International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

# Nanogels: "A Miniature Marvel in Drug Delivery and Beyond"

Athira Florence[1*], Mathan S[2], Shaiju S Dharan[3], Praji SP[4], Shiji SP[4], Tigna Paul PB[4]

*M.Pharm[1*], Department ofPharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala, India, 695124.*

*Professor and HOD[2], Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala, India, 695124.*

*Professor and HOI[3], Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala, India, 695124.*

*M.Pharm[4], Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala, India, 695124.*

Date of Submission: 01-11-2024 Date of Acceptance: 10-11-2024

**ABSTRACT**

Nanogels, a class of nanoparticles composed of cross-linked polymer networks, have emerged as a promising tool in drug delivery and various other biomedical applications. Their miniature size, typically ranging from 10 to 200 nanometers, enables precise control over drug release kinetics, biodistribution, and targeting. Nanogels offer several advantages, including high loading capacity for drugs, proteins, and nucleic acids, as well as protection of encapsulated payloads from degradation. Moreover, their tunable physicochemical properties allow customization for specific therapeutic needs, such as pH or temperature responsiveness. Beyond drug delivery, nanogels hold potential in tissue engineering, diagnostics, and theranostics. This abstract highlights the remarkable versatility and potential of nanogels as miniature marvels poised to revolutionize biomedical science and healthcare.

**KEYWORDS:** Nanogels, cross-linked polymer networks, miniature size, high loading capacity.

## I. INTRODUCTION

Nanotechnology, an innovative methodology, presents vast opportunities for intelligent drug delivery and nanomedicine, encompassing the design, synthesis, and characterization of materials or molecules and devices with functional efficacy at the nanometer scale. This approach primarily emphasizes radical advancements in existing therapeutic and diagnostic methodologies.[1]Theemergence of novel nano-scaled particulate drug delivery systems (DDS) has effectively tackled obstacles by enhancing drug absorption, mitigating drug toxicity, regulating dose release, and curtailing biodegradation.The utilization of nanotechnology in medicine has led to the development of customized nanoparticles capable of encapsulating pharmaceutical agents or genetic material, which can then be precisely delivered to targeted regions of the body via a regulated mechanism.[2]The term "Nano-gel" denotes a nanoparticle hydrogel featuring a cross-linked hydrophilic polymer matrixhave a typical dimension of approximately 100 nanometers. Nano-gels are diminutive, swollen entities composed of pliable hydrophilic or amphiphilic polymer matrices that are physically or chemically interconnected. These polymer matrices may possess anionic or ionic attributes. They function as carriers for pharmaceutical agents and are engineered to readily assimilate biologically active substances through the establishment of bio molecular interactions like salt bonds, hydrophobic interactions, or hydrogen bonding. They are meticulously crafted to facilitate the encapsulation of a diverse array of biomolecules by refining molecular composition, size, and morphology to ensure precise control over drug release within living organisms.[3] They possess a substantial water content, an expansive specific surface area, and excellent stability. Nanogel-based platforms are precisely engineered to prolong the cargo's circulation half-life within the body and facilitate its targeted delivery to desired sites in biomedical applications.[4],[5]When nanogels disperse in the aqueous solution, their expanded networks soften and have the capability to encapsulate a specified amount of water.Preferred biological or pharmaceutical compounds can be encapsulated within nanogels through the facilitation of spontaneous interactions between the polymer matrix and the agents, leading to the creation of

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

finely dispersed hydrophilic particles. This resultant architecture offers substantial physical shielding to the encapsulated biomolecules, safeguarding them from degradation. Consequently, nanogelsrepresent a versatile platform for both the encapsulation of drugs and their controlled release at specific target sites. [6],[7]

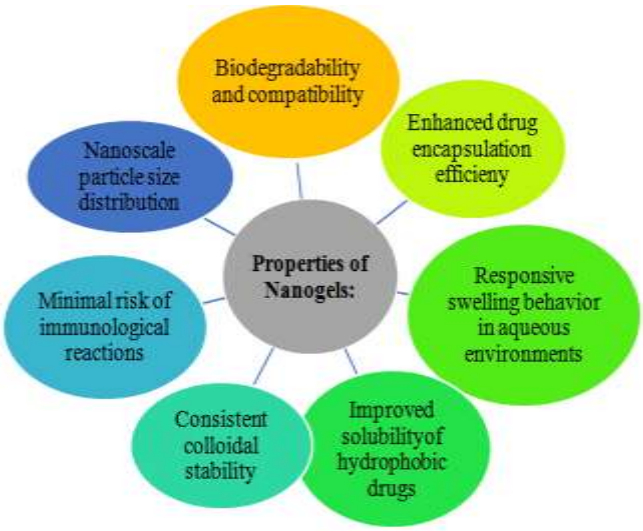


Figure 1: Properties of Nanogels[8]

**Benefits of Nanogel-based Drug Delivery Strategy**

- Provides shielding against drug degradation within the body.
- Allows simple and precise adjustment of nanogel size to match the specific delivery requirements.
- Decreases the required drug dosage and frequency of administration.
- Enhances drug bioavailability and mitigates drug toxicity.
- Enables safe and effective delivery of drugs encapsulated within nanogels, with minimal or no adverse effects, both systemically and topically.
- Facilitates crossing of physiological barriers such as the blood-brain barrier and skin barrier.
- Nanogels elicit no immunological responses due to their inert nature within the bloodstream and internal aqueous context.[9]

**Limitations of Nanogel:**

- Expensive methodologies are necessary to fully eliminate solvents and surfactants at the conclusion of the process.
- Residual surfactants may sporadically induce toxicity.
- Scaling up isn't straightforward due to average size and mass.
- Nanogels exhibit restricted drug-loading capability and inadequate control over drug release. [10]

**DRUG LOADING IN NANOGELS**

Nanogel drug delivery systems have proven to be effective strategies owing to their impressive drug encapsulation ability and minimal carrier numbers; listed below are a few examples of such approaches.

Chemical Bonding:Nanostructures within biological agents can be formed through chemical bonding i.e. covalent bond. Acrylic units are aligned with enzymes and polymerized alongside acrylamide in a dilute aqueous solution or a reverse micro emulsion to generate nanoscale hydrogels. The inclusion of lipophilic compounds into nonpolar regions led to the creation of a lipophilic sequence, which is present in certain nanostructures. For instance, prostaglandin E2 dissolves readily in pullulan modified with cholesterol. Another illustration involves N – hexyl carbamoyl – 5 – fluorocil incorporated non-covalently into NIPAAM & N – vinylpyrrolidone copolymer cross-linkednanostructures. Doxorubicin was also encapsulated within pluronicF127-based amphiphilic cross-linked

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

nanostructures. The hydrophobic interaction typically leads to relatively modest levels of drug encapsulation within the nanostructure (in most instances, below 10%).[[11],[12]]

Auto-assembly: Involves the autonomous organization of components into well-defined structures, offering advantages such as minimal energy consumption, adaptability, simplicity, and cost-effectiveness. Many-molecule self-assembly relies on non-covalent interactions like diffusion, hydrophobicity, or electrostatics. Despite its weak nature due to numerous interactions, self-assembly governs the structural and conformational aspects of assembly. Electrostatic attractions and interactions between oppositely charged polysaccharides can disrupt self-assembly, but chemical modification may induce it. Highly water-soluble polysaccharides can form nanoparticles through hydrophobic interactions. Amphiphilic polymers, with hydrophilic and hydrophobic components, exhibit three forms: grafted polymers, polymers with alternating hydrophilic-hydrophobic segments, and block polymers. In water, these polymers self-aggregate into nanoparticles to minimize interfacial energy, with hydrophobic sections forming the core and hydrophilic parts exposed to the aqueous environment. The critical micelle concentration, or the concentration at which polymer chains aggregate, plays a crucial role in this process.[[13]]

## DRUG RELEASE FROM NANOGEL

The release of drugs is influenced not only by the physicochemical characteristics of the nanogels but also by the manner in which active ingredients are encapsulated within them.When it comes to nanogels, mechanisms governing drug release can be classified as[[14]]:

i. Swelling-Mediated
ii. Diffusion-Mediated
iii. Chemically-Mediated

Macromolecular therapeutics are frequently enclosed within nanogels through physical encapsulation. In such instances, once the nanogels swell, the drug can diffuse provided the mesh size permits. Essentially, the release characteristics primarily hinge on the mesh sizes embedded within the nanogel matrix.[[15]]

The most basic mechanism involves diffusive liberation, a process utilized in clinical applications of nanomedical techniques. Upon physiological or chemical breakdown of the nanogel structure, medications can also be liberated.As an illustration, the release of doxorubicin from pH-responsive nanogels was significantly hastened at lower pH levels, thereby augmenting the uptake of the drug by non-small cell lung cancer cells within a mildly acidic pH milieu.Moreover, substances that are sensitive to different environmental stimuli can also be discharged through nanogels.[[16]]

Reactive oxygen species interact with platinum nanoparticles embedded in a nanogel matrix, influencing both their catalytic activity and the protonation of acidic core polymers (2 – (N, N –diethyl amino) and PEG. The polymers, composed of methacrylic acid and ethyl acrylate, form insoluble 3D structures under acidic conditions. However, as the pH increases, the acidic groups within the polymers undergo ionization due to repulsions between polymeric chains. This leads to a distinct release profile of procaine hydrochloride.[[17]]

As a result of the temperature retention surpassing the lower critical solution temperature, polymers possessing thermo sensitive characteristics, such as poly(N-isopropyl acrylamide), induce initial contractions in gel volume and the efflux of indomethacin. Owing to its capability for release at body temperature despite being stored at low temperatures, the polymer (N-isopropyl acrylamide-co-acrylamide) combined with 5-fluorouracil demonstrates favorable outcomes in rats.[[18]]

## CLASSIFICATION OF NANOGELS

1. Structure based nanogels
2. Linkage based nanogels
3. Polymer basednanogels
4. Stimuli basednanogels

### Structure Based Nanogels:

According to the structure, nanogels are categorized into 4;

i. **Hollow Nanogels:**Nanogels containing a void within their gel structure display an enhanced surface area in contrast to traditional nanogels. This provides precise targeting at specific sites. Moreover, the increased surface area might enhance the drug-carrying capability of the nanogel structure. The synthesis of hollow nanogels, utilizing Poly (N, N-dimethyl amino ethyl methacrylate) co-polymer, resulted in superior drug loading capacity compared to a hybrid hollow nanogel. [[19]]The uniform dispersion of the drug within the polymer

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

crevices, facilitated by its hollow structure, could account for this. Additionally, it might augment drug liberation from the polymer matrix by increasing free energy.

ii. **Multi-Layered Nanogels:** These nanogels primarily consist of numerous layers of either a singular polymer or multiple polymers. The choice of polymer is crucial for achieving precise targeting. The sequence of polymers utilized in fabricating multi-layered nanogels substantially impacts the pattern of drug release. Substances that are exceedingly toxic or particularly vulnerable to bodily fluids can be administered using this method.For aiming at potent or drugs with a narrow therapeutic index, these nanogels may offer significant advantages due to their adjustability, enabling precise targeting compared to alternative nanogels. Nevertheless, the fundamental challenge lies in the complexity of the process, yield, scalability, and expenses associated with their development, hindering their transition into clinical research. Additionally, they demonstrate utility in transporting peptides, oligopeptides, and nucleotides to the intended site of action.[[20]]

iii. **Core Shell Nanogels:** These nanogels serve as the progenitors of nanogels when structural classification is employed.They are designed to gradually release the medication through surface degradation mechanism. Drug incorporation takes place on the core-shell creating component through surface adsorption, ionic bonding, or covalent bonding. These nanogels were synthesized to enhance biocompatibility, prolong drug release, and impart thermo-responsiveness.[[21]]

iv. **Hairy nanogels:** The nanogels consist of slender filamentous extensions on their surface. These are synthesized employing regulated radical polymerization or macro-RAFT (reversible addition fragmentation) agents. These filamentous extensions are generated by the polymers that are subsequently covalently bonded to the central gel matrix.[[22]]

**Linkage Based Nanogels:**

According to the linkage, nanogels are categorized into 2;

i. **Non-Covalent Linkage:** This involves spontaneous self-assembly through physical interactions without the need for any cross-linking agents.[[23]]Interactions at the surface/interface, Van der Waals attractions, adsorption, ionic bonding, etc., act as fundamental mechanisms for non-covalent connections. They possess specific advantages such as reversibility, lack of chemical reactions, and potential avoidance of detrimental bioactive agents or cells. However, their stability is compromised due to frail connections.[[24]]

ii. **Covalent Linkage:**Covalent bonding entails the formation of firm covalent bonds through exact stoichiometric reactions to yield steadfast and consistent connections. This process illuminates the components, empowering them to adapt to the environment while facilitating controlled release.[[25]]

**Polymer Based Nanogels:**

Polyethers and polyesters are compostable polymers formed from monomers linked by ether and ester bonds. Polyethylene glycol (PEG) is a widely used polyether known for its biocompatibility and water solubility, making it a standard in drug delivery. PEG prolongs circulation time by reducing endocytosis, phagocytosis, hepatic uptake, and clearance. Poloxamers, which are block copolymers, comprise two hydrophilic polyethylene oxide chains and one hydrophobic polypropylene oxide chain. The commercialized variant, Pluronic™, is available in various grades distinguished by polymer block lengths.[[26],[27],[28]]

Polyacrylates arise from acrylic acid modifications, resulting from changes in vinyl and/or carboxyl hydrogen atoms. Under particular temperature, charge, and pH circumstances, these polymers exhibit proton donation and assume a negative charge. They experience swelling as counter ions exchange with the surrounding environment.[[29]]

Peptide chains, known as amide polymers, are biodegradable macromolecules linked by amide bonds. They are useful for delivering small molecules due to their customizable amino acid sequences. Common examples include poly(glutamic acid), poly(aspartic acid), and poly(L-lysine). However, controlling release is challenging due to their susceptibility to hydrolysis and enzyme-driven degradation, influenced by the

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

hydrophilic nature of their amino acids. Modifying the biodegradation process is possible by incorporating benzyl, hydroxyl, or methyl groups during polymerization.[[30]]

Polysaccharides are macromolecules formed by linking long chains of monosaccharide units via glycosidic bonds. When these units are identical, they are classified as homo-oligomers (e.g., starch, cellulose, pullulan, etc.), whereas if they vary, they are referred to as hetero-oligomers (e.g., heparin, chitosan, hyaluronic acid, and dermatan sulfate).[[31], [32], [33]]Polysaccharides from various sources have reactive clusters like -OH, -NH2, and -COOH. They can be chemically modified to create diverse derivatives with different structures and functions. These molecules are abundant in nature, and they are biocompatible, biodegradable, non-toxic, water-soluble, and bioactive.[[34],[35]]

**Stimuli Based Nanogels:**

Depending on their reaction to stimuli, nanogels are categorized into 2;

**Responsive nanogels** exhibit changes in their physicochemical characteristics such as structural composition and matrix integrity, consequently initiating the release upon exposure to external stimuli.

**Non-responsive nanogels** liberate the medication regardless of the external stimuli.

Temperature triggers drug release through temperature-responsive polymers with a specific temperature point known as VPTT. This causes changes in polymer structure and release patterns. Polymers sensitive to stimuli undergo phase transitions when stimulated externally, with categories like Van der Waals, hydrophobic, hydrogen bonding, and attractive interactions. [[36]]

The temperature below which the polymer dissolves is the Lower critical solution temperature (LCST), whereas above it, the polymer undergoes a phase change from a dissolved (random coil state) to an insoluble (collapsed state) state.[[37]]Temperature and solubility have an inverse relationship, so nanogels are called negative temperature-responsive. Polymers dissolve at the Upper Critical Solution Temperature (UCST), showing positive thermo sensitivity because solubility increases with temperature.

## APPROACHES FOR NANOGEL SYNTHESIS

**Solvent Evaporation Technique**

For a duration of two hours, the blend of drug and polymer is administered into the specified region of the liquid phase by continuous agitation at 1000 rotations per minute, aided by a magnetic stirrer.[[38]]The nanosponges acquired consequently undergo filtration, followed by a drying procedure in a hot air oven set at a temperature of 40°C for 24 hours.[[39]]Ultimately, the desiccated nanosponges are delicately relocated into vials for preservation. For uniform distribution, it is advisable to submerge the polymer in water for a duration of 2 hours prior to commencing gel formation.[[40]]Afterward, the polymer needs to undergo agitation at a rotational velocity of 6000 rpm. The pH is adjusted using a pH-modifying substance. Following this, the aqueous dispersion is blended with the finely-tuned nanosponge suspension and permeation boosters.[[41],[42]]

**Emulsion Solvent Diffusion Technique**

The drug's aqueous solution is emulsified within an organic layer. Polymer and gelling agent are dissolved in aqueous medium to create the drug phase, which is slowly added to the organic phase and homogenized for 30 minutes at 6000 rpm. Emulsification of an oil/water emulsion into nanodroplets is achieved through homogenization using a homogenizer.[[43]]The nanogel is formed by incorporating Triethanolamine into the oil-in-water emulsion, which is then stirred constantly for one hour at a speed of 8000 rotations per minute.[[44]]

**Nano Precipitation Technique**

When the mixture of medication and polymer in the organic phase interacted with the surfactant aqueous layer, the polymer underwent precipitation. Subsequently, upon eliminating surplus solvent, polymeric nanoparticles remained.[[45]]After moistening the particles, a gelling agent and appropriate quantities of nanoparticle dispersion are introduced, with pH stabilization achieved through the application of Triethanolamine.[[46]]

**Modified Diffusion Emulsification Technique**

A mixture of the medication and a polymer, in a carefully measured proportion, is blended together. This blending occurs within the aqueous phase, where the drug-polymer combination is constantly stirred at a rotational speed ranging from 5000 to 10,000 rpm, resulting

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

in the formation of the organic phase.[[47]]A needle-equipped syringe administers the organic phase into the stabilizing aqueous solution at a pace of 0.5 mL every minute. Following agitation for six minutes at a rotational speed between 10,000 and 25,000 rpm, the mixture undergoes sonication for a duration of five to ten minutes.[[48]]

**Reverse Micellar Technique**

A polymer, drug, and emulsifier are dissolved in an organic solvent. Following the addition of the cross-linking agent, it necessitates inclusion over an extended duration overnight. Once the nanoparticles have been purified, the solvent is removed through evaporation, resulting in a desiccated mass.[[49]],[[50]]The nanogel was formed through the dissolution of the gelling agent in water. When nanoparticles are mixed with an aqueous solution containing a gelling agent, nanogel is produced. The pH is altered by the addition of a neutralizing agent.[[51]]

## EXPLORATION OF NANOGEL APPLICATIONS

**Utilizing Nanogel for NSAIDs**

Carbopol and Methylcellulose (MC) formulated nanogels mimicking chitosan and PLGA bilayered nanoparticles with oleic acid. These nanogels carried anti-inflammatory drugs, spantide II and ketoprofen, for allergic contact dermatitis and psoriatic plaque. Topical application showed enhanced drug absorption into deeper skin layers, promising for treating inflammatory skin conditions.[[52]]

**Enhancing Antimicrobial Efficacy through Nanogels**

Nanoparticles aid in augmenting the permeability rate within cells and boosting drug retention within the bacterial cell membrane, resulting in heightened antimicrobial efficacy. A study noted an improvement in the antimicrobial capacity of berberine.[[53]]

**Nanogel for Autoimmune Disorders**

Cyclodextrin helped encapsulate mycophenolic acid in liposomes with PEG oligomers and a photo initiator. UV light triggered polymerization of PEG oligomers. Nanogels showed better accumulation in the body, binding to immune cells, boosting mycophenolic acid concentrations. This delivery method improves patient compliance and slows kidney damage in lupus.[[54]]

**Utilizing Nanogel for Stopping Bleeding**

A protein compound designed for Nanogel synthesis has proven effective in halting bleeding even in deep lacerations. These proteins possess a nanoscopic self-organization process enabling the creation of a biodegradable gel.[[55]]

**Ophthalmic Nanogel Formulation**

The PVP/PAAc Nanogel is synthesized through radiation-triggered polymerization of polyvinyl pyrrolidone-poly(acrylic acid) nanogel, enabling the sustained localization of pilocarpine at the intended site for an extended duration.[[56]]

**Nanogel for Nasal Drug Delivery**

Nanogel pharmaceutical distribution systems possess great promise in overcoming several obstacles in delivery. Nanogels are effectively absorbed by nasal mucosa and thus, could serve as effective conduits and delivery mechanisms for medication through nasal passages. Utilizing nanogels for vaccine distribution via the nasal route represents a novel strategy to manage disease progression.[[57]]

**Nanogel as Carrier for Antifungal Agents**

In cases of fungal infections, the preferred route for both physicians and patients is primarily the topical method. A chitin-fluconazole nanogel was formulated through innovative chemistry reconstruction and thus the wet-edge approach. Nanogels derived from polysaccharides were reinvented from a polysaccharide solution. This chitin-fluconazole nanogel exhibits a controlled release pattern, which is optimal for sustained fluconazole availability over an extended period, ensuring effective treatment against fungi.[[58]]

**Nanogel for Anticancer Therapy**

Numerous composite nanogels are employed in cancer therapy. Embedding chemotherapeutic agents within the nanogel not only enhances bioavailability but also augments permeability and retention.[[59]]The uptake of Doxorubicin was accelerated by grafting Glycol chitosan with a pH-responsive mechanism and incorporating 3-diethyl amino propyl groups.[[60]]

Nanogels are increasingly utilized for more efficient medication delivery in cancer treatment. A polymeric nanogel approved by the

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 232-241 www.ijprajournal.com ISSN: 2456-4494

FDA for breast cancer patients is Genexol-PM [[61]]

**Nanogels for Diabetics**

A newly created Nano-Network, injectable and responsive to aldohexose, has been engineered. It comprises a blend of countercharged nanoparticles that mutually attract, maintaining gel integrity and preventing nanoparticle dispersion within the body. In vivo trials conducted on diabetic rats in 2012 revealed that nanogels laden with insulin reduced glucose levels by fifty-one percent from baseline for nearly two hours. Remarkably, compared to free insulin, these insulin-loaded nanogels effectively stabilized glucose levels, mitigating fluctuations in sugar levels. [[62]]

## II. SUMMARY AND OUTLOOK ON THE FUTURE OF NANOGELS

Nanogels, versatile nanoscale structures composed of cross-linked polymer networks, have emerged as promising platforms in various fields such as drug delivery, tissue engineering, and diagnostics. Their unique properties, including high water content, tunable size, and stimuli-responsive behavior, make them attractive candidates for targeted drug delivery and controlled release applications. Moreover, advancements in synthesis techniques and the exploration of novel materials have facilitated the development of nanogels with enhanced stability, biocompatibility, and functionality.Looking ahead, the future of nanogels appears bright with numerous opportunities and challenges. Continued research efforts are expected to focus on optimizing nanogel properties for specific applications, such as improving drug loading capacity, achieving targeted delivery to diseased tissues, and enhancing biodegradability for reduced toxicity. Additionally, the integration of nanogels with other nanotechnologies, such as imaging agents and therapeutics, holds promise for advancing personalized medicine and diagnostics.Nanogels represent a rapidly evolving field with significant potential to revolutionize drug delivery and biomedical technology. With ongoing research and technological advancements, nanogels are poised to play a pivotal role in addressing key healthcare challenges and improving patient outcomes in the future.

## REFERENCE

[1]. Tawade PV, Wasewar KL. Nanotechnology in biological science and engineering. InEnvironmental Applications of Microbial Nanotechnology. 2023; 43-64.

[2]. Pei J, Yan Y, Jayaraman S, Rajagopal P, Natarajan PM, Umapathy VR, Gopathy S, Roy JR, Sadagopan JC, Thalamati D, Palanisamy CP. A review on advancements in the application of starch-based nanomaterials in biomedicine: Precision drug delivery and cancer therapy. International Journal of Biological Macromolecules. 2024; 130746.

[3]. Kumi M, Ejeromedoghene O, Wellington SD, Zhang Z. Unlocking the biological response of smart Stimuli-Responsive hydrogels and their application in biological systems. European Polymer Journal. 2024:112906.

[4]. Ayoubi-Joshaghani MH, Seidi K, Azizi M, Jaymand M, Javaheri T, Jahanban-Esfahlan R, Hamblin MR. Potential applications of advanced Nano/hydrogels in biomedicine: static, dynamic, multi-stage, and bioinspired. Advanced Functional Materials. 2020;30(45):2004098.

[5]. Abedi F, Ghandforoushan P, Adeli F, Yousefnezhad M, Mohammadi A, Moghaddam SV, Davaran S. Development of stimuli-responsive nanogels as drug carriers and their biomedical application in 3D printing. Materials Today Chemistry. 2023;29:101372.

[6]. Altuntaş E, Özkan B, Güngör S, Özsoy Y. Biopolymer-based nanogel approach in drug delivery: basic concept and current developments. Pharmaceutics. 2023;15(6):1644.

[7]. Ma B, Li Q, Mi Y, Zhang J, Tan W, Guo Z. pH-responsive nanogels with enhanced antioxidant and antitumor activities on drug delivery and smart drug release. International Journal of Biological Macromolecules. 2024;257:128590.

[8]. Duan QY, Zhu YX, Jia HR, Wang SH, Wu FG. Nanogels: Synthesis, properties, and recent biomedical applications. Progress in Materials Science. 2023; 101167.

[9]. Hoque M, Saha SN, Akram T. Nanogels Based Drug Delivery System: A Promising Therapeutic Strategy.

International Journal of Pharmaceutical Sciences. 2023;1(10):1.

[10]. Ghaywat SD, Mate PS, Parsutkar YM, Chandimeshram AD, Umekar MJ. Overview of nanogel and its applications. GSC Biological and Pharmaceutical Sciences. 2021; 16(1):040-61.

[11]. Rajput D, Singh M, Sahu P, Jain D, Kashaw SK, Patil UK. Advances in Nanogel as Drug Delivery System for Cancer Therapeutics: An Overview. Mini Reviews in Medicinal Chemistry. 2023;23(21):2053-72.

[12]. Li F, Chen X, He Y, Peng Z. Mucoadhesive Thiolated Hyaluronic Acid/Pluronic F127 Nanogel Formation via Thiol–Maleimide Click Reaction for Intravesical Drug Delivery. ACS Applied Bio Materials. 2024; 7(3):1976–1989.

[13]. Vardaxi A, Forys A, Trzebicka B, Pispas S. Nanogel-type nano-objects from a random polyelectrolyte through intermolecular cross-linking. Nano-Structures & Nano-Objects. 2024;38:101122.

[14]. Yuniarsih N, Chaerunisaa AY, Elamin KM, Wathoni N. Polymeric Nanohydrogel in Topical Drug Delivery System. International Journal of Nanomedicine. 2024:2733-54.

[15]. Yabuuchi K, Katsumata T, Shimoboji T, Hashimoto Y, Kimura T, Akiyoshi K, Kishida A. Variable swelling behavior of and drug encapsulation in a maleimide-modified hyaluronic acid nanogel-based hydrogel. Polymer Journal. 2024; 1-1.

[16]. Rohtagi P, Garg U, Jain N, Pandey M, Amin MC, Gorain B, Kumar P. Chitosan and hyaluronic acid-based nanocarriers for advanced cancer therapy and intervention. Biomaterials advances. 2023:213733.

[17]. Chelu M, Musuc AM. Polymer gels: Classification and recent developments in biomedical applications. Gels. 2023;9(2):161.

[18]. Shah S, Rangaraj N, Laxmikeshav K, Sampathi S. Nanogels as drug carriers–Introduction, chemical aspects, release mechanisms and potential applications. International Journal of Pharmaceutics. 2020;581:119268.

[19]. Adlsadabad SY, Pourbadiei B, Doroudian M, Pourjavadi A. Photo-responsive doxorubicin delivery: Nanogel systems based on azobenzene and host-guest interactions enhanced by squeezing action. Polymer. 2024; 126900.

[20]. Aumnate C, Saengow C, Okhawilai M. Gelation and fabrication of bioresorbable-based hydrogels for drug-release applications. InBioresorbable Polymers and their Composites 2024; 147-168.

[21]. Ghosh D, Peterson BW, de Waal C, de Vries J, Kaper H, Zu G, Witjes M, van Rijn P. Effects of sterilization on nanogel-based universal coatings: An essential step for clinical translation. Materials & Design. 2024;238:112689.

[22]. Basak S, Mukherjee I, Das TK. Injectable Biocompatible RAFT mediated Nitroxide Nanogels: A Robust ROS-Reduction Antioxidant Approach. Colloids and Surfaces B: Biointerfaces. 2024; 113790.

[23]. Kayra N, Aytekin AÖ. Chitosan nanogel for drug delivery and regenerative medicine. InPolysaccharide Hydrogels for Drug Delivery and Regenerative Medicine 2024; 215-232.

[24]. Khattak S, Ullah I, Xie H, Tao XD, Xu HT, Shen J. Self-healing hydrogels as injectable implants: Advances in translational wound healing. Coordination Chemistry Reviews. 2024;509:215790.

[25]. Wang P, Cai F, Li Y, Yang X, Feng R, Lu H, Bai X, Han J. Emerging trends in the application of hydrogel-based biomaterials for enhanced wound healing: A literature review. International Journal of Biological Macromolecules. 2024:129300.

[26]. Idumah CI. Recently emerging advancements in polymeric nanogel nanoarchitectures for drug delivery applications. International Journal of Polymeric Materials and Polymeric Biomaterials. 2024;73(2):104-16.

[27]. Shi L, Zhang J, Zhao M, Tang S, Cheng X, Zhang W, Li W, Liu X, Peng H, Wang Q. Effects of polyethylene glycol on the surface of nanoparticles for targeted drug delivery. Nanoscale. 2021;13(24):10748-64.

[28]. De Castro KC, Coco JC, Dos Santos ÉM, Ataide JA, Martinez RM, do Nascimento MH, Prata J, da Fonte PR, Severino P, Mazzola PG, Baby AR. Pluronic® triblock copolymer-based nanoformulations for cancer therapy: A

10-year overview. Journal of Controlled Release. 2023;353:802-22.
[29]. Chaudhari A, Vadodariya P, Vyas A, Patel D, Teli D. Composition of Nanoparticles. Nanocarrier Vaccines: Biopharmaceutics-Based Fast Track Development. 2024; 25-62.
[30]. Gupta SS, Mishra V, Mukherjee MD, Saini P, Ranjan KR. Amino acid derived biopolymers: Recent advances and biomedical applications. International Journal of Biological Macromolecules. 2021;188:542-67.
[31]. Li L, Zhang Y, Wu Y, Wang Z, Cui W, Zhang C, Wang J, Liu Y, Yang P. Protein-Based Controllable Nanoarchitectonics for Desired Applications. Advanced Functional Materials. 2024:2315509.
[32]. Rashwan AK, Osman AI, Abdelshafy AM, Mo J, Chen W. Plant-based proteins: advanced extraction technologies, interactions, physicochemical and functional properties, food and related applications, and health benefits. Critical Reviews in Food Science and Nutrition. 2023; 2:1-28.
[33]. Das S, Kudale P, Dandekar P, Devarajan PV. Asialoglycoprotein receptor and targeting strategies. Targeted Intracellular Drug Delivery by Receptor Mediated Endocytosis. 2019:353-81.
[34]. Basu A, Halder M, Das A, Das R, Bhattacharjee C. Nanomaterials in Drug Delivery: Application of Polysaccharides and Protein-Based Nanomaterials in Modern Drug Delivery. InBiogenic Nanomaterials for Environmental Sustainability: Principles, Practices, and Opportunities 2024; 293-317.
[35]. Tan J, Luo Y, Guo Y, Zhou Y, Liao X, Li D, Lai X, Liu Y. Development of alginate-based hydrogels: Crosslinking strategies and biomedical applications. International journal of biological macromolecules. 2023; 124275.
[36]. Shah S, Rangaraj N, Laxmikeshav K, Sampathi S. Nanogels as drug carriers–Introduction, chemical aspects, release mechanisms and potential applications. International Journal of Pharmaceutics. 2020;581:119268.
[37]. Zou Z, Xu X, Zhao HT, Cheng JN, He WW, Zhang LF, Cheng ZP. Manipulating the phase transition behavior of dual temperature-responsive block copolymers by adjusting composition and sequence. Chinese Journal of Polymer Science. 2024;42(2):176-87.
[38]. Mohamed JM, Alqahtani A, Kumar TV, Fatease AA, Alqahtani T, Krishnaraju V, Ahmad F, Menaa F, Alamri A, Muthumani R, Vijaya R. Superfast synthesis of stabilized silver nanoparticles using aqueous Allium sativum (garlic) extract and isoniazid hydrazide conjugates: molecular docking and in-vitro characterizations. Molecules. 2021; 27(1):110.
[39]. Silva EC, Pina J, Pereira RF, Murtinho D, Valente AJ, Fajardo AR. Synthesis and characterization of fluorescent poly (α-cyclodextrin)/carbon quantum dots composite for efficient removal and detection of toluene and xylene from aqueous media. Environmental Pollution. 2024; 16:123778.
[40]. Sindhu RK, Gupta R, Wadhera G, Kumar P. Modern herbal nanogels: formulation, delivery methods, and applications. Gels. 2022; 8(2):97.
[41]. Massella D, Argenziano M, Ferri A, Guan J, Giraud S, Cavalli R, Barresi AA, Salaün F. Bio-functional textiles: Combining pharmaceutical nanocarriers with fibrous materials for innovative dermatological therapies. Pharmaceutics. 2019;11(8):403.
[42]. Nagalakshmi S, Tejas DS, Yamini M, Taaha ZN, Monisha RL, Anumita G, Logeswaran K. Fabrication and Characterization of Tolnaftate Loaded Topical Nanoemulgel for the Treatment of Onychomycosis. International Journal of Drug Delivery and Technology. 2023; 13(2):461-7.
[43]. Aderibigbe BA. Nanotherapeutics for the delivery of antifungal drugs. Therapeutic Delivery. 2024;15(1):55-76.
[44]. Umeyor CE, Okonkwo AU, Ejielo OD, Umeyor IC, Uronnachi EM, Nwakile CD, Okeke IJ, Attama AA. Formulation design and preclinical evaluations of surface modified lipid nanoparticles-coupled gel encapsulating dihydroartemisinin for treatment of localized inflammation. Lett. Appl. NanoBioSci. 2021;11:3745-69.
[45]. Desu PK, Karmakar B, Kondi V, Tiwari ON, Halder G. Optimizing formulation of

green tea extract-loaded chitosan nanogel. Biomass Conversion and Biorefinery. 2024; 14(3):3209-22.

[46]. Kuchukuntla M, Palanivel V, Madhubabu A. Tofacitinib Citrate-loaded Nanoparticle Gel for the Treatment of Alopecia Areata: Response Surface Design, Formulation and In vitro-in Vivo Characterization. Recent Advances in Drug Delivery and Formulation: Formerly Recent Patents on Drug Delivery & Formulation. 2023;17(4):314-31.

[47]. Ribovski L, de Jong E, Mergel O, Zu G, Keskin D, van Rijn P, Zuhorn IS. Low nanogel stiffness favors nanogel transcytosis across an in vitro blood–brain barrier. Nanomedicine: Nanotechnology, Biology and Medicine. 2021; 34:102377.

[48]. Chouhan C, Rajput RP, Sahu R, Verma P, Sahu S. An updated review on nanoparticle based approach for nanogel drug delivery system. Journal of Drug Delivery and Therapeutics. 2020; 10(5-s):254-66.

[49]. Kareemi AF, Likhitkar S. Applications and Advancements of Polysaccharide-Based Nanostructures for Enhanced Drug Delivery. Colloids and Surfaces B: Biointerfaces. 2024; 30:113883.

[50]. Soni S, Kori SK, Sahu P, Kashaw V, Dahiya R, Iyer AK, Soni V, Kashaw SK. Herbal nanogels: Revolutionizing skin cancer therapy through nanotechnology and natural remedies. European Journal of Medicinal Chemistry Reports. 2023; 19:100126.

[51]. Srivastava S, Saha S, Jakhmola V. Nanogel: Types, Methods of Preparation, Limitation, Evaluation and Application - A Systematic Review. International Journal of Drug Delivery Technology. 2023;13(4):1231-1239.

[52]. Narang JK, Dogra A, Ali J, Baboota S, Narang RS. Polymeric nanocarriers for delivery of combination drugs. InNanocarriers for the Delivery of Combination Drugs. 2021; 85-118.

[53]. Zong TX, Silveira AP, Morais JA, Sampaio MC, Muehlmann LA, Zhang J, Jiang CS, Liu SK. Recent advances in antimicrobial nano-drug delivery systems. Nanomaterials. 2022;12(11):1855.

[54]. Gorle AP, Tatar TD. Nanogels: an overview of properties, pharmaceutical applications and drug loading technique. European Journal of Biomedical. 2020;7(8):203-9.

[55]. Wu Y, Tao Q, Xie J, Lu L, Xie X, Zhang Y, Jin Y. Advances in nanogels for topical drug delivery in ocular diseases. Gels. 2023;9(4):292.

[56]. Sahu P, Sau S, Iyer AK, Kashaw SK. Nanogels: The Emerging Carrier in Drug Delivery System. InRecent Trends in Nanomedicine and Tissue Engineering 2022; 121-156.

[57]. Jetha KL, Bharadia PD, Patel MP. Nanotechnology and Vaccine Development. Nanocarrier Vaccines: Biopharmaceutics-Based Fast Track Development. 2024;63-93.

[58]. Verma S, Nainwal N, Kikon NY, Ali A, Jakhmola V. Hopes and hurdles of nanogels in the treatment of ocular diseases. Journal of Applied Pharmaceutical Science. 2024;14(2):001-12.

[59]. Yu J, Liu Y, Zhang Y, Ran R, Kong Z, Zhao D, Liu M, Zhao W, Cui Y, Hua Y, Gao L. Smart nanogels for cancer treatment from the perspective of functional groups. Frontiers in Bioengineering and Biotechnology. 2024;11:1329311.

[60]. Iacob AT, Lupascu FG, Apotrosoaei M, Vasincu IM, Tauser RG, Lupascu D, Giusca SE, Caruntu ID, Profire L. Recent biomedical approaches for chitosan based materials as drug delivery nanocarriers. Pharmaceutics. 2021;13(4):587.

[61]. Yao J, Li T, Shi X, Wang Y, Fang S, Wang H. A general prodrug nanohydrogel platform for reduction-triggered drug activation and treatment of taxane-resistant malignancies. Acta Biomaterialia. 2021;130:409-22.

[62]. Lu Y, Yu H, Wang L, Shen D, Chen X, Huang Y, Amin BU. Recent advances in the smart insulin delivery systems for the treatment of diabetes. European Polymer Journal. 2021;161:110829.