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Overview of nanogel and its applications

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Abstract

Nanogel have emerged as a versatile drug delivery system for encapsulation of guest molecules. A nanoparticle which is composed of hydrophilic polymer network known as Nanogel having range from 100-200nm. Nanogel have swellable and degradation properties with high drug loading capacity, high stability, sustained and targetable manner, large surface area. Therefore, nanogel are more productive than conventional and micro-sized delivery. In recent year in the field of biotechnology nanogel were prominently used to deal with genetics, enzyme immobilization and protein synthesis. Moreover, it has productive asset for the development of novel therapeutic system in medicine. These are soft materials capable of holding small molecular biomacromolecules, therapeutics, and inorganic nanoparticles within their crosslinked networks, which allows them to find applications for therapy as well as imaging of a variety of disease conditions. These properties not only enhance the functionality of the carrier system but also help in overcoming many challenges associated with the delivery of cargo molecules. This review aims to highlight the distinct and unique capabilities of nanogels as carrier system, Synthesis of nanogels, Types of Physical and chemical crosslinked nanogels, Stimuli responsive behavior, *In vivo* behavior, Therapeutic drug carrier, marketed formulation of Nanogels and the last part of review summarizes the applications of nanogels in various diseases. Transdermal drug delivery, diabetes, anti-inflammatory, vaginal drug delivery, neurodegenerative diseases, ocular diseases, autoimmune disease, and anticancer treatment for specially targeting the cancer cells, thereby reducing uptake into healthy cells. This nanogel drug delivery is a phenomenal system, and further depth study is required to explore their interaction at cellular and molecular levels and minimize the challenges.

Keywords: Nanogel; Micromolecules; Anticancer Therapy; Neurodegenerative Diseases; Antibody Conjugation

1. Introduction

The term 'nanogels' defined as the nanosized particles which forms crosslinked polymer by physically or chemically. It was first introduced by cross-linked bifunctional networks of a polyion and a non-ionic polymer for delivery of polynucleotides [1]. Nanogel are soluble in water, but have properties different from linear macromolecules of similar molecular weight. Such structures, along with their bigger analogues [2]. Nanogels are typical formulations usually size range of 100 nm, to maintain the three-dimensional structure by varying solvent quality and branching the volume fraction can be altered. Since the of gene delivery has now become possible within cellular organelles for gene silencing therapy therefore, Nanogels have transformed the field of gene therapy [3]. Nanogels are expanded in nano-sized framework formulated of hydrophilic or amphiphilic polymer chains, which can be ionic or non-ionic. In spite of drug delivery system, the nanogel has been scrutinized from longer period of time in making miscellaneous agents like quantum dots, dyes and other diagnostic agents [4]. As a result of specific delivery system anticipation, the nano-sized microgel and hydrogel has arisen. A large variety of polymer systems and the easy alteration of their physico-chemical characteristics have given advantageous form of nanogel formulations [5]. Nanogels are nanoparticles composed of a

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hydrogel with cross-linked hydrophilic polymer with 100–200 nm particle size [6]. The chemically and physically cross-linked synthetic polymers [7] or biopolymers constitute nanogels [8]. Micro molecules or macromolecules through filled the pores of nanogels [9]. Nanogels have expandability and degradation properties with flexible size, large surface area and high-water content [10]. Nanogels are mostly used in sensing, diagnostics, and bioengineering, but in spite of that it is also used in drug delivery [11]. Nanogels having high stability, high drug loading capacity, prolonged contact time with the skin surface which leads to more convenient as a transdermal drug delivery system. Hence nanogel are more productive than conventional and macro-sized delivery. Water-soluble non-ionic polymers like hydroxyl propyl methylcellulose as well as ethyl cellulose are especially used to stabilize nanogel dispersions [13- 17].

The separation of phase could be found in drug-loaded nanogels due to interactions (electrostatic, hydrophobic van der Waals) between the polymeric matrix and the active agent, which could be impeded by dispersing hydrophilic polymers. To the skin surface by forming the protective layer around the nanogel the dispersed hydrophilic polymer becomes exposed and allowing to drug particles to remain dispersed in the gel matrix [18- 20].

For the formulation of biopolymer-based nanogels, modified natural biopolymers possess a high degree of functional groups with additional functional crosslinkers used Innovative techniques such as, chemical cross-linking, photopolymerisation, chemistry-based cross-linking etc., these all are used to attain the self-assembly and cross-linking of hydrophilic block copolymers. Between internal and external layers of nanogels, block polymers permit the control of drug release from a polymer matrix [21, 22].

The adaptability of their architecture allows for consolidation of a plethora of guest molecules ranging from inorganic nanoparticles to biomacromolecules like proteins and DNA with suitable modifications of the materials used for their construction, without compromising with their gel-like behaviors [17, 23- 25]. Modified with ligands to permit receptor mediated drug release at the site of action for target specific or cell-specific drug delivery [26-27]. Drug or biologically loaded nanogels can cross biological barriers and release the therapeutic agent inside cells [28-30].

In the field of biotechnology in recent year the nanogel were prominently used to deal with genetics, enzyme immobilization and protein synthesis, therefore it has provided an effective asset for the novel therapeutic system in medicine.

To the effective cancer therapy polyacrylamide used as a polymer for core shell magnetic nanogel. For the transdermal delivery system Pluronic poly (ethyleneimine) was used to prepare a thermo-responsive nanogel. In Anticancer drug as well as many drugs it has enhanced the efficacy and safety due to chemical composition of Nanogel-based drug delivery which has been confirmed by *in vivo* studies in animal models. Nanogel is a promising and innovative drug delivery system that can have crucial role in overcoming the problem associated with nonspecific effect and poor stability of old or new therapeutics [31- 35].

For prolonged and controlled release manner nanogels are used to deliver all biologically active agents. Nanogels forms three-dimensional structures in which drugs, polymers and dispersed phase of liquid can be entrapped [36-37].

Availability of various polymer systems and respite of alteration of their characteristics have contributed nanogels formulations advantageous.

Nanotechnology, it is a novel technique, provide a comprehensive scope for a smart drug delivery and drug manufacturing (nanomedicine) approach involving the synthesis and characterization of materials or molecules, Design and devices that have constructive function at manometer scale. The researches in academic laboratories and pharmaceutical companies all over the world reported that on the disease prevention, diagnosis and treatment progression of novel nano-sized particulate drug delivery systems (DDS) have shown the keen impact [38].

2. Advantages of nanogels

- Highly biocompatible (due to high water content and hence behave like natural tissue) and therefore immunological responses
- Nontoxic because of biodegradable carrier.
- Loading capacity of drug is high.
- Easily escape entrapment by reticuloendothelial system.
- Crosslinking densities of drug delivery can be controlled by tuning
- Better permeation via biological membranes due to extremely small size

- Easily can incorporate both hydrophilic and hydrophobic drugs and charged solutes
- Excellent transport features
- Because of tiny volume drug can reach to the smallest capillary vessels, and to penetrate the tissues either through the transcellular or the paracellular pathways [39-40].
- Prolonged release of drug from the formulation by the addition of a polymeric network [41].
- In aqueous media the free-flowing pearlescent solution of the nanogels can easily disperse [41-43].
- Easy for administration in parenteral and mucosal [44].
- From the solution reduced the premature leakage of the drug [45].

3. Disadvantages of nanogels

- Expensive strategy to altogether eliminate the solvents and surfactants toward the finish of arrangement.
- Adverse impact can be granted because of Surfactant or monomer follows can be remain.
- Some small particles of particles are in the micrometer range
- Scale up isn't simple because of mean size and weight [46-47]
- Nanogels has limited drug-loading capacity and suboptimal regulation of drug release [48].

Sometimes collapse the structure due to strong interaction between drug and polymer decreases the hydrophilicity of the nanogels, leads to irreversibly entrapping the drug molecules and enhancing the hydrophilicity of the nanogel matrix [49-50].

4. Properties of nanogels

4.1. High water content/swellability

Nanogels have rapid swelling and de-swelling properties due to their high affinity functional group of polymers [1, 51].

4.2. Softness

In the biomedical field and biodistribution the softness of nanogel is crucial parameter and it can be adjusted by variation on the structure of nanogel [52].

4.3. Colloidal stability

Prevent the development aggregation into the bloodstream due to the surface charge of polymers inhibits the development along with their associated problems. This could be due to higher repulsive forces between particles leading to nanogel stabilization which is altered by increasing the zeta potential. Polyethylene glycol is also chemical method use to integration of surfactants which produce a steric effect and hydration forces to give a stable nanosuspension [1, 53].

4.4. Biocompatibility and degradability

Nanogel are synthesize by using natural or synthetic polymers. For preventing the deposition in systemic circulation this polymer plays vital role as of these are biocompatible and biodegradable. In addition to this, formulation of nanogel Chitosan, poly-acrylic acid, methyl cellulose, sodium alginate, and several polysaccharide-based polymers like dextran, pullulan, and cyclodextrin can be used. Carbohydrate based polymer like Polysaccharides are typically formed of repeating monosaccharide units linked by glycosidic bonds. These polymers are biodegradable, stable, hydrophilic, non-toxic in nature [54].

4.5. Particle size

In endothelial area of skin tissue nanogel can easily diffused and in some cases through a specific pathway. Due to particle size, many routes of administration face the challenge of crossing the Blood Brain Barrier (BBB). So, to overcome this issue, nanogels were developed which have a size in the diameter range from 20-200 nm [1, 55]

Nanogels are effective in avoiding the rapid renal exclusion due to range of size in 10-100 nm. However small enough to avoid the uptake by the reticuloendothelial system [56]. Small particle size resulting good permeation capabilities [1]. On the basis of physiological parameters like hepatic filtration, tissue extravasation, tissue diffusion, and kidney excretion Size of nanoparticle is a vital factor in the biodistribution of long-circulating as well [57].

4.6. Higher Drug Loading Capacity

The higher drug loading capacity of nanogels depend on the functional group present in the polymeric unit. These functional groups are very helpful in a drug carrying and releasing, despite of these some functional groups having ability to conjugate the drug and antibodies for targeting purpose. These hanging functional groups of polymeric chain provide the initiating the hydrogen bonding and wander wall forces of interaction within the gel network. Therefore, ease the drug carrying capacity [1].

4.7. Solubility

Nanogels are able to solubilize diagnosis agent and hydrophobic agents in their core or networks of gel [1]. In addition, lyophilic molecules can be solubilized into lipophilic domains presented in some nanogels. For example, in cholesterol-modified pullulan nanogel prostaglandin E2 was solubilized. Doxorubicin was also loaded in amphiphilic cross-linked nanogels based on Pluronic F127 or poly [oligo (ethylene oxide)-methyl methacrylate]. Notably, in most cases loading due to hydrophobic interactions alone results in relatively low loading capacities [57].

4.8. Electromobility

Nanogels is prepared without harsh condition and employing energy like sonication or homogenization, which is critical for encapsulating biomacromolecules [1].

4.9. Colloidal Stability

Over the surfactant micelles nanogels or polymeric micellar nanogel systems have a higher stability exhibit slower rate of dissociation, lower critical micelle concentrations, and longer retention of loaded drugs [1].

4.10. Non-immunologic Response

This nanogel drug delivery system usually doesn't produce any immunological responses [1].

5. Synthesis of nanogels

Especially nanogel was classified by either (covalently) crosslinking of physically or chemically method. Some are the techniques used to allowing the preparation of nanogel like conventional and controlled/living radical polymerization with different composition, dimensions, and architectures including core-shell and hollow nanogel particles. For the incorporation of functionalities in the interior or posterior, that allows the initiators and macroinitiators, which provide multivalent bioconjugation [58- 62].

By performing the core-shell self-assemblies like polymer micelles should allow introducing the high degree of special domain organization into nanogel for the variety of other crosslinking reactions carried out [63-64].

Recently, in nanoscale fabrication methods various unique feature has been developed for fabricating well-defined nanogel like precise control over size, shape, deformability and surface chemistry in a high-comprehensive manner [65-67].

6. Types of physical crosslinked nanogels

Nanogels	Examples	References
Hybrid	<p>Composite of nanogel particles dispersed in organic or inorganic matrices.</p> <p>Ability to create complexes with various proteins, drugs and DNA; may coat the surface of liposomes, particles and solid surfaces including cells.</p> <p>Ready to deliver insulin and anticancer drugs.</p> <p>Cholesterol-bearing pullulan composed of pullulan backbone and cholesterol branches. The molecules self-aggregate and form stable nanogels through physical crosslinking points by the association of hydrophobic groups.</p> <p>Nanogel in aqueous medium by self-assembly or aggregation of pullulan-poly (N-isopropylacrylamide), hydrophobized polysaccharides and hydrophobized pullulan.</p>	[68- 70].

Micellar	<p>Obtained by supramolecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions.</p> <p>Core-shell morphological structures obtained through hydrogen bonds, with core hydrophobic block segment surrounded by shell hydrophilic polymer block that stabilizes the complete micelle</p> <p>Micelle's core provides enough space for drugs/biomacromolecules encapsulation. The drug molecules within the hydrophobic core are protected against hydrolysis and enzymatic degradation.</p> <p>N-isopropylacrylamide based micelle systems, evaluated as drug delivery devices.</p>	[71]
Liposome modified	<p>Liposomes bearing succinylated polyglycidol undergo chain contracting beneath pH 5.5 and deliver calcein to the cytoplasm</p> <p>Liposomes adjusted with poly (N-isopropylacrylamide) make temperature and pH sensitive nanogels, researched for transdermal drug delivery.</p>	[72-73]

7. Type's chemical cross-linked nanogels

7.1. Inverse Emulsion Polymerization

For the continual emulsification, Inverse emulsion polymerization could be a polymerization reaction initiated in water-in-oil emulsifiers within the oil phase. Various factors can regulate the sizes of nanogels like surfactant, feed ratio of the monomer, crosslinker and pH [74].

7.2. Reversible Addition-Fragmentation Chain Transfer (RAFT) Polymerization

Reversible Addition-fragmentation Chain Transfer (RAFT) during the radical polymerization, a polymer undergoes various reactions administrated of dithioester compounds; these reactions include reversible addition, reversible degradation of adducts, chain transfer reactions and control the mass of the polymer.

By altering the length, configuration and properties of the polymers, RAFT technology can change the micelle structure of amphiphilic polymers. Poly (N-vinylcaprolactam) (PVCL) has become a stimulating biocompatible and temperature-sensitive polymer [75].

7.3. Click Chemistry Crosslinking Polymerization

Click chemistry, it's a most optimistic approach for the formulation of nanogel. Which involves the copper-free click reaction, pseudo-click chemistry, and copper (I)-catalyzed azide-alkyne (CuAAC) click. As an example, a pH-responsive nanogel was obtained through thiol-ene click chemistry, an efficient method of nanogel preparation without by products, by polymerization with methoxy polyethylene glycol acrylate (mPEGA), pentaerythritol tetra (3-mercaptopropionate) (PT) and ortho ester diacrylamide (OEAM) [76].

7.4. Photo-Induced Crosslinking Polymerization

within the process of irradiation, intermolecular crosslinking, resulting in formation of radical and atom potentially polymer get convert into microradicle through breakdown of water molecules which develop nanogel [77].

Therefore, by regulating the wavelength or energy of the laser the crosslinking density are often adjusted [78].

7.5. Stimuli-Responsive Behavior

Stimuli-responsive systems nanogels has been widely used on their stability, high drug-loading capacity, simple synthesis and talent to be modified in multiple ways. Importantly, As compared to other drug delivery system (DDSs), nanogels are more highly aware of mutative environments through their unique 3D network structures, which may be easily adjust in several environments to regulate drug release [79].

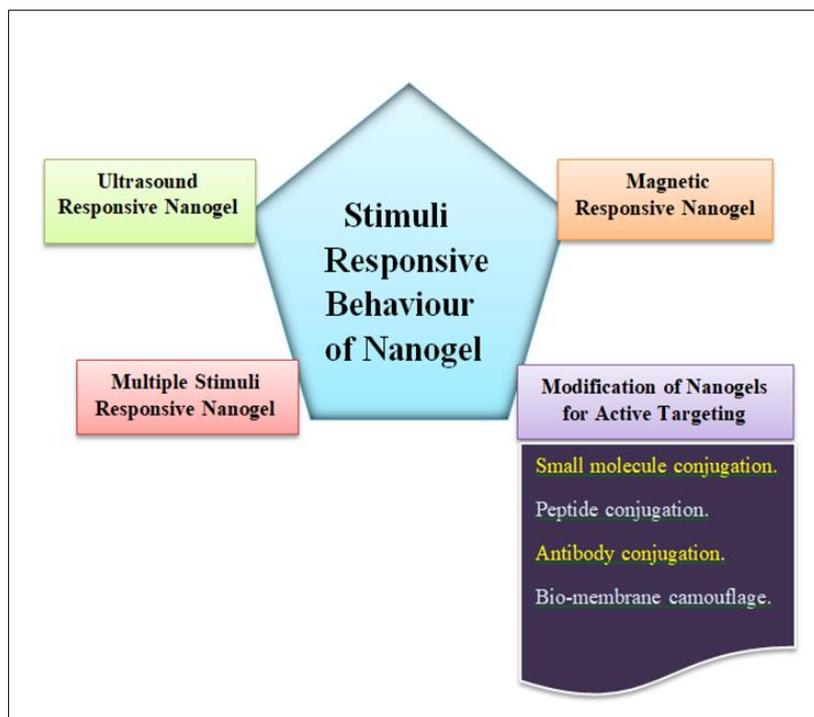


Figure 1 Mechanism of nanogel

8. Thermo-Responsive Nanogel

Thermo-responsive nanogels are one of the finest specific responsive DDSs. Thermoresponsive nanogels are control release rate of drug loaded inside due to present shrinkage-swelling behaviour with changes the environmental temperature. Furthermore, Microenvironment diseases associated deposition and enhanced the intracellular efficiency can be achieved by the reduction of particle size and further benefit the pharmacological outcomes. N-isopropylacrylamide-co-N-isopropylmethacrylamide nanogels (NIPAm) are a typical thermosensitive derivative that has been widely applied in biomedicine [80- 85].

In the contemporary report, polymerization initiating of NIPAm with AA and N-[3-(dimethylamino) propyl] methacrylamide (DMPMA), the quantity natural process temperature (VPTT) of pNIPAm-based nanogels was adjusted to close the physiological temperature (37°C). With APS as an inissiaer and sodium dodecyl sulfate (SDS) as an emulsifier. For protein loading this thermo-sensitive nanogel was introduced by aqueous imprinting precipitation. More importantly, the template protein lysozyme exhibited imprint-release property accompanying with the temperature-dependent shrinking-swelling of nanogel, indicating the promising controlled delivery ability [86].

9. Magnetic-Responsive Nanogels

Besides the magnetic-targeting, hyperthermia magnetic nanoparticles can assist under extra magnetic field, undergoing the conditions of alternative magnetic field (AMF) [87-88].

Therefore, temperature-sensitive nanogels and the MNPs were applied to construct the hybrid nanogels and loaded with DOX (DOX-MagNanoGels). Nanogels provide 3D network structure due to co-encapsulation of MNPs and chemical drugs. Furthermore, when the drug applied the shrinking-swelling property of nanogels guarantees stimuli-drug release. The DOX-MagNanoGels despite of displayed enhanced internalization of cancer cells and release of DOX because of the shrinkage of nanogels by MNPs-induced magnetic hyperthermia, but also possess the possibility for magnetic resonance imaging (MRI) and magnetic targeting in cancer diagnosis and therapy [89].

10. Ultrasound-Responsive Nanogels

In transdermal administration and central nervous system (CNS) treatment Ultrasound (US)-mediated drug delivery systems are mostly used [90-91].

The liquid US agent perfluorohexane (PFH) evaporated to gas, benefitting the triggered drug release when US was applied [92].

The synthesis of a redox-sensitive hybrid nanogel (MSNss-gel) by the mesoporous silica nanoparticles' which is utilized for the hydrophilic drug like DOX and the hydrophobic PFH co-loading having core and polymer shell, In the tumour region of cancerous cell polymer shell promote the controlled release of DOX and enhanced the US contrast imaging in cell line [93].

11. Multi-stimuli-Responsive Nanogels

The multi-responsiveness combinations have been studied with some modification approach like pH–temperature dual-sensitivity combinations [94].

At the moment of circulation, the thermo-responsive nanogels could reduce the Cl–-triggered drug release, simultaneously the acidic environment in the tumour region would achieve the controlled release of CDDP, improving antitumor efficacy and minimizing adverse effects.

12. Modifications of Nanogels for Active Targeting

The interaction between the ligand and specific cellular or subcellular receptors can be achieved by the active targeting. Furthermore, the pharmaceutical modification of the NPs through the biological ligands such as small molecules, proteins, peptides, polysaccharides were formulated.

12.1. Small-Molecule Conjugation

The antitumor targeted latest therapies reveal that the folic acid (FA) has become a promising approach that can specifically interact with cells overexpressing folate receptors (FRs). FRs are situated in ovarian cancer cells of human, but are hardly expressed in normal tissues. The differential expression of FR in ovarian cancer and other tumour tissues makes it an attractive biomarker for the diagnosis and treatment of tumours [95].

The intracellular uptake rate of FA nanogel in FA- negative cells reported that (approximately 20%). While the intracellular uptake results shown in FA-positive cells (approximately 80%) was much higher than in FA-negative cells. *In vivo* data detected that CDDP- loaded FA-nanogel shows reduced the toxicity in kidney, where an increase the therapeutic effect in ovarian cancer cells in animal model.

12.2. Peptide Conjugation

Recently, the active targeting with some peptide ligands has been extensively investigated in both therapy and imaging. In the peptide conjugation with nanoparticles could elevate the tumour targeting. Example, the tumour-homing peptide LyP-1, which was reported to bind precisely with p32 protein of a series of tumour cells [96].

In addition to LyP-1, the RGD peptide, a tripeptide consisting of L-arginine, glycine and L-aspartic acid, is a cell adhesion sequence that mimics cell adhesion proteins and can bind to integrin receptors on angiogenic endothelial cells and tumour cells, such as malignant glioblastoma cells, bladder cancer cells and $\alpha V\beta 3$ integrin receptor-overexpressing breast cancer cells [97].

12.3. Antibody Conjugation

In the development of nanogel the antibody used mostly because of higher affinity for binding sites, higher targeting and precision, additionally to the current the antibody is used as a ligand modification [98-99].

In addition to cell adhesion sequence like LyP-1, the RGD peptide a tripeptide consisting of L-arginine, glycine and L-aspartic acid, that mimics cell adhesion proteins and might bind to integrin receptors on angiogenic endothelial cells and tumor cells, like malignant glioblastoma cells, bladder cancer cells and $\alpha V\beta 3$ integrin receptor-overexpressing carcinoma cells [97]. Furthermore, maintain the affinity to tumor cell the cyclic RGD (cRGD) peptide has also been detected. Therefore, for tumor targeting the cRGD-modified nanogels may be the versatile and prominent drug carriers.

The combining the tumor region enrichment with controlled drug release within the tumor environment, the twin drug-loaded nanogels displayed enhanced therapeutic outcomes in MBA-MD-231 carcinoma model [100].

12.4. Bio membrane Camouflaged

A bio membrane-camouflaged it is a new strategy of nanomedicine has been invented. Membrane-camouflaged DDSs can imitate the structure and function of cell membranes. It exhibits the superior passage through physiological barriers, more precise accumulation, prolonged circulation time and improved drug efficacy compared with conventional ligand-modified delivery systems [101-102].

Mesenchymal stem cell membrane-coated gelatin nanogels (SCMGs) were loaded with DOX and exhibited considerable tumor-targeting ability because of tumor recognition by mesenchymal stem cells. Compared to the free DOX-treated group, the enhanced antitumor efficiency was observed in the group administrated by nanogels with mesenchymal stem cell coating, as well as the excellent biocompatibility with organs [103-104].

12.4.1. *In vivo Behavior*

Nanogels are macromolecular systems having ability to realize long circulation half lives of their delivery *in vivo*, together with their ability to deliver this cargo at the specified site.

Nanogels are designed on the premise of route of administration and overcome associated barriers and reach the circulation intact. Nanogels having sustained circulation half-life of their cargo by 1) in case of small molecules preventing their fast clearance and 2) prevent quick distortion or metabolism which is more relevant for biomolecules. One amongst the foremost crucial hurdles is by their clearance via organs of MPS like spleen, liver, to achieving prolonged circulation opsonization of the nanogels. Where, they're obsessed by the resident monocytes and macrophages [105].

Nanogel partially liquefies the splenic filtration for their softness and deformity. This is the humonguous properties of nanogel. This can be brief by an instance in nature, namely erythrocytes which in spite of having a size range in microns are easily able to pass through the splenic filtration bed that has a pore size of few hundred nanometers, due to their flexibility and deformability [106-107].

To the targeted delivery of nanogel and other nanomedicine in tissue or cells associated manner, there are many small molecules, peptides, aptamers, antibodies or antibody fragments have been exhibited. On the Biodistribution profile of the nanogel ligand-mediated targeting influences the more as compared to nontargeted nanogel. The high expression of the receptor to targeted nanogel this can assist to prevent the excessive deposition of the nanogel at target site and therefore reduce the associated side effects [108].

12.4.2. *Nanogels as a Therapeutic Drug Carrier*

Nanogels can incorporate 30% weight and highly expandable property. No. of biological molecules Interacted with the electrostatic, van der Waals and or hydrophobic/covalent interaction occur with the polymer chain. These loading capabilities are unorthodoxly high and exceed those of liposomes and polymeric micelles. As a outcomes of drug loading, the nanogels collapse forming stable nanoparticles, during which biohazard is entrapped. Aggregation will be prevented by Introducing dispersing hydrophilic polymers (e.g., PEG) in a very nanogel structure. Hydrophilic polymer chain become exposed during the collapse of the drug-nanogel complex and forms the protective layer round the nanogel. The control and flexibility of polymer chemistry allows designing and development of broad range of drug formulations and inclusion of multiple therapeutic cargos within the identical nanogel carrier [109-110].

12.4.3. *Nanogels for Small Therapeutic Molecule Delivery*

The cargos of swelling nanogels easily allows in an aqueous environment. The advance design of the nanogel could be a productive asset to tune the drug release rate, affect carrier cell interaction, improved the desired therapeutic effect of the drug. One of the most significant features of weakly-crosslinked polyelectrolyte nanogels is their ability to incorporate molecules of the opposite charge. For instance, for immobilization of negatively charged biological active compound like retinoic acid, Indomethacin, valproic acid explored by the cationic crosslinked PEG-polyethyleneimine (PEG-PEI) nanogels [111-112].

It was detected that in mammary cancer cells of animal model these drug-loaded nanogels inhibited the tumor growth by delivering the active triphosphates of therapeutic nucleoside analogs [113].

Recently, the same group studied that the beneficial advantage of cationic nanogel incorporated active 5'-triphosphates of nucleoside reverse transcriptase inhibitors over free drugs in the antiviral therapy of HIV-1 infection in the central nervous system (CNS) [114].

To the local drug delivery of dexamethasone for the prevention the acute pulmonary inflammation the nanogel which use having biocompatible physically crosslinked hybrid nanogels consisting of a partially denaturated lysozyme cores and dextran shells. The nanogels were coated with antibodies directed to endothelial determinant for target the pulmonary vasculature [115-116].

13. Nanogel for oligonucleotide delivery

Therapeutic oligonucleotides designed for targeted inhibition of specific mRNA sequence which is useful measure for the treatment and diagnosis of cancer and neurodegenerative disorders which includes antisense oligodeoxynucleotides (ODNs), small interfering RNAs (siRNAs), and the more recently discovered micro RNAs (miRNAs) [117-125].

The incorporation of the ONs delivery into targeted cells it remains big obstacle to realizing their full therapeutic potential due to ONs are negatively charged, hydrophilic molecules that difficult to penetrate cell membranes on their own, it can stimulate the innate immune system and can be destored by endogenous nucleases. Thus, to reach the the site of action without side effects ONs require a delivery vehicle. Cationic nanogels are one of the prominent new classes of nanomaterial to domicile the hurdles of *in vivo* ONs delivery [126].

14. Nanogels for delivery of protein therapeutics

Nanogels having self-ability to encapsulate high amounts of biomacromolecules and prevent them from degradation, also for the delivery of proteins and peptides they have been widely explored. The nanogels depend on the molecular weight and hydrophobicity of the protein. The complexation size the thermal denaturation and eventually aggregation of proteins and protected it from enzymatic degradation [127-128]

14.1. Nucleic Acid Delivery

The powerful ability of siRNAs to silence genes and effectively and specifically inhibit gene expression. Hence, application of small interfering RNA (siRNA) has become an important treatment aspect for gene-related diseases. It cannot penetrate the cell surface and their applications are specific like low transfection rates and short half-lives due to rapid enzymatic degradation [129-130].

To target these problems, naked siRNA can be enriched by the biomolecule cholesterol, loaded in liposomes, or linked with polymer nanoparticles during nucleic acid treatment [131].

The siRNA therapy was perceived by a nanogel-based delivery system. Furthermore, for other functional oligonucleotides therapies it was clearly soft signal. In nanogel the nonviral vector like tetrahedral DNA- based was introduced for siRNA assembly and provided protection during delivery. This strategy could be enabling to cell transfection effectively in in-vitro and in-vivo and prevent ribonuclease degradation as well. Therefore, this is the favourable environment for incorporating multiple devices for increased efficiency [132].

14.2. Nanogels for Combination Drug Delivery

The nanogel structure is without delay adjusted to integrate options of various materials and, thus, provide benefits for combinatorial encapsulation of medicine with varied chemistry properties like little molecules, proteins and nucleic acids. The event of liposomal nanogels of drug-complexed cyclodextrins and protein-encapsulating perishable polymers that may deliver little hydrophobic molecular TGF- β substance and soluble supermolecule cytokine (IL-2) in an exceedingly sustained operate to the growth microenvironment. These synergistic effects at the same time delivered IL-2 and TGF- β substance on activation of the innate arm of the system crystal rectifier to delayed growth and increased survival of skin cancer tumour bearing mice once general administration.

Binary drug combination in nanogels exhibited synergistic cytotoxicity against human ovarian A2780 cancer cells and exerted a superior anticancer activity in cancer heterograft models *in vivo* as compared to individual drug-loaded nanogels or free medicine. The advantages of synchronic co-delivery of the platinum-taxane drug combination via single carrier is any increased by targeting nanogels to B vitamin receptor, that are overexpressed in most ovarian cancers [133].

Dual drug-loaded nanogels displayed potent toxicity in a very carcinoma cell panel and exerted selective synergistic antineoplastic activity against ErbB2-overexpressing carcinoma cell lines. This synergistic impact was attributed to the

action of 17-AAG, HSP90 substance, that induces degradation of the many of the proteins needed for DNA- harm response likewise as attenuates active ErbB2 downstream oncogenic communication, thereby rendering cancer cells a lot of prone to the cytotoxic effects of DOX. In step with the *in vitro* findings, combination treatment with nanogels exhibited superior anticancer effectivity, each in terms of growth inhibition and survival, in associate ErbB2-driven transplant model compared to the cocktail of free medicine at equivalent drug concentrations.

14.3. Nanogels in diagnostics and imaging

Encapsulation of magnetic nanoparticles like iron compound into crosslinked nanogels has been shown to confer each mixture stability and better sensitivity than once these agents are administered as non-encapsulated entities. Nanogels yield the encapsulation of an oversized load of the magnetic nanoparticles, which could lead to generation of abundant stronger native magnetic fields due to the cluster impact [134-138].

The gel coating additional will increase the relativities by lowering the diffusion constant of water near the particles and sustaining the interaction between the water protons and so the high magnetic fields at the surface of the particle. The extent of reduction within the diffusivity of the water molecules depends on the thickness of the gel coating around the magnetic particle [138-140].

14.4. Nanogel for PET Imaging

Polyacrylamide-based nanogel crosslinked with polydentate chelating ligands that were developed by Allmutairi and co-workers may be co-jointly used as a scaffold for metal radionuclides to get PET radiotracer. Numerous crosslinkers supported DTPA, DOTA or 1, 4, 7-triazacyclononane-1,4,7-triacetic acid (NOTA) were synthesized to optimize the chelation stability of nanogels. Experiments in mouse humour indicated that NOTA-based nanogels maintained ⁶⁴Cu most stably, with little or no trans-chelation compared with the opposite 2 crosslinkers. ⁶⁴Cu-DOTA-crosslinked nanogels showed high accumulation within the neoplasm further as lower signal within the liver and spleen compared to DOTA-based nanogels. In some cases, the build-up of ⁶⁴Cu-DOTA in metastases was even above within the primary connective tissue neoplasm. These knowledge counsel that nanogels incorporating metal-chelating crosslinks may be helpful as PET agents in cancer identification and medical care watching. A bonus of such systems is that the isotope may be simply incorporated into preformed nanogels like a shot before their clinical application [141].

15. Nanogel for Optical Imaging

In vivo fluorescence-based optical imaging is only by mistreatment agents that emit within the NIR region (> 700 nm) because of the marginal auto-fluorescence from the tissues during this wavelength vary and deep tissue penetration of excitation lightweight [142, 143].

16. The application of nanogels

Nanogel-based drug delivery formulations improve the therapeutic effect of anti-fungal drugs, anti-cancer drugs, and anti-diabetic drugs, because of their physicochemical properties, and improving the ease of administration as well which is authenticate by *in vivo* studies. Nanogels have minimal toxicity to close tissues and high healing effects in cancer treatment at the site of action [144].

16.1. Transdermal Drug Delivery of an Antipyretic Drug

The nanosized dispersion of aceclofenac was developed by emulsion-solvent diffusion ways and so incorporated into a Carbopol 940. The formulation showed optimum porosity properties and stability, and achieved a sustained drug unleash [145].



Figure 2 Application of nanogels

16.1.1. Carrier for antifungal agents

In fungal infections, physicians and patients like the mostly stratum route. A fluconazole-chitin nanogel was developed by using reconstructed chemistry and therefore the wet edge methodology. polyose nanogels were redeveloped from polyose resolution. Fluconazole-chitin features a controlled unleash pattern that is ideal for the continual accessibility of fluconazole over an extended amount for effective fungous treatment [146]. The synthesis of an antioxidant (Vit E) nano emulsion-based nanogel consisting of the high relative molecular mass chemical agent antibiotic B has been effectively used for connective tissue fungal infections; the nanogel showed an almost 4-fold higher skin deposition through porcine ear skin [147].

16.1.2. Vaginal Drug Delivery

In vaginal infection nanogel containing antibacterial drugs have been used to prevent various infections [148].

They can even be wont to scale back vaginal irritation, discharge and alternative sexual issues. Some disadvantages of vaginal nanogel are that they're contraindicated throughout menses and gestation. Researchers have found that sure vaginal nanogel having antiretroviral medication could decrease the severity of HIV infection among ladies [149].

Tenofovir vaginal gel has been investigated within the prevention of HIV. Gelatin nanoparticles of Tenofovir were ready by 2 step desolvation methodology HPMC K15M was used as a bio adhesive compound in addition as a gelling agent [150].

16.2 Diabetics

“An injectable Nano-Network that responds to aldohexose and Releases Insulin” has been developed. It contains a combination of oppositely charged nanoparticles that attract one another. This keeps the gel along and stops the nanoparticles drifting away once within the body. *In vivo* experiments conducted in diabetic rats in a pair of 2012 disclosed that insulin-loaded nanogels faded the glucose levels by fifty-one from the baseline level for pretty much 2 hours. Considerably, in comparison with free insulin the insulin-loaded nanogels might keep glucose levels stable and avoided sugar changes [151].

16.3 Anticancer Therapy

Many compound nanogels are utilized for cancer medical aid. Incorporating chemotherapeutical medicine into the nanogel not solely will increase the bioavailability however additionally increased permeableness and retention [152].

Nanogels are being employed to deliver medication a lot of effectively in cancer therapy. One among the polymeric nanogels to be used in patients with breast carcinoma, that has received federal agency approval conjointly, is Genexol-PM [153].

16.4 Tumor therapy

During the past few decades, several drug delivery systems, particularly the nanoparticles, are investigated to beat the limitation of typical therapy agents like poor solubility, slim therapeutic window, and toxicity to traditional tissues. Nanogel, a sort of special nanoparticle, expresses wonderful advantage for anticancer drug delivery. First, the consistency of nanogel network provides a perfect storage cavern for loading medication avoiding early unharness further as a shielding to environmental degradation and hazards [154].

For example, nanogel considerably sustained the potency of decitabine because of their ability of bypassing the glycoside transporters and increased stability [155].

Second, nanogels yield a modification in carrier shape, from a sphere to oval, similar to a red blood cell [156].

This property is crucial to try the rise of the duration of blood circulation through microcapillaries. At a high shear rate, the nanogels could become elongated, any reducing the apparent viscousness of the blood. Besides, nanogels will simply be passive and active targets to neoplasm tissue. The nano-size nanogels endow themselves associate increased EPR impact, whereas active targeting may be effectively achieved through introducing specific purposeful teams into nanogels [157].

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Additionally, to the targeting, alternative options of nanogels are explored in cancer medical aid, like sensitivity and chargeability. As mentioned higher than, nanogels have glorious pH-responsive ability and growth could be a special tissue with slightly acidic living thing microenvironment, thus pH-sensitive nanogels will effectively improve the effectiveness of the loaded drug whether or not the drug act on extracellularly or intracellularly [158-159]. Prepared promising PEG-chitosan nanogels for cancer medical aid, that couldn't solely answer nice changes in setting pH scale, however can also be modulated by external cooling/heating. The surface charge of the 5-FU loaded nanogels varied from nearly neutral to positive around tumour extracellular pH scale (6.0–6.2). The positive charged nanogels will facilitate cell learning and later on the magnified acidity in endosome and organelle would cause a big unharness of 5-FU [160]. Prepared a pH, thermal, and reaction potential triple-responsive expandable nanogel system (TRN) for neoplasm and mitochondria targeted photo-sensitizer delivery by victimization artificial polymers, which may swell at acidic pH, with temperature more than their transition temperature, and reducing surroundings. The nanogels quickly expand from 108 nm to over 1200 nm (in diameter) among two h in very reducing surroundings at blood heat. Besides, TRN additionally functionalized with sigma-2 receptor targeting-ligand which may effectively target head and neck neoplasm. The photodynamic medical care (PDT) assessment of necrobiosis once PDT showed that TRN killed the majority cancer cells twelve h post irradiation that immensely increased the PDT effectuality. Additionally, to effective delivery of the hydrophobic photosensitizer, the nanogel is additionally the best delivery system for encapsulating the high number molecules (such as gold and platinum) which may enhance the biological impact of X-irradiation. Recently, loads of ways for delivering a curative dose of radiation by nanogels to neoplasm are evaluated [161-162]. Developed higher stabilized and neoplasm selective gold nanoparticles by encapsulating them with PEGylated poly (2- [N, N, -diethylamino] ethyl methacrylate) (PEAMA) nanogels.

One nanogel with a diameter of around 106 nm encapsulated 15 gold nanoparticles (GNG). Except the upper accumulation potency, the GNG within the nanogels additionally showed appreciably high stability compared with the commercially accessible citrate-stabilized gold nanoparticles and PEGylated GNG. The results incontestable that the novel PEGylated nanogel containing gold nanoparticles would be a promising nanomedicine for cancer photothermal medical aid

As we have a tendency to all apprehend, nanoparticles will passively target neoplasm through EPR result, however typically, the unfold of them is restricted to the neoplasm peripheral region and that they cannot penetrate into the deep neoplasm interstitial space [163].

16.5 Nanogels in Diagnostics and Imaging

Nanogels have properties such as high-water content, structural flexibility, fluid-like transport, biocompatibility, and biodegradability. Gadolinium-assembled nanogels were synthesized by the crosslinking of branched polyethyleneimines with metallic element ions. Inverse microemulsion followed by surface functionalization with synthetic resin glycol chains was performed to extend the blood circulation time [164].

16.6 Neurodegenerative Diseases

Nanogel could be a promising system for delivery of oligonucleotides (ODN) to the brain. For treatment of neurodegenerative disorders systemic delivery of oligonucleotides (ODN) to the central systema nervosum is required. Macromolecules injected in blood square measure poorly transported across the barrier (BBB) and speedily cleared from circulation. Nanogels sure or encapsulated with negative charged ODN ends up in formation of stable liquid dispersion of electrolyte complicated with particle sizes but a 100 nm which may effectively transported across the BBB. The transport efficaciousness is more enlarged once the surface of the nanogel is changed with siderophilin or insulin [165].

16.7 Anti-Inflammatory Action

3-acetyl-11-keto- β -boswellic acid (AKBA) and AKBA loaded nanoparticles were accustomed prepare nanogel. Carbopol with the specified consistence were used to arrange the nanogels. AKBA loaded nanoparticles were accustomed ready the treatment of inflammation. 3-acetyl-11-keto- β -boswellic acid (AKBA) is that the most potent pentacyclic triterpenic acid present in gum of *Boswellia serrata* for anti-inflammatory activity. The result showed abundant higher medicine activity of AKBA [166].

16.8 Other Applications

16.8.1 Ocular Problems

Polyvinyl pyrrolidone – poly (acrylic acid) (PVP/PAAc) nanogel is hydrogen ion concentration sensitive and prepared by γ – radiation induced polymerisation. it's accustomed encapsulate alkaloid (pilocarpine) so as to take care of associate degree adequate concentration of the pilocarpine at the location of action for sustained of time [167].

Curcumin-loaded cationic nanostructured supermolecule carriers (CNLC) were ready by film-ultrasonic techniques and also thermosensitive gelling agents were wont to improve pre-ocular retention and the ocular permeation capability of curcumin. Muscone has most drug loading within the colloidal gel, and also the physics results showed that the phase change temperature was 34°C. Blinking of eyes was resisted because of the thixotropy; the recovery time indicated that colloidal gel was effective [1, 168].

16.8.2 Autoimmune Disease

A study conducted designed and tested a unique nanogel drug delivery vehicle for the immunosuppressive drug mycophenolic acid (MPA). The consequences of this study ended that there's a much better efficaciousness of nanogel primarily based native drug delivery for lupus erythromatous because it targets antigen-presenting cells. This new drug delivery system will increase the longevity of the patient and delays, the onset of renal failure, a typical complication of lupus [169].

16.8.3 Stopping Bleeding

A protein supermolecules that is in solutions & been used for formation of nanogel has been accustomed stop trauma, even in severe gashes. The proteins have mechanism of self – assemble on the nanoscale in to a perishable gel [170].

16.8.4 Nasal Drug Delivery

Nanogel drug delivery systems hold nice potential to beat a number of the barriers in delivery. Nanogels ar with efficiency obsessed by nasal mucous membrane and thus, might be used as efficient transport and delivery systems for medical specialty through nasal mucous membrane. The employment of nanogels for vaccine delivery via nasal route may be a new approach to regulate the illness progression. Nanogels are high-viscosity systems containing nanoparticulates (NPs, microcapsules, NEs, etc.) during a compound polymeric network [171].

17 Marketed Formulation of Nanogels

Sr. No	Product Name	Application
1	Skin perfect brightening nanogel	It brightens the skin and gives complete hydration. It repairs, tones, and protects the skin
2	Oxalginnanogel	It gives deeper action and quicker penetration
3	Aqua Multi Effect Nano Gel Cream	It's a moisturizing gel that gives complete hydration for a long time. It also works as anti-wrinkle cream
4	Augen Nanogel Eye-care Gel	It is an eye care gel with deep penetration properties
5	Revivagenix Pro Collagen Nano Gel	It is an anti-wrinkle cream, gives complete hydration to the skin for longer time
6	Sane care nanogel	Reduces accumulated fats on the abdomen, arms, legs, thighs.
7	HA nanogel	Excellent alternative to regular toothpaste. Reducing risk of decay and also reduced bad breath

18 Conclusion

Nanogels are reassuring and modern drug delivery system that have effective role by sermonizing the drawback associate with old and modern therapeutics like nonspecific effects and poor stability. Modification of Nanogel for targeting through the biological ligand like proteins, peptides, polysaccharides were formulated for excellent interaction between ligand and specific cells. Nanogels are used as therapeutic drug carrier because of high incorporation capacity and swelling property and no. of biological molecules interacted with the electrostatic, van der wall interaction occurs with polymer chain leading to form stable nanoparticles and thus drug can be entrapped easily. Nanogels appear to be excellent candidates for tumor targeting. Therefore, future objective of this review is to improve the design of nanogel with specific targeting residue to facilitate highly selective uptake into particular cancer cells, thereby minimize the uptake in normal cells.

Compliance with ethical standards

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Disclosure of conflict of interest

There was no conflict of interest in this study.

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