Review Article

Nanogel – A Future Drug Delivery Tool

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ABSTRACT

Nanogels, potent nanogels, are made from a dispersion of hydrogel. Employing a network of polymers, which are cross linked either physically or chemically in a suitable solvent. Nanogels have emerged as the next generation drug delivery tools owing to either promising properties like minimal toxicity, high drug loading capacity, tuneable size, simplicity of preparation, uniformity and stability. In addition, nanogels provide feasibility of drug delivering then to multiple organs in the body due to unique properties like high biocompatibility and biodegradability. They have proven themselves to be safer for encapsulating both hydrophilic and liphophilic drug moieties in into them and are design such that at the specific target site, nanogel releases the active material either in a sustained or controlled manner. Recent studies have proven suggest nanogel as an appropriate carrier for the delivery of variety materials like vaccines, proteins hormones and genetic material. Nanogels have shown in field like diagnosis, chemotherapy organ targeting gene delivery etc. The present review concentrates our properties, preparation, evaluation and applications of nanogels.

Keywords: Nanogels, Hydrogel, Diagnosis, polymers, Sustained, biocompatibility.

INTRODUCTION

Nanogels are three dimensional hydrogel materials that are extremely cross linked. These are either co- polymers or monomers which can be either ionic or non- ionic. The nanoscale formed by cross linked swellable polymers is interconnected with a great volume to grasp the water without liquefying into the aqueous medium. The size of nanogels ranges from 20- 200nm and can be prepared by a method that involves either chemical or physical cross linking. Nanogels act as carrier molecules for drugs and designed in which a manner they can efficiently adobe by biologically active compounds through bio-molecular interactions like salt bonds, hydrophobic or hydrogen bonding. The characteristics of nanogels such as size, charge, porosity, amphiphilicity, softness and degradability can be calibrated by shifting the chemical composition of the nanogels. Nanogels may release the drugs and biological molecules, so they can be greatly employed in protein and gene delivery. The properties of nanogels that make them unique are their self healing ability and more than 98 % drug loading capacity. Nanogel formulations are used in fold in nanomedicines, biosensors, artificial muscles, biomaterials and anti cancer therapy etc.[1, 2]

Advantages of nanogels: [3, 8, 11]

Nanogels offer the following advantages:

1. Nanogels reduce premature leakage of the drug from the solution

2. Good permeation capabilities due to extreme small size

3. Provides feasibility of incorporating both hydrophilic and hydrophobic drugs

4. High biocompatibility and biodegradability

5. Capability to cross the blood brain barrier

6. Enhances permeation capability

7. Easily administered through parenteral and mucosal

8. Rapid response to the environmental changes such as pH and temperature.

9. Good transport characteristics.

Limitations: [2, 3, 8]

1. It is Expensive technique to completely remove the solvent and surfactants at the end of Preparation process.

2. Adverse reactions may occur if any traces of monomers or surfactants remain in the body.

3. Nanogels have limited drug-loading efficiency and suboptimal regulation of drug release.

Properties of Nanogels:

Biocompatibility and Degradability:

Nanogel based drug delivery system is highly biocompatible and biodegradable as it is made up of each of two, natural or synthetic polymers. Nanogels are highly biocompatible and biodegradable by avoiding its accumulation in the organs. Polymers like chitosan, methylcellulose and polysaccharides like dextron, Pullulan can be used to formulate the nanogel as they are safe, stable, nontoxic and biodegradable, hydrophilic in nature.[2]

Solubility:

Nanogels are capable to solubilize either hydrophobic drugs or diagnostic agents in their networks of gel.[3]

***Swelling property**:*

The greatest benefit of nanogels is their quick or rapid swelling and de-swelling characteristics, because nanogels are small in size, soft materials, they have capability to swell in presence of an aqueous medium. It is consider being the fundamental property influencing the mechanism of action followed by drug delivery system[2]. It depends up on:

- ✓ The structure of Nanogels.
- ✓ Environmental parameters.[4]

Particle size and permeability:

Particle size of nano carrier plays a vital role in its permeability. Few modifications such as surface charge, hydrophobicity and particle size enhances the permeation of the nanoparticles. Though nanoparticles have capability to diffuse through some specific transport systems, but they pose a problem in crossing blood brain barrier (BBB). To overcome this situation, nanogels are typically formulated in the way that they possess a diameter of 20-200nm which is actually enough to cross blood-brain-barrier at the same time to avoid rapid renal clearance mechanism.[5]

***Electromobility*:**

Nanogels can be prepared without the application of any energy or any hard conditions such as sonication or homogenization, which is critical for encapsulating bio-macromolecules.[3]

***Non-immunologic response*:**

Nanogels usually does not produce any immunological response, thus are non immunologic in nature. Any foreign agent if enters into systemic circulation, is rapidly stamped out by phagocytosis or Opsonization. Opsonization is a method of just marking the foreign agents and makes them visible to phagocytosis.[6]

***Higher drug loading capacity**:*

Drug loading capacities of nanogels depend on the functional group present in the polymeric unit. Nanogels are expected to have greater loading capacity compared to conventional dosage forms. The functional groups have tremendous effect on drug carrying and releasing properties and some are potentially conjugated with drugs for targeting applications. Drug releasing property of nanogels is mainly due to swelling of polymers allowing large quantities of water to absorb. Therefore, upon incorporation and loading the water will provide cargo space sufficient to contain salts and biomaterials. Loading takes place through three methods:

1} Physical entrapment: linkage between hydrophilic chains and hydrophobic regions of the polymer.

2} Controlled self assembly: provides interaction between oppositely charged electrolytes.

3} covalent attachment: which leads to the formation dense drug-loaded core[7]

CLASSIFICATION OF NANOGELS

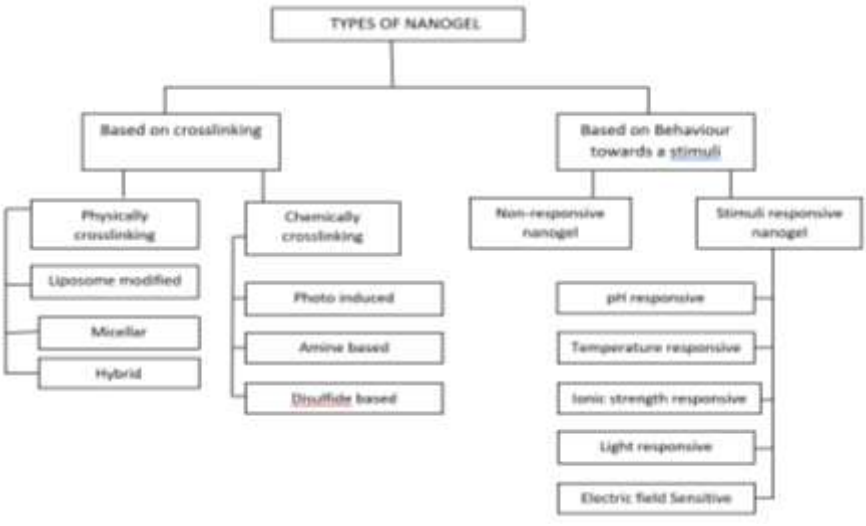


Figure 1: Classification of nanogels

Based on cross linking, nanogels are of two types. They are:

- ➢ Physically cross linking and
- ➢ Chemically cross linking

Chemical cross-linking

Chemically cross linking is the linking of polymer chain through covalent bonding and assembling them in a tridimensional network. This particular linking scales down the flexibility of the structure and commonly elevate its mechanical and barrier properties and it's water resistance.

Chemically cross linking nanogels are arranged by networks of strong covalent bonds and other permanent chemical linkages. The chemical cross linking is sub categorized into 3 types. They are:

- Photo induced cross linking
- Amine based cross linking
- Disulfide Based Cross Linking

***Photo Induced Cross linking**:*

Photo induced cross linking is a clean method and used to purify and remove the un-reacted cross linking agent and by-products, compared to the chemical methods.

It has been used to preserve polymer accumulation that is functionalized with polymerizable or dimerizable units.

Amine Based cross linking:

Amino groups play a major role in the preparation of nanogels due to their reactivity towards carboxylic acids, activated esters isocyanates, iodides and others.

The amino cross linking is used in the development and the preparation of shell cross linked knedel like structures (SCKs) in the Woolley group. SCKs are truly, unimolecular polymer micelles which are prepared by stabilizing the basic structure of the spherical Micellar assembly through linking together of the hydrophilic portions of the chains with in the micelle shells.

Disulfide Based Cross Linking:

Disulfide bonds play an important role in the structural stability and rigour, and it can be initiated in natural peptides and proteins.

The disulfide – thiol chemistry is popularized in conventional polymer synthesis and provides a facile route to the preparation of recyclable cross linking of micelles. In the environment of thiol concentration, the disulfide undergoes reversible reduction.[8]

Physically cross linking

Physically cross linking nanogels, mainly depends on the characteristics of the polymer. Hence it is so called pseudo-gels. Factors that govern the production of physically cross linked nanogels include polymer composition, temperature and the ionic strength of medium. Such nanogels are formed by the weaker linkages through either electron static interaction or vanderwals forces or hydrogen bonding. Thus, the stability of nanogels is relatively less compared to chemically cross linked nanogels. Examples of physical cross linking nanogels are polysaccharide such as dextron, mannon and polyaminoacids modified with cholesterol, derivatives of chitosan with de-oxycholic acid etc. Physical crosslinking is of following types:

Liposomal Modified Nanogels:

Liposome's with succinylated poly glycidol group undergoes chain wilting reaction under pH of below 5.5, may transfer calcin to the cytoplasm upon modifying them with poly (N-Iso propyl acrylamide).

Micellar Nanogels:

Micellar nanogels are obtained from the supramolecular self assembly of amphiphillic blocks on graft co-polymer in aqueous solution. Micelles provide appreciable space by physical entrapment for the penetration of various drugs or macromolecules encapsulation. Highly versatile Y – shaped micelles of poly (oleic acid Y- N (Iso propylacrylomide) has an application in drug delivery.

The hydrophobic core block, surrounded by hydrophilic polymer blocks stabilizer the whole micelle.

Hybrid Nanogels:

Hybrid nanogels consist of inorganic and organic matrices in which components of nanogels have been spreaded. Various studies have been performed on nanogels form an aqueous medium; where the polymers self assemble themselves.

Eg: example of such a nanogel is cholesterol bearing Pullulan nanogels.

Cholesterol bearing Pullulan (CHP) polymers self assemble themselves to form stable mono disperse gels via physical cross linking. Such nanogels can associate with various protein, drug and DNA. Further they have provided feasibility of coating them to liposome's cell and particulate surfaces. They also find application in delivering the insulin and anti-cancer drugs.[3]

SYNTHESIS OF NANOGELS

Synthesis methods of nanogels include:

Modified Pullulan technique:

A mixture of Cholesterol in dimethyl sulfoxide and pyridine is used in the synthesis cholesterol Pullulan nanogel.

Cholesterol is surrogated with Pullulan and the nanogel is designed by allowing the cholesterol isocynate in dimethyl sulfoxide to react with pyridine. The final step of every CHP (cholesterol based Pullulan) nanogel should be freeze drying. Freeze drying operation is carried in the aqueous phase to result in a nanogel. In the treatment of osteological disorders, nanogel obtained after freeze drying technique is complexed with W-9peptide, TNF-alpha and Rankl antagonist. Research is in progress globally to evaluate the efficiency of nanogels in cancer therapy and alziemers disease.[9]

Inverse (mini) emulsion polymerization technique:

The above technique is a W/O polymerization process where the internal phase i.e., the aqueous droplets are dispersed uniformly in a continuous organic medium with the aid of oil soluble surfactants to produce a stable dispersion.

A Fluorescein labelled nanogel i.e., Fluorescent dye Rhodamine B nanogels was made by inverse mini emulsion polymerization technique at ambient temperatures. The process involves activators generated electron transfer atom transfer free radical polymerization (ATRP) of Oligo

monomethymerizl ether methacrylate, where the polymerization reaction was initiated and controlled by hydroxyl containing ATRP initiator. The reaction results in the formation of functional HO-POEO300MA nanogel. Construction of a stable dispersion in inverse emulsion process employs a mechanical stirrer. Nanogel, at the final step, is purified by centrifugation. Precipitate obtained is washed with isopropanol and other organic solvents. particle size of the nanogels can be controlled by variables like amount of surfactant and crosslinking agents used and also stirring speed, to a lesser extent, while formation of inverse emulsion.[10]

Membrane emulsification technique:

Membrane emulsification technique, a technique where the dispersed phase-to-be, is made to pass through a membrane like glass, having uniform pore size, to give out a microgel with specific morphology on membrane surface, with the external phase streaming crossways the membrane.

The produced microgels can be picked up into desired container. Such formulated droplets can be either of O/W type or W/O type and O/W/O or W/O/W type. The droplet size of the constructed nanogels can be controlled by process variables like pore size of the membrane, velocity of the dispersion passed and membrane pressure.[3]

Precipitation polymerization technique:

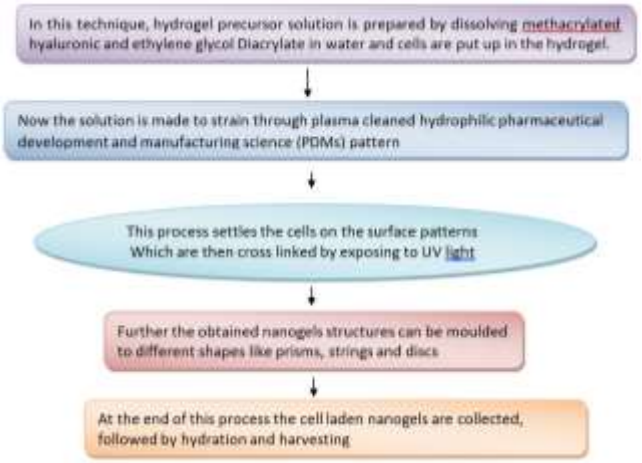
In this technique, a homogenous mixture is formed at the initial stages followed by the commencement and polymerization within the formed homogenous solution. since the polymers formed within the mixture are soluble but not swellable in the medium, thus the use of a crosslinking agent is advised. a crosslinking agent helps to crosslink the polymer chains and produces a poly-dispersion of particles with irregular shapes.

An example supporting the above context is the polymethyl arcylicacid–ethylene glycol (polyMAAgEG) nanospheres, prepared through precipitation polymerization for oral delivery of proteins. Better control over particle size and particle size distribution can be controlled by controlling the monomer concentration in water. The study also revealed that any increase in cross-linker concentration during polymerization, decreases thermo-equilibrium swelling of nanospheres.[4]

Free radical crosslinking polymerization technique:

A new development in the theranostic diagnosis and delivery of nano-biomaterials to target organ is the use of Photocross-linked biodegradable photo-luminescent polymers. PBPLPs nanogel can be prepared by free radical cross-linking of a vinyl-containing florescent pre-polymer for cell imaging and drug delivery.[3]

Micromolding method:



This method resembles photolithographic technique where the need of costly equipment and clean room was reduced by a precursor solution and plasma cleaned pattern.[4]

Photolithography technique

The fabrication of 3D hydrogel particles and nanogels rings for drug delivery has been explored by the photolithography. This method is critically important in developing the mechanism for surface treatment of stamps

It includes 5 steps they are

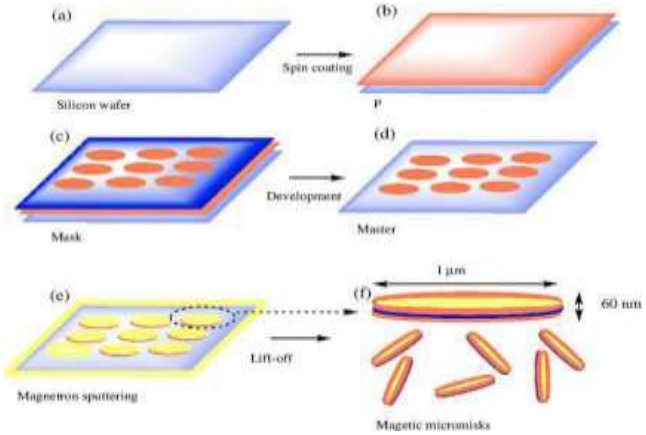


Figure 2: Schematic diagram of five steps involved in photolithography

Process starts with a UV cross -linkable polymer substrate, that owns the low surface energy is released on the pre-baked photo resist coated water.

In the second step, the polymer is moulded into patterns on a silicon wafer and exposing it to the intense UV-light by pressing the quartz template

At step 3, quartz template is removed to expose out the particles interconnected with a thin residual film. The next step employs a plasma containing oxygen that oxidizes the residual film. Finally, the particles are collected by subjecting the substrate to dissolution in buffer.[4]

MECHANISM OF DRUG RELEASE

1. PH Responsive mechanism:

In this mechanism drug release depends on the changes of pH at the surrounding environment. Simply the release of drug takes place in different physiological environments that have different pH values. This mechanism is based on the fact that the polymers selected in the synthesis of a nanogel contain pH sensitive functional groups that deionise in the polymer network.

For instance, the dextron nanoparticles loaded with nanogel exhibit on and off catalytic activity for insulin delivery. Polymers employed here are insoluble at neutral pH but pH becomes acidic as the polymer swells and drug release takes place through this mechanism.[10]

2. Diffusion mechanism:

Diffusion mechanism tends to form a controlled release device when the active agent is made to pass through a polymer. The process carries on a macroscopic scale through pores in the polymer matrix. The polymer and drug have been mixed to form a homogeneous system referred to as a matrix system. For example, Doxorubicin release from copolymer of puronic block through diffusional mechanism in a hydrogel nanoparticle. This mechanism is simple and various nanomedicines follow this mechanism for it drug release.[11]

3. Photochemical internalization and Isomerization:

Photoisomerization is referred to a process in which bond of restricted rotation under goes some conformational changes as it is exposed to light. Photo sensitive loaded nanogels produce singlet oxygen and reactive oxygen species which oxidizes cellular compartment walls such as endosomal barrier that inturn effects release of Therapeutic agent into cytoplasm. Azodextran nanogel loaded with aspirin is subjected of this kind of drug release studies.

On observation, it was found, cis-trans Isomerization of azobenzene causes the formation of E-configuration of AZO group leading the better release of drug (aspirin) than Z configuration.[6]

APPLICATIONS

1. Skin Diseases:

The nanogels can be able to apply directly on the exaggerated area or part topically. The permeability of drug is improved by its renovation to the nanoparticle size range. Nanoparticle of clindamycin and neomycin are the antibacterial and integrated in the gel and they prove that the efficacy of the drug. The naturally available antifungal and antibacterial drugs are used to prepare nanogels for topical application with suitable soothing agents.[12]

2. Gastro Intestinal Disorders:

Nanogels are used in gastrointestinal disorders, such as umbilical infections, ulcers for this purpose the nanogel zwitter ionic poly nanogel are used to treat umbilical infections.[13]

3. Wound healing:

Nanogel provides many advantages under conventional therapy used for healing of wounds. The nanogels have a great ability, greater retention time when applied on surface and also improve healing capability due to its moisturing nature.

Hirokimaeda et al prepared NanoClick by using polyethylene glycol and acroyal group solution CHP nanogel. Finally they reported the rate and extend is better than other groups after implamiation of 7 to 14 days.[14]

4. Cancer treatment:

In cancer treatment nanogels used for specific target in drug delivery with less toxicity and more therapeutic action. Cancer cells have a Ph more acidic than normal tissues and cells. The nanogel swelling property depends upon the pH changes release the drug only in the affected tissue or cell. If the functional group of nanogel is a amine group leads to decrease in pH and increase the swelling. If the functional group is carboxylic an increase in pH and increase the swelling .Nanogel can be prepared by cross linking of PEI and PEG used for 5'- triphosphorylated ribavirin reduced toxicity. Doxorubicin loaded self-established nanogel used for cancer treatment.[15]

5. Antipyertics:

Nanogel has been advanced based on interpenetrating networks of thermo-sensitive polymers and modified nonporous silica. Nanogels are used to antipyretic especially in children's by supportable positive thermo-responsive drug release attained. When temperature increases, the gel shirks, holding the drug into porous channels and at the same time opening to the pores outside media the drug slowly spread out of the porous channel. The overall rate can be adjusted by changing the composition of the gel.[16]

6. Anti-inflammatory:

In today's era, nanogels have established themselves as topical delivery systems for Non-steroidal anti Inflammatory drugs (NSAIDS) The Spantide and Ketoprofen are two anti inflammatory drugs which are potent against allergic contact dermatitis and Psoriatic Plague.

Nanogels can be prepared by methods that involve chemical cross-linking and polymerisation. The desired viscosity of nanogels can be obtained by using polymers such as Carbopol and Hydroxy Propyl Methyl Cellulose. Nanogels loaded with anti-inflammation drugs are used in the treatment of different inflammatory disorders.[17, 10, 4]

7. Neuro-Degenerative Disease:

Parkinson's disease and Alzheimer's disease has no treatment to cure but based on nanoscale network of cross-linking poly (Ethylene Glycol) and Poly Ethylenimine. These

are delivered by Oligonucleotide from there they are rapidly cleared by Renal excretion.

A nanogel of Oligonucleotide is designed by cross-linking poly (Ethylene Glycol) and Poly Ethylenimine. It has the potency to form stable aqueous dispersion of poly electrolyte complex with molecular size less than 100nm which can be effectively transported across the Blood Brain Barrier.[9, 2]

8. *Auto Immune Disease*:

Auto immune disorder can be cured by delivering a therapeutic agent that has capability of disabling the immune cells that mediate in immune response. Research is still in progress in studying the ability at which the immune suppressants can be loaded in to nanogel system.

The immune suppressant loaded nanogels be get the antigen presenting cells effectively and aid in immuno suppressant. An example supporting the above is, **n**anogels with mycophenolic and KN93 can be prepared by a chemical process that involves polymerization and cross-linking of Diacrylate terminated co - blocker polymer of poly (Lactic acid co -Ethylene Glycol). Among the two therapeutic moieties KN93 lowered auto immuno encephalomyelitis by targeting particularly. The CD4+T cells where as the former found effectively in curing lupus by lowering cytokinin production.[6, 15, 3]

9. *Ophthalmology:*

The nanogels have a different route of administrations like oral, topical, parenteral, intra-ocular. If an ophthalmic infections the nanogels can be administered intra-ocularly. Dexamethasone containing eye drops is prepared by emulsification method and solvent evaporation using 2-hydroxypropyl gama cyclodextrin medium containing clclodextrin (CD) nanogel for sustain release.

Polyvinylpyrrolidone-poly (PVP/PAAc) nanogels, formulated by gama radiation induced polymerization of acrylic acid in aqueous solution of (PVP) were used to encapsulate pilocarpine, thus enhancing the bioavailability as well as stability of pilocarpine and maintain an sufficient concentration of the drug at the site of action.[6, 17]

10. *Bleeding*:

Protein because of their self-gathering characteristic at nanoscale level, can be made into nanogels and used in the stoppage of bleeding.[4]

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