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Nanogel: Synthesis and uses is an optimized drug delivery systems

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ABSTRACT
Nanogels are nanoparticles that are three-dimensional hydro gel materials with a nanoscale size range of 10–100 nanometers. They are made up of cross linked polymer networks that can swell and hold a lot of water without dissolving in an aqueous medium. Nanogels are capable of absorbing and retaining water or water-based fluids.nanogels can be used in drug delivery systems, and they can be tuned to match the physicochemical properties of their biomedical application.It is used to deliver active drug compounds in controlled drug delivery applications. Nanogels drug delivery system is more effective and safer for both hydrophilic and hydrophobic drugs due to their chemical composition and formulations that are inappropriate for other formulations. This review aims at providing general introduction on nanogels, Advantages, Limitations, classification according to structures, recentsynthesis techniques and their novel application in different fields.

KEYWORDS: Nanogel, Controlled drug delivery, Synthesis, applications.

INTRODUCTION:
A nanogel is a polymer-based, cross linked hydro gel particle on the sub-micron scale. These complex networks of polymers present a unique opportunity in the field of drug delivery at the intersection of nanoparticles and hydro gel synthesis. Nanogels can be natural, synthetic, or a combination of the two and have a high degree of tunability in terms of their size, shape, surface functionalization, and degradation mechanisms. Nanogels are a promising strategy to treat disease and dysfunction by serving as delivery vehicles capable of navigating across challenging physiological barriers within the body.[1, 2, 3]
Nanogels are used to deliver all biologically active agents and are drugs in a controlled and sustained release manner. Nanogels occur in the form of three-dimensional structures in which drugs, polymers and dispersed phase of liquid can be entrapped.[4]

Figure 1.Nanogel

ADVANTAGES OF NANOGELS:[5, 6, 7, 8, 9]

1. Nanogels are highly biocompatible and biodegradable, which helps prevent accumulation in organs and toxicity.
2. Nanogels are inert in the bloodstream and internal aqueous environment, so they don't trigger an immune response

4. Nanogel are free-flowing pearlescent solution of the nanogels is easily dispersed in aqueous media

3. Nanogels can carry 40–60% of their weight in drugs, which is higher than other systems.

4. Nanogels can release drugs based on stimuli response, and they can be modified to suit different treatment needs.

5. Nanogels can reach small capillary vessels and penetrate tissues through transcellular or paracellular pathways.

6. Nanogels protect drugs from biodegradation and can pass through the blood-brain barrier.

7. Nanogels is reduced premature leakage of the drug from the solution

8. Both hydrophilic and hydrophobic drugs can be formulated in nanogels formulation.

DISADVANTAGES OF NANOGEL: [10, 11]

1. Nanogels may have limited efficiency in loading drugs, and they may not regulate drug release well.

2. A strong interaction between a drug and a nanogel's polymer can cause the nanogel's structure to collapse, trapping the drug molecules. This can also make the nanogel matrix more hydrophilic.

3. It can be difficult to make nanogels with particles smaller than 100 nanometers using emulsion membranes.

4. The size and shape of nanogels can also be affected by the size of the microchannels used to make them, as well as the flow rate of the solutions and the polymerization reaction time

5. Surfactants and monomers in nanogels can cause adverse effects.

6. Even small amounts of surfactants can be toxic if they remain in the body. Removing solvents and surfactants from nanogels can be expensive and time-consuming.

CLASSIFICATIONS OF NANOGEL: Multiple factors influence the design and development of nanogels which include the tuning of nanogels for desired functions, point of action, polymeric constituents required for production, and the long-term releasing behavior of the loaded drugs. This classification of nanogels based on various factors.

Figure 2. A schematic view of the classification of nanogels based on various aspects.

STRUCTURE OF NANOGEL: [12-14]

Nanogels are classified on the basis of their structures. Different types of nanogels are simple nanogels (artificial chaperons), hollow nanogels including pH- or temperaturesensitive nanogel; cross-linked core shell nanogels also used to prepare stimuli-responsive nanogel, hairy crosslinked nanogels, multilayer nanogels and functionalized nanogels.Hollow nanogels, which are those possessing a cavity at their centre matrix. This structure imparts a relatively greater surface area which can be advantageous for site-specific targeting whereas multi-layered nanogels are designed by interwinding different layers of polymers, which may be constituted of either single or multiple polymers. Such nanogels have exemplary benefits to deliver high toxicity bearing drugs and slow drug release can be prolonged. In addition to the above two categories, there are core–shell nanogels, that can be embedded with a core of Au–Ag nanorods, carbon dots, etc. and the fourth common category is hairy nanogels, which possess hair-like projections on their surface.

Types	**Structure**
1. Hollow nanogel	
2. Multilayered nanogel	

3. Core-cross linked nanogels

4. Hairy nanogels

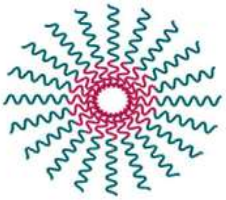

Figure 3. Structure of Nanogel

Nanogels can be categorized based on the linkage present in network chains of the gel structure into two categories primarily:

(a) Physically cross-linked nanogels: these types of nanogels are formed either by weaker linkages like van der Waals interactions, hydrophobic forces of attraction, or by hydrogen bonding but have a poor preference in comparison to chemically cross-linked nanogels owing to the stability factor. The nanogels can be those that are liposome modified, micellar type, and hybrid nanogels. These types of nanogels have the ability to form a complex with various substances like proteins, drugs, and DNA moleculesand possess various desirable features such as reversibility, no chemical reactions, and/or toxic bioactive agents.When utilizing associating polymers, it might be challenging to create stable physically cross-linked nanogels with regulated sizes due to the relative weakness of their non-covalent contacts.

(b) Chemically cross-linked nanogels: these nanogels are characterized by permanently joined polymer chains *via* strong covalent linkages at different junctions. The permanent chemical linkages across the gel networks in chemical cross-linked nanogels and the functional groups present in the gel networks determine their characteristics. These nanogels are of several types based on the mode of synthesis like inverse emulsion polymerization, photo-induced cross linking polymerization, reversible addition–fragmentation chain transfer (RAFT) polymerization, click chemistry cross linking polymerization, *etc.* Out of these, click chemistry cross linking polymerization is the optimistic mode for the synthesis and formulation of nanogels due to its promising.[15-21]

SYNTHESIS METHOD OF NANOGELS: Methods for nanogel synthesis can be divided into chemical and physical as shown in Figure .4 generally, the former gives rise to nanonetworks characterized by strong covalent bonds that improve the colloidal stability under in vitro and in vivo conditions, essential for limiting the leakage of the payload induced by unwanted dissociation of the gel network.

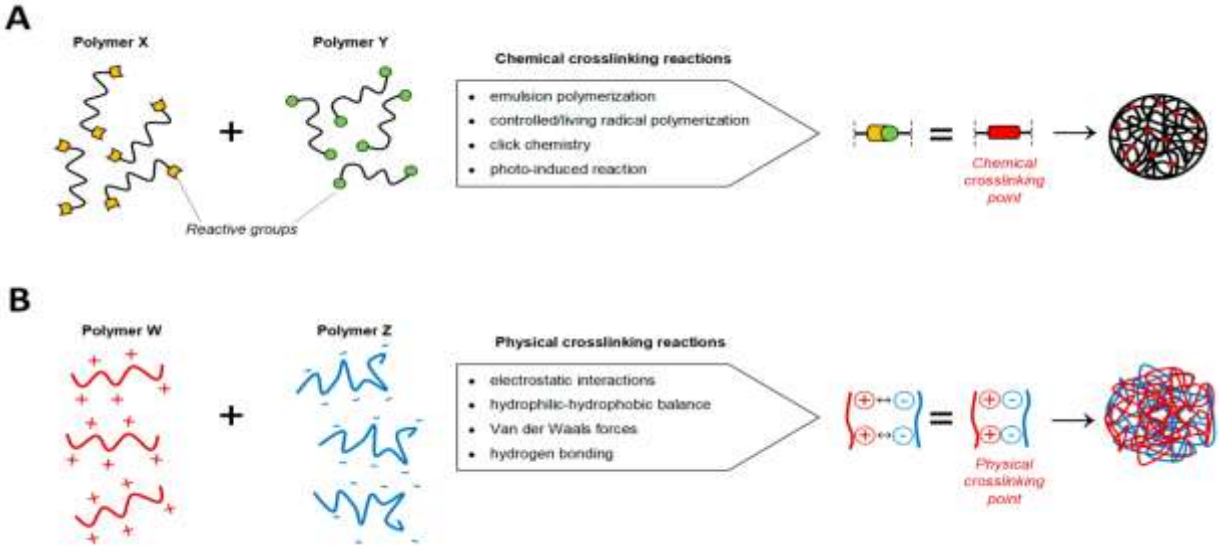

Figure 4. Schematic representation of chemical and physical cross linking methods in nanogels design

The synthesis of nanogels can be achieved using a vast array of different methods. However, two critical steps typically included in each method are polymerization and cross linking, with physical and chemical cross linking the most common. These steps can be completed concomitantly or in sequential order depending on the synthesis method and eventual nanogel application. Here, several different synthesis mechanisms are described briefly.[22]

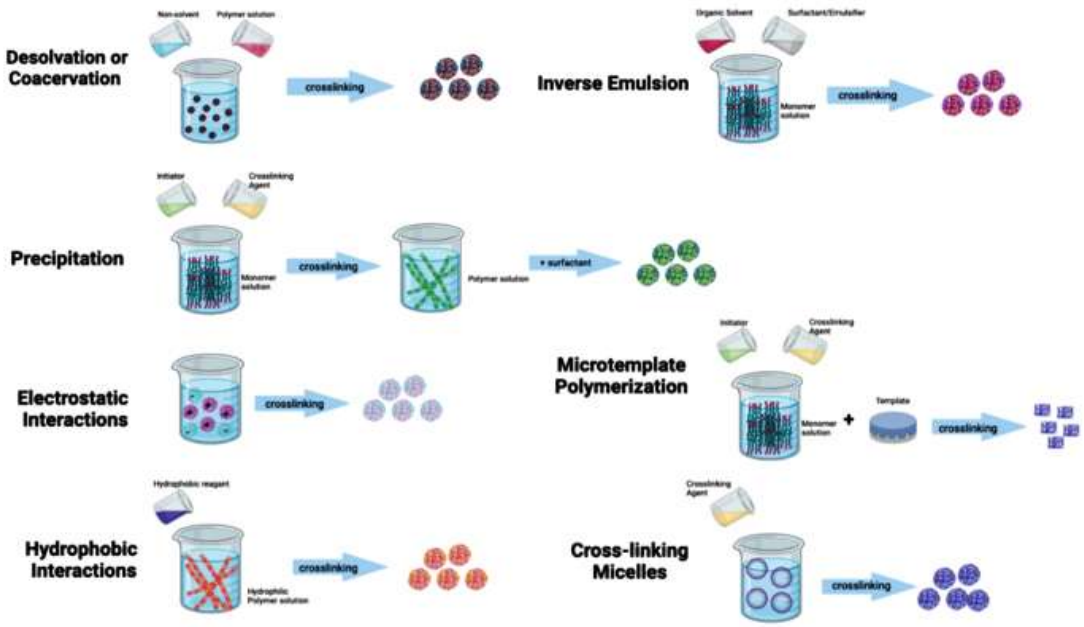

Figure 5. Graphical representation of Different methods of synthesizing polymeric nanogels.[23-28]

1.Desolvation or Coacervation: Desolvation or coacervation, a non-solvent is added to a homogeneous polymer solution to produce individual, nanosized polymer complexes dispersed in the same solution. These complexes then undergo cross linking to form nanogels with surface functionalization an optional next step.

2. Precipitation: In precipitation, initiators and cross linking agents are added to a homogenous monomer solution to induce a polymerization reaction. When the polymer chain reaches the desired length, the reaction is halted and a polymer colloidal suspension is formed. Surfactants are the final addition to produce nanosized polymers.

3. Electrostatic Interactions: Electrostatic interactions can form nanogels through the combination of anionic and cationic polymers in an aqueous solution. The size and surface charge of the resulting nanogels can be modulated by changing the molecular weight or the charge ratio of the two different polymers.Ionotropic gelation can also leverage electrostatic interactions between multivalent anions and cations to form nanogels.

4. Hydrophobic Interactions: Hydrophobic interactions rely heavily on physical cross linking to form nanogels. In this method, hydrophobic groups are added to hydrophilic polymers in an aqueous solution to induce their self-assembly into nanogels. When thiolated polymers (thiomers) are used for this preparation process, nanogels can be further stabilized by the formation of inter- and intrachain disulfide bonds due to oxidation. In the following the oppositely charged oligo- or polymers can even be removed.

5. Inverse-emulsion: Inverse-emulsion, or reverse miniemulsion, requires an organic solvent and a surfactant or emulsifying agent. Nanosized droplets are produced when an aqueous monomer solution is dispersed in the organic solvent in the presence of the surfactant or emulsifying agent. Upon removal of the organic solvent and further chemical and physical cross linking of the droplets, nanogels are formed. The size of nanogels synthesized using this method can vary greatly depending on the type of surfactant and reaction medium used. Purifying nanogels produced using an emulsifying agent may also pose a challenge.

6. Micro template Polymerization: The addition of a monomer precursor solution and cross linking agent to a microtemplate, or mold-type device, can initiate polymerization and the formation of nanogels. This method can be used to create nanogels in specific shapes and load them with various small molecules. Lithographic microtemplate polymerization is a similar process that uses a photoinitiator and light to trigger the formation of nanogels. Lithographic microtemplate polymerization can produce smaller nanogels on a length scale of <200 nm, which has a higher resolution compared to microtemplate polymerization that does not require a photoinitiator.

7. Cross-linking Micelles: Polymer-based micelles that undergo cross linking reactions can induce the formation of nanogels. Cross linking either the core or the shell of preexisting micelles can synthesize nanogels with a “high degree of spatial organization”.

APPLICATIONS OF NANOGEL: Nanogels have many uses in biomedical applications, including:

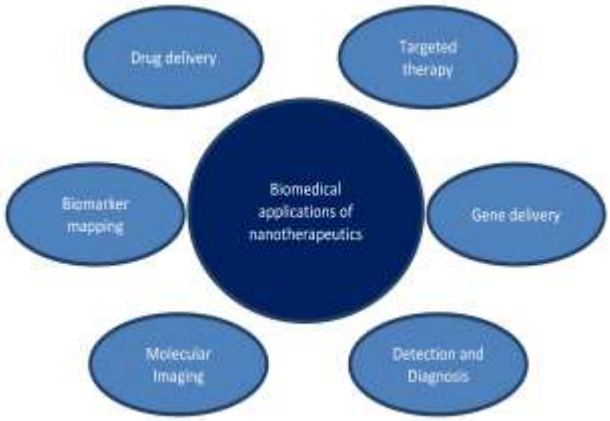

Figure.6 Applications of Nanogel

1. Drug delivery: Nanogels can deliver drugs to specific sites, such as the brain, without crossing the blood-brain barrier. They can be used to treat brain diseases like Alzheimer's, migraines, schizophrenia, and depression. Nanogels can also be used to deliver small therapeutic molecules, oligonucleotides, and proteins.

2. Regenerative medicine: Nanogels can be used in cell behavior analysis, 3D cell culture, bone tissue regeneration, and wound healing. For example, after brain tumors are surgically removed, nanogels can be used to fill the cavities left behind.

3. Imaging: Nanogels can be used as MR contrast agents, PET imaging agents, and optical imaging agents.

4. Other applications: Nanogels can be used in cancer therapy, anti-inflammatory therapy, anti-diabetic therapy, and anti-virus therapy. They can also be used to detect ions, proteins, and bioactive small molecules.

CONCLUSIONS: Nanogel systems have been studied. They are widely used for controlled delivery system, targeted delivery system, coatings purpose, and for the cosmetics products. Over numerous literature instances, the current review has highlighted the advantages, disadvantages, different types of nanogels, nanogel's preparation methods, their applications as drug delivery. Based on the resultant data, nanogels high drug loading capability, good biologic stability, high permeability, and the excellent ability to react to external stimuli. The tremendous potential of functional nanogels as unique polymeric platforms in biomedicine.

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