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NOVEL NANOGEL APPLICATIONS: A REVIEW

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ABSTRACT

The term Nanogels (NGs) refers to a hydrogel nanoparticle with a network of cross-linked hydrophilic polymers. NGs 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 NGs systems that have capability to supply medicaments in a targetable, controlled, and sustained 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 NGs applications, drug loading techniques, and drug release mechanisms. Furthermore, the current state of NGs, 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 considerable importance in illness diagnosis, prevention and treatment. By enhancing drug absorption, lowering drug side effects, managing drug release, and decreasing biodegradation, this method has surmounted the obstacles. It also decreases the likelihood of immune cell stimulation following drug administration within human organs. The use of NGs in pharmacy has resulted in the creation of functionalized nano-scale particles that may be filled with drugs or genetic and delivered to specific areas of the body through a controlled mechanism. As an advanced DDS, different nanotechnological methods such as lipid nanoparticles, protein nanoparticles, nanocrystals, nanodiamonds, nanoemulsions, nanosuspensions, carbon nanotubes, and NGs have been used, with NGs being the most advantageous over other DDS techniques.[2]

The term "NGs "refers to aqueous nanoparticle conjugated with aqueous polymer network. NGs (nanosized hydrogels) are small, swollen particles of flexible amphiphilic or hydrophilic polymer networks that are physically or chemically cross-linked. These networks may be ionic or anionic in nature. They act as drug carriers and are developed in such manner that they can absorb active materials through chemical interactions such as hydrogen or hydrophobic bonding and salt formation. They are formed in such manner that these NGs can easily loaded with a variety of bio-molecules through optimization of molecular components, morphology and size to ensure in-vivo sustained drug release.[3]

When NGs are suspended in water, their networks swollen and are capable of encapsulate high percent of water. Through the interactions between drug and gel matrix, desired drug can be encapsulated inside NGs, leading to formation of suspended hydrophilic nano-particles. This structure is capable of protecting the desired loaded biomolecule from degradation.

As a result, NGs are a flexible structure for drug loading as well as drug sustained release at the desired site.[4]

NGs have been shown to be a viable form for injectable medication delivery, the design of functional nano-carriers such as sustained drug release at the desired site during the first decade of their development. Because to their enormous surface area and changeable sixe, NGs may incorporate a wide range of compounds.

Advantaged of NGs

- It protects against degradation of active ingredient within the body.
- Physical characteristics of NGs, like size, may be maintained and adjusted as requested delivery of active ingredient.
- A small quantity of active ingredient is required, and the number of doses is reduced.
- Increases drug molecule absorption and decreases drug toxicity.
- Drug-encapsulated NGs can be reached inside the body without causing any side effects and also can be used transdermally.
- These have the ability to pass the barriers as blood-brain barrier and skin.

DRAWBACKS of NGs

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

NGs pores can be filled with small molecules or macromolecules; NGs varied in size from one to hundreds of nanometers in diameter. Furthermore, some properties of NGs, such as swelling, degradation, and chemical functionality, can be controlled.[5] NGs 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 NGs 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 NGs has a promising value; besides, NGs are used in gene therapy because gene delivery is now possible to silence genes within cellular organelles. The volume fraction of a NGs can vary by changing the solvent quality and by branching to maintain a three-dimensional structure, as shown in Figure 1.[7]

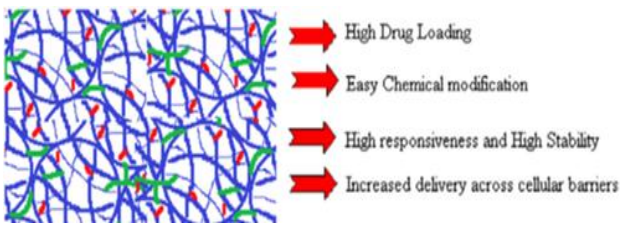

Figure 1: 3D Structure of Nanogels.

ROUTES OF ADMINISTRATION

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

NGs AS A DRUG ENCAPSULATEDTECHNIQUE

NGs can be used as an excellent techniques or methods due to their high drug loading capacity and low carrier count; below are some such methods.

Covalent Conjugation

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

Self-assembly

It occurs when groups of ingredients assemble into well-defined structures; it will have some benefits such as minimal thermodynamics, adaptable, simple and low-cost option. Many-molecular self-assembly is differentiated by diffusion which followed by hydrophobic, electrostatic or non-covalent molecule binding. Because of the large number of interactions, self-assembly is weak and it dominates the assembly's conformational and structural 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.

Aqueous soluble polysaccharides may produce nanoparticles through hydrophobic reactions. Such 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 dispersed in water, they aggregated by formation of intra molecular bonds of moieties primarily to decline interfacial free energy.
The hydrophobic moiety aggregates inside the core while the hydrophilic moiety interacted with water. The critical micelle concentration, also known as the critical

aggregates concentration, is the concentration at which polymeric chains aggregate.

METHODS of DRUG EFFLUX from NGs

Thermo-sensitive and Volume Transition Method

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

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

Internalization and Isomerization

Free radical oxygen is obtained by the stimulation of photosensitizer-loaded NGs 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. Photo regulation was used to observe the cis – trans isomerization of azobenzene, and an azo dextran encapsulated NGs associated by acetyl salicylic acid as an example drug demonstrated that the E – configuration of the azo functional group resulted in an excellent drug release model than the Z – configuration at 360 nm.[12]

Diffusion Mechanism

DOX 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 NGs 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, DOX release was significantly increased.[13]

Displacement by Ions Found in the Environment

Most researchers are focusing on producing NGs capable of releasing biological agents at the area of impact when stimulated by the surroundings. Aqueous polymers, such as POEOMA NGs, are deteriorated in water by the aid of glutathione tripe-tide, which located in cells. When activated with a anionic drug, cationic NGs form complexes in the cell-membrane and clarify the accumulation of medicine delivered with NGs.[14]

APPLICATIONS OF NGs

NGs in Ophthalmic

PVP/PAAc NGs is a radiation-induced polymerization of polyvinyl pyrrolidone-poly (acrylic acid) NGs; it can be used to encapsulate pilocarpine so that the pilocarpine is kept at activity site and give sustained release effect.[15]

NGs in Prevention of Hemorrhage

A solution protein molecule for NGs production has demonstrated that it prevent severe haemorrhage. Like proteins have a nano-scale self-assembly mechanism that allows them to form a biodegradable gel.[16]

NGs **as NSAIDS**

The NGs were made with carbomer and hypromellose in the optimized viscosity. Bilayered nanoparticles were created by using chitosan and poly- (Lactide-co-glycolic acid), by the aid of oleic acid. Two different formulae were prepared in NGs and applied topically to treat psoriatic plaque and allergic contact dermatitis. The researchers found that NGs sustain the transdermal absorption of these two formula into different skin layers for the healing of skin inflammations.[17]

NGs in Autoimmune disorders

The liposomes encapsulated with mycophenolic acid, was 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 disposition of mycophenolic acid. Delivery of such drug improves individual adherence and postpones the incidence of urinary system destruction, that is a common lupus complication.[18]

NGs in Cancer

NGs are used in cancer treatment to deliver specific targeted drugs with low toxicity and improve its efficacy.

According to the Mechanism of Action

pH sensitive chitosan glycol was interlaced with a 3-diethyl amino propyl group and this improve DOX delivery. Mechanisms of thermo-sensitivity and size transition DNA / pluronic polyethylene mine complexes are employed in thermo-responsive endosomal rupture and medication release via NGs. Poly (N-isopropyl acrylamide-co-acrylamide) is an insitu gelatinized thermo sensitive NGs employed for medicament encapsulating capacity of 5-Flourouracil was greater than

that of macromolecules, bovine serum albumin.[19] Poly (N-isopropylacrylamide) and chitosan are thermosensitive magnetically modalized NGs employed in targeted drug delivery and cancer prevention. Hydroxypropyl cellulose (HPC)-poly (acrylic acid) and cholesterol bearing pullulan modified with amino group is a NGs quantum dot hybrid pH and temperature responsive cadmium II ions quantum dots which employed for optical pH sensing, imaging probe, temozolomide drug loading , and cell imaging.[20]

Based on the Self Assembly Heparin pluronic, a self-assembling NGs used in the internalization of RNase an enzyme. A quarternized, amine and size dependent NGs 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-arranged NGs employed to transport DOX. 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 NGs 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 macro RAFT agent used to create a one-step PEGlylated cationic NGs. Endosomal escape of SiRNA is achieved by creating photo chemically internalized NGs 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 NGs 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 NGs is used to treat Alzheimer's disease by inhibiting amyloid – protein aggregation.[23]

CLINICAL TRIAL STATUS of NGs

Cholesteryl pullulan (CHP) NGs have seen a great promise in the delivery of peptides. The CHP-HER-2 vaccine was given 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 NGs of poly (4-vinylphenylboronic acid-co-2-(dimethylamine) ethyl acrylate) have been formulated for diabetes management, ushering in a new era in medical 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

NGs have primarily been employed in cancer treatment. Cholesteryl pullulan angel has been used in medical experiments to be effective for peptidase delivery. The cholesteryl-HER-2 vaccine was given to 9 patients in 300g doses, with boosters every two weeks. According to this, skin sensitivity at the site of subcutaneous injection, as well as CD4+ and CD8+ T-cells, show improved therapeutic effect. In the prevention of Alzheimer's disease, cholesterol pullulan angels have been shown to reduce adverse effects to CNS cells while increasing association 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 NGs was recently developed. NGs are now associated with antibiotics for targeted medicament delivery at the single cell level.[26]

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

CONCLUSION

NGs are sophisticated pharmaceutical nanocarriers for both pharmaceutical and therapeutic agents. NGs 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 NGs systems. NGs can also encapsulate biopolymers and low molecular mass hydrophobes. The discovery of a new polymeric system is critical to the advancement of NGs. Advanced polymerisation or cross-linking approaches have the potential to play a role in therapies. This is a novel method for synthesizing NGs assemblies. As a result, we can anticipate that these advanced nanocarrier systems will be prioritized in future pharmaceutical developments.

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