Drug

Aceclofenac is a non-steroidal anti-inflammatory drug that was prepared as nanogels using emulsion-solvent diffusion and then entrapment into carbopol 940. The prepared formulation demonstrated good stability and permeability properties, as well as long-term release (Table 1).[31]

Nanogel in Opthalmic

From poly (acrylic acid)-polyvinyl pyrrolidone (PAAc/PVP) can prepare pH sensitive nanogel by γ-radiation-induced polymerization method.

This type of nanogel is used to deliver of pilocarpine as sustain release which maintaining the drug release at the site of action (Table 1).[32]

Diabetics Application

As diabetics diseases becomes more and more predominant in the world's population, developed new techniques are being used for treatment of diabetics. Smart insulin nanogel where injected, which is sensitive to changes in blood glucose levels and insulin release at desired amounts accordingly has been requirement. This types of nanogels containing oppositely charged of nanoparticles, so attraction of nanoparticles oppositely charge each other lead to formation intact gel matrix that responds to pH changes. By using of dextran nanogels containing the insulin and other enzymes and these enzymes responsible for the conversion of glucose into gluconic acid. In case of hyperglycemia, there is high level of glucose, the glucose pass through gel network of a nongel and by action of enzymes convert glucose into gluconic acid,

Table 1: Applications of nanogels in the cancer therapy

Nanogel constitution	*Type of nanogel*	*Drug used*	*Applications*
Maleic acid poly-(*N* isopropylacrylamide) Polymer	pH-sensitive nanogel as sustained release	Doxorubicin	At a normal physiological pH of 7.4 and a temperature of 37°C, dual-responsive doxorubicin hydrochloride delivery (pH and temperature) resulted in low drug release and high drug release in cancer cells (pH 4, temperature 41°C).[40]
Conjugation between carboxyl group and sodium hydroxide in nanogel used as catalyst	pH- and temperature responsive Nanogel	Cisplatin	Dual responsive-mechanism nanogel (pH and temperature), it used for treatment breast cancer.[41]
Chitin nanogels	Polymerized nanogel	Doxorubicin	This nanogel is used to treat prostate cancer, liver cancer, lung cancer, and breast cancer.[42]
Acetylated chondroitin Sulfate	Self-organizing nanogel	Doxorubicin	Used for treatment cancer cell.[43]
Hydroxypropylcellulose poly (acrylic acid)	Dual-responsive (pH- and temperature responsive) cadmium ions quantum dots	Temozolomide	Temozolomide drug loading, cell imaging, and optical pH sensing.[44]
Glycol chitosan grafted with 3 diethylaminopropyl groups	pH-responsive	Doxorubicin	Doxorubicin uptake Accelerated.[45]
Reducible heparin with disulfide linkage	Reducible nanogel	Heparin	Internalization of heparin to induce melanoma cell apoptosis[46]
Poly(*N* isopropylacrylamide *co* acrylamide)	*In situ* gelatinized thermosensitivenanogel	5-Flurouracil	Low molecular weight 5-Flourouracil has a higher drug-loading potential than bovine serum albumin and other biomacromolecules.[47]

As a result, the pH of the medium is lowered. As a result, the insulin release will be triggered. Even though this approach is effective in the treatment of diabetes, it is still a new technique that needs further research before it can be used in clinical trials.[33-36]

Nanogel in Cancer

The use of nanogel as a targeted drug in cancer treatment is for the specific delivery with high therapeutic efficacy and low toxicities as shown in Table 1.[37-40]

CONCLUSION

Nanogel systems have been studied for both practical and theoretical aspects. Nanogels formed by physical crosslinking or chemical self-assembly reveal the ability to deliver hydrophobic or hydrophilic drugs.

It most commonly used for targeted, controlled delivery system, cosmetics products, and for the coatings purpose. Nanogels systems have a bright future ahead of them, with new technologies and drug delivery possibilities.

Recent advance of nanogel have delivered greater vision in the applications of nanogels, especially within the management of cancer, gene transfection,gastrointestinal complications, enzymology and protein folding.

Considering the advancement of nanogels, we believe that future research and clinical evaluation of nanogels with smart properties based on regulated physico-chemical properties of the device has greater potential.

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