

# Nanogels: An overview of properties, biomedical applications, future research trends and developments

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**Abstract-** A nanoparticle which is composed of a hydrogel with a cross linked hydrophilic polymer network is known as “Nanogel”. The term „nanogels” defined as the nanosized particles formed by physically or chemically cross-linked polymer networks that is swell in a good solvent. Nanogel is a nanoscale drug delivery systems with enhanced surface area not only are capable of transmitting hydrophobic drugs in vitro and in vivo with improved drug bioavailability but also help to reduce side effects of drug Here we summarize emerging research of nanogels for biomedical applications and provide an overview of the state-of-the-art, recent developments as well as emerging trends in the field of nanogel. Nanogels have enabled enlargement of functionalized nanoparticles, which act as a drug carriers that can be loaded with drugs and other active material to be released in a controlled manner at specific site

**Keywords-**Nanogel, controlled drug release

## Introduction-

Nanogels are currently considered as promising nanosized drug delivery carriers. Nanogels are made of a crosslinked polymeric network which could encapsulate both hydrophilic and hydrophobic drugs due to their tunable nature. The ability of nanogels to control drug release is vastly described in the literature and researchers are consistently improving the control of drug release from nanogel by designing new polymers having specific sensitivity to a chemical or physical stimulus. In this review, we briefly discuss the definition of nanogels, their release profiles, their specific gel-based characteristics and the pathways of drug release from nanogels, we have focused on the stimuli responsive nanogels and their release profile. This compilation opens the window for understanding the influence of chemical composition and design of various nanogel on their release in the presence and absence of corresponding stimuli such as temperature, pH, enzymes and others. The uniqueness of this review is that it highlights the data of release profiles in terms of the different nanogel composition and triggers. It also points the high potential of nanogels in the list of candidates for drug delivery systems, thanks to their properties regarding drug encapsulation and release, combined advantages of nano-size and swelling characteristics of hydrogen

## Advantages of nanogel

- A. Nanogels occur with have high biocompatibility and biodegradable formulation.
- B. Nanogels can be controlled for sustained release of drug from the formulation by the addition of polymeric network. Polymeric networks also control the particle size of the formulation<sup>(1)</sup>
- C. The free-flowing pearlescent solution of the nanogels is easily dispersed in aqueous media<sup>(2)</sup>
- D. Nanogels can be easily administered in parenteral and mucosal administration<sup>(3)</sup>.
- E. The biggest advantage of nanogels is reduced premature leakage of the drug from the solution<sup>(4)</sup>.
- F. Both hydrophilic and hydrophobic drugs can be formulated in nanogels formulation<sup>(5)</sup>

## Drug Release Mechanism for Nanogels

Drug delivery systems, aiming to enhance the drug concentration at the pathological site, are usually designed to carry drug and to provide its controlled release. To achieve an optimal therapeutic effect, the factors affecting drug release should be considered during the design stages.

These factors are related to i) drug-material interactions which are determined by several features including hydrophilicity/hydrophobicity of drug and carrier, and ii) biodegradability mechanisms and clearance time of the carrier<sup>(6)</sup>

Regulating the rate of both drug release profile and biodegradation along with stability in systemic circulation is rather challenging. In addition, a burst release phenomenon, which is an initial large bolus release of drug after the administration of the drug delivery system, or its placement in release medium, is observed for many drug delivery systems<sup>(7,8)</sup>

The nanogels have the tendency to release the drug quickly in the form of burst release as shown in Figure 2. This leads to the loss of hydrophilic and 5 hydrophobic drugs in the circulation just after the administration. A small amount of drug remain intact within the nanogel and is able to reach the target site<sup>(9)</sup>To control the release of the drug, a combination of polymer or modified polymers should be used to slow the release from the nanogel, preferably in a controlled manner. The various mechanisms governing drug release have been well reviewed by<sup>(10,11)</sup> From nanogels, the release of the drug can be due to the aqueous phase at the surface of the nanogel, aqueous penetration, drug dissolution, change of excipient transition phase, excipient degradation, change in microenvironment, or simple diffusion. Trigger is the way to control the release. Nanogels with responsive behavior and triggered drug release are reported in the literature and termed as Smart nanogels as shown in **Figure 3**. Chemical or physical triggers lead to a change in their swelling behavior or cause the degradation of polymeric network and structure which influence the drug release profile. The main physical triggers reported are temperature, pressure, electrical and magnetically fields, whereas chemical triggers are pH, ionic change, enzymes and chemical agents, that changes the polymer-solvent interactions<sup>(12)</sup>.

Three main release mechanisms have been reported including simple diffusion, chemical and physical triggers:

- i) drug release by diffusion is governed by Fick's law<sup>(13)</sup>

The polymer chain retards the solute release by reducing the average free volume available to the solute, acting as physical obstructions. Therefore, the density of polymer chain is a means to control drug release by diffusion<sup>(14)</sup>. Physical triggers such as temperature, irradiation and others can also cause swelling or degradation of polymeric network to control the release, which influences drug diffusion. The kinetics of release is controlled by the increase of matrix area that exposed to the dissolution medium produced by the triggering phenomenon<sup>(15)</sup>. Chemically release mechanism of drug is based on the degradation of the polymeric chain, inducing hydrolysis of the gel network, leading to surface erosion and drug diffusion<sup>(16)</sup>.

### Classification of Nanogels

Nanogels are more commonly classified into two major ways. The first classification is based on their responsive behaviour, which can be either stimuli-responsive or non-responsive. In the case of non-responsive microgels, they simply swell as a result of absorbing water.

1. Stimuli-responsive nanogels swell or deswell upon exposure to environmental changes such as temperature, pH, magnetic field, and ionic strength.

2. Multi-responsive nanogels are responsive to more than one environmental stimulus. The second classification is based on the type of linkages present in the network chains of gel structure, polymeric gels (including nanogel) are subdivided into two main categories

#### 1) Physically Cross-Linked Nanogels

##### 1) Hybrid Nanogels

Hybrid nanogels are defined as a composite of nanogel particles dispersed in organic or inorganic matrices<sup>(17)</sup>.

Group of studies have demonstrated nanogel formation in an aqueous medium by self assembly or aggregation of polymer amphiphiles, such as pullulan-poly(N-isopropylacrylamide) (PNIPAM), hydrophobized polysaccharides, and hydrophobized pullulan<sup>(18)</sup>

Pullulan is extensively used in food, cosmetic and pharmaceutical industries because it is easily modifiable chemically, non-toxic, non-immunogenic, non-mutagenic, and non-carcinogenic<sup>(19)</sup>.

The merits of pullulan are that it is biocompatible, biodegradable, blood compatible and non-immunogenic<sup>(20)</sup>

It can be chemically modified to various derivatives to endow amphiphilic property. Another advantage of Pullulan is that it binds strongly to asialoglycoprotein receptor and is internalized via receptor-mediated endocytosis. This group has investigated cholesterol-bearing pullulan (CHP) Nanogels<sup>(21)</sup>

##### 2) Micellar Nanogels-

Polymeric micelles are nanosized particles with a typical core-shell structure where the core can solubilise the hydrophobic drug and the corona stabilizes the interface between the core and the outside medium<sup>(22)</sup>.

Polymer micellar nanogels can be obtained by the supramolecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions. Since the use of block polymer micelles as drug-carrying vehicles was proposed in 1980s, micellar drug delivery systems (DDSs), which are aimed to deliver drugs at predetermined rates and predefined periods of time, have attracted increasing research attention<sup>(23)</sup>

They possess unique core-shell morphological structures, where a hydrophobic block segment in the form of a core is surrounded by hydrophilic polymer blocks as a shell (corona) that stabilizes the entire micelle. The core of micelles provides enough space for accommodating various drug or biomacromolecules by physical entrapment. Furthermore, the hydrophilic blocks may form hydrogen bonds with the aqueous media that lead to a perfect shell formation around the core of micelle<sup>(24)</sup>.

Therefore, the drug molecules in the hydrophobic core are protected from hydrolysis and enzymatic degradation. Researchers successfully developed highly versatile Y-shaped micelles of poly(oleic acid-Y-Nisopropylacrylamide) for drug delivery application. In this study, the delivery of prednisone acetate above its lower critical solution temperature (LCST) was demonstrated.

Liposome Modified Nanogels- When liposomes are mixed with the succinylated poly (glycidol); these liposomes can be efficiently deliver calcein to the cytoplasm by fusion the chain below pH 5.5. Liposomes which are the thermo and pH responsive nanogel like as poly (N isopropylacrylamide) are being investigated for transdermal drug delivery<sup>(25)</sup> Liposomes are simple microscopic vesicles in which lipid bilayer structure is present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecules. There are number of components present in liposomes, with phospholipid and cholesterol being the main ingredients<sup>(26)</sup>.

In particular, liposomes have been used as carriers for many kinds of molecules such as anticancer, anti-bacterial, anti-fungal and anti-viral agents, and bioactive macromolecules<sup>(27)</sup>.

#### 2) Chemically Cross-Linked Gel

Chemical gels are comprised of permanent chemical linkages (covalent bonds) throughout the gel networks. The properties of cross-linked gel system depend on the chemical linkages and functional groups present in the gel networks<sup>(28)</sup>

Chemically crosslinked hydrogels are synthesized by chain growth polymerization, addition and condensation polymerization and gamma and electron beam polymerization. Chain-growth polymerization includes free radical polymerization, controlled free radical polymerization, anionic and cationic polymerization. It is done by three process viz., initiation, propagation, and termination. After initiation, a free radical active site is generated which adds monomers in a chain link-like fashion<sup>(29)</sup>.

The crosslinking agent is explained by the e.g. by using the disulfide cross linking in the preparation of nanogel (20 – 200 nm) the pendant thiol groups are achieved “environmentally friendly chemistry.”<sup>(30)</sup>

### Synthesis

Nanoparticle composed gels can be combined by various procedures. Since an inside and out conversation of the relative multitude of accessible methods is past the extent of this audit, a short review of the procedures is given, alongside reference to

more nitty gritty sources. Generally, nanoparticle composed gels have been grouped dependent on the technique for naturally or synthetically (covalently) cross-linked nanoparticle composed gels. The most widely utilized techniques for planning artificially crosslinked nanoparticle composed gels use heterogeneous polymerization responses within the sight of bifunctional<sup>(31)</sup>.

Ordinary and restricted revolutionary polymerization procedures take into account readiness of nanoparticle composed gels with various syntheses, measurements, and designs including center shell and empty nanoparticle composed gel particles. Arranging the nanogels by such polymers is difficult because of its authority on molecular size, which needs the tweaking of the polymer fixations or else ecological boundaries, like pH, ionic strength and temperature. One of the investigations by Nielsen and team suggested that these difficulties can be tended by using a microfluidics-based methodology<sup>(32,33)</sup>.

Nanogel networks based on synthetic or natural polymers can be mainly classified into two categories according to their crosslinked structure: chemically crosslinked nanogels which form crosslinking by covalent bonds and physically crosslinked nanogels which form self-assembling through weaker linkages by noncovalent bonds. Crosslinking due to chemical interactions leads to permanent, stable and rigid link in the polymer network. Physical interactions are obtained by polymer chain entanglements or by physical interactions, such as: hydrogen bonds, electrostatic, van der Waals and hydrophobic interactions<sup>(34,36)</sup>.

While the chemical nanogels are difficult to change, in the physical nanogels the sol-gel transitions can precede as a result of the environment stimuli changes. Due to the multitude of potential applications, a lot of research in designing and synthesizing of the nanogels is in progress. As a result, in the last decade comprehensive presentations of the nanogel methods of preparation are reviewed<sup>(37,40)</sup>.

[1] In this context, polymer synthesis domain offers the options of different techniques in getting products that meet the relevant medical parameters: size, shape, yield. These methods have their specific positive aspects but limitations, too. The review makes only a short presentation of them. In the synthesis of nanogels with narrow size distribution of the particles, the stability of the gel particles in dispersion is a very important feature in relation with biomedical applications<sup>(41,42)</sup>.

This stability is influenced by the control of the particles' size, nature and chemical composition of the polymer matrix and the crosslinking type of the polymer chains. While the chemically crosslinked nanogels are attractive because of the reproducibility and size stability, in the physical crosslinking by non-covalent interactions between polymer chains, the weak field strength affects the stability of gels and the control over size during synthesis<sup>(43)</sup>

The nanometer-scale in nanogels can be created according to two major approaches: "top-down" and "bottom-up"<sup>(44)</sup>.

The "top-down" approach generates nanoparticles from large particles or clusters by physical, chemical or mechanical methods such as imprint photolithographic techniques (Particle Replication in Nonwetting Templates, PRINT)<sup>(45,46)</sup>.

The undesirable problem with "top down" approach is the imperfection of particles' surface. Also, the method having now few references is more appropriate for synthesizing micron-sized particles<sup>(47,48)</sup>.

The "bottom-up" approach is realized by designing molecular structures and assemblies, starting from molecules or clusters that are subsequently cross-linked by chemical or physical bonds. Practically, the most convenient and common way is achieved via classically direct cross-linking copolymerization of monomers or from polymer precursors by assembling them, as it is illustrated in Fig. 1 and 2



## DESIGN AND APPLICATIONS OF NANOGEL-

**BASED CHAPERONE INSPIRED SYSTEMS** 1. Amphiphilic Polysaccharide Nanogels as Artificial Chaperones in Cell-Free Protein Synthesis The application of the cell-free protein synthesis (a promising technique for the rapid production of proteins) requires the development of an artificial chaperone that prevents aggregation of the protein and supports its correct folding. Here, nanogelbased artificial chaperones are introduced that improve the folding efficiency of rhodanese produced in cell-free systems. Although rhodanese suffers from rapid aggregation, rhodanese was successfully expressed in the presence of the nanogel and folded to the enzymatically active form after addition of cyclodextrin<sup>(49)</sup>.

1. Protein refolding assisted by self-assembled nanogels as novel artificial molecular chaperone Molecular chaperone-like activity for protein refolding was investigated using nanogels of self-assembly of cholesterolbearing pullulan. Nanogel of cholesteryl group-bearing pullulan (CHP) selectively interact with proteins as a host and are useful as artificial molecular chaperones and drug carriers such as cancer immune therapy<sup>17</sup>. Nanogels effectively prevented protein aggregation (i.e. carbonic anhydrase and citrate synthase) during protein refolding from GdmCl denaturation. Enzyme activity recovered in high yields upon dissociation of the gel structure in which the proteins were trapped, by the addition of cyclodextrins. The nanogels assisted protein refolding in a manner similar to the mechanism of molecular chaperones, namely by catching and releasing proteins. The nanogels acted as a host for the trapping of refolded intermediate proteins. Cyclodextrin is an effector molecule that controls the binding ability of these host nanogels to proteins. The present nanogel system was also effective at the renaturation of inclusion body of a recombinant protein of the serine protease family. CHPA nanogels were cross-linked with PEGSH to prepare a biodegradable hydrogel (CHP-PEG gel). Gelation occurred within 10 minutes when the final concentration of CHPA nanogel was 30mg/ml in hydrogel. The nanogel structure was maintained after gelation and nanogels distributed homogeneously in the hydrogel. The CHP-PEG hydrogel was an efficient delivery system for bone anabolic agent, PEG2 and also cytokines.
2. Polysaccharide nanogel-cyclodextrin system as an artificial chaperone for in vitro protein synthesis of green fluorescent protein Polysaccharide nanogels have been demonstrated to aid the refolding processes of chemically or thermally denatured proteins, a function that is similar to that of natural molecular chaperones. In this study, the possibilities of using the nanogel chaperone system to mediate protein folding in a cellfree (in vitro) protein synthesis system containing transcription/translation factors are examined. High-performance liquid chromatography showed that a polysaccharide nanogel comprising cholesteryl group-bearing pullulan (CHP) trapped unfolded or partially folded green fluorescent protein (GFP) expressed in the cell-free system. The protein release and refolding processes, which are induced by ATP in natural molecular chaperone systems, were also simulated by methyl- $\beta$ -cyclodextrin (M- $\beta$ -CD). The CHP nanogels dissociate on complexation with M- $\beta$ -CD to yield dissociated CHP. Thus, the dissociation of the CHP nanogel-protein complex subsequently allows for the release and folding of GFP. The folding kinetics in the presence of the CHP nanogel and M- $\beta$ -CD was comparable to that of spontaneous folding in the absence of CHP/M- $\beta$ -CD, indicating that the CHP nanogels did not affect protein synthesis in the cell-free system, providing correctly folded active proteins<sup>(50)</sup>

#### Application of Nanogels

Nanogel in Ophthalmic Polyvinyl pyrrolidone – poly (acrylic acid) (PVP/PAAc) nanogel is Ph sensitive and prepared by  $\gamma$  – radiation – induced polymerization. It is used to encapsulate pilocarpine in order to maintain an adequate concentration of the pilocarpine at the site of action for prolonged of time<sup>(51)</sup>

Nanogel in Stopping Bleeding A protein molecules which is in solution & been used for formation of nanogel has been used to stop bleeding, even in severe gashes. The proteins have mechanism of self – assemble on the nanoscale in to a biodegradable gel<sup>(52)</sup>.

Nanogel as NSAIDS Carbopol and Hydroxypropylmethyl cellulose (HPMC) with the desired viscosity used to prepare the nanogels. Same like another polymer chitosan & poly – (Lactide – co – glycolic acid) used to prepare bilayered nanoparticles and surface was modified with oleic acid. For eg. Two anti – inflammatory drugs spantide II & ketoprofen drugs are effective against allergic contact dermatitis and psoriatic plaque were prepared in nanogel and applied topically. The results show that nanogel increases the absorption through percutaneous of these two drugs deeper skin layers for the treatment of various skin inflammatory disorders<sup>(53)</sup>

Nano gel in Autoimmune Diseases Cyclodextrin easily solubilized the loading liposomes with mycophenolic acid, oligomers of lactic acid – poly (ethylene glycol) that were terminated with an acrylate end group and Irgacure 2959 photo initiator. After it is exposed to ultraviolet light to produce photo polymerization of the PEG oligomers. Nano gel is having greater systemic accumulation due to their intrinsic abilities and bind to immune cells in vivo than free fluorescent tracer and permit high localized concentration of mycophenolic acid. By this types of drug delivery system there will increase patient compliance & delays the onset of kidney damage and common complication of lupus<sup>(54)</sup>.

Nanogel in Cancer Nanogel in cancer is used for the specific targeted drug delivery with low toxicities with high therapeutic efficacy. Based on the Mechanism of Action PH responsive mechanism Glycol chitosan grafted with 3 – diethyl amino propyl group & used Doxorubicin uptake accelerated<sup>(55)</sup>.

Thermosensitive & Volume Transition Mechanism Pluronic polyethylene mine / DNA complex which are used in thermoresponsive endosomal rupture by nanogel and drug release. Crosslinking of oligo (L –lactic acid) – poly (ethylene oxide) – poly (propylene oxide) – poly (ethylene oxide) – poly (lactic acid) grafted poly (1 – lysine) these all are used in the traumatic cell death due to physical stress and good source for loading anticancer drugs<sup>(56)</sup>

. Poly (N – isopropyl acrylamide – co – acrylamide) is a insitu gelatinized thermosensitive nanogel used for drug loading capacity of low molecular weight of 5 – Flourouracil was higher than that of macromolecules, bovine serum albumin<sup>(57)</sup>.

Poly (N – isopropylacrylamide) and chitosan is a thermosensitive magnetically modalized nanogel & used in hyperthermia cancer treatment and targeted drug delivery<sup>(58)</sup>.

Hydroxypropyl cellulose – poly (acrylic acid) and cholesterol bearing pullulan modified with amino group is a nanogel quantum dot hybrid PH and temperature responsive cadmium II ions quantum dots which is used for probe for imaging<sup>(59)</sup> optical PH sensing, cell imaging and drug loading of temozolomide<sup>(60)</sup>. Based on Sustained Release Cholesterol bearing pullulan nanogels is controlled by sustained release nanogel and used for recombinant murine interleukine–12 sustained tumour immunotherapy<sup>(61)</sup>.

Reducible heparin with disulfide linkages nanogel is used for internalization of heparin for apoptotic death of melanoma cells<sup>(62)</sup>.

Based upon the Self Assembly Heparin pluronic which is a self-assembling nanogel and used in RNase an enzyme delivery internalized in cells<sup>(63)</sup>.

Polymer with cross linked poly (2 – (N, N – diethylamino) methacrylate) core & PEG is a quarternized, amine and size dependent nanogel which is used for efficient SiRNA delivery<sup>(64)</sup>.

Acetylated chondroitin sulfate is self-organizing nanogel and used for Doxorubicin loaded<sup>(65)</sup>.

Acrylate group modified cholesterol bearing pullulan is nanosized cationic hydrogel which is used enhancing oral and brain Bioavailability of oligo nucleotides<sup>(66)</sup>.

Based on Gene Delivery Controlled delivery of plasmid DNA by using the polymer Di – acrylated pluronic 127 and glycidyl methacrylate chitoooligosaccharides and making Photo crosslinking nanogel<sup>(67)</sup>.

Potential in gene therapy by using the polymer poly (2 – (N, N – diethylaminoethyl) methacrylate) PEGlyted macroRAFT agent for making one step PEGlylated cationic nanogel [38]. Used in Endosomal escape of SiRNA by using the polymer Dextran hydroxyl ethyl methacrylate – co – (2 – methacryloyloxy) – ethyl) trimethyl ammonium chloride for making nanogels with photochemical internalization<sup>(68)</sup>.

SiRNA delivery to HCT – 116 cells by using the polymer thiol functionalized hyaluronic acid for making specific target and degradable nanogel. Based on Protein Treatment of alzheimer’s disease by inhibiting aggregation of amyloid  $\beta$  – protein by using cholesterol bearing amino group modified for making artificial chaperone nanogel<sup>(69)</sup>.

Based on the Enzymes  $\alpha$  – chymotrypsin immobilized on aminated nanogel by using methyl acrylic acid and N, N– methylene – bis – (acrylamide) for making super magnetic nanogel functionalized with carboxyl group<sup>(70)</sup>.

Assisted protein refolding of carbonic anhydrase and citrate synthase during GdmCL denaturation by using cholesterol bearing pullan for making self-assembled artificial molecular chaperone<sup>(71)</sup>

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