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# In Depth Review on Nanogel and its Applications

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## ABSTRACT

Nanogel have emerged as a versatile drug delivery system for encapsulation of guest molecules. A nanoparticle which is composed of hydrophilic polymer network known as Nanogel having range from 100-1000 nm. With a high drug loading capacity, high stability, sustained and targetable approach, and huge surface area, nanogel has swell able and degradation characteristics. Therefore, nanogel are more productive than conventional and micro-sized delivery. Recent years have seen a significant increase in the use of nanogel in the fields of genetics, enzyme fixation, and protein synthesis. Moreover, it has productive asset for the development of novel therapeutic system in medicine. These soft materials can contain therapeutics, inorganic nanoparticles, and small molecular biomacromolecules within their crosslinked networks, enabling them to be used for imaging as well as therapy for a range of disease conditions. This review aims to highlight the distinct and unique capabilities of nanogels as carrier system, Types of Physical and chemical crosslinked nanogels, the applications of nanogels in various diseases diabetes, auto immune diseases, local anaesthesia, nasal drug delivery and anticancer treatment for specially targeting the cancer cells, thereby reducing uptake into healthy cells. This phenomenal drug delivery method using nanogels needs more in-depth research to better understand how cells and molecules interact with them and how to overcome limitations.

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## INTRODUCTION

Nanogels are defined as nanoscale particles that, either physically or chemically, create crosslinked polymers. In order to transport polynucleotides, cross-linked bifunctional networks of a polyion and a non-ionic polymer were first developed [1]. Although soluble in water, nanogels differ from linear macromolecules with comparable molecular weights in their properties. These structures along with their larger equivalents [2]. Nanogels are typical formulations that typically range in size from 1000 nm, and their three-dimensional structure can be maintained by altering volume proportion and solvent quality. Nanogels have revolutionized the field of gene therapy because they have made it possible to deliver genes within cellular organelles for gene silencing therapy [3]. Nanogels are composed of ionic or non-ionic polymer chains that are hydrophilic or amphiphilic and grow into nanoscale structures. Despite its use as a drug delivery system, nanogel has been studied for longer periods in the production of other substances like quantum dots, dyes, and other diagnostic agents [4]. The development of nano-sized microgels and hydrogels as a result of specific delivery system anticipation has been made possible by the wide range of polymer systems and the simple modification of their physico-chemical properties [5]. The voids of nanogels were filled with micro- or macromolecules [6]. Nanogels have flexible size, a large surface area, and a high-water content, which contribute to their expandability and degradation characteristics [7]. Nanotechnology is an innovative technology that offers a broad range for a smart drug manufacturing and delivery (nanomedicine) approach that involves the synthesis and characterization of materials or molecules, Design, and devices that have constructive function at manometer scale. the studies conducted in university labs and pharmaceutical companies from around the globe reported that novel nano-sized particulate drug delivery systems (DDS) have had a significant effect on disease prevention, diagnosis, and treatment [8].

**Advantages of nanogels**

- Highly biocompatible (due to high water content and hence behave like natural tissue) and therefore immunological responses
- Nontoxic because of biodegradable carrier.
- Loading capacity of drug is high.
- Easily escape entrapment by reticuloendothelial system.
- Crosslinking densities of drug delivery can be controlled by tunning
- Better permeation via biological membranes due to extremely small size.
- Easily can incorporate both hydrophilic and hydrophobic drugs and charged solutes.
- Excellent transport features.
- The inclusion of a polymeric network prolongs the drug's release from the formulation [9].
- The freely circulating pearlescent nanogel solution can be readily dispersed in aqueous media [9]

**Disadvantages of nanogels**

- Expensive strategy to altogether eliminate the solvents and surfactants toward the finish of arrangement.
- Adverse impact can be granted because of Surfactant or monomer follows can be remain.
- Some small particles of particles are in the micrometre range.

**Properties of Nanogels**

**1. Biocompatibility and Degradability**

Nanogel based drug delivery system is highly biocompatible and biodegradable due to this characteristic it is highly promising field now a days.

**2. Swelling Property in Aqueous Media**

The ability of nanogels to quickly expand and disperse is their most advantageous quality. Soft nanoparticles are known as nanogels [1]. Swelling of nanogels in aqueous environment is controlled by both nanogel structure chemical nature of polymer chains, degree of cross-linking, charge density for polyelectrolyte gels and environmental parameters for polyelectrolyte gels - pH, ionic strength and chemical nature of low molecular mass ions for thermo-responsive gels – temperature. It is widely accepted that the physical dimensions of a hydrogel particle are determined by a balance between the osmotic pressure and the polymer's elasticity [10].

**3. Higher Drug Loading Capacity**

The properties of higher drug loading capacity of nanogels depend on the functional group present in the polymeric unit. These functional groups have a tremendous effect on drug carrying and drug-releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications. These pendent functional groups of polymeric chains contribute toward establishing hydrogen bonding or vander Waals forces of interactions within the gel network and thus facilitate the drug-carrying efficiency. Moreover, the presence of functional groups at interface with drug/protein molecules is also responsible for higher loading [1].

**4. Particle Size**

Nanogels are usually between 10 and 100 nm in size, making them effective at preventing rapid renal exclusion while remaining small enough to prevent uptake by the reticuloendothelial system [11]. Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB) [1]. On the basis of physiological parameters such as hepatic filtration, tissue extravasation, tissue diffusion, and kidney excretion, size is a crucial factor in the biodistribution of long-circulating nanoparticles [12].

**5. Solubility**

Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel [1]. Additionally, some nanogels contain hydrophobic regions that can be used to solubilize hydrophobic molecules. For instance, prostaglandin E2 was soluble in pullulan nanogels treated with cholesterol. Doxorubicin was also put into Pluronic F127- or poly [oligo(ethylene oxide)-methyl methacrylate]-based amphiphilic cross-linked nanogels. Notably, the majority of the time, loading caused solely by hydrophobic interactions has comparatively low loading capacities [12].

**6. Electromobility**

Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating biomacromolecules [1].

**7. Colloidal Stability**

In comparison to surfactant micelles, nanogels or polymeric micellar nanogel systems show superior stability, lower critical micelle concentrations, slower rates of dissociation, and longer retention of loaded drugs [1].

**8. Non-immunologic Response**

This type of drug delivery system usually does not produce any immunological responses [1].

**9. Others**

Nanogel can be used to administer both hydrophilic and hydrophobic medications as well as charged

solutes. Temperature, the presence of hydrophilic and hydrophobic groups in the polymeric networks, the cross-linking density of the gels, surfactant concentration, and the type of cross-links present in the polymer networks all have a major impact on the properties of nanogels [1].

**Routes of administration of Nanogel**

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

**Classification of Nanogels**

There are two main categories into which nanogels are typically divided. The first categorization is based on their responsive behaviour, which can be either stimuli-responsive or non-responsive Nanoscience and Nanotechnology Research 27. Non-responsive microgels merely swell after absorbing water, in this case.

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.

**A. Physically Cross-Linked Nanogels**

**1. Hybrid Nanogels**

A mixture of nanogel particles dispersed in organic or inorganic matrices is referred to as a hybrid nanogel [13]. A number of studies have shown that hydrophobic polymer amphiphiles like pullulan-poly (N-isopropylacrylamide) (PNIPAM), hydrophobized polysaccharides, and hydrophobized pullulan can self-assemble or aggregate to create nanogels in an aqueous medium [1]. Because pullulan is chemically easy to modify, non-toxic, non-immunogenic, non-mutagenic, and non-carcinogenic, it is widely used in the food, cosmetic, and pharmaceutical industries [14]. Pullulan has the advantages of being non-immunogenic, nontoxic, biodegradable, and blood compatible [15]. These nanogels can bind to different proteins, medications, and DNA; they can also coat the surfaces of liposomes, particles, and solid surfaces, including cells. Additionally, these hybrid nanogels can transport insulin and cancer treatments more efficiently. Pullulan backbone and cholesterol limbs make up CHP. Through the connection of hydrophobic groups that serve as physical crosslinking points, the CHP molecules self-associate to create mono-dispersed stable nanogels [1]. As shown in Figure 1.

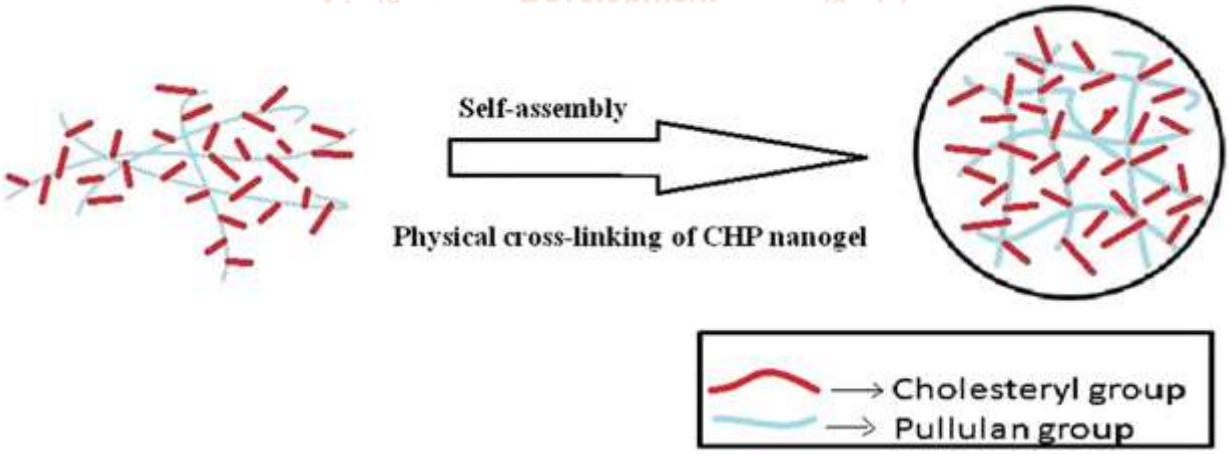


**Figure 1 Schematic representation of CHP nanogel preparation by physical cross-linking (self-assembly)**

**2. Micellar Nanogels**

The hydrophobic drug can be dissolved in polymeric micelles, which are nanosized particles with a typical core-shell structure. The corona stabilizes the contact between the core and the surrounding medium [16]. Amphiphilic block or graft copolymers can be assembled supramolecularly in aqueous liquids to form polymer micellar nanogels. Since the 1980s, when the idea of using block polymer micelles as drug-delivery systems first emerged, micellar drug delivery systems (DDSs), which seek to deliver drugs at predetermined rates and over predetermined periods of time, have drawn growing research interest [17]. They have special core-shell morphological structures, where a hydrophobic block segment serves as the core and is surrounded by hydrophilic polymer blocks to create the micelle's stabilizing shell (corona). The interior of micelles has enough room to physically entrap a variety of drugs or biomacromolecules. A perfect shell may develop around the micelle core as a result of hydrogen bonds that the hydrophilic blocks may make with the aqueous medium [18].

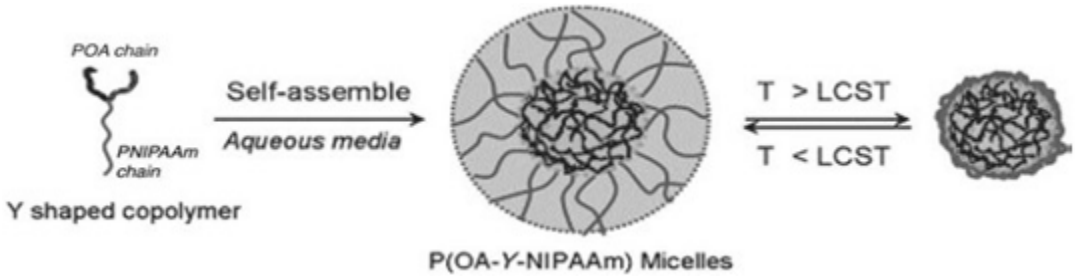


**Figure 2. Y-shaped copolymer self-assembly to give micelle structures**

### 3. Liposome Modified Nanogels

By fusing the chain below pH 5.5, liposomes can effectively transport calcium to the cytoplasm when combined with succinylated poly (glycidol). Transdermal drug administration using liposomes, a thermo- and pH-responsive nanogel similar to poly (N-isopropylacrylamide), is being researched [4]. Simple microscopic vesicles called liposomes have an aqueous capacity completely surrounded by a membrane made of lipid molecules and a lipid bilayer structure. Liposomes contain a variety of ingredients, the two major ones being phospholipid and cholesterol [19]. Particularly, liposomes have been used as carriers for a variety of molecules, including bioactive macromolecules and anticancer, antibacterial, antifungal, and antiviral drugs [20].

## B. Chemically Cross-Linked Gels

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 [1]. Chain growth polymerization, addition and condensation polymerization, gamma and electron beam polymerization are the processes used to create chemically crosslinked hydrogels. Free radical polymerization, regulated free radical polymerization, anionic and cationic polymerization are all examples of chain-growth polymerization. Three processes—initiation, spread, and termination—are used to accomplish this. Following initiation, a free radical active site is produced that adds monomers in a way that resembles a chain link [21]. 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." [4].

## Mechanism of Drug Release from Nanogels

### 1. Diffusion Mechanism

Example: stable hydrogel nanoparticles based on pluronic block copolymer [1]. They have the ability of releasing doxorubicin through diffusion. This method and straightforward process are used in many different types of nanomedicine, including polymeric micelles that have already entered the clinical stage [4].

### 2. Nanogel Degradation

It has been demonstrated that the breakdown of these nanogels causes the release of molecules that have been enclosed, such as the fluorescent dye rhodamine 6G and the anticancer drug doxorubicin, as well as makes empty carriers easier to remove [1]. Due to the grafting of the diethylaminopropyl group, the glycol chitosan nanoparticles' sensitivity to pH stimuli was greatly increased, which increased the release of the chemotherapy drug [3]. Due to pH sensitivity, a significant mesh size change has been observed in diethylaminoethyl methacrylate cationic nanogel for release of medium-sized compounds [22].

### 3. Displacement by Ions Present in the Environment

The development of nanogels that can release biological agents in reaction to environmental indications at the intended site of action is gaining more attention. For example, in the presence of the glutathione tripeptide, which is frequently present in cells, disulfide cross-linked POEOMA nanogels biodegraded into water-soluble polymers [23]. It was also suggested that cellular accumulation of an NTPs drug supplied with nanogels could be explained by cell membrane-triggered release of negatively charged drugs from complexes with cationic nanogels [1].

### 4. pH Responsive Mechanism

Because of the protonation of crosslinked poly (2 - (N, N - diethylamino) methacrylate) core and PEG, platinum nanoparticles containing nanogel are able to eliminate reactive oxygen species in the acidic skin pH [24]. Methacrylic acid and ethyl acrylate are polymers that are insoluble in 3D when the pH is too low. However, as the pH levels rise, acidic groups start to ionize as a result of the polymeric chains' repulsions, which results in a specific release profile of procaine hydrochloride [25]. The substance temozolidine exhibits a controllable release kinetics mechanism as a result of the pH-sensitive polyacrylic acid chains' swelling action [26]. However, owing to the pH sensitivity of glycol chitosan nanoparticles and the grafting of diethylaminopropyl groups, the release of doxorubicin was significantly increased [4].

**5. Photochemical Internalization and Photoisomerization**

The oxidation of cellular compartment walls, such as endosomal barrier walls, results from the excitation of photosensitizer-loaded nanogels and produces singlet oxygen and reactive oxygen species, which affect the release of medicines into the cytoplasm [3]. Polyelectrolyte hydrogels that contain biological agents via electrostatic bonds enable the release of biological agents in response to environmental changes. It was demonstrated that the E-configuration of the azo group produced a better drug release profile than the z-configuration under 365 nm radiation by using aspirin as the model drug in a cis-trans isomerization of azobenzene by photoregulation in azo-dextran nanogel [27].

**Application of Nanogels**

Nanogels have been transforming the field of curative medicines. In the short duration since the appearance of the concept, these non-conventional drug delivery systems have served as potential candidates for wide spectrum of applications.

**1. Anticancer Therapy**

Numerous polymeric nanogels have been used as cancer treatments. Chemotherapeutic drug incorporation into nanogel improves permeability and retention as well as absorption [5]. In cancer chemotherapy, nanogel is used to transport drugs more successfully. Genexol-PM is one of the polymeric nanogels that has been approved by the FDA for use in breast cancer patients [28].

**2. Autoimmune Disease**

In research, a novel nanogel drug delivery method for the immunosuppressant mycophenolic acid was developed and tested. (MPA). According to the study's findings, local delivery of medications based on nanogels is more effective at treating lupus erythematosus because it specifically targets antigen-presenting cells. By delaying the onset of kidney damage, a frequent complication of lupus, this new drug delivery method prolongs patient life [29].

**3. For Local Anaesthesia**

One of the top objectives in therapeutics for dental care is pain management. By including them in drug delivery devices, local anaesthetic regional administration could be improved [5].

**4. Stopping Bleeding**

A protein supermolecules that is in solutions & been used for formation of nanogel has been accustomed stop trauma, even in severe gashes. The proteins have mechanism of self – assemble on the nanoscale in to a perishable gel [4].

**5. Diabetics**

A nano-network that can be injected and reacts to aldohexose by releasing insulin has been created. It includes a mixture of nanoparticles with opposing charges that are drawn to one another. This keeps the gel along and stops the nanoparticles drifting away once within the body. In vivo experiments conducted in diabetic rats in a pair of 2012 disclosed that insulin-loaded nanogels faded the glucose levels by fifty-one from the baseline level for pretty much 2 hours. Considerably, in comparison with free insulin the insulin-loaded nanogels might keep glucose levels stable and avoided sugar changes [30].

**6. Nasal Drug Delivery**

Nanogel drug delivery systems hold nice potential to beat a number of the barriers in delivery. Nanogels are with efficiency obsessed by nasal mucous membrane and thus, might be used as efficient transport and delivery systems for medical specialty through nasal mucous membrane. The employment of nanogels for vaccine delivery via nasal route may be a new approach to regulate the illness progression. Nanogels are high-viscosity systems containing nanoparticulates (NPs, microcapsules, NEs, etc.) during a compound polymeric network [32]

**Conclusion**

Nanogels are reassuringly modern drug delivery systems that effectively mitigate drawbacks associated with both old and new therapeutics, such as poor stability and nonspecific side effects. Biological ligands like proteins, peptides, and polysaccharides were formulated with modifications to nanogel for outstanding interaction with target cells. Because of their high incorporation capacity, swelling ability, and number of biological molecules that interact with the electrostatic van der wall interaction that happens with the polymer chain to form stable nanoparticles, nanogels are used as therapeutic drug carriers. This makes it simple to entrap drugs within them. Nanogels appear to be excellent candidates for tumour targeting. Therefore, future objective of this review is to improve the design of nanogel with specific targeting residue to facilitate highly selective uptake into particular cancer cells, thereby minimize the uptake in normal cells.

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**CONFLICT OF INTEREST:**

All authors declared no conflict of interest for the work.

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