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NANOGELS AS HIGHLY EFFECTIVE NANOCARRIERS: A MINI REVIEW

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ABSTRACT
Nanogels show promise as a suitable nanomedicine carrier as compared to other nanoparticles especially in terms of drug loading. Nanogels can be prepared or synthesized even in the absence of the drug to be loaded as drug loading in nanogels can be efficiently done later on when the nanogels are swollen and equilibrated in water or biological fluid. Drug loading occurs spontaneously in nanogels. As compared to other conventional nanoparticles, nanogels allow much higher drug loading (up to 50% of weight). Two of the approaches most commonly used for preparation of nanogels are physical self-assembly of interactive polymers and chemical cross-linking of preformed polymers. The physical self-assembly of polymers involves controlled aggregation of hydrophilic polymers capable of bonding with each other. Physical cross-linking in nanogel formation occurs via non-covalent attractive forces, such as hydrophilic–hydrophilic, hydrophobic–hydrophobic, ionic interactions and/or hydrogen bonding.
Keywords: Chitosan- Based Nanogel, Alginate Based Nanogel , PVA Based Nanogel

INTRODUCTION
Recently, nanotechnology is very significant in drug delivery process. Polymer nanogels play an important role in tumor treatment among different types of nanoscale drug delivery system. This is because they have a cross-linked three-dimensional network structure that provides good water-retaining property and colloidal stability. [1] Specific types of nano particle vehicles have employed including ionic-complexed nano particles, biodegradable nano particles, and gel-formed nano particles called nanogels for the intracellular delivery of drugs. [2] Nanogels is defined as the nanosized particles formed by physically and chemically cross linked polymer networks that is swell in a good solvent. The term "nanogel" was first introduced to define cross linked bifunctional networks of the polyion and a nonionic polymer for delivery of polynucleotides. [3]

Nanogels can release the drug as a result of diffusion. For instance, doxorubicin is released from hydrogel nanoparticles through diffusional release. This is based on block copolymer. This release mechanism is simplex and easily employed. There is an elevated concern in producing nanogels that can release drug in response to environmental cues at the targeted site of action. Nanogels are premium drug delivery system due to:

- Rapid clearance by phagocytic cells can be avoided by manipulating particles size and surface properties.
- Drug release at the target size can be controlled and sustained to increase therapeutic action.
- It is highly biodegradable and biocompatible.
- It is able to reach the thin small capillary vessels due to small volume.
- The drug loading is high and achieved without any chemical action

Administration of nanogels can be using different route such as oral, pulmonary, nasal, parenteral, intra-ocular, and topically.

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ADVANTAGES OF NANOGELS [4]

- It enhanced brain and oral bioavailability of low molecular weight drugs
- Helps in achieving target specific delivery
- Nanogels can help to prevent reticuloendothelials as they are invasion in nature
- It produced non immunological responses
- It is highly biocompatible and biodegradable

- It has good permeation capabilities because of extremely tiny size
- It is perfect for transport characteristics and specific target
- It can be applied to both hydrophilic & hydrophobic drugs and charged solutes.

DISADVANTAGES OF NANOGELS [4-6]

- It is an expensive technique
- Toxicity can be imparted by surfactant and monomer.

CLASSIFICATION OF NANOGELS

Nanogels are classified into three types:
A) Based on the polymers.
B) Based on responsive behavior.
C) Based on linkages present in the network chains of gel structure.

A. Based upon the polymers

Chitosan- based nanogel:
Chitosan, α (1-4)-2 amino-2-deoxy β-D-glucan, is a polysaccharide which is a deacetylated form of chitin and present in crustacean shells. It is discovered in 19th century. It has been used as agents for biomedical and drug delivery system and as a polymers from last two decades. [7] Drug delivery and the carriers for macromolecules can be imparted by the physicochemical and biological properties. [8]

The polymer chitosan carried the positive charge and hydro-soluble in nature. They interact with negatively charged polymers and have contact with polyanions in aqueous environment. Interactive forces are occurred in between these types of ions. This resulting in sol-gel transitions stages. [9] It can adhere to the mucosal surface within the body. It is capable to open the tight junctions between epithelial cells. This could affect the biocompatibility and toxicity, as the biocompatibility is increased and toxicity is decreased.

Poly (vinyl alcohol) – based nanogel:
PVA plays an important role for nanogel studies. By carrying out using physical and chemical methods, it gives the cross linking characteristics. For example, physical method like freezing or thawing and chemical method like cross linking agents and electron beam. It is useful for many types of application in pharmaceutical fields although the cross linking method is difficult. [10]

For instance, biodegradable polymers having short polyactone chains grafted to PVA. This type of polymers undergoes and assembling to produce the nanogel. This is a stable complexes with a number of protein such as cytochrome C. [11]

Alginate – based nanogel:
Sodium alginate is used to make up a new drug carrier. This is proposed by Rajaonarivony et al in the year of 1993. [12] The sodium alginate, calcium chloride and polu-lysine are used to prepare alginate nano particles which gives a wide range of particle sizes around 250-850nm. The concentration of both opposite ion solution and polymer were less than regularly used in gel formation. Recently the studies involving alginate-based nanoparticles are increasing. This type studies are used as therapeutic drugs like insulin, antifungal drugs and antitubercular drugs. [13]

B. Based On Their Responsive Behaviour[*14]*

Stimuli – responsive:
It maybe swell of de-swell in this type of nanogel. These changes depended upon the exposure to environmental changes like pH, temperature magnetic field and ionic strength. The nanogels have the multi-responsive character because it gives more than one environmental stimulus.

Non – responsive:
These have a characteristic like absorbing of water and swelling.

Based on their linkages in the network chains:
Based on their linkage it is capable to form a gel structure. These can be divided as follows:

Physical Cross-linked Gels:
It is also known as pseudo gels. They are formed by weaker linkages through vander waals forces, hydrogen bonding, hydrophobic or electron static interactions. Their sensitivity are depend on temperature, ionic strength, concentration og polymer and cross linking agents. The combination of amphiphilic block copolymers and complexation of oppositely- charged polymeric chains can easily form the nanogels.

Chemically Cross-linked Gels:
They are linked through the covalent bonds permanently. It gives the properties like cross linked gel system. This is depending on the functional groups present. Properties of synthesized different types of nanogels are given by different types of chemical linking. The hydrophilic polymners and hydrophilic-

hydrophobic copolymers are obtained by the polymerization of vinyl monomers in the presence of multifunctional crosslinkers. The total physicochemical properties of the gel system are allowed to alter by these types of crosslinking points. [15] For example, by using the disulfide cross linking in the preparation of nanogel, the pendant thiol groups are achieved environmentally friendly chemistry. [16]

SYSTHESIS OF NANOGELS

Synthesis of Nanogels by Free Radical Polymerization (FRP):

The monomers which may be hydrophilic plays an importat role. They are either difunctional or multifunctional cross linkers. Different methods by this free radical polymerization (FRP) are as follows:

Dispersion Polymerization:

The organic solvent is act as continuous phase. It is capable to soluble the polymeric stabilizers, monomers, and initiators. Firstly, the formed polymer is insoluble in continuous medium when the polymerization takes place in homogenous reaction mixtures. Finally, the stable dispersion is formed by adding colloid stabilizers hydrophilic monodisperse micro-sized of PHEMA. This can be prepared by dispersion polymerization in the presence of PEO – b – poly (1,1,2,2 – tetrahydroperfluorodecyl acrylate) diblock copolymer as a stabilizer in super critical carbon dioxide and methacryloyl – terminated PMMA in a 55/45 (wt/wt) mixture of 2 – butanol / tolune. These types of gels are effective in drug delivery carriers and DNA application. [17]

Inverse (mini) Emulsion Polymerization:

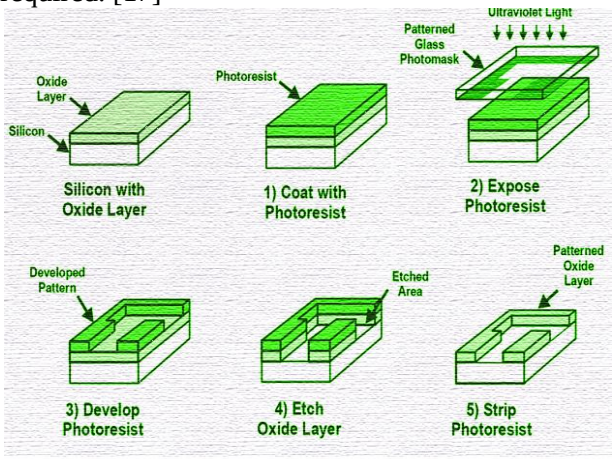
This type is also called as w/o polymerization. Aqueous droplets are dispersed in oil soluble surfactant in a continuous organic medium. Stable dispersion of polymerization is formed by using mechanical stirring and by sonification. Polymerization occurs within the aqueous droplets producing colloidal particles by adding of radical initiators.

Inverse Micro emulsion Polymerization:

The inverse micro-emulsion also can produce by adding emulsifier above the critical threshold and thermodynamically stable when the inverse emulsion polymerization is formed the stable macro-emulsion which is below the critical micellar concentration. This process is also giving the same disperse and continuous phase but producing stable hydrophilic and water soluble colloidal nano-particles. Synthesis of stable nanogels is invented by using inverse micro-emulsion polymerization. [18-19]

Photolithographic techniques:

3D hydrogel particles and nanogels for drug delivery can be revealed by this method. The stamps or replica mold for release of the gels are required. [17]



This method involved 5 steps. Firstly, the UV crosslink able polymer is used. This possesses low surface energy and acts as a substrate which is released on the pre-backed photo resist coated water. Next, the polymer is molding the silicon water and it is exposed to the intense UV light. Thirdly, the quartz template is removed to uncover the thin interconnecting film layers. Fourthly, plasma containing oxygen removed the remaining thin layer and oxidizes it. Lastly, the fabricated particles are collected from the buffer solution of the dissolution. [20]

APPLICATION OF NANOGELS

Cancer treatment:

Nanogels give high therapeutic efficacy in cancer treatment. This involved the targeted delivery of drugs with low toxicities to other tissue.

Brain diseases:

Carrier for oligonucleotides to the brain has been identified by nanogels. This can be carried to the brain by using polarized monolayers of bovine BMEC. Increased level of oligonucleotides across the cell monolayers is shown in the model of blood barin barrier. This is due to the incorporation with nanogels. The further increased in transport of oligonucleotides is shown by nanogels modified with insulin or the ligands transferred. In addition,

No toxic effects on the model mice is shown by the nanogels. [21]

Anti-inflammatory action:

Skin permeating nanogel system is developed for effective drug delivery in skin imflammatory diseases. This type of nanogel system is composed of a surface of modified polymeric bilayered nanoparticles in addition with a gelling agent. In this skin permeating nanogel system, bilayered nano-particles and oleic acid are prepared by Poly-(lactide-*co*-glycolic acid) and chitosan. After maintaining the desired viscosity, hydroxypropyl methyl cellulose and carbopol was used for nanogel formation. Effective percutaneous delivery of drug for skin diseases is shoen by these researches. [22] In the cases of arthritis, Diclofenac is mainly used. It is a non-steroidal anti-inflammatory drug. Hydrogels of diclofenac sodium liposomal gel have better outcomes as an anti-inflammatory agent. [23]

Stopping bleeding:

It is a protein molecule in solution. It has been used for formation of nanogel to stop bleeding. It can be used even in severe gashes. The proteins have mechanism of self – assemble on the nanoscale in to a biodegradable gel.

In autoimmune diseases:

The loading liposomes with mycophenolic acid are easily solubilized by cyclodextrin. Nanogel has greater systemic accumulation. This is because the intrinsic abilities and bind to the immune cells in vivo. It also permits high localized concentration of mycophenolic acid. These will increase the patience compliance and this lower the onset of kidney damage by these types of drug delivery system. [24-25]

CONCLUSION

Recent years have witnessed an extraordinary expansion in drug delivery research in the area of cancer. There is an increasing assurance that nanotechnology applied to medicine will bring significant advances in the diagnosis and treatment of cancer. When most of the chemotherapeutics fail to show effect clinically in the treatment of cancer due to their toxic side effects, nanogels as nanomedicine yield more effective therapies.

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