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A Comprehensive Review of Nanogel – Based Drug Delivery System

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Abstract: *Imagine a microscopic, water-filled sponge—perfectly structured to carry therapeutic cargo and release it exactly where and when it's needed. This is the essence of nanogels , a truly advanced nano-technological system that is revolutionizing drug delivery. By combining the high water content and flexibility of hydrogels with the ultra-small size of nanoparticles (typically 100 to 200 nm), nanogels have emerged as the "ideal" vehicle for next-generation pharmaceuticals .The core of their success lies in their distinctive properties: they are built from crosslinked hydrophilic polymer networks, granting them a unique swelling ability to absorb substantial amounts of water while maintaining structural integrity. This structure translates into a phenomenal high drug-loading capacity, excellent biocompatibility, and crucial biodegradability, making them safe for use both inside the body and for topical applications. The goal of ongoing research is to fine-tune their operation by controlling their swelling behavior to achieve truly sustained and targeted drug release. This release is a complex, elegant dance governed by three factors: the simple diffusion of the drug, the gradual degradation of the polymer network, and the dynamic swelling behavior of the gel itself. high-water-content polymer platforms are unquestionably poised to transform the landscape of modern medicine*

Keywords: Nanogel, classification, release mechanism, drug loading technique, properties , application , Types , Advantages , Disadvantages , Application

I. INTRODUCTION

Nanogels are fascinating, nanosized particles that represent a significant advancement in drug delivery and biotechnology. Simply put, they are tiny polymer networks—either physically or chemically interlinked—that have the remarkable ability to swell in a good solvent, often water. While they dissolve, their properties are distinct from simple, linear polymers of the same size. These structures were initially introduced to define specialized cross-linked networks used for delivering polynucleotides.Nanogels are proving to be invaluable assets in modern medicine and biotechnology. They are capable of delivering a wide range of biologically active agents in a prolonged and controlled release manner. Their unique three-dimensional structure allows them to entrap drugs, polymers, and a liquid phase. Nanogels offer several distinct advantages over traditional delivery systems: their size is tunable, their synthesis is facile, and they are highly physiologically compatible and hydrated. Crucially, they possess a remarkable responsiveness to environmental changes such as variations in temperature, pH, light, or biological agents, allowing for smart, on-demand drug release. This makes them a prominent tool in fields like genetics, enzyme immobilization, and protein synthesis, establishing nanogels as a highly effective component in novel therapeutic systems.[1,2,3,4,5,10]

Route of Administration :[6]

Nanogels, with their tunable size and structure, offer incredible flexibility in drug delivery. They can be administered through a wide array of routes to target specific tissues or provide systemic effects:

Route of Administration	Delivery focus
Oral	Systemic/ Gastrointestinal

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Pulmonary	Lung Disease / Systemic
Nasal	Brain Targeting / Systemic
Parenteral	Systemic [IV, SC , IM]
Intra-Ocular	Ocular Diseases
Topical	Skin / Mucosal (Dermal)

Properties of Nanogel :[1,6,7,8,9]

Biocompatibility and Degradability

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

Swelling property in aqueous media

Nanogels are tiny, soft materials that are incredibly useful because they can quickly puff up (swell) and shrink down (de-swell). This ability to change size rapidly makes them very desirable for various applications. Their swelling behavior in water is a delicate balance.

Higher drug loading capacity

Nanogels are outstanding drug carriers largely because of the special \text{chemical groups} they contain. These functional groups on the polymer chains are crucial; they act like tiny molecular "hooks" or "magnets." They boost drug-carrying capacity by forming weak, temporary bonds—like hydrogen bonds or van der Waals forces —with the drug molecule, locking it inside the gel network.

Importantly, these same groups can be used to attach the nanogel to targeting molecules (like antibodies), ensuring the drug is delivered precisely where it's needed in the body. Ultimately, the presence of these active functional groups, both throughout the gel and at its surface, is the key to achieving high drug loading and controlled release.

Particle size

Nanogels are tiny, versatile drug carriers that offer a sweet spot for medical applications! Ranging from 10 to 100 nm, their size is crucial: they're small enough to sneak past the kidneys (avoiding rapid excretion) but large enough to dodge the body's immune clean-up crew (the reticuloendothelial system). This precise sizing gives them long circulation times and excellent tissue penetration, even allowing them to cross the tough blood-brain barrier (BBB), making them highly effective for targeted delivery and improving the biodistribution of therapeutics.

Solubility

Nanogels are powerful carriers for water-hating (hydrophobic) drugs ! They essentially act as tiny, friendly containers, either trapping the drug inside their core or within the gel network. Some nanogels are even designed with hydrophobic domains to boost this ability, allowing them to effectively solubilize molecules like prostaglandin I2 or the chemotherapy drug Doxorubicin. While super helpful for drug delivery, relying only on these hydrophobic interactions usually leads to a relatively modest drug loading capacity.

Colloidal stability

In short: Nanogels are superior drug carriers because they are very stable, require less concentration to stay formed, and keep the drug safe and contained for a longer time.

Electro mobility

Nanogels can be prepared mildly—without using energy or harsh methods (like sonication or homogenization)—which is key for encapsulating biomacromolecules.

Non- immunologic response

This drug delivery system usually doesn't cause immune reactions.

Others

Nanogels are versatile drug carriers that can deliver all kinds of drugs—water-loving {hydrophilic}), water-hating {hydrophobic}), and {charged} ones!

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Their effectiveness is easily tuned by factors like:

* Temperature
* Polymer components (water-loving/hating groups)
* Gel tightness {cross-linking density}
* Surfactant amount
* Type of cross-links

Advantages of Nanogel:[2,11,12,13,14]

- Targeted Delivery and Enhanced Efficacy: They enable the drug to reach the desired site specifically, improving therapeutic outcomes.
- Controlled Release: Drug release kinetics can be precisely regulated by tuning crosslinking densities or incorporating a polymeric network, providing a sustained effect.
- High Biocompatibility and Low Toxicity: Due to high water content, they mimic natural tissue and are biodegradable, minimizing adverse immunological responses and toxicity.
- Versatile Drug Loading: They can easily incorporate both hydrophilic and hydrophobic drugs and charged solutes, making them suitable for a wide range of pharmaceuticals.
- Excellent Transport Features & Penetration: Their extremely small size allows them to easily escape the reticuloendothelial system (RES), penetrate tissues via transcellular or paracellular pathways, and reach the smallest capillary vessels.
- High Drug Loading Capacity: They can carry a significant amount of the therapeutic agent.
- Improved Imaging Potential: Their structure can be leveraged for better diagnostic applications alongside drug delivery.
- Reduced Premature Leakage: The formulation helps in retaining the drug until release is desired.
- Applicability in Regenerative Medicine: Their unique properties make them valuable tools in tissue repair and regeneration.
- Easy Administration: They are easy to disperse in aqueous media and suitable for parenteral and mucosal administration.

Disadvantages of Nanogel:[15,16]

- Toxicity and Biocompatibility Concerns: Residual trace amounts of monomers, solvents, or surfactants used in the synthesis process can remain in the final product and may cause toxicity or adverse biological effects.
- Immunogenicity: The polymer components of the nanogels can sometimes be recognized by the immune system, leading to an unwanted immune response.
- Scalability Issues: Transitioning the nanogel synthesis process from a small-scale laboratory batch to a reliable, cost-effective, and reproducible large-scale industrial manufacturing process is often difficult.
- Characterization Difficulties: Due to their soft, dynamic, and hydrated nature, precisely characterizing the structure, swelling state, cross-linking density, and mechanical properties of nanogels can be analytically difficult.
- Limited Stability (Physical and Chemical): Nanogels can suffer from poor physical or chemical stability during storage, sterilization, or in the complex biological environment, leading to aggregation, degradation, or loss of function.

Classification of Nanogel:[5,6,17,18,19]

Nanogels are more commonly classified into two major ways. The firstclassification is based on their responsive behavior, which can be either stimuli-responsive or non-responsive.

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1.Stimuli-responsive microgels swell or deswell upon exposure to environmental changes such as temperature. pH.magnetic field, and ionic strength. Multi-responsive microgels are responsive to more than one environmental stimulus.

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.

Hybrid Nanogels

Hybrid Nanogels are composites where nanogel particles are dispersed in organic or inorganic matrices. A popular example involves cholesterol-bearing pullulan (CHP) . The pullulan polymer, a safe, biocompatible polysaccharide, is chemically modified with cholesterol groups. In water, these hydrophobic cholesterol groups self-associate, forming stable, mono-dispersed nanogels with physical crosslinks. They are incredible complexing agents, capable of binding to proteins, DNA, and drugs, making them ideal for enhanced delivery of agents like insulin and anticancer drugs, even targeting specific cell receptors.

MicellarNanogels

MicellarNanogels are formed by the supramolecular self-assembly of amphiphilic block or graft copolymers in water. They naturally arrange into a core-shell structure .

* The hydrophobic core acts as a safe haven, physically entrapping and solubilizing hydrophobic drugs, protecting them from degradation.

* The hydrophilic shell (corona) stabilizes the entire structure in the aqueous environment.

These unique structures have made polymeric micelles a highly attractive platform for sophisticated drug delivery systems, allowing drugs to be delivered at a controlled rate and time

Liposome Modified Nanogel

are being studied as a drug delivery system.

Here's a simpler breakdown:

® What They Are

These systems combine liposomes—tiny spheres with a fatty shell and a water center, often made of phospholipids and cholesterol—with a nanogel, which is a microscopic, cross-linked polymer network.

®How They Work

* pH-Responsive Delivery: When liposomes are mixed with succinylated poly(glycidol), they can deliver substances (like the model drug calcein) directly into a cell's cytoplasm. This happens because the components fuse together when the environment's pH is below 5.5 (acidic).

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Types of Nanogels

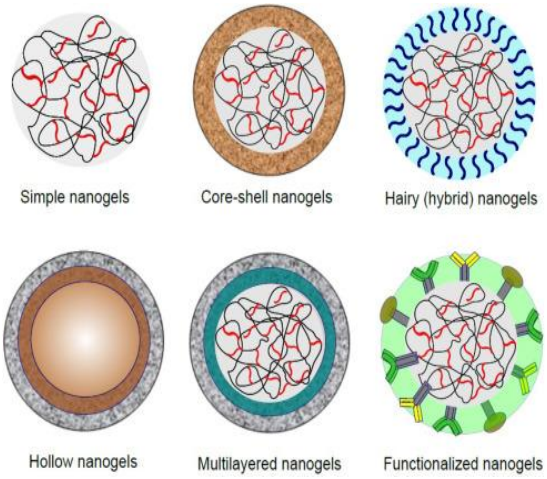

Figure no 1 types of nanogel

Preparation Method of Nanogel :[6]

Dispersion Method

Spread of the Gelling Substance
Last-Minute Homogenization

Emulsification Method

Emulsifier
Mixing process
Gelling Agent

Sol-Gel Method

Ingredient Mixing
Gel Formation
Drying and Shaping

Gelatin Gel Preparation

Let the Gelatin Bloom
Gel the Gelatin Dissolve
Pour the Set

Coacervation Method

Dissolove Polymer
Induce Coacervation
Nano Gel Formation
Stabillization
Purification and Drying

Microemulsion Method

Making Water-in-oil or Oil-in-water
Gelation or Polymerization Procedure

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Nanogel Formation and Purification

Spray Drying Method
Preparation
Automization
Drying
Gathering

High-Shear Homogenization Method
Crosslinking and Stabilizatin
Last-Minute Processing and Storage

Mechanism of Drug Release from Nanogels:[9,17,20,21,22,23]
Nanogels control drug delivery through various internal changes and responses to external stimuli at the target site, ensuring therapeutic efficacy while minimizing side effects. Key mechanisms include:

1. Diffusion Mechanism
* Core Principle: The drug simply moves out of the nanogel matrix, often driven by a concentration gradient.
* How it Works: The drug escapes through the existing pores or "mesh" of the stable nanogel structure without the nanogel itself changing significantly.
* Example: Release of Doxorubicin from stable hydrogel nanoparticles based on Pluronic block copolymer. This is a common and straightforward method, utilized by many nanomedicines, including successful polymeric micelles.

2. Nanogel Degradation
* Core Principle: The nanogel physically breaks down, which liberates the encapsulated drug.
* How it Works: The chemical bonds holding the nanogel structure together cleave (e.g., in response to specific enzymes or conditions), causing the nanogel to fall apart and release its payload and facilitate the removal of empty vehicles.
* Example: Increased release of Doxorubicin from glycol chitosan nanoparticles due to their sensitivity to {pH} changes (due to the grafting of a diethylaminopropyl group).

3. Displacement by Ions in the Environment
* Core Principle: Biological agents are released when specific ions or molecules at the target site interact with and alter the nanogel structure.
* How it Works: An external molecule displaces the drug or cleaves cross-links in the nanogel. For example, disulfide cross-links in nanogels can be broken by the high intracellular concentration of the tripeptide glutathione {GSH}), a common {redox} cue in cells.
* Example: Disulfide cross-linked POEOMA nanogels degrade into water-soluble polymers in the presence of {GSH}, triggering the release of the drug.

4. pH Responsive Mechanism
* Core Principle: A change in acidity (\text{pH}) causes the nanogel to swell or shrink, altering its mesh size and releasing the drug.
* How it Works: Polymers within the nanogel contain acidic or basic groups that ionize (become charged) when the {pH} changes. This ionization leads to repulsion of the polymer chains, causing the nanogel to swell significantly and expel the drug.
* Example: The controlled release of Temozolidine due to the swelling action of {pH}-sensitive polyacrylic acid chains. Also, mesh size alteration in diethylaminoethyl methacrylate cationic nanogel to release medium-sized molecules.

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5. Photochemical Internalization (PCI) and Photoisomerization

* Core Principle: Light energy is used to trigger drug release.
* PCI: Exciting photosensitizers loaded in the nanogel produces reactive oxygen species and singlet oxygen (a highly reactive form of oxygen). These reactive species damage the cell compartment walls (like the endosomal barrier), allowing therapeutics to escape into the cytoplasm.
* Photoisomerization: Light causes a molecule within the nanogel (a photoisomer) to change its shape, which in turn alters the nanogel's overall structure and drug-holding capacity.
* Example: Cis-trans isomerization of an azobenzene group in an aro-dextran nanogel, which changed its configuration upon 365 nm radiation to control the release of Aspirin.

Drug Loading Techniques in Nanogel:[6,24,25,26,27]

Drug loading into nanogels is essential for a great delivery system. To keep the required amount of carrier low, a successful system needs a high drug-loading capacity.

Covalent conjugation:

attaching bioactive molecules—can happen in two powerful ways: either during nanogel synthesis or by using preformed nanogels.

For example, scientists can modify acrylic groups with enzymes. Then, by mixing this with acrylamide in a dilute solution or inverse microemulsion, they create tiny, custom-built nano-sized hydrogels. This allows for the precise integration of agents right into the nanogel structure.

Physical Enterapment:

Nanogels act like miniature, porous sponges for drugs and proteins. In one common method, molecules are simply trapped inside the nanogel's structure, like catching a bug in a net.

* For Proteins: Nanogels made of pullulan, when treated with cholesterol, can physically trap and hold proteins.
* For Other Molecules (like siRNA): Hydrophobic (water-repelling) molecules are added to certain nanogels (like HA nanogels) to create non-polar, water-resistant domains—essentially, little oily pockets—that successfully enclose hydrophobic drugs or genetic material like siRNA. This method was used to solubilize drugs like prostaglandin E2 (pge E2) in cholesterol-modified pullulannanogels, and to incorporate N-hexylcarbamoyl-5-fluorouracil (HCFU) into special PNIPAAm/VP copolymer nanogels.

The success of this trapping technique primarily depends on the matching sizes of the nanogel's internal pores and the molecule being loaded. Alternatively, some nanocarriers use active parts on their surface to bind molecules instead of just trapping them inside.

Self Assembly:

Self-assembly is a fascinating biological phenomenon where molecular units spontaneously and reversibly organize into highly ordered, stable aggregates. Think of it as molecules "snapping" together perfectly, achieving a thermodynamically stable structure with minimal flaws, much like building blocks clicking into place.

Key Features and Driving Forces:

* Adaptable and Affordable: This process is efficient and cost-effective.
* Sturdy Structures: It naturally occurs near thermodynamic minima, resulting in robust and stable arrangements.
* Weak Forces Rule: The process is governed by a precise balance of weak, non-covalent interactions, including hydrogen bonds, van der Waals forces, and hydrophobic/electrostatic associations. These weak forces direct molecules to "affiliate" and control the final structure.

Amphiphilic Polymers: A Perfect Example

A great illustration is the self-assembly of amphiphilic polymers (molecules with both water-loving/hydrophilic and water-fearing/hydrophobic parts). In water, these polymers automatically organize into nanoparticles to minimize the energy where the water meets the hydrophobic part.

* They arrange their hydrophobic segments into a hidden core.
* They expose their hydrophilic portions to the watery environment.

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This assembly begins when the polymer concentration reaches the critical micelle concentration (CMC), spontaneously forming these well-defined aggregates.

Upon administration, gastrointestinal fluids permeate through the semipermeable membrane because of the osmotic gradient between the external medium and the core (Shivam-Gavandare et al., 2020).

Water influx dissolves or suspends the drug inside the core, forming a saturated drug solution or gel inside the tablet (Patel et al., 2024).

As more water enters, osmotic pressure builds up within the system, producing a controlled, constant internal hydrostatic force (Khan et al., 2022).

This pressure pushes the drug solution out through a laser-drilled orifice or in-situ generated pores, depending on the device type (Singh et al., 2023).

In push–pull systems (PPOP), the push layer swells significantly when hydrated, generating mechanical pressure to expel the drug from the drug layer, especially for poorly soluble drugs (Kumar et al., 2023).

Controlled-porosity osmotic pumps (CPOP) allow drug release through micropores formed in the membrane, eliminating the need for orifice drilling (Azhar et al., 2021).

Because the driving force (osmotic pressure) remains constant, the drug release rate becomes independent of gastric variables like pH, food, agitation, or motility (Shao et al., 2020).Drug release continues until the entire core is depleted, after which the exhausted shell is excreted intact (Khan et al., 2022)

Marketed Formulation of Nanogel:

1)Oxalginnanogel: It gives deeper action and quicker penetration
2)Skin perfect brightening nanogel: It brightens the skin and gives complete hydration. It repairs, tones, and protects the skin
3)HA nanogel Excellent alternative to regular toothpaste. Reducing risk of decay and also reduced bad breath
4)Revivagenix pro collagen Nano gel: It is an anti-wrinkle cream, gives complete hydration to the skin for longer time
5)Aqua multi Effect Nano gel cream: It's a moisturizing gel that gives complete hydration for a long time. It also works as anti-wrinkle cream
6)Sane care nanogel: Reduces accumulated fats on the abdomen, arms, legs, thighs.
7)AugenNanogel Eye-care Gel: It is an eye care gel with deep penetration properties

Application of Nanogel:[2,6,29,30,31,32]

1. Uses in cancer therapy.
2. Diabetes Treatment.
3. Neurodegenerative Diseases.
4. Nasal drug delivery.
5. Vaginal Drug delivery.
6. Ocular problems.
7. Anti - Inflammatory Action.
8. Tumor therapy.
9. carrier for Antifungal agents.
10. stopping Bleeding.
11. Nanogel in Diagnostics and imaging.

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II. CONCLUSION

Nanogels represent a promising and modern drug delivery system that effectively overcomes key limitations of older and current therapies, such as non-specific effects and poor stability.These innovative systems are excellent therapeutic drug carriers due to their high drug incorporation capacity and swelling property. By modifying their surface with biological ligands—like proteins or peptides—nanogels can achieve specific targeting, making them especially effective for treating conditions like cancer. The future aim is to perfect nanogel design with specific targeting residues to ensure highly selective uptake into cancer cells while minimizing impact on healthy ones. Furthermore, recent advancements have expanded nanogel applications to managing a variety of issues, including ocular problems, and nasal and vaginal drug delivery, securing their vital role in the future of medical therapies.

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