Nanotechnology is an ingenious drug delivery method with nanometer-sized materials. Nanogel has captivated as scrutiny as one of the most multifaceted drug delivery systems especially for site-specific and/or time-controlled delivery of bioactive agents owing to their combining features of hydrogel and nanoparticle. Physically synthesized nanogels can offer a platform to encapsulate various types of bioactive compounds, particularly hydrophobic drugs and bio macromolecules, but they have poor mechanical stability, whereas nanogels prepared by chemical cross-link have a wider application and larger flexibility. As an ideal drug-delivery carrier, nanogel has excellent drug loading capacity, high stability, biologic consistence and response to a wide variety of environmental stimuli. This review throws an insight into recent advancements in nanogel.

**Keywords:** Nanogel, macromolecules, hydrogel.

1. **INTRODUCTION**

A nanogel is a nanoparticle comprises of a hydrogel a crosslinked hydrophilic polymer network. Hydrogel nanoparticles referred as nanogel soluble in water but possess properties varied from linear macromolecules. Uttermost synthetic polymers or biopolymers constitute the nanogel and the polymers are physically or chemically crosslinked by non-covalent bonds by hydrogen bonds, electrostatic and hydrophobic interactions. The size of nanogel commonly exists in the tens to hundreds of nanometer in diameter. Owing to their small size it evade renal clearance and prolonged half-life period. Nanogels are three dimensional hydrophilic network and have susceptibility to imbibe water or physiological fluid in enormous quantity without changing in the internal network structure. Further for integrating ligands to achieve targeted drug delivery change in chemical modification is essential. Small molecules or macromolecules can be filled in the nanogel and various properties like swelling nature, degradation can be controlled effectively.

Nanogel based materials constitute good biocompatibility and biodegradability enables greater potential to design the drug delivery system effectively. Due to very high drug encapsulation capacity nanogel makes a promising drug delivery system. Even multiple combinations of drugs can be loaded in nanogel like vaccines, nucleic acids and other immune disorders without affecting the gel like structure. They are designed to incorporate and drug release of bioactive molecules ex. Drug, proteins, peptides and antigens inorganic molecules like quantum dots.

1.1. **Advantages of nanogel drug delivery system**

- High drug encapsulation efficiency
- Ability to encapsulate variety of drugs
- Widely acceptable drug delivery system
- Greater potential to encapsulate in same carrier more than one bioactive substance with diverse physical properties
- Site targeting action
- Simplicity in preparation
- Minimal toxicity
- Good responsive to environmental stimuli
1.2. Route of administration [14-16]

- Oral
- Nasal
- Intra-ocular
- Pulmonary
- Topical
- Parenteral
- Topical.

1.3. Properties of nanogel

1.3.1. Swellable characteristic in aqueous media

It has good swelling nature exposed to aqueous media owe to polymer chain nature, degree of crosslinking, charge density for polyelectrolyte gels-pH. It also depends upon strength of ion and chemical nature of low molecular mass ions and temperature. Moreover existence of good balance between the osmotic pressure and elasticity nature of polymer ascertain the hydrogen particle physical dimension. Charge density and polymer chain’s chemical nature determines the structure of nanogel. Temperature is a trigger of swelling in thermoresponsive gels. In certain conditions like osmotic pressure exerted by medium ions and the pressure exerted polymer network swelling pressure are imbalanced.

1.3.2. Biocompatibility and degradability

Nanogel drug delivery system encompass high biocompatible and biodegradable nature since it is made up of natural or synthetic polymers. Moreover it avoids hoarding in the organs. Owing to this nanogel marks greater attention in drug delivery system. Ex: Chitosan, methyl cellulose, ethyl cellulose and polysaccharide based polymers like dextran, pullulan can be incorporated for formulation of nanogel. Being non-toxic, stable, hydrophilic and biodegradable in nature nanogel meets all the essential criteria for novel drug delivery system.

1.3.3. Prominent drug loading capacity

Functional groups present in thenanogel plays vital role and determines the efficiency of drug loading capacity. Some of the functional groups have the ability to conjugate with drug/antibodies for specific action like drug targeting nature. The higher loading capacity due to absorption of large quantity of water hence when incorporating and loading sufficient space will be afforded by water to contain salts and biomaterials. Drug loading in nanogel occurs by three steps

1.3.4. Physical entrapment:

Hydrophilic chains and hydrophobic region present in polymer provide an association and facilitates drug loading

1.3.5. Covalent attachment

Bioactive molecules has been attached covalently and forms a dense drug-loaded core. Controlled self-assembly: Customarily it is for polyelectrolyte basednanogel. The underlying fact behind drug loading capacity due to correlation between oppositely charged electrolytes.

1.3.6. Other factors

Existence of different functional groups in polymeric unit. Composition, molecular weight of polymer.

1.3.7. Particle size

Nanogels exhibit particle size in the range of 20 -200 nm and effectively uptaken by the reticuloendothelial system. Nanogels explicit proficient permeation nature owes to its utmost small size. Depending on parameters like hepatic filtration, tissue extravasation, tissue diffusion biodistribution of nanoparticlesoccur expertly. Additionally nanogels can cross blood brain barrier (BBB).

1.4. Types of nanogel

1.4.1. Physical cross-linked gels

Physically crosslinked nanogels are formed by vanderwal’s forces, hydrophobic, electrostatic interactions or by hydrogen bonding. It is also formed by the assemblage of chain of polymers. These systems are perceptive in nature and it is based on polymer composition, temperature, ionic strength of the medium and concentration of polymer and cross-linking agent chains. Physically crosslinked hydrogel are synthesized by ionic interaction, crystallization ,sterio complex formation, protein interaction, hydrophobized polysaccharides and hydrogen bond. Ex for polysaccharidesare chitosan, dextran, pullulan etc.

1.4.2. Chemically cross-linked gels

Chemically cross-linked hydrogels are formed by covalent crosslinking of polymers. Chemically crosslinked hydrogels are synthesized by chain growth polymerization, addition and condensation polymerization and gamma and electron beam polymerization. The functional groupspresent in gel networks has greater impact on the properties of gel system. The entire physicochemical properties were altered by the
crosslinking points of the gel system. Hydrophilic groups NH₂, COOH, OH present in hydrophilic polymers account for formation of hydrogel. Amine-carboxylic acid or an isocyanate OH/NH₂ reaction or Schiff’s base formation enable to identify the covalent linkages between polymer chains. Examples for crosslinking agents are glutaraldehyde, formaldehyde etc. [30,31]

1.4.3. Drug loading in nanogel

The exorbitant drug loading in nanogel is associated with self-assembly and in comparatively imperceptible conditions compared to other carriers, which is essential criteria for conservation of biological activity of labile drugs and macromolecules like proteins and peptides. [32]

Drug loaded innanogel by

- Physical entrapment
- Covalent conjugation
- Controlled self-assembly

1.4.4. Mechanism of drug release from nanogels

Drug release from nanogel occurs by

Simple diffusion

The key factor behind diffusion was the polymeric micelles attains a clinical stage.

Ex: The diffusional release of doxorubicin from stable hydrogel nanoparticles based on pluronic block copolymer.

Temperature responsive

Specific polymersexert sensitivity for temperature ultimately leads in the expansion of polymeric chains allowing the process of drug diffusion. [34]

pH responsive

Alteration of pHcauses swelling deswelling of polymers that contain acidic and basic functional groups amount of swelling depends upon extent of ionization by polymer that in turn is determined by pH of the medium5 hence by regulating extent of swelling of pH governs the rate and extent of release of drug. [35]

Volume transition: Increase in volume when subjected to pHchange.

Displacement by ions present in the environment

Degradation of disulfide cross-linked poly [oligo(ethylene oxide)methyl methacrylate] in the presence of tripeptide triggered and release of encapsulated solutes, rhodamine 6G and doxorubicin. Polyelectrolyte hydrogels incorporating drugs via electrostatic bonds can also release them in response to environmental changes. [36]

1.5. Synthesis of nanogel

1.5.1. Photolithographic techniques

In this technique 3D nanogel are prepared. UV cross linked polymer acts as substrate but possess low surface energy and it is released on pre-baked photo resist-coated water. Subsequently polymer molding on the silicon wafer done and the quartz template is pressed on to polymer and immediately exposed to UV light. Later quartz was removed and the particles with a thin residual interconnecting film layer are uncovered and plasma containing oxygen that oxidizes. Finally the product was collected by the dissolution of substrate in water or buffer. [37-38]

1.5.2. Disulfide-based cross linking

To maintain structural stability disulfide bonds are essential which occur naturally in proteins and peptides. [39-40]

Thayumanavan and coworkers formulated the nanogel based on reversible addition fragmentation transfer - synthesized copolymers of oligo(ethylene glycol) methacrylate (OEMGA) and pyridyl disulfide derived methacrylate(PDS-MA) comprise of disparate compositions and molecular weights. Incorporation of deficient quantity of dithiotheritol (DDT) diminishes controlled percentage of PDS groups to thiol, which eventually reacted with analogous quantity of remaining PDS groups to provoke disulfide cross links and consequently nanogels were formed. [41-43]

1.5.3. Emulsion photopolymerisation process

Cationic dextran nanogel was prepared exerting ultraviolet rays dextran hydroxyethylmethacrylate made in to emulsion utilizing ABIL EM-90 emulgent in mineral oil. The obtained product was acetone: hexane(1:1) and the precipitate was further subjected to centrifugation followed by lyophilization and finally dessicated. To initiate deterioration of endosomal membranes in cell and release of genes in cytoplasm and nuclease mesotetraphenylpropinedisulfonate a photosentizer was added to incarnation of genetic material. [44].

1.5.4. Novel pullulan chemistry modification

Pullulan is a polysaccharide polymer comprising maltotriose units and it acts as a good protein carrier. Cholesterol isocyanate in dimethyl sulfoxide and pyridine reaction yielded cholesterol based pullulan nanogel. Pullulan was substituted with 1.4 cholesterol moieties per 100 anhydrous glucose units. Resultant product was freeze dried and in aqueous phase nanogel was
formed further complexed with W-9 peptide for delivery in osteological disorders. [45]

1.5.5. Photo induces cross-linking

This method procure certain advantages like devoid from cross-linking agent and byproducts formation. This method consists of stabilization of polymer assemblies which are functionalized with polymerizable units. [46]

1.6. Applications of nanogel

1.6.1. Neurodegenerative disease

Nanogel of oligonucleotide formulated my cross-linking polyethylene glycol and polyethyleneimine and possess good stability forming a aqueous dispersion of polyelectrolyte complex. The mechanism behind the process was encapsulation of negatively charged particles of the drug. To reinforce transport potency modification of surface with insulin or transferrin is suggested. To cure neurodegenerative diseases like Alzheimer's and Parkinsonism disease oligonucleotides marks good potential as diagnostic aid. [47]

1.6.2. Autoimmune disease

Liposomes was loaded with mycophenolic acid solubilized within cyclodextrin oligomer of lactic acid-polyethylene glycol with terminated group of acrylate and Igracure 2959 photo initiator used for the formulation of nanogel. Exposure to ultraviolet light to persuade process of photo polymerization of PEG oligomers. It exhibit greater systemic accumulations and capable to bind more immune cells in vivo than free fluorescent tracer. The novel nanogel delays the onset of kidney damage. [48]

1.6.3. Local anesthetics

The major crisis in local anesthetics is over dosage leads to high toxicity hence controlled release drug delivery system is essential. Aminoster local anesthetic, a procaine hydrochloride loaded with methacrylic acid ethylacrylatenanogel by hydrophobic and hydrogen bonds which exerts high release rate at high pH. The key mechanism behind was increase in osmotic pressure and swelling nature and increases porosity hence drug release is initiated. [49]

1.6.4. Transdermal drug delivery

Oral drug delivery system possesses certain disadvantages like ulcers and gastric bleeding. Nanogel transdermal drug delivery of aceclofenac by solvent diffusion method enhances drug penetration in plasma and patient compliance proved to effective alternative drug delivery system. [50]

1.6.5. Cancer treatment

Doxorubicin loaded self-organizing nanogel formulated by acetylated chondroitin sulphate for cancer treatment. Sustained release nanogel made from cholesterol bearing pullulan finds its application in sustained tumor immunotherapy. Cholesterol bearing pullulan with modified amino group used for bio-imaging. [51]

1.6.6. Vaccine delivery

Protection from enzymatic degradation is achieved by novel nanogel vaccines. Subsequently target specificity is also enhanced by surface modified nanogels with attached antibodies and other ligands. [52]

1.6.7. Anti-inflammatory action

Nanoparticles were prepared with chitosan and poly-(lactide-co—glycolic acid) and to formulate a nanogelhydroxypropylmethyl cellulose and carbopol with desired viscosity were incorporated. Anti-inflammatory drugs like Spantide and ketoprofen were applied topically alongwith nanogel. Promising result achieved with spantide and ketoprofen drugs since it exhibited potential deep penetration to skin. [53]

1.6.8. Antibacterial and anti-microbial activity

Dextran cross-linked polyacrylamide nanogel loaded with zinc nitrate prepared by mini-emulsion method used as antibacterial agent. Methacrylated hyaluronic acid was utilized as cross-linking agent. The main aspiration was targeting action to methicillin-resistant strains of staphylococcus aureus. [54]

1.6.9. Antifungal drug delivery

Fluconazole loaded with colloidal chitin nanogel showed sustained release and exhibited good anti-fungal activity to candida tropicalis without inducing any toxicity problems. Further nanogels did not impede with plasma coagulation pathway and ex vivo studies showed no signs or symptoms regarding inflammation to corneal cells. [55]

1.6.10. Ophthalmic drug delivery

By γ radiation induced polymerization pH sensitive polyvinyl pyrrolidone poly (acrylic acid nanogel was prepared and the drug pilocarpine was encapsulated which exerted prolonged drug release. [56]

1.6.11. Diabetics

An injectable nanogel releases precise amount of insulin was formulated with network of oppositely charged nanoparticles. It leads to gel formation and respond to pH change. The nanogel
will bear insulin and other enzymes essential for conversion by employing dextran. In hyperglycaemia condition it stimulates the insulin release. It still needs further work to find suitable for human trials. [60]

2. Conclusion

Nanogels unveil excellent thermodynamic stability, high solubilization capacity, low viscosity, and potential to combat sterilization techniques, and these properties make nanogels as fascinating drug delivery systems. Nanogels are strong nanoparticles that could be used to deliver active drug compounds in controlled drug delivery applications. Futurisic approach of research in nanogels should be the improved design of nanogels with specific targeting residues to empower highly selective uptake into particular cells. Nanogel drug delivery system is most efficacious and impregnable for both hydrophilic and hydrophobic drugs due to their chemical composition and formulations that are inappropriate for other formulations. Hence nanogel-based delivery systems paved a futuristic approach for drug delivery applications.

3. REFERENCE


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