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Review Article

A Comprehensive Review of Nanogel Formulations and their Pharmaceutical Applications in Drug Delivery

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ABSTRACT

Nanotechnology has emerged as a transformative field with significant applications in pharmaceutical sciences, particularly in the development of advanced drug delivery systems. Among various nanocarriers, nanogels have gained considerable attention due to their unique physicochemical properties, including high drug-loading capacity, biocompatibility, biodegradability, enhanced stability, and controlled drug release characteristics. Nanogels are nanosized hydrogel particles composed of cross-linked polymeric networks capable of encapsulating a wide range of therapeutic agents, such as small molecules, proteins, enzymes, genes, and herbal extracts. They can be synthesized from natural or synthetic polymers and classified based on their cross-linking mechanisms and responsiveness to external stimuli. Various polymer-based nanogels, including chitosan, pullulan, hyaluronic acid, alginate, cyclodextrin, and gum acacia nanogels, have demonstrated promising potential in targeted and site-specific drug delivery. Recent advancements have led to the development of multifunctional and stimuli-responsive nanogels for applications in cancer therapy, gene delivery, protein transport, gastrointestinal disorders, and theranostics. This review highlights the fundamentals of nanotechnology, nanoparticle and nanogel systems, classification of nanogels, formulation developments, significance, and diverse pharmaceutical applications. The growing interest in nanogel-based drug delivery systems suggests their potential to overcome limitations of conventional therapies and improve therapeutic outcomes in modern medicine.

INTRODUCTION

The pharmaceutical industry is not an exception to the growing trend of nanotechnology, which is driving advancements in almost every area of

technology. For many years, it has been applied to synthetic medications. However, traditional treatments are the main focus these days. [1] Despite the scientific community's fascination with the topic of nanoscience, the majority of

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current conversations, definitions, and attention are directed toward nanotechnology, which is a mentality. As a result, it is a general phrase that illustrates the pinnacle of man's insatiable desire for knowledge with useful applications. Any technology that operates at the nanoscale and has practical applications, such as using individual atoms and molecules to create functional structures, is referred to as nanotechnology.[2] The synthesis and application of chemical, physical, and biological systems with structural characteristics ranging from single atoms or molecules to submicron dimensions, as well as the integration of the resulting nanostructures into larger systems, are all included in the topic of nanotechnology [3], [4]. "Technology on the nanoscale" is the most basic definition of nanotechnology. As a result, different definitions of nanotechnology have developed. This initial definition has to be expanded upon, for example, by defining what is meant by "nanoscale." Therefore, without defining "nanoscale," or a scale encompassing 1–100 nm, we are unable to adequately define nanotechnology. Nanotechnology can be defined as "atomically precise technology" or "engineering with atomic precision." [5].

1.2 Nanoparticle

Microscopic objects with at least one dimension smaller than 100 nm are called nanoparticles.[6] The medication is encapsulated, dissolved, trapped, or affixed to a matrix of nanoparticles. Nanoparticles, nanospheres, or nanocapsules can be produced, depending on the preparation technique. [7] Nanoparticles frequently have unique size-dependent characteristics because of their comparatively huge surface area. [8]. Furthermore, a nanoscale particle is shorter than either the wavelength of light or the de Broglie wavelength of the charge carrier (holes and

electrons). Therefore, the periodic boundary conditions of crystalline particles disappear at that length. Because of this, the physical characteristics of nanoparticles differ significantly from those of bulk materials, leading to novel and intriguing applications. For instance, drug molecules are delivered by injecting nanoparticles into matrix materials.[9,10]

1.3 Nanogel

Polymer nanoparticles having three-dimensional networks, known as nanosize hydrogels or nanogels, are created when polymer chains are cross-linked chemically or physically.[11] A variety of synthetic and natural polymers, or mixtures of them, make up nanogels, which aid in the encapsulation of proteins, oligonucleotides, and tiny molecules.[12] The nanosized particles created by chemically or physically crosslinked polymer networks that expand in a suitable solvent are referred to as "nanogels." Cross-linked bifunctional networks of a polyion and a nonionic polymer for the transport of polynucleotides were initially referred to as "nanogel." [13] Although they have different characteristics from linear macromolecules with comparable molecular weights, they are soluble in water. These structures and their larger counterparts.[14] Hydrophilic or amphiphilic polymer chains, which can be ionic or non-ionic, swell into nanoscale networks to form nanogels. Nanogels have been studied for a longer time to make various agents such as quantum dots, dyes, and other diagnostic agents, in addition to drug delivery. [15] The expectation of particular delivery systems has led to the importance of nano-sized hydrogel and microgel. A wide range of polymer systems and the ease with which their physico-chemical properties can be changed have made nanogel compositions flexible.

[16] As nanoscopic drug carriers, nanogels have garnered a lot of interest, especially for the site-



specific or time-controlled administration of bioactive mediators. Multipurpose forms of nanogel preparations have been made possible by a wide variety of polymer systems and the straightforward alteration of their physico-chemical characteristics.[17]

1.4 Drug Delivery System

New therapeutic compound development is costly and time-consuming. Numerous strategies, including dose titration, individualized medication therapy, and therapeutic drug monitoring, have been tried to improve the safety efficacy ratio of "old" pharmaceuticals. Other extremely appealing approaches that have been actively studied include targeted delivery, gradual delivery, and controlled medication delivery. It's interesting to note that Indian researchers have written a significant amount of work and numerous publications from the United States and Europe.[18,19,20] One of the most important projects of the twenty-first century is the development of drugs that target particular organs and tissues. One of the frontier areas that requires a comprehensive scientific approach to provide significant advancements in enhancing therapeutic index and bioavailability at site-specific administration is the search for novel drug delivery strategies and novel mechanisms of action.[21,22,23,24]

In pharmacological and biomedical research, the most frequently mentioned kinds of nanogels include:

1. Natural nanogels
2. Synthetic nanogels
3. Physically cross-linked nanogels
4. Chemically cross-linked nanogels

5. Stimuli-responsive nanogels (pH-, temperature-, redox-, photo-, enzyme-responsive)
6. Core-shell and hybrid nanogels.

2. Classification of Nanogels based upon polymers

Polysaccharide-based nanogel

Polysaccharides like chitosan, sodium alginate, sodium hyaluronate, chondroitin, and cyclodextrin are used to create nanogels with oppositely charged polymers by intermolecular electrostatic interaction that produces ionic complexes. Nanogels having this characteristic can be used to sense and account for physiological pH variations.[25] Hydrophilic polysaccharides are modified by hydrophobic groups. Amphiphilic polymers are also used to create nanogels in an aqueous setting. [26]

Chitosan-based nanogel

Chitosan is a promising alternative for creating chitosan-based nanogels using oil-in-water lipid emulsion technology because of its ability to increase emulsion stability and prevent coalescence via steric and electrostatic mechanisms. Notably, chitosan eliminates the requirement for proteins or surfactants. Highly stable matrices could be created by chemically crosslinking chitosan nanogels. Certain chitosan nanogels were produced by reactions with bi-functional agents, such as di-isocyanate, di-epoxy compounds, dialdehyde, and glutaraldehyde.[27] employing genipin as a crosslinking agent to create chitosan nanogels via reverse microemulsion for use in biomedical applications.[28] Pullulan-based nanogel Pullulan-based nanogels that have been treated with cholesterol to produce functional groups may



be a useful tool. The pullulan backbone has been linked to several functional categories in different investigations. These consist of urocanic acid, acryloyl groups, and tricarboxylate..[29] The size and density of the pullulan-based hydrogel nanoparticles were associated with the amount of cholesterol that replaced the hydrophobic moiety. The nanogels, which are extremely durable and efficient in reducing protein side effects by, among other things, preventing aggregation and shielding against enzymatic degradation, were made from self-associating hydrophilic polymers.[30,31] Nanogel based on hyaluronic acid Animal-derived polysaccharide HA has advantageous properties that make it a good choice for creating nanogels. These characteristics, which may be related to its particular glucuronic acid and N-acetylglucosamine composition, include biocompatibility, mucoadhesion, and non-immunogenicity. It's also important to remember that HA has a high level of bioactivity, mostly due to its distinct binding to particular cell receptors. The most well-known of these receptors is CD44 (cell surface adhesion receptor 44).[32]

Alginate-based nanogel

Alginate is a polysaccharide that contains alternating blocks of alpha guluronic and beta mannuronic acid residues. Alginate's highly reactive groups (OH, COOH) make it chemically susceptible to oxidation, amidation, esterification, and sulfation. Chemical modifications can regulate solubility and lipophilicity, increasing the range of potential applications. Alginate nanogels can shield the proteins during oral administration even though they are infamously unstable in the stomach's acidic environment. [33]

Cyclodextrin-based nanogel

Biologically compatible cyclic structured oligosaccharides comprising D-glucopyranose

units connected by α -1,4 glycosidic linkages are known as cyclodextrins.[32]. The nanogels absorbed the hydrophobic phenolphthalein quite well. [34]

Gum acacia-based nanogel

The biological source of gum acacia, often known as arabic gum, is *Acacia nilotica*. It was used to make microparticles and nanoparticles. This polysaccharide's excellent water solubility, biocompatibility, and low cost are its main benefits for this application. To create nanogels, gum acacia was mixed with polysaccharides like alginate and chitosan or proteins like gelatine.[35]

3. Why Nanogels?

Nanogels are employed because they effectively address a number of major issues that traditional medication delivery methods are unable to. The primary causes are:

The medicine is delivered gradually over time rather than all at once thanks to nanogels' controlled and sustained drug release. This lessens adverse effects and increases treatment efficacy.

They can load a wide range of medications, including poorly soluble pharmaceuticals, proteins, and DNA, thanks to their porous network structure and extremely large surface area.

Nanogels can safely interact with biological systems and decompose without producing long-term harm since they are biocompatible and biodegradable.

They can be made to be stimuli-responsive systems (pH, temperature, enzyme, or redox-sensitive), which implies that medications are only released at the intended location, such a tumor or inflammatory tissue. This lessens harm to healthy cells and enhances targeting.



Their tiny size improves medication availability at the site of action by enabling better penetration through biological barriers, such as tissues and occasionally cellular membranes.

Lastly, because they may be created from synthetic or natural polymers and altered for a variety of medicinal uses, including protein transport, gene delivery, and cancer treatment, nanogels are incredibly adaptable.

4. Formulations of nanogel

1. PEG–PEI Nanogel (2003)

Formulation-Polyethylene glycol (PEG), Polyethyleneimine (PEI), Antisense oligonucleotide [36]

2. CHP Nanogel (2004)

Formulation-Pullulan, Cholesteryl groups [37]

3. Nanogel–Quantum Dot Hybrid (2005)

Formulation-CHP nanogel Quantum dots [38]

4. IL-12 Loaded Nanogel (2008)

Formulation-CHP nanogel, Interleukin-12 [39]

5. pH-Responsive Nanogel (2011)

Formulation-pH-responsive polymer network, Hydrophobic/cationic drugs [40]

6. Ophthalmic Nanogel (2013)

Formulation-Polyvinylpyrrolidone (PVP), Poly (acrylic acid), Pilocarpine [41]

7. Vaccine Delivery Nanogel (2014)

Formulation-P(HEMA-co-MAA), Surface modifiers [42]

8. Gelatin Nanogel (2016)

Formulation-Gelatin nanoparticles, HPMC gel, Tenofovir [43]

9. Theranostic Nanogel (2018)

Formulation-Fluorescent polymeric nanogel, Imaging agent [44]

10. Controlled Release Nanogel (2020)

Formulation-Stimuli-responsive polymer, Drug-loaded nanogel network [45]

11. Herbal Nanogel (2023)

Formulation-*Beta vulgaris* extract, Polymeric nanogel matrix [46]

12. Propranolol Chitosan Nanogel (2024)

Formulation-Chitosan, TPP, Propranolol [47]

13. Advanced Multifunctional Nanogels (2025–2026)

Formulation-Stimuli-responsive polymer, Targeting ligand, Imaging probe, Therapeutic payload [48].

5. Significance of Nanogel

The primary significance lies in the nanogel's high degree of drug loading capacity, biocompatibility, and biodegradability, improved therapeutic stability, decreased side effects, and improved permeation capabilities due to its smaller size—all of which are essential for creating an effective drug delivery system. The new drug delivery methods for both hydrophilic and hydrophobic medications are called nanogels.[49,50]

6. Applications of nanogel

Applications in cancer therapy



Doxorubicin, cisplatin, 5-fluorouracil, temozolomide, heparin, and other medications are incorporated into nanogels to treat cancer. Doxorubicin-loaded nanogels, such as pH- and temperature-responsive nanogels in the presence of maleic acid poly-(N-isopropylacrylamide) polymer, are widely employed in cancer treatment formulations where doxorubicin is released at a particular pH and temperature. Prostate, breast, lung, and liver cancers are treated using chitin-polymerized doxorubicin nanogels.[51]

Applications of nanogels in gene delivery, enzymology, and protein folding

Additionally, proteins, enzymes, and genes can be delivered to a specific location using nanogel formulations. One technique for delivering various proteins and enzymes is the artificial chaperon. The artificial chaperon approach uses modified polymers. Different nanogel formulations are employed in gene delivery methods, protein folding, and enzymology.

Nanogel applications in gastrointestinal disorder

Additionally, conjugated nanogels or other nanogel formulations are employed to treat gastrointestinal diseases. [52]

Marketed formulations

There are numerous nanogel formulations on the market. A number of tooth paste formulations that lessen tooth decay issues are accessible, the majority of marketed formulations are cosmetic cures, and a number of formulations are personal care items that are frequently used for skin care issues..

Limitations of nanogel

- a) Nanogels exhibit poor drug release regulation and a low drug loading efficiency. [53].
- b) Occasionally, a strong drug-polymer interaction reduces the hydrophilicity of the nanogels and causes the structure to collapse, permanently trapping the drug molecules and increasing the hydrophilicity of the nanogel matrix. [54,55].
- c) The presence of monomers or surfactants in nano gel may have negative impacts on the formulation. [56]

CONCLUSION

A particularly promising class of nanoscale drug delivery methods, nanogels bridge the gap between traditional hydrogel systems and cutting-edge treatments based on nanotechnology. A variety of therapeutic agents, including as proteins, genes, tiny medication molecules, and bioactive natural chemicals, can be effectively encapsulated in their special three-dimensional, cross-linked polymeric network, which also provides regulated and sustained release patterns. Because of their adaptability, nanogels made from synthetic, natural, and hybrid polymers can have adjustable physicochemical characteristics, which makes them appropriate for a variety of biological uses.

The potential for site-specific and targeted drug administration has been greatly increased by recent advancements in stimuli-responsive and multifunctional nanogels, especially in complicated disease states like cancer, gastrointestinal disorders, and genetic diseases. To ensure safe and successful clinical translation, issues such restricted drug-loading efficiency in some systems, probable polymer–drug interactions, and potential formulation-related toxicity still need to be addressed, despite their many benefits.



Overall, it is anticipated that continued study and technical developments in nanogel formulation and design will get over current constraints and enhance their functionality. By enabling more accurate, effective, and patient-friendly therapeutic approaches, nanogels are expected to play a significant role in the future of nanomedicine and ultimately improve clinical outcomes in contemporary healthcare.

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