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Review Article

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NANOGEL AS A DRUG DELIVERY SYSTEM: A REVIEW

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ABSTR ACT

The term "Nanogel" refers to a hydrogel nanoparticle with a network of cross-linked hydrophilic polymers. Nanogels are nanoparticles made up of cross-linked polymer that expand in a suitable solvent. For polynucleotide delivery, cross-linked networks of a poly ion, a nonionic polymer (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG). The creation of Nanogel systems that have proven their ability to deliver drugs in a sustained, controlled, and targetable manner has been necessitated due to the sudden explosion in the field of nanotechnology. As clinical trials progress, it is now unavoidable to develop smart nano-systems that can be used for treatment due to the growing field of polymer sciences. The goal of this brief review is to provide comprehensive examples of novel Nanogel applications, drug loading techniques, and drug release mechanisms. Furthermore, the current state of Nanogels, the status of clinical trials and future prospects have been summarized.

KEYWORDS: Nanoparticles; Nanogels; Nanotechnology; Polymers.

INTRODUCTION

Nanotechnology, a unique technique, opens up a plethora of opportunities for drug production and delivery (nanomedicine) approaches that include the characterization, synthesis and design of molecules or materials, as well as devices, with effective function at the nanometer scale. The primary goal of this technique is to improve current therapeutic and diagnostic procedures.[1]

According to studies conducted in academic labs and pharmaceutical companies around the world, the introduction of new nano-sized particulate drug delivery systems (DDS) has had a significant impact on disease diagnosis, prevention and treatment. This technique has overcome the challenges by improving drug absorption, lowering drug toxicity, controlling dose release, and reducing biodegradation. It also reduces the likelihood of immune cell activation following drug administration inside the body. The use of nanotechnology in medicine has resulted in the creation of functionalized nanoparticles that may be loaded with pharmaceutical drugs or genetic material and delivered to specific areas of the body through a controlled mechanism. As an advanced DDS, various nanotechnological techniques such as protein-based nanoparticles, lipid-based nanoparticles, nanoemulsions, nanocrystals, nanodiamonds, carbon nanotubes, nanosuspensions, and Nanogels have been introduced, with Nanogels being the most advantageous over other DDS techniques.[2]

The term "Nanogel" refers to a hydrogel nanoparticle with a cross-linked hydrophilic polymer network. Nanogels (nanosized hydrogels) are small, swollen particles made up of flexible hydrophilic or amphiphilic polymer networks that are physically or chemically cross-linked. These polymer networks may be anionic or ionic in nature. They act as drug carriers and are designed in such a way that they can easily absorb biologically active compounds through the formation of biomolecular interactions such as salt bonds, hydrophobic or hydrogen bonding. They are designed in such a way that these Nanogels can easily encapsulate a wide range of biomolecules by optimizing molecular composition, size, and morphology to ensure controlled drug release in vivo.[3]

When Nanogels are dispersed in aqueous media, their swollen networks soften and are able to encapsulate the required volume of water. By allowing the formation of spontaneous interactions between the polymer matrix and the agents, desired biological or drug molecules can be loaded into the Nanogels, resulting in the formation of highly dispersed hydrophilic particles. This resulting structure is capable of protecting the desired loaded biomolecule from degradation.

As a result, Nanogels are a versatile structure for drug encapsulation as well as drug controlled release at the target site.[4]

Nanogels were demonstrated to be a promising structure for systemic drug release, the design of multifunctional nanocarriers such as controlled drug release at the target site during the first decade of their development. Because of the large surface area and adjustable sixe of Nanogels, these molecules can incorporate a variety of molecules.

BENEFITS of NANOGEL DRUG DELIVERY APPROACH

- It protects against the biodegradation of drugs within the body.
- Physical properties of Nanogels, such as size, can be easily adjusted and maintained in accordance with the desired delivery molecule.
- A small amount of drug is required, and the number of doses is reduced.
- Increases drug molecule absorption and decreases drug toxicity.
- Drug-loaded Nanogels can be reached inside the body without causing any adverse or side effects and they can also be applied transdermally.
- These have the ability to pass the blood-brain barrier as well as physiological barriers such as the skin.

DRAWBACKS of NANOGEL

- At the end of the process, expensive techniques are required to completely remove the solvents and surfactants.
- Surfactant traces can occasionally cause toxicity.

Nanogel pores can be filled with small molecules or macromolecules; Nanogels typically range in size from one to hundreds of nanometers in diameter. Furthermore, some properties of Nanogels, such as swelling, degradation, and chemical functionality, can be controlled.[5] Nanogels have been studied for a long time not only for drug delivery but also for the production of various agents such as dyes and other diagnostic agents such as quantum dots.[6]

The importance of Nanogels has grown as a result of specific delivery system expectations, a diverse range of polymer systems, and the ease with which physical-chemical properties can be altered. Clinical studies have shown that Nanogel has a promising value; besides, Nanogels are used in gene therapy because gene delivery is now possible to silence genes within cellular organelles. The volume fraction of a Nanogel can vary by changing the solvent quality and by branching to maintain a three-dimensional structure, as shown in Figure 1.[7]

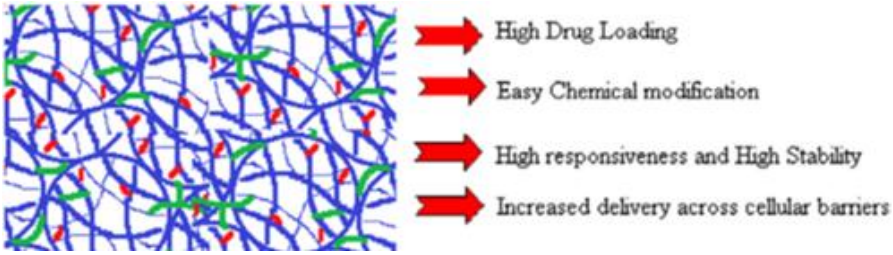

Figure 1: 3D Structure of Nanogels.

ROUTES OF ADMINISTRATION

Pulmonary, oral, parenteral, nasal, topical and intra-ocular are common routes of Nanogel administration.

NANOGELS AS DRUG LOADING TECHNIQUE

Nanogel drug delivery systems can be used as successful techniques or methods due to their high drug loading capacity and low carrier count; below are some such methods.

Covalent Conjugation

Nanogels in biological agents can be created by using covalent conjugation. Acrylic groups are arranged with enzymes and copolymerized with acrylamide in a dilute aqueous solution or an inverse microemulsion to produce nanosized hydrogels. The incorporation of hydrophobic molecules into nonpolar domains resulted in the formation of a hydrophobic chain, which can be found in some Nanogels. Prostaglandin E2, for example, is easily soluble in cholesterol-modified pullulan. Another example is N – hexyl carbamoyl – 5 – fluorocil (HCFU) noncovalently incorporated in NIPAAM & N – vinylpyrrolidone (VP) copolymer cross – linked Nanogels. Doxorubicin was also loaded into pluronic F127-based amphiphilic cross-linked Nanogels. The hydrophobic interaction results in relatively low levels of drug molecule loading with the Nanogel in most cases (less than 10 %).[8]

Self-assembly

As self-assembly occurs when autonomous organizations of components are aggregated into structurally well-defined structures, it will have some benefits such as minimal thermodynamics, adaptable, simple and low-cost option. A many-molecule self-assembly is distinguished by a diffusion followed by specific molecule association of non-covalent, hydrophobic, or electrostatic interactions. Because of the large number of interactions, self-assembly is weak and it dominates the assembly's structural and conformational behavior. Hence, because of electrostatic attractions and oppositely charged and readily associated[9] polysaccharides, interactions with neutral polysaccharides weaken or

eliminate self-assembly. However, chemical modification may necessitate assembly.

Polysaccharides that are highly water soluble could result in the formation of nanoparticles via hydrophobic interactions. This amphiphilic polymer has three uses.

- Hydrophilic chains with a hydrophobic backbone (grafted polymer).
- A hydrophilic backbone connected hydrophobic chains.
- Segments alternated between hydrophilic and hydrophobic (block polymers).

When amphiphilic polymers are exposed to water, they form self-aggregated nanoparticles by intra or intermolecular bonds of hydrophobic moieties primarily to decrease interfacial free energy.

The hydrophobic portion aggregates in the internal core while the hydrophilic region is exposed to the polar or aqueous medium. The critical micelle concentration, also known as the critical aggregates concentration, is the concentration at which polymeric chains aggregate.

MECHANISM of DRUG RELEASE from NANOGELS

Thermo-sensitive and Volume Transition Mechanism

Due to temperature retention above the lower critical solution temperature, polymers with thermosensitive properties, such as poly (N – isopropyl acrylamide), cause initial shrinkages in gel volume and indomethacin efflux. Because of the low temperature and release at body temperature, the polymer (N – isopropyl acrylamide – co – acrylamide) with 5 – fluorouracil is advantageous in rats.[10]

The pluronic superficial modification of polyethylene amine Nanogels has thermo-responsive properties in terms of size and has successfully used a gene delivery system. It is expanded up to 1 m in Nanogel size by thermally triggered volume of poly alkylene oxides Nanogels by physical destruction of cellular network. Nanogels with lower critical solution temperatures, such as poly (N – isopropyl acrylamide) and chitosan, could be modified by changing the polymer ratio and used in hyperthermic cancer treatments.[11]

Photochemical Internalization and Photo Isomerization

Singlet oxygen and reactive oxygen are produced by the excitation of photosensitizer-loaded Nanogels and may lead to oxidation of cellular walls like endosomal barrier walls, allowing therapeutics that would otherwise be hampered by intracellular compartment to be released into the cytoplasm. Photoregulation was used to observe the cis – trans isomerization of azobenzene, and an azo dextran loaded Nanogel with aspirin as the model drug demonstrated that the E – configuration of the azo group resulted in a better drug release pattern than the Z – configuration at 360 nm.[12]

Diffusion Mechanism

Doxorubicin is released through diffusion of stable copolymer block hydrogel nanoparticles. In a variety of Nano-medicines, this mechanism and simple procedures is used.

pH Sensitive Mechanism

Reactive oxygen species scavenge platine nanoparticles containing nanogel on and off catalytic activity as well as the protonation of acidic core polymers (2 – (N, N – diethylamino) and PEG. The polymers methacrylic acid-ethyl acrylate form insoluble 3D structures when the pH is low. When the pH is raised, acidic groups ionize due to polymeric chain repulsions, resulting in a specific procaine hydrochloride release profile.[8] The pH-sensitive polyacrylic acid chain swelling controls the kinetics of the drug temozoline's release. However, because of the pH sensitivity of glycol chitosan nanoparticles and the grafting of diethylaminopropyl groups, doxorubicin release was significantly increased.[13]

Displacement By Ions Found in The Environment

Most researchers are focusing on producing Nanogels capable of releasing biological agents at the area of impact when stimulated by the surroundings. Water-soluble polymers, such as POEOMA Nanogels, are biodegraded in aqueous environments in the presence of glutathione tripe-tide, that is found in cells. When activated with a negatively charged drug, cationic Nanogels form complexes in the cell-membrane and explain the cellular accumulation of drug delivered with Nanogel.[14]

APPLICATIONS OF NANOGELS

Nanogel in Ophthalmic

PVP/PAAc Nanogel is a radiation-induced polymerization of polyvinyl pyrrolidone-poly (acrylic acid) nanogel; it can be used to encapsulate pilocarpine so that the pilocarpine is kept at the site of activity for a longer period of time.[15]

Nanogel in Prevention of Bleeding

A solution protein molecule for Nanogel production has demonstrated that it stops bleeding even in severe gashes. The proteins have a nanoscale self-assembly mechanism that allows them to form a biodegradable gel.[16]

Nanogel as NSAIDS

The Nanogels were made with carbopol and hydroxypropylmethyl cellulose (HPMC) in the desired viscosity. Bilayered nanoparticles were created by using chitosan and poly- (Lactide-co-glycolic acid), and the surface was treated with oleic acid. Two anti-inflammatory drugs were prepared in Nanogel and applied topically to treat psoriatic plaque and allergic contact dermatitis. The researchers found that Nanogel increases the percutaneous absorption of these two drugs

into deeper skin layers for the healing of skin inflammatory disorders.[17]

Nanogel in Autoimmune Diseases

The loading liposomes with mycophenolic acid, oligomers of lactic acid-poly (ethylene glycol) terminated with an acrylate end group, and Irgacure 2959 photo initiator were easily solubilized by cyclodextrin. The PEG oligomers are then photo polymerized after being exposed to ultraviolet light. Nanogels have a greater systemic accumulation than free fluorescent tracers due to their inherent ability to bind to immune cells in vivo and allow for high localized concentrations of mycophenolic acid. This type of drug delivery system improves patient adherence and postpones the onset of kidney destruction, that is a common lupus complication.[18]

Nanogel in Cancer

Nanogel is used in cancer treatment to deliver specific targeted drugs with low toxicity and high therapeutic efficacy.

Based on the Mechanism of Action

pH sensitive chitosan glycol was grafted with a 3-diethyl amino propyl group and used to accelerate Doxorubicin uptake. Mechanisms of thermo-sensitivity and volume transition pluronic polyethylene mine / DNA complexes are used in thermo-responsive endosomal rupture and drug release via Nanogel. Poly (N-isopropyl acrylamide-co-acrylamide) is an insitu gelatinized thermosensitive nanogel used for drug loading capacity of 5-Flourouracil was greater than that of macromolecules, bovine serum albumin.[19] Poly (N-isopropylacrylamide) and chitosan are thermosensitive magnetically modalized nanogels used in targeted drug delivery and cancer prevention. Hydroxypropyl cellulose (HPC)-poly (acrylic acid) and cholesterol bearing pullulan modified with amino group is a Nanogel quantum dot hybrid pH and temperature responsive cadmium II ions quantum dots which used for optical pH sensing, imaging probe, temozolomide drug loading , and cell imaging.[20]

Based on the Self Assembly Heparin pluronic, a self-assembling Nanogel used in the internalization of RNase an enzyme. A quarternized, amine and size dependent Nanogel with a cross linked poly (2-(N, N-diethylamino) methacrylate core and PEG is used for efficient SiRNA delivery.[21]

Acetylated chondroitin sulfate is a self-organizing Nanogel used to transport Doxorubicin. A nanosized cationic hydrogel containing acrylate group modified cholesterol bearing pullulan is used to improve oral and brain health.[14]

Gene Delivery is at the heart of A photo crosslinking Nanogel was created by using the polymers Di-acrylated pluronic 127 and glycidyl methacrylate chitoolgosaccharides to control the delivery of plasmid DNA.[22] Gene therapy potential exists for the polymer poly (2-(N, N-diethylaminoethyl) methacrylate) PEGlyted macroRAFT agent used to create a one-step PEGlylated cationic nanogel. Endosomal escape of SiRNA is achieved by creating photochemically internalized Nanogels from the polymer Dextran hydroxyl ethyl methacrylate – co-(2-methacryloyloxy)-ethyl) trimethyl ammonium chloride.[15]

The polymer thiol functionalized hyaluronic acid was used to create a specific target and degradable Nanogel for the delivery of SiRNA to HCT-116 cells. Based on protein, a cholesterol-containing amino group modified for the production of an artificial chaperone Nanogel is used to treat Alzheimer's disease by inhibiting amyloid – protein aggregation.[23]

CLINICAL TRIAL STATUS of NANOGELS

Cholesteryl pullulan (CHP) nanogels have shown a great promise in the delivery of peptides. The CHP-HER-2 vaccine was administered in 300g doses every two weeks to nine patients, with booster doses in between. With only minor skin sensitivity at the injection site, the vaccine was well tolerated. All of the patients had a CD8+ T-cell and CD4+ response, indicating that the therapy was working. Recently, optically sensitive insulin-loaded silver nanoparticle nanogels of poly (4-vinylphenylboronic acid-co-2-(dimethylamine) ethyl acrylate) have been designed for diabetes management, ushering in a new era in clinical trials 50. The development and application of antibiotic conjugated angels in vivo has provided a promising solution to two problems.[24]

ANGELS' CURRENT SITUATION AND FUTURE PROSPECTS

Nanogels have primarily been used in cancer therapy. Cholesteryl pullulan angel has been shown in clinical trials to be effective for peptidase delivery. The cholesteryl-HER-2 vaccine was given to nine patients in 300g doses, with boosters every two weeks. According to this, skin sensitivity at the site of S.C injection, as well as CD4+ and CD8+ T-cells, show better therapeutic efficacy. In the prevention of Alzheimer's disease, cholesterol pullulan angels have been shown to reduce toxicity to nervous system cells while increasing binding capacity to AB oligomer.[25]

To control diabetes, a poly (4-vinyl phenyl boronic acid-co-2-(dimethylamine) ethyl acrylate) optically sensitive insulin-loaded silver nanoparticle nanogel was recently developed. Nanogels are now conjugated with antibiotics for targeted drug delivery at the single cell level.[26]

In the future, the mechanisms of the blood-brain barrier and cytosolic destination over endosomal or nuclear delivery will need to be studied for specific and targeted drug delivery.

CONCLUSION

Nanogels are sophisticated pharmaceutical nanocarriers for both pharmaceutical and therapeutic agents. Nanogel systems could be easily prepared with biomacromolecules to achieve maximum entrapment ability and dispersion stability. Pharmaceutically active compounds with various drug structures are controlled by Nanogel systems. Nanogels can also encapsulate biopolymers and low molecular mass hydrophobes. The discovery of a new polymeric system is critical to the advancement of Nanogels. Advanced polymerisation or cross-linking approaches have the potential to play a role in therapies. This is a novel method for synthesizing Nanogel assemblies. As a result, we can anticipate that these advanced nanocarrier systems will be prioritized in future pharmaceutical developments.

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