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Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

REVIEW ARTICLE

HYBRID HYDROGELS INCORPORATING NANOPARTICLES, THEIR TYPES, DEVELOPMENT, AND APPLICATIONS: A COMPREHENSIVE REVIEW OF NANOGELS

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Article Info:

Article History:
Received: 6 July 2024
Reviewed: 11 September 2024
Accepted: 19 October 2024
Published: 15 November 2024

Cite this article:
Nadeem A, Saqib Z, Arif A, Abid L, Shahzadi H, Saghir A, Khan E, Afzaal T, Saadat S, Rasheed N, Mustafa MA, Iqbal MZ. Hybrid hydrogels incorporating nanoparticles, their types, development, and applications: A comprehensive review of nanogels. Universal Journal of Pharmaceutical Research 2024; 9(5): 142-149.
http://doi.org/10.22270/ujpr.v9i5.1202

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Abstract

Nanogels have become significant in biomedical science research due to various unique characteristics. Hydrogels are three-dimensional crosslinked polymer networks that swell by absorbing aqueous solvents. These polymeric networks with sizes from nanometers to micrometres incorporate features of both hydrogels and nanoparticles, exhibiting high efficiency in drug delivery, tissue engineering, and biosensing. The synthesis process involves the chemical and physical crosslinking process, and the nanoparticles can be incorporated either during gelation or in situ. The resulting hydrogel nanoparticle composites exhibit high drug encapsulation capacity, adjustable swelling behaviour, biocompatibility, and responsiveness to stimuli like pH, temperature, and enzymes. They are of uniform size and less toxic, ideal for controlled and targeted drug delivery, and improved therapeutic effectiveness. Newer developments have highlighted its applications in cancer therapy, cardiovascular treatment, wound healing, and neurodegenerative disease management. This review provides a comprehensive analysis of the types of nanogel, the development process and wide-ranging applications, along with insights into future developments in this promising field.

Keywords: Controlled system, drug delivery, hydrogels, nanoparticles, nanogels, nanocomposites, polymerization, stimuli-responsive.

INTRODUCTION

According to Wichterle and Lim, the first synthetic hydrogel was able to accept or release water severalfold[1]. Hydrogels, with their long history of exploration spanning more than half a century, are known as the earliest source of monomers of hydroxyethyl methacrylate (HEMA)[2]. They are transparent, 3D, water-absorbing, soft, cross-linked particles made of hydrophilic polymers. These polymers are nontoxic, biocompatible, and bio-degradable and are often used in various medical and pharmaceutical applications[3].

Nanoparticles are micro-sized particles ranging from 1 to 100 nanometers (nm); however, they differ in their physicochemical properties. Because of their large surface area, they are used in drug administration, biological detection, and CO_2 collection, among other processes. Because of their distinctive characteristics over bulk materials, nanoparticles are now used in everyday consumer products and appliances. This trend has sparked public discussion over the safety of nano-particle technology, and regulatory bodies have stepped in to address the issue in several nations[4].

Thereby, these can function as an alternative to some drug delivery systems that exhibit biocompatibility, good mechanics, control the drug delivery, bio-degradability, excellent flexibility, and great permeability[5]. Furthermore, it was believed that a novel combination of these two completely distinct material

types would produce multiple property improvements in addition to structural variety. Consequently, with the advancement of nanotechnology, drug carriers that are based on hydrogels and nanoparticles are invented to solve drug administration issues[6]. Nanoparticles can load onto the hydrogel-forming matrix by gelation process or developed in an in-situ manner within the hydrogel swellable matrix, thus making them suitable for application in the delivery of drug[7]. Their qualities, which are mostly linked to swelling, elasticity, rigidness, mechanical strength, and viscosity, are utilized to determine their smartness and functioning.

In biomedical research, nanogels open the way for advanced drug carrier systems and possess many advantages of high drug-carrying capacity, stability, uniformity, and low toxicity[8]. The novel drug delivery systems are used in biotechnology methods involving enzyme immobilization, genetic engineering, and recombinant protein synthesis[9]. They are also investigated as contact lenses, bacterial applications, and targeted drug delivery agents for the early detection and treatment of cancer cells[10,11].

The review paper provides a comprehensive overview of hydrogel synthesis, types, and applications, highlighting the potential of hydrogel-containing nanoparticles for controlled drug delivery and tissue engineering. Future research may focus on biocompatibility, drug release kinetic optimization, and regenerative medicine applications, leading to more sophisticated therapies.

METHODS

The study was conducted over four months, from February 5, 2024, to June 3, 2024, with ethical approval from the Research Ethics Committee at the University of Biological & Applied Sciences (UBAS) in Lahore, Pakistan (reference number RMEC/AM/09866). Adhering to the PRISMA flow statement guidelines, this review primarily utilized Google Scholar and Pubmed databases.

The search terms used to select articles for the current review are Nanoparticles Containing Hydrogels, Nanogel Composition and Structure, Synthesis of Hydrogel-Nanoparticle Composites, Characterization of Hydrogel-Nanoparticle Systems, and Applications of Nanoparticle-Loaded Hydrogels (2001–2024). Other searches were made from electronic sources, including the Scopus and Science Direct databases. The flow chart of this systematic review according to the PRISMA guideline is shown in Figure 1.

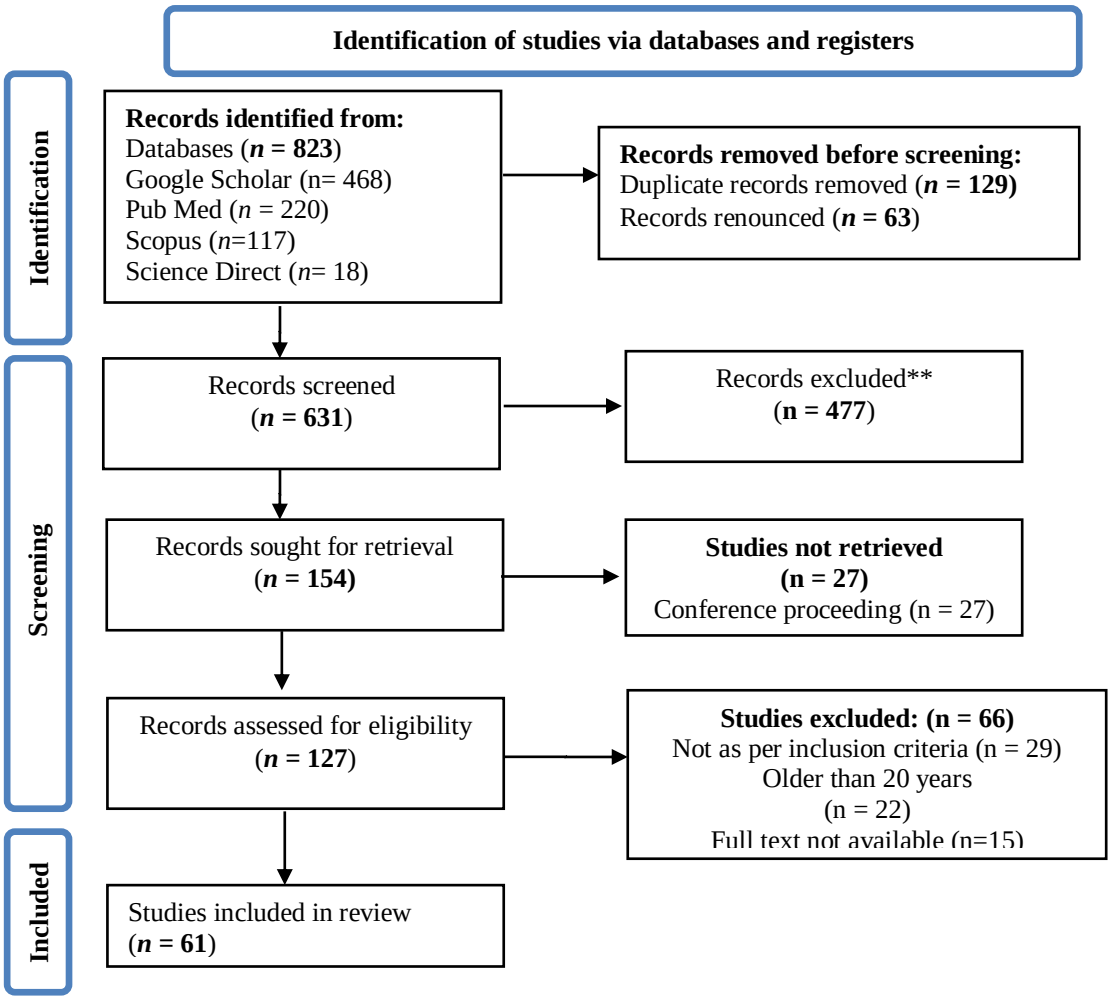


Figure 1: PRISMA flow diagram for systematic review.

Inclusion criteria

The type of studies searched for the inclusion criteria was restricted to articles published in English dealing with nanoparticles incorporated in hydrogels, the characteristics of nano-gel synthesis and the process of nano-gels, and the application of nanoparticles incorporated in hydrogels from 2001 to 2024.

Exclusion criteria

- Other related carrier systems, like nanoemulsions, in situ gels, liposomes, etc.
- Research articles in languages other than English.
- Studies conducted before 2001.

Data extraction

The extracted data included author details, the year of the study, nanoparticle-hydrogel systems, their history, types, composition, structure, synthesis, and applications.

Nanogel

Hydrogel nanoparticles (NPs) are a family of nanoscale materials being researched for drug delivery techniques. They possess a long half-life, targeting biophases, hydrophilicity, flexibility, versatility, high water absorptivity, and biocompatibility.

Table 1: Types of nanoparticles containing hydrogels.

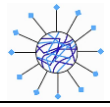
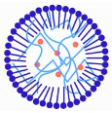
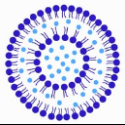
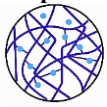
Types	Composition	Application	Polymer used	Example
Simple[12] 	Natural polymers, synthetic polymers, or both polymers.	Skin infections, neurodegenerative disorder.	Polyethylene glycol, Polyvinyl alcohol, Chitosan.	Antibiotics
Core-shell[13] 	It is comprised of two layers: an inner and an outer layer. The inner layer is the core fabricated to stabilize the drug by increasing the formulation capability. The outer layer is the shell exposed to the environment, and it protects the core.	Cancer therapy	Polyacrylic acid, Polyethylene glycol, Poly-N-isopropyl acrylamide	Cisplatin
Hairy[14] 	Linear polymer chains consisting of high polar groups bonding with dispersion medium catalyst such as silica.	Anti-tumor effect.	Poly (ethylene glycol) methyl ether methacrylate	Stimuli-responsive nanogel
Hollow[15] 	They are made by cross-linking of temperature sensitive polymers and they show swelling behavior by small angle neutron scattering (SANS).	Cancer therapy, acute ischaemic shock therapy.	Poly-N-isopropyl acrylamide (PNIPAM).	Thermo-responsive nanogels
Multi-layered[16] 	They formed by layer-by-layer hydrogen bonding and acrylic acid crosslinking using EDA/AAD.	Use of sodium diclofenac for arthritis treatment.	Polyvinyl pyrolidone (PVPON)	Thermo-responsive nanogels
Functionalized[17] 	They contain polymers that are crosslinked.	Diagnostic purposes.	Poly EA-MAA-BDDA, Poly MMA-MMA-ESDMA.	Thixotropic gel
Micellar nanogels[18] 	Micelles are large polymeric molecules with both hydrophilic and hydrophobic characteristics similar to those of lipids. They are in cylindrical shapes.	Cancer therapy as Controlled drug delivery systems	Polyethylene glycol, Polyacrylic acid Diblock copolymer	Sodium dodecyl water
Liposome modified[19] 	These are microscopic vesicles that contains membrane of lipid molecules around the aqueous region. Cholesterol and phospholipids are the two main components.	oral delivery of steroids, cancer therapy	Cyclodextrin, Polyethylene glycol, Poly amido amines, Chitosan.	Immunological adjuvants
Stimuli responsive[20,21] 	Different polymers are conjugated to get the stimuli response of hydrogels	Chemotherapy, use in MRI for diagnostic purpose.	Poly-N-isopropyl acrylamide (PNIPAM), Chitosan, 2-(2-methoxyethoxy) ethyl methacrylate	Thermo responsive hydrogels, pH responsive nanogels
Hybrid[22,23] 	Copolymers of polyethylene glycol-polyglutamic cid-polyphenylalanine.	Gene therapy, Drug delivery	Polyethylen glycol (PEG), Diblock polymer.	Caesin based hybrid hydrogels

Table 2: Ingredients and components of nano gels.

Monomers	pH stabilizer	Polymers	Initiator	Gelling Agents	Reducing Agents
Vinyl Pyrrolidone	Histadine	Chitosan	Sodium mono hydrogen phosphate	Guar gum	Silver nitrate
Nanoshell-Au-NPs	Triethanolamine	Polyacrylamide	Ferrous ammonium sulfate	Sodium Hydroxide	Sodium horohydride
2-hydroxy ethyl methacrylate	Acetic acid	Gelatin	Ammonium sulphate	Acacia	Citrate
Acrylic acid	Potassium hydroxide	Polyvinyl alcohol	Ammonium persulphate	Food-grade sodium alginate	Tetrakis (hydroxyl methyl) phosphonium chloride
PEG methyl ether methacrylate	Povidone	Poly Beta iactam	Potassium persulfate	Hydroxy ethyl cellulose	Urea
Oligo (ethylene glycol) mono methyl ether methacrylate	Collagen	Ammonium persulphate	HCl	Carbomers	Graphene oxide
Dihydrogen phosphate	HCL	Collagen	Ammonium persulphate	Carbomers	Graphene oxide
Diallyl dimethyl ammonium chloride	Phosphate buffer saline	HPMC	Dihydrogen phosphate	Pectin	H_2
Acrylamide	Sodium dodecyl sulphate	Polyvinyl pyrrolidone	Dihydrogen phosphate	Carbapol	Sodium citrate
Disulphide-linked	Glycin	Alginate	Tetra methyl ethylene diamine	Triethoxysilane (APTES:≥98%)	Sodium CMC

Combining hydrogels and nanoparticles could enhance drug loading capacity and provide sustained therapeutic agent release, potentially revolutionizing drug delivery systems and improving patient outcomes[1]. It was believed that the innovative combination of these two radically distinct types of materials would produce structural diversity and numerous property improvements. Research on hydrogel-nanoparticle composite materials, which produced better mechanical strength and stimuli response, was primarily focused on enhancing these properties. For instance, compared to hydrogel without nanoparticles, a recently reported silica nanoparticle-hydrogel composite consisting of modified polyethylene glycol and silica nanoparticles showed notable increases in tissue adhesion properties, mechanical stiffness, and bioactivity[1].

Components and Ingredients of nanogel

The components and ingredients of a hydrogel containing nanoparticles vary depending on the desired application and type of nanoparticles used. Generally, these are the main components given in Table 2.

Methods of nanogel development

The development and process of nanogels involve the design of nanoscale hydrogel particles that could swell in aqueous environments.

1. Photopolymerization

The nanoparticles are synthesized by chemically reducing a metal salt solution with the help of a suitable reducing agent. Stabilizers are added to stabilize the nanoparticles, and concentration is adjusted. Hydrogels are prepared by dissolving biopolymers such as gelatin and chitosan in an appropriate solvent. Then, nanoparticles are added to this solution. To facilitate the formation of a gel network cross-linking agents such as poly (ethylene glycol) diacrylate (PEGDA) are also added along with a photoinitiator or any other initiator to start the process. Polymerization is induced by UV radiation triggers in hydrogels. The formed nanoparticles are then dried at room temperature and stored in suitable conditions[24].

2. Microwave-assisted synthesis

Synthesis of hydrogel is done by preparing a monomer solution. Add the monomer (e.g. acrylic acid) to the base solution and cool to the specified temperature (30°C). Add crosslinking agent (e.g. NMBA), initiator (e.g. ammonium persulfate), and other required additives (e.g. PEG). Polymerization of hydrogel is performed by microwave irradiation for the set duration. Microwave heating helps in the formation of rapid 3D polymer network structure. Nanoparticles are prepared by chemical reduction method. Hydrogel composites are formed by introducing the nanoparticles during the addition of initiator, cross-linker and other additives[25].

3. Emulsion polymerization

The process involves preparing a chitosan solution (aqueous phase), oil phase and making an oil in water emulsion. The aqueous phase is prepared by dissolving chitosan in an acidic solution overnight, along with adjusting the pH. The surfactant is added for homogeneity. The preparation of the oil phase is done by mixing the oil component with an emulsifier and another surfactant solution for a homogeneous oil phase. Mix the oil phase into an aqueous chitosan solution to create an oil-in-water emulsion under high-speed homogenization. Now, a crosslinking agent is added to the emulsion to induce ionic gelation. Sonicate the mixture to enhance the formation of the nanoparticle. Nanoparticles are then collected by centrifugation, washed thoroughly with surfactant solution and water and lyophilized to store in dry conditions at room temperature. A hydrogel matrix is prepared by dissolving the polymer like PVA in water. Then, add a cross-linking agent to form a semi-solid hydrogel. The nanoparticles are then mixed with the hydrogel solution. A crosslinking agent is added for the

finalization of hydrogel-containing nanoparticles. Store them at room temperature[26].

4. In situ polymerization

Nanoparticles are prepared by the reduction process by combining a reducing agent and a metal salt solution. Dissolve monomer in distilled water along with a crosslinking agent to form hydrogel. Stir until homogeneous and purging with an inert gas. Add an initiator and allow polymerization to occur at a controlled temperature for an extended time period. Hydrogels are then cut into desired shapes and washed thoroughly to remove unreactive materials. Hydrogels are loaded with metal salt by placing them in the metal ion solution and then transferred into the reducing agent solution. This converts the absorbed ions into nanoparticles[27].

5. Interfacial synthesis

A hydrogel mixture is formed by dissolving a suitable polymer in the appropriate solvent, such as water and acetic acid. Stirring of the solution is done to ensure complete dissolution at the appropriate temperature. According to the desired properties of the hydrogel, the crosslinking agent and gelling agent are added to the polymer solution. Stir the solution for homogeneity of the mixture. The mixture is poured into the moulds and allowed to be set by cooling, heating, or chemical reaction to form the hydrogels. After setting, the hydrogels are removed from the moulds and immersed into the secondary solution (e.g. calcium chloride solution) to enhance stability. For nanoparticle incorporation, a solution containing a nanoparticle (e.g., silver nanoparticle, gold nanoparticle) is prepared using a chemical reduction method. Hydrogels are then immersed in the solution, and sufficient time is allowed to incorporate the nanoparticles into the hydrogels either by diffusion or chemical interaction. Optimized conditions are provided for maximum incorporation. Finally, the nanoparticle-containing hydrogels is removed from the solution[28].

6. Sequential polymerization:

This method outlines the procedure for dual network hydrogels. The first hydrogel network is formed by dispersing nanoparticles into the water and sonicating them until fully dispersed. Prepare the monomer solution with an adjusted pH and disperse the nanoparticles in this solution. Add a cross-linker (N, Methylene Bisacrylamide), an enzyme initiator (glucose oxidase), and a chemical initiator (cerium (IV) ammonium nitrate). The solution is then distributed into the moulds and placed at a controlled temperature to ensure homogeneous dispersion and polymerization.

The second hydrogel network is formed by soaking the hydrogels in a second monomer solution containing nanoparticles, a cross-linker, an initiator enzyme, and a chemical initiator. Then, these hydrogels are again placed into molds and incubated. Dry and rehydrate the hydrogels for swelling[29].

APPLICATIONS

Biomedical applications

Currently, nanogels are a rising material in biomedical research. These structures include hydrogel nanoparticles conjugated with the polymeric structure. Some of the properties of nanogels that make them an advanced drug delivery system are high drug encapsulation efficiency, monodispersity, ease of synthesis, biocompatibility, stability in serum media, and sensitivity to changes in the environment. Their ability to be used in various settings makes them indispensable in a great number of biomedical uses, which include chemotherapy, diagnostic procedures, organelle targeting, or delivery of biologically active material[8].

Due to their ability to circumvent the drawbacks of traditional drug carrier systems, hydrogels containing nanoparticles are becoming more and more popular as novel carriers[30]. Prime threatening comorbidity is cancer, which greatly affects the functioning of the human body[31]. Frontline techniques used for the treatment of cancer are radiotherapy, surgery, and targeted drug delivery. Nano gels have been enhanced and are the most used in designing drug delivery systems as they can provide the proper formation of these nanoparticles. Thus, employing novel functionalization strategies to target cancer cells directly is a successful strategy that can effectively mitigate many side effects that occur from other treatments[32]. This way, the properties of Nano dextrin are altered by conjugating it with an AMD3100 (plerixafor) CXCR4 chemokine receptor for selective cellular targeting. Besides, the characteristics of Nano gel concerning the loading and releasing of doxorubicin prove the efficacy of this concept and it becomes clear that this approach reveals high effectiveness concerning cancer eradication and the primary prevention of metastasis[33]. Both single-target and two-target systems, including technology, can be incorporated into similar processes. For instance, a nanosized assembly is depicted that encodes the chemical molecule named saporin and delivers it into the cancer cells, comprising hyaluronic acid nano gel incorporating EGFR and CD44 protein. The *in vivo* testing on the cancer model of the breast was designed[34]. Nano gels have cured different kinds of cancers that are difficult to treat from old techniques like, and the grading of fibrosarcoma is done with the help of IL-12-carrying pullulan-cholesterol nanogels[35]. Nanogels can effectively deliver an active therapeutic agent to the glioblastoma cells in the brain. This can be synthesized by specific T-lymphocytes delivering thermo-responsive poly (ethylene glycol)-g-chitosan copolymers[36].

Injuries of the spinal cord

Hydrogel containing nanoparticles have shown promising results in promoting tissue regeneration and reducing inflammation in preclinical studies for spinal cord injuries. This innovative approach improves outcomes by providing a scaffold for cell growth and delivering therapeutic agents directly to the injury site. Nanogels can cross the Blood-Brain Barrier, allowing drugs to bypass it. Polyethylene grafted with amines has been tested for its efficacy in controlling inflammatory responses. *In vivo* experiments show nanogels modulate neuron regeneration, increase voluntary function, and decrease inflammation[37].

Treatment of Alzheimer's disease

Another chronic neurodegenerative problem that poses a severe pathology is Alzheimer's disease. There is recent research that shows there is a connection between insulin dysfunction and Alzheimer's disease. In some cases, insulin administration is now used in the management of Alzheimer's disease. For example, polycarbonyl (N-vinyl pyrrolidone) nano gels are produced through ionizing radiation and capped with insulin, which acts as an insulin agonist to interact with insulin receptors, stimulate insulin signal transduction, and transport through the blood-brain barrier. This helps in the management of Alzheimer's disease by providing insulin[38].

Thrombolytic therapy

One application of nanogels is in enhancing the serine proteases by the addition of urokinase, which appears to be beneficial in thrombolysis. pH-sensitive nano gels and PEG sprays nano gel are synthesized for thrombolysis treatment. In thrombolytic events, microcirculation clots developand oxygen deficiency occurs which results in pH lowering so these nanogels have been utilized for thrombolytic injuries[39].

Cardiovascular diseases

Cardiovascular illnesses have been treated with nano gel formulations, namely N-Isopropylacrylamide-methyl methacrylate; in particular, N, α-L-rhamnopyranosyl vincosamide, possesses heart-protective properties. Doxorubicin-induced models have shown effectiveness in suppressing toxicities related to heart[40].

In Hypertension:

Nanogels, specifically a positively charged cholesterol group (cCHP) have been used in hypertension therapy due to their ability to carry angiotensin II type 1 receptor (AT1R). These receptors have proven to lower blood pressure in rat models effectively[41].

Wound healing

The wound healing process involves replacing damaged tissue with new ones. Drugs and active ingredients can enhance this process by speeding up regeneration and inhibiting infections. Controlled transmission of substances is essential for drug success. Chitosan nanogel loaded with silver sulfadiazine has shown potential in treating burn wounds. Lysine-containing nanogels encapsulated within hydrogels with antiseptic species, such as chlorhexidine diacetate, have been used on face wounds. *In vivo* assessments have demonstrated the viability of these nanogels and their increased effectiveness in wound healing[42].

Stimuli-Responsive hydrogels

The preparation techniques for conventional nanogels and stimulus-responsive nanogels are comparable. Nanogels are commonly prepared by polymerization of monomers and chemical cross-linking of preformed polymers in heterogeneous colloidal environments, especially in water-in-oil inverse microemulsions. This method easily entraps macromolecules and small-molecule medications into the nanogels. Encapsulating bioactive macromolecules was made possible by the physical self-assembly of polymers, which were employed to create a variety of nanogels in aqueous mediums and mild environments[43].

Nanogel durability depends on concentration and weak interactions between polymer chains. Highly diluted substances may dissociate into hydrophilic polymers, causing early release and side effects. Physical self-assembly/chemical cross-linking is a viable technique for stable nanogels without surfactants or solvents, but low efficiency needs to be fixed before widespread drug administration[43].

Materials known as hydrogels have the potential to alter their structural properties in response to biological and environmental stimuli, including pH, biomolecule recognition, and bioreduction. Although their primary usage is in the biomedical domain, these materials have also been applied to imaging, targeted delivery, and sensing agents. The main purpose of pH-responsive hydrogels, which are widely used in biomedicine, is to react to changes in pH. Because of their versatility, they are widely used in many different fields. Usually, responsive polymers—which maintain their properties even inside the finished structure—are used to develop these systems. Hydrogels that are sensitive to pH and temperature are essential nanodevices, and because of their versatility and use, hydrogels for ion detection are becoming more and more significant[43].

Environmental applications

The protection and restoration of the environment are current topical problems and concerns of the future timeframe.Environmental preservation and protection are crucial issues in today's society and the future. Chemical sciences are important and valuable for their non-chemical hazards. Natural polymer-based materials have proven powerful adsorbents of particles and pollutants due to their non-toxic character, high biodegradation, binding ability, and immobilization convenience. Nanogels have gained attention for their stretchability, large surface area, high-strength structure, and ability to hold fluids. Research is focused on how sorption can happen on the surface of MgO (magnesium oxide), and the adsorption of heavy metal ions, dyes, and other compounds[43].

Limitations of the study

The article's limitations include not covering extensive characterization, variability in methods, not providing insights into long-term stability, and focusing on biomedical applications only.

FUTURE PERSPECTIVES

The most significant potential for nanoparticles containing hydrogels is in the medical field, particularly for targeted drug delivery, controlled release, advanced wound healing, tissue engineering and regeneration, biosensing and diagnostics. These hydrogel drug carrier systems help transport drugs to specific target cells or tissues via controlled drug release and thus help reduce side effects. They create a moist environment that promotes cell growth and infection control for the healing of wounds. In tissue engineering, they serve as a matrix on which tissue regeneration takes place, providing biomolecules and growth factors. Future developments are aimed at promising nanocarriers for targeted drug delivery, developing multi-functional hydrogels for the

simultaneous delivery of the drug, imaging and detectable stimuli-sensitive changes, and biodegradability of the hydrogels to counter persistent accumulation in tissues. It is also important yet challenging to develop cost-effective production processes for large-scale use in clinics. Collectively, they may transform a few different industries: personalized medicine, materials science, medical provision, and environmental monitoring. It could bring about a revolution in the different sectors if the interaction of the nanoparticles with hydrogels is further tackled and enhanced as more research is conducted.

CONCLUSIONS

Hydrogel-containing nanoparticles are novel drug delivery systems with extensive applications in various fields, including biomedical and industry. This review article has comprehensively described the types and materials used for preparation, synthesis and biomedical applications. The functionalities of hydrogels can be improved by incorporating them with nanoparticles for targeted drug delivery, enhanced therapeutic efficacy, and stimuli responsiveness. The development of hydrogels, which show controlled release of drugs as a response to specific physiological conditions like temperature, pH, magnetic rays, enzymes, etc, is notable. This system has led to significant advancements in customized medications according to individual patient needs. Some challenges in hydrogel nanoparticle composite, such as precise targeting, cost-effective production, and long-term biocompatibility, need to be overcome in fields such as healthcare, environmental restoration, and improvement of human health and well-being.

ACKNOWLEDGEMENT

We want to extend our sincere gratitude to the Deanship of the Faculty of Pharmaceutical Sciences at Lahore University of Biological & Applied Sciences (UBAS) for providing the necessary resources and support that made this research possible. Their commitment to fostering academic excellence has been invaluable.

AUTHOR'S CONTRIBUTIONS

Nadeem A: Literature search, collected & analyzed data, wrote the manuscript**, Saqib Z:** Literature search, methodology**, Arif A:** Collected & analyzed data, methodology. **Abid L:** Concepts or Ideas, experimental studies. **Shahzadi H:** Collected & analyzed data, Wrote manuscript**, Saghir A:** Collected & analyzed data, wrote manuscript**, Khan E:** Collected & analyzed data , wrote the manuscript, **Afzaal T:** Collected & analyzed data, wrote the manuscript**, Saadat S:** Wrote the manuscript, **Rasheed N:** Wrote the manuscript**, Mustafa MA:** Conceived & designed, collected & analyzed data, wrote manuscript, Manuscript editing, **Iqbal MZ**: Data curation, investigation. All authors revised the article and approved the final version.

DATA AVAILABILITY

This article is available to anyone upon request from the corresponding authors.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Thoniyot P, Mein Jin Tan, *et al*. Nanoparticle-hydrogel composites: Concept, design, and applications of these promising, multi-functional materials. Adv Sci (Weinheim, Baden-Wurttemberg, Germany) 2015; 2 (1–2): 1400010. *https://doi.org/10.1002/advs.201400010*
2. Seow, Wei Yang, Charlotte A. E. Hauser. Short to ultrashort peptide hydrogels for biomedical uses. Mater Today (Kidlington, England) 2014; 17 (8): 381–88. *https://doi.org/10.1016/j.mattod.2014.04.028*
3. Tyliszczak B, Anna D, Kudłacik-Kramarczyk S, *et al*. *In vitro* cytotoxicity of hydrogels based on chitosan and modified with gold nanoparticles. J Polym Res 2017; 24 (10). *https://doi.org/10.1007/s10965-017-1315-3*
4. Khan I, Khalid S, Khan I. Nanoparticles: properties, applications and toxicities. Arab J Chem 2019; 12 (7): 908–31. *https://doi.org/10.1016/j.arabjc.2017.05.011*
5. Delia Mihaela R, Cadinoiu AN, Popa M, *et al*. Biocomposite hydrogels for the treatment of bacterial infections: Physicochemical characterization and *in vitro* assessment. Pharmaceutics 2021; 13 (12): 2079. *https://doi.org/10.3390/pharmaceutics13122079*
6. Débora N, Stéphanie A, Ramalho MJ, *et al*. Polymeric nanoparticles-loaded hydrogels for biomedical applications: A systematic review on *in vivo* findings. Polymers 2022; 14 (5): 1010. *https://doi.org/10.3390/polym14051010*
7. Gholamali I, Yadollahi M. Bio-nanocomposite polymer hydrogels containing nanoparticles for drug delivery : A Review. Review 2022. *https://doi.org/10.1007/s40883-021-00207-0*
8. Stanislawska I, Wioletta L, Marek L, *et al*. Recent advances in degradable hybrids of biomolecules and NGs for targeted delivery. Molecules (Basel, Switzerland) 2019; 24 (10): 1873. *https://doi.org/10.3390/molecules24101873*
9. Rajput R, Narkhede J, Naik J. Nanogels as nanocarriers for drug delivery: A review. ADMET DMPK 2020; 8 (1): 1–15. *https://doi.org/10.5599/admet.724*
10. Gurpınar SS, Devrim B, Eryılmaz M. *In-vitro* antibacterial activity of lactobacilli metabolites loaded hydrogel formulations against Pseudomonas aeruginosa. Universal J Pharm Res 2019; 4(4): 9-11. *https://doi.org/10.22270/ujpr.v4i4.29*
11. Zare I, Taheri-Ledari R, Esmailzadeh F, *et al*. DNA hydrogels and nanogels for diagnostics, therapeutics, and theragnostics of various cancers. Nanoscale 2023; 15 (26): 10882–903. *https://doi.org/10.1039/d3nr00425b*
12. Botha NL, Mushonga P, Onani MO. Review on nanogels and their applications on dermal therapy. Polym Polym Compos 2023; 31: 1–15. *https://doi.org/10.1177/09673911231192816*
13. Kaewruethai T, Chavee L, Yue P, Luckanagul JA. Multifunctional polymeric nanogels for biomedical applications. Gels (Basel, Switzerland) 2021; 7 (4): 228. *https://doi.org/10.3390/gels7040228*
14. Fu W, Chunhui L, Morin EA, *et al*. UCST-type thermosensitive hairy nanogels synthesized by RAFT polymerization-induced self-assembly. ACS Macro Lett 2017; 6 (2): 127–33. *https://doi.org/10.1021/acsmacrolett.6b00888*

15. Dubbert J, Honold T, Pedersen JS, *et al*. How hollow are thermo responsive hollow nanogels?" Macro-molecules 2014; 47 (24): 8700–8708. *https://doi.org/10.1021/ma502056y*
16. Zavgorodnya O, Carmona-Moran CA, Veronika K, *et al*. Temperature-responsive nanogel multilayers of poly(N-vinylcaprolactam) for topical drug delivery. J Colloid Interface Sci 2017; 506: 589–602. *https://doi.org/10.1016/j.jcis.2017.07.084*
17. Milani AH, Saunders JM, Nguyen NT, *et al*. Synthesis of polyacid nanogels: pH-responsive Sub-100 Nm particles for functionalisation and fluorescent hydrogel assembly. Soft Matter 2017; 13 (8): 1554–60. *https://doi.org/10.1039/c6sm02713j*
18. Discher DE, Adi E. Polymer vesicles. Science (New York, N.Y.) 2002; 297 (5583): 967–73. *https://doi.org/10.1126/science.1074972*
19. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov 2005; 4 (2): 145–60. *https://doi.org/10.1038/nrd1632*
20. Zha, L, Brittany B, Frank A. Stimulus responsive nanogels for drug delivery. Soft Matter 2011; 7 (13): 5908. *https://doi.org/10.1039/c0sm01307b*
21. Yadav HK, Halabi A, Alsalloum NA. Nanogels as novel drug delivery systems-A review. J Pharm Res 2017.1.
22. Morimoto N, Takao E, Michiko O, *et al*. Hybrid nanogels with physical and chemical cross-linking structures as nanocarriers. Macromol Biosci 2005; 5 (8): 710–16. *https://doi.org/10.1002/mabi.200500051*
23. Khaled SZ, Cevenini A, Iman K, *et al*. One-pot synthesis of ph-responsive hybrid nanogel particles for the intracellular delivery of small interfering RNA. Biomaterials 2016; 87: 57–68. *https://doi.org/10.1016/j.biomaterials.2016.01.052*
24. Mohammed AA, Li S, Sang T, Jones JR, Pinna A. Nanocomposite Hydrogels with Polymer Grafted Silica Nanoparticles, Using Glucose Oxidase. *Gels*. 2023; 9(6):486. *https://doi.org/10.3390/gels9060486*
25. Tyliszczak B, Krzysztof P. Novel hydrogels containing nanosilver for biomedical applications - Synthesis and characterization. J Polym Res 2013; 20 (7). *https://doi.org/10.1007/s10965-013-0191-8*
26. Ngampunwetchakul L, Supitsara T, Pitt S, Orawan S. Semi-solid poly (vinyl alcohol) hydrogels containing ginger essential oil encapsulated in chitosan nanoparticles for use in wound management. J Polym Res 2019; 26 (9). *https://doi.org/10.1007/s10965-019-1880-8*
27. Murali MY, Thathan PK, Lee K, Geckeler KE. Fabrication of silver nanoparticles in hydrogel networks. Macromol Rapid Commun 2006; 27 (16): 1346–54. *https://doi.org/10.1002/marc.200600297*
28. Gazil O, Gancheva T, Bilodeau-Calame M, *et al*. Controlling the distribution of nanoparticles in hydrogels: Via interfacial synthesis. Nanoscale Adv 2020; 2 (11): 5263–70. *https://doi.org/10.1039/D0NA00488J*
29. Ali M, Siwei Li, Tian, *et al*. Nanocomposite hydrogels with polymer grafted silica nanoparticles, using glucose oxidase. Gels (Basel, Switzerland) 2023; 9 (6). *https://doi.org/10.3390/gels9060486*
30. Qureshi MA, Khatoon F. Different types of smart nanogel for targeted delivery. J Sci Adv Mater Devices 2019; 4 (2): 201–12. *https://doi.org/10.1016/j.jsamd.2019.04.004*
31. Barani M, Bilal M, Sabir F, *et al*. Nanotechnology in ovarian cancer: Diagnosis and treatment. Life Sci 2021; 266 (118914): 118914. *https://doi.org/10.1016/j.lfs.2020.118914*
32. Yang, Muyue, Jipeng Li, Ping Gu, Xianqun Fan. The application of nanoparticles in cancer immunotherapy: Targeting tumor microenvironment. Bioact Mater 2021; 6 (7): 1973–87. *https://doi.org/10.1016/j.bioactmat.2020.12.010*
33. Zhang F, Siman G, Wu J, *et al*. CXCR4-targeted and redox responsive dextrin nanogel for metastatic breast cancer therapy. Biomacromolecules 2017; 18 (6): 1793–1802. *https://doi.org/10.1021/acs.biomac.7b00208*
34. Chen J, He H, Deng C, Yin L, Zhong Z. Saporin-loaded CD44 and EGFR dual-targeted nanogels for potent inhibition of metastatic breast cancer *in vivo*. Int J Pharm 2019; 560: 57–64. *https://doi.org/10.1016/j.ijpharm.2019.01.040*
35. Acebes-Fernández V, Landeria-Viñuela A, Juanes-Velasco P, *et al*. Nanomedicine and onco-immunotherapy: From the bench to bedside to biomarkers. Nanomaterials (Basel, Switzerland) 2020;10 (7): 1274. *https://doi.org/10.3390/nano10071274*
36. Tsao CT, Kievit FM, Ravanpay A, *et al*. Thermoreversiblepoly (Ethylene Glycol)-g-chitosan hydrogel as a therapeutic T Lymphocyte depot for localized glioblastoma immunotherapy. Biomacro-molecules 2014; 15 (7): 2656–62. PMID: 24890220
37. Papa S, Valeria V, Mauri E, *et al*. Functionalized nanogel for treating activated astrocytes in spinal cord injury. J Cont Rel 2021; 330: 218–28. *https://doi.org/10.1016/j.jconrel.2020.12.006*
38. Aderibigbe BA, Naki T. Design and efficacy of nanogels formulations for intranasal administration. Molecules (Basel, Switzerland) 2018; 23 (6): 1241. *https://doi.org/10.3390/molecules23061241*
39. Bernardo-Castro S, Inês A, Barrera-Sandoval AM, *et al*. Therapeutic nanoparticles for the different phases of ischemic stroke." life (Basel, Switzerland) 2021; 11 (6): 482. *https://doi.org/10.3390/life11060482*
40. Xie J, Feng-Xian L, Chong-Ying S, *et al*. *Moringa oleifera* alkaloids inhibited PC3 cells growth and migration through the COX-2 mediated Wnt/β-catenin signaling pathway. Front Pharmacol 2020; 11: 523962. *https://doi.org/10.3389/fphar.2020.523962*
41. Azegami T, Yuki Y, Hayashi K, *et al*. Intranasal vaccination against angiotensin II Type 1 receptor and pneumococcal surface protein A attenuates hypertension and pneumococcal infection in rodents. J Hypertens. 2018; 36 (2): 387–94. *https://doi.org/10.1097/HJH.0000000000001519*
42. Dreiss CA. Hydrogel design strategies for drug delivery. Curr Opin Colloid Interface Sci 2020; 48: 1–17. *https://doi.org/10.1016/j.cocis.2020.02.001*
43. Pinelli F, Marjan S, Zare EN, Makvandi P, *et al*. A perspective on the applications of functionalized nanogels: Promises and challenges. Int Mater Rev 2023; 68 (1): 1–25. *https://doi.org/10.1080/09506608.2022.2026864*