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A Brief Study on Nanogel: A Review

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Abstract **Review Article**

Strong nanoparticles called nanogels may be utilized in controlled drug delivery applications to distribute active pharmaceutical ingredients. Because of their chemical makeup and formulations that are unsuited for other formulations, nanogels provide a safer and more effective drug delivery mechanism for both hydrophilic and hydrophobic medicines. Functionalized nanoparticles, which serve as drug carriers and can be loaded with medications and other active materials to be released in a regulated way at a specific spot, can now be larger thanks to nanogel technology. The objective of this paper is to present a broad overview of nanogels, their innovative applications across several domains, and their latest synthesis process.

Keywords: pharmaceutical ingredients, drug delivery mechanism, Nanogel, Functionalized nanoparticles.

INTRODUCTION

In the nanoscale size range, nanogels are three-dimensional hydrogel materials made of crosslinked swellable polymer networks that have a high water-holding capacity without really dissolving into the aqueous media. A range of manufactured, naturally occurring or a combination of polymers can be used to create nanogels. You can fine-tune the properties of the nanogels, including size, charge, porosity, amphiphilicity, softness, and degradability, by tuning their chemical composition. The majority of them are spherical particles, however new developments in synthetic techniques enable the creation of nanogels with a variety of morphologies [1, 2]. In order to maintain structural integrity they can also be created with a minimum of one crosslinked layer and a core-shell or core-shell-corona structure. With a large loading capacity for guest molecules and a mostly hydrophilic nature, nanogels are extremely biocompatible and have a particular advantage over other forms of nanomaterials in biomedical applications due to their unique physical features. Due to their unique characteristics, such as their softness, swelling, and behaviour that responds to stimuli, nanogels not only shield the cargo from deterioration and removal but also actively assist in the delivery process by assisting in the achievement of a regulated, triggered response at the target site [3-9].

The rapid advancement of nano drug delivery methods in the last few years has given many conventional chemotherapy medications a new avenue for application. In particular, anti-cancer medication delivery makes extensive use of nanocarriers, including liposomes, micelles, nanogels, and nanoparticles, which are potent substitutes for conventional radiation and chemotherapy (Fig 1). Nevertheless, a number of flaws exist in these nanocarriers as well, such as inadequate targeting [10], medication leakage, inadequate stability and biocompatibility, rapid blood circulation [11], and so forth. Even worse, a few biological and physical barriers including the endothelium and the mononuclear phagocyte system (MPS) make it more difficult for drugs to reach tumours, which lowers administration efficiency and produces an inadequate therapeutic effect. Consequently, there is a strong need to create a fresh diagnostic and therapeutic approach that defies accepted.

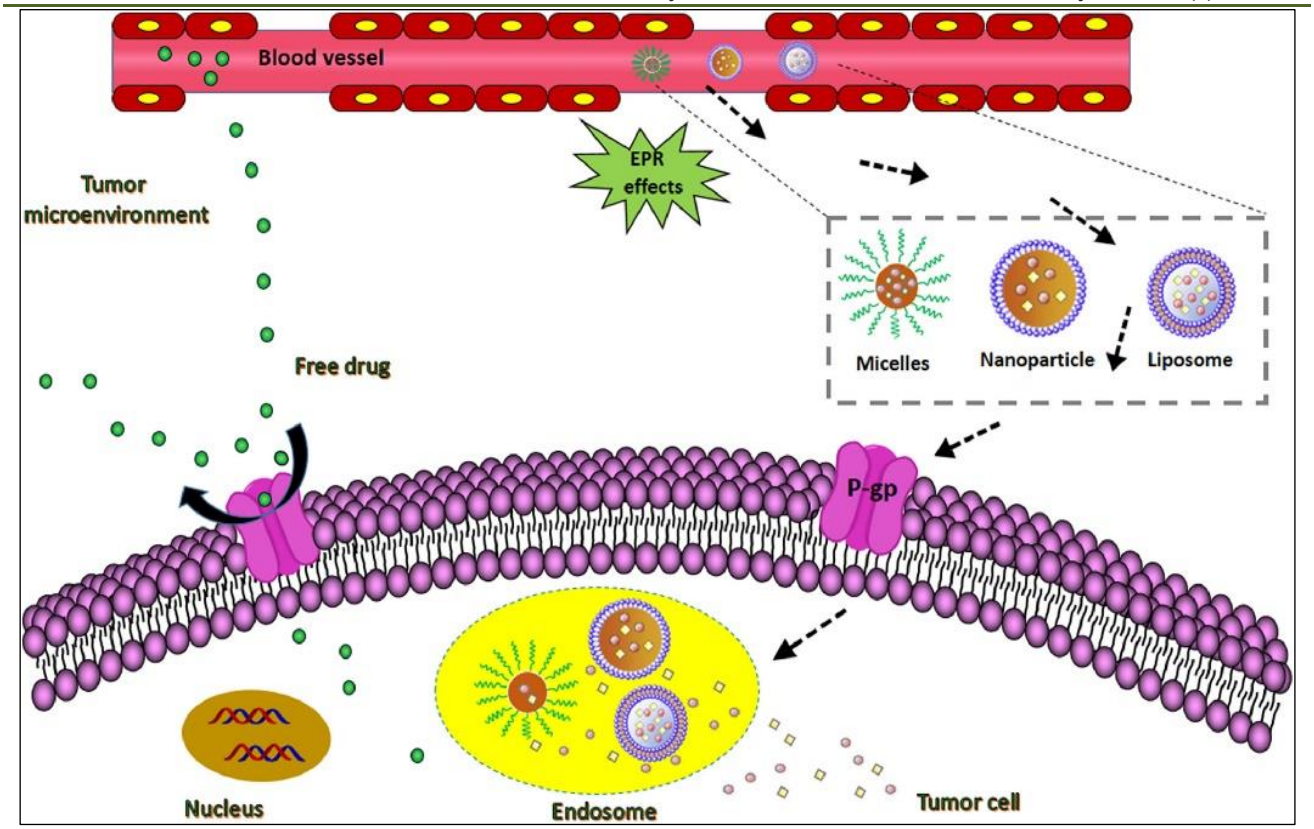

Fig 1: Conventional Radiation and Chemotherapy

Advantages [12]

For a number of reasons, nanogels are thought to be superior to alternative drug delivery methods. These reasons include:

1. **Biocompatibility and degradability:** Natural or synthetic polymers are used to make nanogel. Their excellent biocompatibility and biodegradability prevent them from building up in organs. The nanogel is made using chitosan, methylcellulose, ethyl cellulose, and a variety of polysaccharide-form polymers, including pullulan, dextran, and dextrin. These polymers are biodegradable, hydrophilic, stable, and non-toxic.
2. **Swelling properties in aqueous media:** Nanogels can swell or dwell in an aqueous medium by ingesting water because of their strong affinity for aqueous solutions. Because it gives nanogels the best chance of absorbing and delivering proteins, peptides, and bio-macromolecules, this is their most advantageous featureand heavy medications. Only when medium ions apply osmotic pressure and there is an imbalance in the swelling pressure of the polymer network does swelling occur.
3. **High drug loading capacity**: Compared to conventional dosage forms, nanogels offer a higher drug loading capacity. This is mostly because of the formulation's swelling feature, which enables it to absorb a large amount of water and creates cargo space big enough to hold salts and biomaterials. A few additional elements, such as composition, molecular weight, potential interactions between the medication and the polymer in use, and the various functional groups in each polymeric unit, also play a role in the high loading capacity.
4. **Particle size and permeability Because of their hydrophobicity, surface charge, and nanosize Skin permeability is advantageous for nanogels:** Reduced particle size, surface charge, and hydrophobicity in nanogels can greatly increase permeability. They can penetrate tissues or endothelium by diffusion because of their small particle size, or diameter of 20–200 nm, and occasionally by a specific transport system.
5. **Stability of colloidal particles:** Aggregation is a propensity that occurs when handling nanoparticles and jeopardizes colloidal stability. Raising the zeta potential (to a minimum of ±30 mV), which causes the particles to repel one another more strongly and become electrostatically stabilized. Other methods include adding a surface modification, such as polyethylene glycol (PEG), which hydrates the material and creates steric effects to create a stable nanosuspension.
6. **Non-immunologic response**: This sort of drug delivery system does not give rise to any immunological responses. Nanogels are inert in the bloodstream and the internal aqueous environment and do not induce any immunological responses in the body.
7. **Ease of synthesis:** The synthesis of nanogels is a stress-free process where mechanical energy is not employed and harsh conditions are not involved.

This process does not include the introduction of organic solvents. Hence the drug can be loaded effortlessly without being exposed to any sort of robust conditions throughout the preparation process.

8. **High encapsulation stability**: Drug molecules put into the nanogel must be kept and not be carried out or leak prematurely while circulating in order to give optimum therapeutic effects and minimal toxicity or adverse effects.
9. **Controlled and sustained release of the drug**: Nanogels are designed to release pharmaceuticals at the target site in a predetermined and extended pattern in order to maximize the therapeutic efficacy of the drug and prevent its side effects.
10. **Response to stimuli:** Drugs can be delivered to a specific spot using nanogels without compromising on other properties. The drug then disperses to reach the target site and is released willingly in response to the right stimulus.
11. **Targeting:** By binding to surface ligands, target determinants, or through "passive" targeting strategies such extravasation in the diseased regions and retention in the microvasculature, the nanogels can be employed as a targeted drug delivery system. The incorporation of ligands into nanogels through chemical modification results in targeted and triggered drug release anddistribution.
12. **Low toxicity:** The nanogels should be extremely biocompatible, toxic-free, and biodegradable, producing non-toxic breakdown products that the body can easily eliminate.

The limitations of nanogel

1. Removing the solvent and surfactant at the conclusion of the preparation procedure is costly.
   If any remnants of surfactants or polymers are still inside the body, negative consequences could happen [13].
2. Limited ability to load drugs and inadequate release control.
3. The contact between the drug and polymer may cause the structure to collapse, permanently trapping the drug molecules and enhancing the hydrophilicity of the nanogel matrix [14].

Because of [15], nanogels could be thought of as better drug delivery platforms than the others.

1. It is possible to regulate surface characteristics and size to prevent reticuloendothelial cells from clearing the medication quickly, enabling both passive and active drug targeting.
2. Sustained and controlled drug release at the intended location, improving treatment effectiveness and lowering adverse effects. Drug activity can be preserved thanks to the somewhat high drug loading that can be accomplished without causing chemical reactions.
3. The capacity to enter tissues via either paracellular or transcellular pathways, and to reach the tiniest capillary capillaries due to their tiny space.
4. They are both very biodegradable and biocompatible.

Nanogel Applications [16]

Nanogels have been proven to be extremely effective in treating

- Autoimmune diseases
- Cancer
- Neurological disorders
- Inflammatory disorders
- Diabetes
- Is used to deliver drugs intracellularly;
- Acts as a local anaesthetic;
- Delivers vaccines;
- Promotes bone regeneration

CATEGORIES OF NANOGELS

Two main categories are more frequently used to categorize nanogels. Their response behaviour—which can be either stimuli-responsive or nonresponsive—is the basis for the first classification. When it comes to non-responsive microgels, they just swell when they take in water. 2. In response to alterations in temperature, pH, magnetic field, and ionic strength, stimuli-responsive microgels expand or contract. Multiple environmental stimuli can cause multi-responsive microgels to react (Gupta *et al*., 2002; Sasaki and Akiyoshi, 2010). The second classification divides polymeric gels, including nanogel, into two primary groups according to the kind of connections found in the network chains of gel structure:

Physical gels cross-linked

Weaker links created by (a) van der Waals forces, (b) hydrophobic, electrostatic contacts, or (c) hydrogen bonding result in the formation of physical gels or pseudo gels. There are a few easy ways to make physical gels. Fig 1 Nanogel drug release model. These systems are sensitive, and their sensitivity is dependent on the concentrations of the cross-linking agent and polymer, as well as the temperature and ionic strength of the medium. In a matter of minutes, micro- and nanogels are formed through the complexation of oppositely charged polymeric chains and the association of amphiphilic block copolymers. Polymeric chains can also aggregate and/or self-assemble to generate physical gels.

Nanogels Modified with Liposomes
Liposomes Modified Nanogels

Liposomes containing succinylated poly(glycidol)s have been reported by Kono *et al*., They have been demonstrated to effectively transport calcium to the cytoplasm via chain fusion occurring below pH 5.5. For thermo- and pH-responsive nanogels, which are

being researched for transdermal drug administration, liposomes modified or anchored by poly (N isopropylacrylamide)-based copolymeric groups are appropriate (Labhasetwar *et al*., 2007).

Micellar Nanogels

The supramolecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions can yield polymer micellar nanogels. Their distinct morphological formations are characterized by a hydrophobic core segment encircled by hydrophilic polymer blocks that serve as a corona, stabilizing the micelle as a whole. Micelles' cores have sufficient room to physically entrap different drugs or biomacromolecules. Moreover, the hydrophilic blocks might establish hydrogen bonds with the aqueous medium, which would complete the creation of a perfect shell around the micelle's core. As a result, the hydrophobic core shields the drug molecules from enzymatic and hydrolytic breakdown.

For the purpose of drug distribution, researchers (Li *et al*., 2006) successfully created extremely adaptable Y-shaped micelles of poly(oleic acid-Y-N-isopropylacrylamide). Prednisone acetate was shown to be delivered above its lower critical solution temperature (LCST) in this investigation.

Hybrid Nanogels

A composite of nanogel particles scattered in either organic or inorganic matrices is known as a hybrid nanogel. Studies by a group of researchers (Akiyoshi *et al*., 1999; Akiyoshi *et al*., 2000) have shown that polymer amphiphiles, such as pullulan PIPAM, hydrophobized polysaccharides, and hydrophobized pullulan, can self-assemble or aggregate to create nanogels in an aqueous media. This group has studied pullulan (CHP) nanogels that contain cholesterol. These nanogels can coat the surfaces of liposomes, particles, and solid surfaces, including cells. They can also form complexes with different proteins, medications, and DNA (Nishikawa *et al*., 1996; Kuroda *et al.,* 2002). Additionally, these hybrid nanogels can more efficiently carry insulin and anticancer medications. The pullulan backbone and cholesterol branches make up CHP.

Chemically crossed-linked gels

Covalent bonds, which are long-lasting chemical connections between molecules, make up chemical gels. The functional groups and chemical bonds found in the gel networks determine the characteristics of the cross-linked gel system. Various techniques have been employed to create distinct nanogels by the chemical joining of polymeric chains. The polymerization of vinyl monomers in the presence of multifunctional cross-linkers, which serve as the initial cross-linking locations inside and between the polymeric chains, is typically how hydrophilic polymers and hydrophilic–hydrophobic copolymers are produced. The gel systems' entire physicochemical properties can be changed thanks to these crosslinking locations. There have been some published reports of adaptable cross-linking agents (Labhasetwar *et al*., 2007).

Example

As an illustration A simple method for creating nanogels (20–200 nm) has been shown, wherein the polymeric chains are endowed with pendant thiol groups, and the "environment" facilitates the subsequent intramolecular disulfide cross-linking of these chains.

Nanogels for drug delivery

The majority of nanogel systems are made of crosslinked natural or synthetic biopolymers. It is possible to include tiny molecules or biomacromolecules into the pores of the 3D network in nanogels. The utilisation of polymeric nanogels as drug carriers has several benefits, including the ability to regulate medication dosage artificially through external stimuli, protect against drug odour, enhance therapeutic efficacy, and mitigate side effects [17]. Pharmaceuticals with severe side effects, short half-lives in circulation, and easy degradation by enzymes, like proteins and anticancer medicines, can be delivered via chemical crosslinking or physical assembly of nanogel systems [18, 19].

Small Molecule Delivery

Because of their water solubility, biocompatibility, and biodegradability, as well as their encapsulation stability and intelligent release, nanogels show great promise as DDSs. In order to deliver tailored medication to the tumor tissue, the primary goal of current nanogel research is to overcome the instability of protein-based medications. It is common practice to examine the encapsulation and delivery characteristics of different nanogels using DOX, a hydrophilic model drug [20]. In the presence of external cues, swelling-collapse variation might readily fulfil the drug-entrapping and controlled release requirements [21]. The nanogel network may also trap some hydrophobic medications in addition to the hydrophilic ones.

The hydrophobic drug rapamycin was intended to be loaded into a Fe3O4 hybrid nanogel system by interaction with the inner core's hydrophobic surface. To build the hydrophilic shell of the hybrid nanogel, 2-aminoethyl methacrylate hydrochloride (AEMA) was added as the pH-sensitive monomer and NIPMAm as the thermoresponsive monomer. Additionally, on the surface of drug-loaded nanogels, a collagen IV targeting peptide (KLWVLPK) was coupled with the amino group of AEMA, allowing the creation of nanogels that targeted the wounded artery and, as a result, achieving the vascular restenosis therapy [22].

Biomacromolecules Delivery

Large molecular weight, complex structure, and biological functions distinguish biological macromolecules from chemical medications;

nonetheless, these features also make it difficult to control the stability and permeability of biomacromolecules [23]. As a result, a range of nanoscale DDSs are used to transport these medications [24, 25]. Among them, nanogels, which are made up of nanometer hydrogels, have the ability to effectively transport pharmaceuticals and exhibit stability, hydrophilicity, and great drug-loading capacity.

Proteins Delivery

Proteins must be pharmacologically altered for therapeutic purposes due to their limited medication release and prolonging drug retention duration can be achieved through encapsulation in a range of polymers [26]. Both synthetic and natural polymers—such as polycaprolactone, acrylic polymers, and polyallylamine—as well as chitosan, dextran, and alginate—were used to create nanogels that delivered insulin; these polymers demonstrated superior biocompatibility, high permeability, and improved glucose-based response. These oral nanogels' outstanding benefits have made it possible to significantly reduce hypoglycemia. When insulin was administered orally as opposed to intravenously, patient compliance was found to be higher, even though the gastrointestinal tract has epithelial barriers [27].

In order to increase the bioavailability of oral insulin, Mudassir *et al*., recently created a pH-sensitive polymethyl methacrylate (MMA)/itaconic acid (IA) nanogel [28].

Nucleic Acids Delivery

Certain hereditary illnesses can be specifically treated using gene therapy, which involves delivering therapeutic DNA or RNA sequences. Small interfering RNA (siRNA) is one of these gene treatments that has gained significant traction in the treatment of gene-related disorders because of its potent capacity to silence genes and precisely and efficiently block gene expression [29]. Since siRNAs are hydrophilic, negatively charged chemicals that cannot pierce the cell membrane, their applicability is restricted by a number of parameters, including their short half-lives owing to enzymatic degradation and poor transfection rates.

In order to overcome these issues, naked siRNA can be attached to polymer nanoparticles during nucleic acid treatment, loaded in liposomes, or adorned by the biomolecule cholesterol. Furthermore, due to its physicochemical properties, decorated siRNA can penetrate particular tissues. A delivery technology based on nanogel was used to achieve siRNA treatment. Furthermore, there is a clear path forward for other functional oligonucleotide medicines with this method. Introduced as a nonviral vector for siRNA assembly, the tetrahedral DNA-based (TET) nanogel offered protection during delivery. This method efficiently prevents ribonuclease degradation and permits both in vitro and in vivo cell transfection, indicating a suitable platform for the integration of numerous devices for enhanced efficacy.

CONCLUSION

Nanogels have garnered significant attention from researchers due to their potential uses in biosensing, targeted drug administration, diagnostics, and biological substance separation. Because of their small particle size—smaller particles have greater surface area and, thus, more action—nanogels have been useful in delivering higher action or potency of the medicine. Because of their hydrogel properties, which enable them to hold large amounts of water and thus increase their drug loading capacities, tissue-like properties, and flexibility, nanogels combine the best aspects of both hydrogels and nanoparticles to create a unique carrier system. Meanwhile, the nanometric size of these particles enables them to enter deeper tissues, evade reticuloendothelial system invasion, provide site-specific delivery, and other benefits.

Thus far, research on nanogels has gathered sufficient evidence to support their promise as targeted carriers for the topical delivery of bioactive chemicals for conditions such as skin cancer, wounds, inflammation, local anaesthetic, etc.

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