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Mechanistic Insights and Emerging Applications of Nanogel-Based Topical Drug Delivery Systems

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Abstract

Purpose: Nanogels (NGs) represent a new generation of nanoscale hydrogel particles with immense biomedical applications, especially drug delivery System (DDS). Nanogels (NGs) are soft and water-retentive materials that deliver drugs in controlled and sustained release while maintaining high biocompatibility and biodegradability.
Method: This review paper primarily focuses on the applications, mechanism, therapies. The capability to react with environmental signals, such as pH, temperature, or enzymatic activity, makes nanogels a promising platform for targeted therapy. Polysaccharide-based nanogels increase biocompatibility and reduce toxicity, allowing for extended therapeutic applications.
Result: This reviews the structural properties, drug release mechanisms, and newer developments in nanogel formulations. It also presents the future outlook for nanogels in precision medicine, highlighting their potential in transcending pharmacological obstacles towards enhancing drug delivery and therapeutic efficacies in various branches of medicine.
Conclusion: By overcoming existing drawbacks, nanogels have the potential to revolutionize drug delivery and therapeutic interventions in diverse clinical settings.

Keywords Nanogels (NGs), Drug delivery system (DDS), Biomedical, Biocompatibility, Precision medicine

Introduction

Nanogels (NGs) are hydrogel particles that can be injected into the circulations to target particular tissue pr organ after being loaded with bioactive substances. They disperse the content intracellularly on local level[1]. For high tech application, nanotechnology offers new nanomaterials[2]. They can be given orally, ocularly, sublingually, topically, or via any other route[3].Release of drugs is provide due to breakdown of diffusion gradient and drugs support structure, selling behaviour, or affinity-based mechanisms [4]. One of the most fascinating soft materials, nanogels are used in drug delivery systems, tissue engineering, wastewater treatment, food packaging, diagnostics, imaging, and emulsion stabilization. Chemical and physical nanogels can be sub-classified depending on the mechanism of crosslinking. Nanogels that undergo chemical crosslinking have gained rigid nanostructures

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through the covalent bonding of molecules within them. Their less stable counterparts, the physically crosslinked nanogels, are characterized by the fragile nature of the non-covalent linkages. The biological and structural characteristics are included in the table 1[5].

Routes of administration of nanogel

I. Topical
II. Nasal
III. Pulmonary
IV. Parenteral
V. Intraocular
VI. Oral[6].

Nanogels are three-dimensional hydrogel nanomaterials of nano-meter size composed of cross-linked swellable polymer networks possessing a high water holding capacity without being dissolved in the surrounding aqueous environment. Nanogels may be synthesized from a broad array of naturally occurring, synthetic polymers, or a both combined [7]. This review provide a general overview of nanogels and enumerates their main applications [8].Nanoparticles such as gold, silver, and liposomes, as well as natural and manufactured hydrogels, are frequently used in clinical settings. Kabanov et al. created the first chemically cross-linked nanogels to transport antisense oligonucleotides by combining PEG and PEI[9].Nanogels can be prepared from almost any crosslinked, synthetic or natural polymer with hydrogen bonding, hydrophobic interactions, and electrostatic interactions with non-covalent bonds. Classification of nanogel illustrated in the table 2 [10].

Nanotechnology is a groundbreaking concept with enormous potential for medicinal delivery. The discovery of novel drug delivery systems has an impact on disease prevention, diagnosis, and treatment. This novel technique overcomes pharmacological challenges by increasing absorption, providing sustained and controlled release, and reducing toxicity. Nanotechnology in medicine entails producing nanoparticles containing medications or genetic material and delivering them to specific target areas in a regulated and sustainable manner. Nanotechnological techniques for drug administration include nano-emulsions, nanosuspensions, nanotubes, and nanogels. However, nanogels are the most popular formulation due to their advantages over other approaches[6]. Nanoparticles have been effective in information retrieval throughout all phases of clinical practice since they are used in a range of new tests to diagnose and treat disease. The intrinsic advantage of the nanoparticles is based on their surface chemistry, which allows proteins to be bound on the surface. Gold nanoparticles, for example, are used as biomarkers and tumor markers in different biomolecule detection assays [7].

Nano-biosensors

Biosensor technology has made significant interdisciplinary contributions around the world. Biosensors have undergone substantial research and development in the medical, environmental, food, and pharmaceutical domains[11]. A biosensor is a receptor-transducer device that converts biological responses into electrical signals. Transducers often generate optical or electrical signals based on analyte-bioreceptor interactions[12].One of the primary reasons nano-biosensors are so effective and inherit an intrinsic nature that is magnified through their unique properties. Nano-biosensors improve illness therapy by expanding the scope of diagnostics into personalized medicine. This technique is likely to increase therapeutic efficacy while reducing the potential of side effects. These nanotechnology-based sensors have the potential to transform disease management by offering early identification, personalized treatment approaches, and better results for infected individuals. Furthermore, nano-biosensors can help personalize treatment by evaluating effectiveness and recognizing relapses early[13].

Nanogel containing polysaccharides

There are numerous kinds of natural polysaccharides, which contain a wide variety of distinct physicochemical features. (Rinaudo, 2008) Polysaccharides are also generally employed in hybrid nanogels to lower man-made polymer toxicity, to trigger cidal bactericidal action, or to decrease inflammation due to bioadhesion due to their high negative charge, enabling interaction with a wide variety of proteins, or as targeting moieties for encapsulation and nucleic acid delivery. Polysaccharides are polymeric carbohydrate molecules comprising repeated units of monosaccharides coupled by glycosidic bonds. They constitute a large category of naturally occurring biopolymers available in a variety of natural and inexpensive sources such as algae (e.g. alginate), plant (e.g. pectins, cellulose, cyclodextrins), microbes (e.g. dextran, pullulan), and animal (e.g. chitosan, hyaluronan) sources. Polysaccharides generally tend to be highly heterogeneous with respect to chemical composition and structure, differentiating between neutral or charged, linear or branched, and low or high molecular weight (Mw) polymers with miscellaneous hydrophilicity. Nucleic acid nanocarriers are often classified as either viral or nonviral vectors. Fig.1 show the advantages of polysaccharide containing nanogel[14].

Drug release From Nanogel

Release of drugs from nanogels relies on hydrophobic and hydrogen linkage interactions, complexation and coordination of drug molecules with polymer chain networks. Nanogel network characteristics, including crosslinking permits cross-link density, polymer molecular weight, degradation rate, and drug-biomacromolecule interaction, affect the drug release profile. Control of the nanogel network by internal for controlled medication release in response to a stimulus, e.g., changes in physiological fluids during drug release. Fig.2 illustrate the schematic representation of drug release from nanogel [15].

Properties of nanogel

1. Nanogel shows swelling property.
2. It has high drug loading capacity.
3. Nanogel size varies between 20 to200 nm in diameter.
4. Nanogel is porous as they have smaller size, hydrophobic nature and surface charge.
5. Solubility
6. Nanogel formulation is expensive since solvent removal of at the end of the process is needed
7. Small residual surfactant or monomer amount can still be present, causing toxicity.
8. There are also micrometre-sized particles among the particles. [16].

Advantages of Nanogels

1. High drug loading capacity.
2. They penetrate into capillaries and tissues both through paracellular and transcellular pathway.
3. Extremely biocompatible and biodegradable.
4. It is capable of entrapping hydrophilic and lipophilic drugs.
5. Due to its small size, it possesses very high permeability[17].
6. Non-immunological reactions restrict invasion by reticuloendothelial cells.
7. Increase the solubility of drugs with very low water solubility.
8. Sustained release of encapsulated drug.
9. Increases the stability of therapeutic agents by chemical or physical means.
10. Concentrate drugs more in target areas through enhanced permeation and retention.
11. Presented site-specific therapies if conjugated with cell-type specific ligands[18].

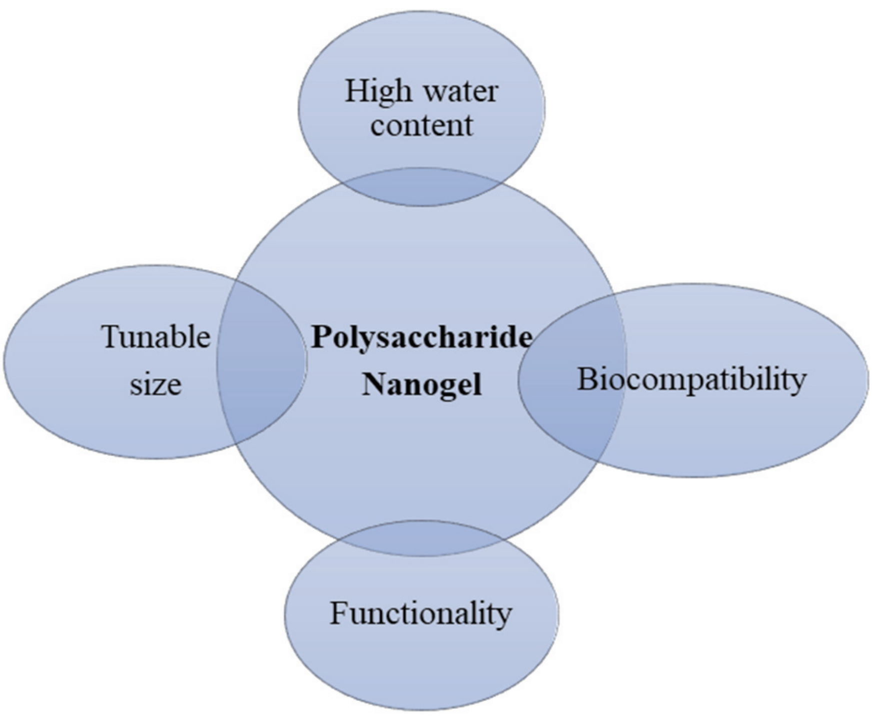

Figure 1. Advantages of polysaccharides containing nanogel: These are the main 4 advantages of polysaccharide nanogels

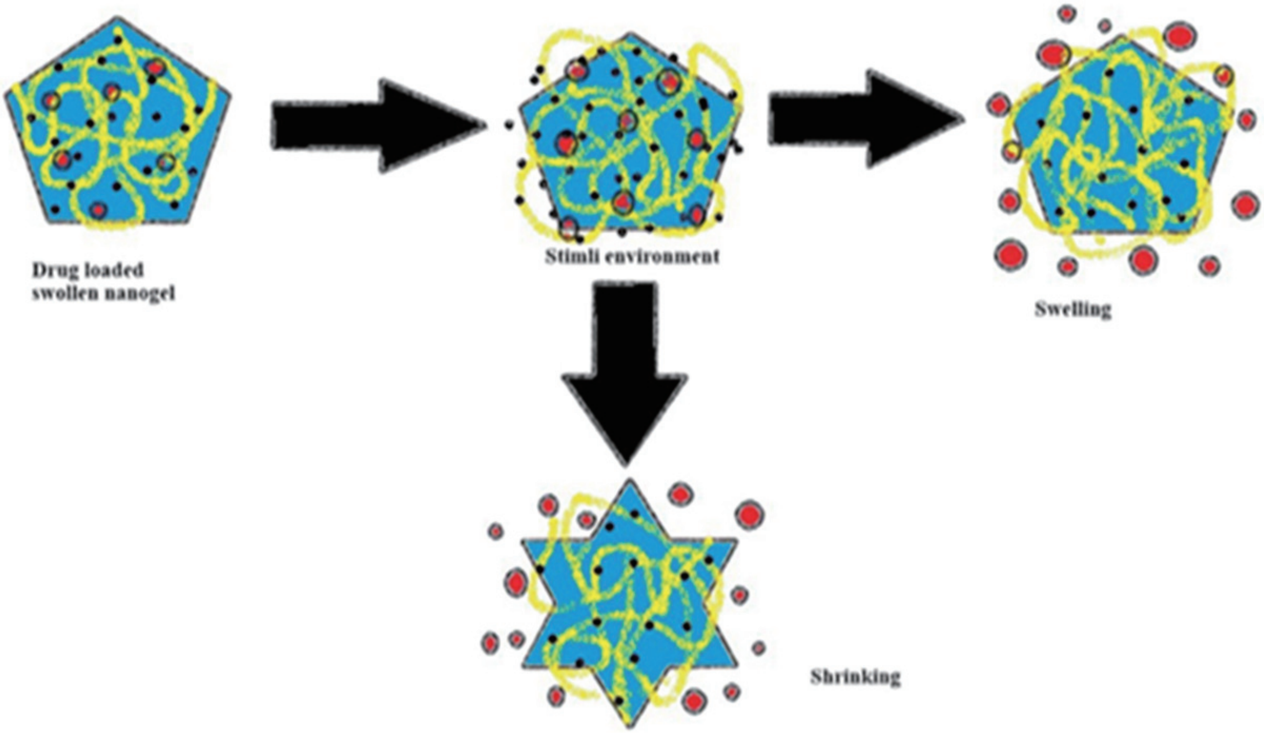

Figure 2. Schematic representation of drug release from nanogel. The figure depicts a stimuli-responsive nanogel drug delivery system. The nanogel first encapsulated drug molecules. When exposed to a stimulus (e.g. pH, temperature), it swells, releasing the drug. Alternatively, it shrinks, regulating drug release for targeted delivery. This intelligent mechanism allows for precise and effective drug administration.

Disadvantages of Nanogel

1. Nanogel systems are expensive as there is a need for solvent removal at the end.
2. Residuals of the surfactant or monomer may be present and be toxic.
3. They have some particles which are micro meter-sized.
4. It is difficult to increase the process because of the average size and weight [19].
5. A percentage of the particle is micrometre in size.
6. They are difficult to scale up due to their average weight and size. Nanogels have low efficacy for drug loading and have no control over drug release.
7. Nanogels are produced using severe polymerization techniques[20].

Characteristics of Nanogel

1. Biocompability and Degradability

Nanogels are either natural or synthetic polymers. Nanogels are biocompatible and biodegradable, thus minimizing organ accumulation. Nanogels are synthesized using polysaccharide-based polymers such as pullulan, dextran, and dextrin, chitosan, methyl cellulose, and ethyl cellulose. Polysaccharides are primarily carbohydrate polymers that are composed of repeating units of monosaccharides that are bound together by glycosidic bonds. Polymers are hydrophilic, non-toxic, stable, and biodegradable in nature [26].

2. Swelling characteristics in water

The most important feature of nanogels is swelling, which can be defined in terms of how much they absorb water or other aqueous solvents. Weight of the swollen nanogel and initial weight are used to measure the degree of swelling, making weight measurement the simplest form of measurement of the swelling equilibrium and kinetics. The type and quantity of monomer, cross-link density, temperature, pH, and ionic strength determine the extent to which the nanogel swells [20].

3. Drug loading capability

The superior drug loading capacity of nanogels is due to the presence of functional groups within the polymeric part. The functional groups are advantageous to drug carrying and drug-releasing behaviour, and some functional groups may be conjugated to drugs/antibodies for targeted

Table1. Difference between structural and biological characteristics of nanogel. This table summarizes the biological and structural properties of the material or system, probably in drug delivery or nanomedicine. These refer to physicochemical properties of material and emphasize the functional features. Such as its composition, charge, biocompatibility and targeting capacity[1].

Structural Characteristics	Biological Characteristics
1. Hydrophilic moieties and aggregates.	1.Biocompatibility, permeability, bioavailability, biodegradability, and low immunogenicity
2. Cationic charge.	2. Recognizes and binds specifically to nucleic acids.
3. Chemical modification allows specific features for desired applications	3. Binds and carrier' s nucleic acids into the cells.
4. Stimuli to sensitive.	4. Adhesive nature.
5. Attached to functional ligands on the surface.	5. Safe transport through biological barriers at targeted sites.
6. Stable in biological fluids.	6. High drug protection.
7. Able to encapsulate drugs, small molecules, peptides, and proteins.	7. Controls dose and release.

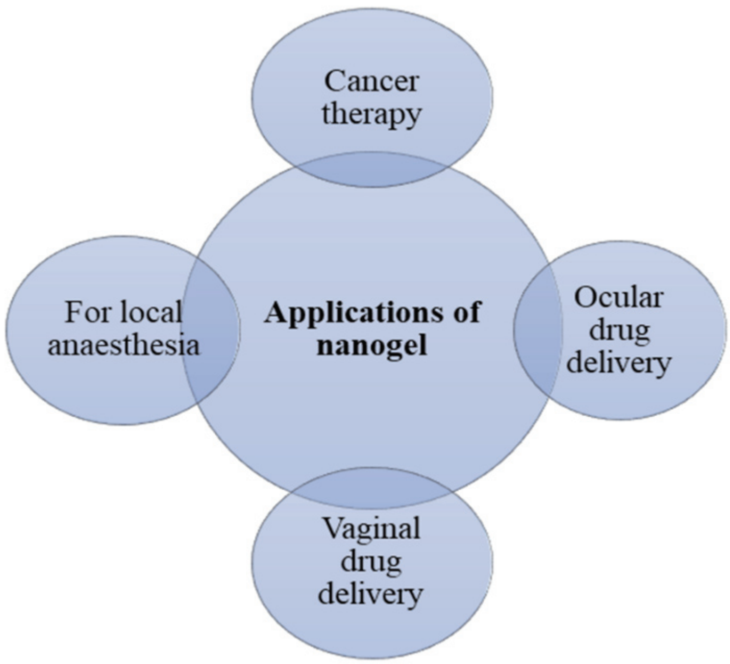

Figure 3. Schematic representation of application of nanogel[21].

application. This dangling functional group of polymeric chains facilitates hydrogen bonding or van der Waals contact forces of the gel linkage, which improves the efficiency of drug transport. Besides, the availability of functional groups at the drug or protein molecule interface is anticipated to result in maximum loading [27].

4. Particle size effectiveness

The particle size ranges of nanogels are also typically 20 to 200 nm in diameter, which is typically related to being efficient in avoiding rapid renal elimination while being small enough to decline uptake by the reticuloendothelial system. Even more very small sizes are related to good permeation abilities, because of which it has been found that it can cross the blood brain barrier (BBB). Size is the key parameter in the biodistribution of long-circulating nanoparticles based on physiological processes like tissue diffusion, tissue extravasation, hepatic filtration, and renal excretion [27].

Nanogel for cancer therapy

Nanogels have recently been proposed as drug delivery systems to overcome the shortcomings of existing conventional cancer therapies. Nanogels exhibit a variety of special properties that make them

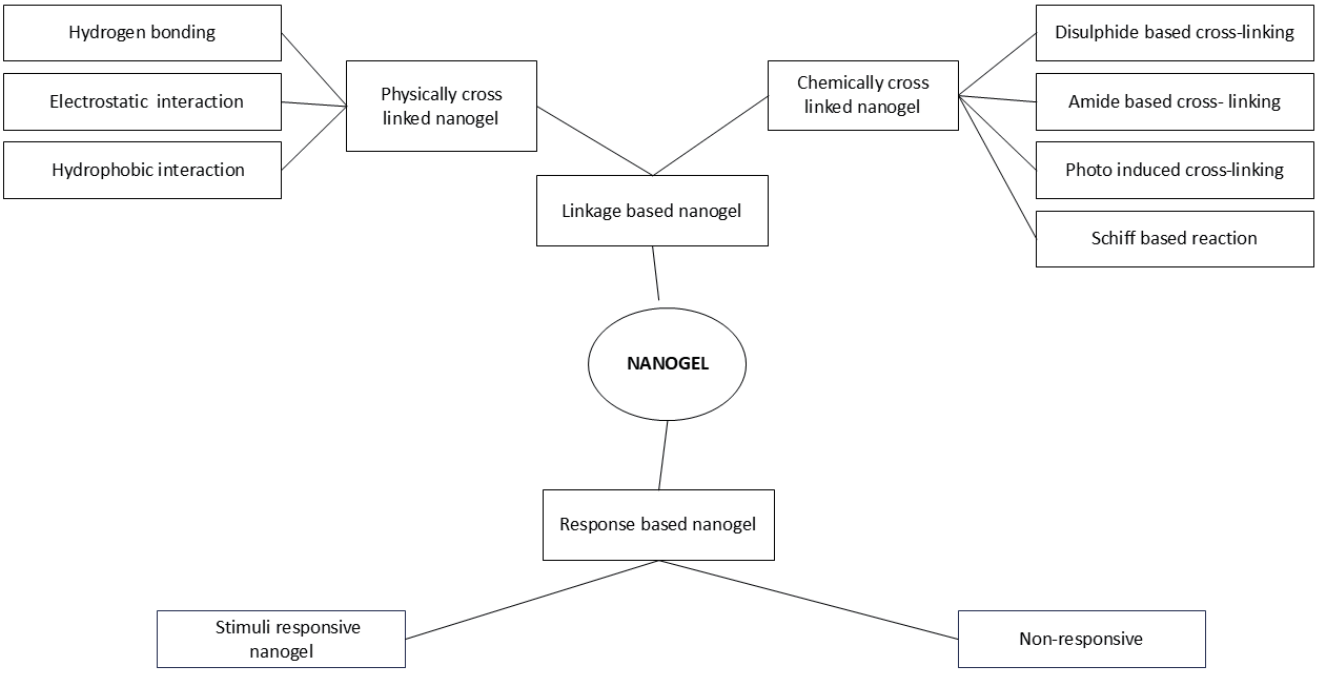

Figure 4. Classification of nanogel. This table classify into the response based and responsive based nanogel and it illustrate the properties of nanogel which include environmental factors, chemical bonds and functional groups, etc [20].

Table 2. Type of nanogel and their properties

Types of nanogel	Properties
1.Response Based Nanogel a. Non-Response Nanogel	1.Its swells through simple absorption when contacting to the aqueous fluids, thus it does not depended on external tiggers to make drug released. [22] 2. It is not dependent on the environmental conditions such as pH and temperature. [23]
2. Responsive Based Nanogel	1. The responsive nanogel may will de-swell depending on environmental conditions such as pH, light, magnetic field, ultrasound and strength of ions. [22]
b. Cross linked nanogel 1.Chemically cross linked	1. This is denoted by the type of chemical bonds and functional groups. 2. This type of cross-linking modifies the physiochemical characteristics of the gel system. [24]
2. Physically cross linked	1. In this combination of nanogel particles spread throughout the organic or inorganic matrix and is referred to as hybrid nanogel. 2.It is water-repelling, possesses electrostatic interaction and hydrogen bonding[25].

versatile and suitable for formulation into a variety of dosage forms for the potential treatment of a variety of diseases, including but not limited to cardiovascular disease, cancer, and other cancers[28].Nanogel enhances the in vivo bioavailability and safety of chemotherapy drugs[29]. Nanogels are an intelligent drug delivery system (DDS) that can improve the efficacy of cancer treatment by avoiding the limitations of conventional medicine. Conventional chemotherapy, employed by a non-selective mechanism, kills cancer and normal cells. This generates more side effects and toxicity. Stimuli-sensitive nanogels deliver chemotherapeutic drugs into cancer cells with fewer side effects and damage [30].Hormone therapy can effectively treat hormone-related malignancies, however some may raise the risk of diabetes and blood clots nanogels designed for targeted medication delivery in specific cancer types do not have these risk considerations.

Classic anticancer therapies are radiotherapy, hormone treatment, and chemotherapy, all of which require delivery in high doses and are not characterized by high tumor-targeting selectivity. This results in nonselective biodistribution, cytotoxicity to normal cells or tissues, cardiotoxicity, and cancer drug resistance[31].Reuse of an approved drug for different applications has proved to be a credible alternative in cancer drug design with the high failure rate, extensive labour, and time-consuming involvement in new drug discovery. It costs an average of $1.8 billion and 13 years of research to make it to clinical practice. Nanotechnology and nanomaterials have inspired innovations in cancer therapy such as tumor-directed drug delivery, imaging, and nanomedicine [32].

Chemotherapy

Chemotherapy remains the primary therapeutic modality in the treatment of cancer. Nanomedicines can be employed in cancer therapy due to the fact that they have characteristics like high tumor accumulation, drug loading, and low toxicity. Crosslinked nanogels have been employed in anticancer drug delivery against cancer in accordance with several studies. Cui et al. have synthesized a potent and simple-to-prepare nanogel for combination therapy.

Alginate (ALG) backbone nanogels were ionic contact cross-linked by calcium ions. Glycyrrhizin (GL) and DOX were loaded by hydrogen and ionic bonds, respectively, in nanogel. DOX release at acidic pH, i.e., in tumor tissue microenvironment, occurs. Loaded GL prevents macrophage phagocytosis of nanogel, which leads to improved tumor accumulation. In vivo results show that co-administration of DOX along with GL with nanogels can improve therapeutic efficiency [33].

Future prospects of nanogels as target drug delivery systems in cancer therapy

Nanogels can be employed for the improvement of drug delivery to cancerous tissue and cells. Patient-drug interaction relies on several factors during cancer therapy. Stability of dosage form in vitro and in vivo is crucial such that it is delivered to the target location in an intact manner. Nanogels are a stable dosage form that have the potential to deliver drugs to cancerous tissue using intravenous injection. Topical nanogel products can be beneficial in the case of localized skin cancers because they are elastic and can be designed to achieve best permeability. Researchers working on drug delivery should accord first priority to the employment of natural polymers that are safe, biocompatible, and biodegradable and investigate new types of nanogel [29].

Nanogels for gene therapy

Gene therapy involves the delivery of foreign genomic material into target host cells with the objective of achieving a therapeutic effect by correcting inherent dysfunction or sustaining the cells with new function. The most challenging step towards the effective delivery of genes seems to be the choice of an effective carrier system. New gene delivery technologies thus heavily depend on non-viral vectors with special focus on polymeric carrier systems. Polymeric nanogels are one class of nano-scale systems made of nanoparticles consisting of hydrogels made up of cross-linked polymer networks. Nanogels are designed for the specific purpose of delivering controlled and responsive release at the target location owing to their soft nature and swelling property [34]. The characteristics of the nanogels can be controlled by adjusting the monomers or polymers used, the process of functionalization and polymerization, and the synthesis condition. Emulsion, precipitation, and template polymerization have been utilized for the preparation of nanogels for gene and drug delivery [35].

Perspectives

Nanogels have been engineered according to that paradigm. For that, positively charged and amine-containing transporters were engineered to complex with nucleic acids and interact with cell membranes for internalization via electrostatic interactions. In place of charged nanogels, ligand-based approaches have been presented for the development of charge-free nanogels. More complex structures should be engineered as well. Development of core-shell nanogels is one of those instances. Engineering the three-dimensional structure could enhance the application of responsive properties. Another innovation of nanogels could be incorporation of charge conversional moieties. Charge changing transporters has been engineered to deliver drug, proteins and genes. Then, use of gene therapy may need a justification; "proper use" and "misuse", "abnormal" and "normal" will have to be defined. Societal value of tolerance could be impacted within this process [36].

Nanogel use in ocular therapy

The eye, being an important, complex, and fragile organ of the human body, has a major bearing on the quality of work, study, and life. As per the Lancet Global Health report, in 2020, almost 433 million individuals were blind and 553 million had various levels of vision impairment globally. People face a huge challenge in preventing and treating ocular diseases. The eye is provided with a multitude of physical and chemical protective mechanisms. Whereas these physical and chemical barriers facilitate the normal functioning of the eye, they present a challenge to the delivery and bioavailability of ocular drugs Conditions that belong to the anterior segment of the eye (ASE), including conjunctivitis, disease of the dry eye, and cataracts, are major contributors to visual impairment, Besides, eye diseases that belong to the posterior segment of the eye (PSE), including the retina and optic nerve, and conditions like glaucoma, diabetic retinopathy, and age-related macular degeneration, also play an important role in producing vision loss[37].

Nanotechnology in ocular drug delivery

Nanotechnology has been utilized for countless applications in medicine, ranging from disease diagnosis to therapy. It has various applications like enhanced ocular drug delivery through the development of effective drug delivery systems (DDSs) for the aim of enhanced bioavailability and drug penetration through the different ocular barriers.

a) Nanoparticles
b) Nanosuspension
c) Nanofibers
d) Nano-micells
e) Dendrimers
f) Nanoliposomes
g) Nanogel

Barriers in ocular drug delivery

Anatomical structure of the eye and physiological properties prevent entry of drugs and other substances into the eye. Three main barriers to ocular drugs are precorneal, corneal and conjunctival, and blood-ocular barriers. Static, dynamic, or metabolic are the categories.

a) Precorneal
b) Corneal and conjunctival barriers
c) Conjunctival
d) Blood-Ocular barrier
e) Blood retinal barrier[38].

Nanogel in vaccine delivery

Vaccination is one method of creating active immunity, which is immunological stimulation to produce cellular immunity (T-cell immunity) and a humoral immunological response (IgG antibodies) of specificity to certain antigens. The primary benefit of vaccinations that employ live, attenuated microbe particles is a high T-cell response; such vaccines are, however, risky. Since protein- and peptide-based vaccinations contain adjuvants such as aluminium salts, this benefit is not claimed for them. Thus, there is a need to formulate better, safer, and more effective vaccinations that do not employ attenuated germs or cause inflammation by aluminium salts. Targeted drug delivery. Nano-systems are one of the areas of research being explored to develop a next generation of vaccinations. To treat or cure infections, cancer, allergy, and/or autoimmune disease, nanogels can be designed to upregulate or downregulate the immune response[20].

Conclusion

Nanogel are a versatile and promising drug delivery method. Nanogel with the unique characteristics by their tuneable dimensions, ease of fabrication, compatibility with biological systems. Its responsive behaviour is highly useful since it facilitates release of the drug at the target site. With the physical, chemical, biological stimuli the nanogel rapidly and reversibly transition from swelling to collapse. The nanogel demonstrates the fantastic potential of gene therapy, cancer therapy and ocular therapy. There are numerous therapeutically genetic substances in existence nowadays, but targeting the right locations within the body is still a significant challenge.

For that, Polymers are handy tools for this. For this crosslinked nanogels may be engineered to assist each step of gene delivery, from transporting the gene to the target location, to deliver it within cells and assist the gene to function correctly. Also, in the development of ocular drug delivery systems there are several challenges to be overcome which are biomaterial compatibility, sterilization; large scale manufacture and drug and device long-term stability. to overcome these challenges the use of controlled release drug delivery has been proven. Recently, nanotechnology of drug delivery in the eyes has been increasing in fact there are approximately 51 nanomedical products are reported in markets and this nanomedical products are present in the different nano-formulations including nanosuspension, nano-emulsion, nano-micelles, etc.

Apart from this future research can be directed towards the application of biodegradable polymeric systems and nanotechnology to develop improved nanodevice to enhance ocular drug delivery. In cancer treatment there are numerous challenges are encountered like the chemotherapy which was administered by the conventional cancer medicine has a non-selective action that targets both cancerous and non-cancerous cells. Such result obtains more undesirable effect and toxicity but stimuli-sensitive nanogels are capable to overcome such challenge and successfully deliver chemotherapeutic drugs. Nanogel enhances drug delivery to cancer cells and tissues. Overall, the detailed review exemplifies the wide potential of drug delivery systems based on nanogel to change the course of therapeutics.

Author's Contribution

MK: Supervision
PS: Conceptual & Supervision
DM: Literature review & Paper Writing
VR: Literature review & Paper Writing
SC: Editing & review
AD: Editing & review

Abbreviations

NGs: Nanogels
DDS: Drug Delivery Systems
PSE: Posterior Segment of the Eye
ASE: Anterior Segment of the Eye
PEG: Polyethylene Glycol
PEI: Polyethylenimine
Nm: Nano-meter
BBB: Blood Brain Barrier

Competing Interest

All the authors declare that they have no competing interests.

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