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Nanogel: An Emerging Drug Delivery System

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ABSTRACT

A nanoparticle that is composed of a hydrogel with a cross-linked hydrophilic polymer network is known as “Nanogel”. The term nanogels is defined as the nanosized particles formed by physically or chemically cross-linked polymer networks that swell in a good solvent. The term “nanogel” was first introduced to define cross-linked bifunctional networks of a poly-ion and a non-ionic polymer for delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG) or PEG-cl-PEI). The sudden outbreak in the field of nanotechnology has introduced the need for developing nanogel systems which proven their potential to deliver drugs in a controlled, sustained and targetable manner. With the emerging field of polymer science, it has now become inevitable to prepare smart nano-systems which can prove effective for treatment as well as clinical trials progress. The brief review aims at providing comprehensive illustrations on the novel applications, drug loading technique, mechanism of drug release from nanogels. Further, the current status, clinical trial status, and future perspective of nanogels have been summarized.

INTRODUCTION [1-10]

Nanogels are three-dimensional hydrogel materials in the nanoscale size range formed by crosslinked swellable polymer networks with a high capacity to hold water, without actually dissolving into the aqueous medium. Nanogels can be composed of a variety of naturally occurring polymers, synthetic polymers, or a combination thereof. Their characteristics such as size, charge, porosity, amphiphilicity, softness, and degradability can be fine-tuned by varying the chemical composition of the nanogels. They are mostly spherical particles but the current advancement in synthetic strategies allows for the fabrication of nanogels of different shapes. They can be also designed to have either a core-shell or a core-shell-corona structure, with at least one of the layers crosslinked for structural integrity. Being mostly hydrophilic, nanogels are highly biocompatible with a high loading capacity for guest molecules and their unique physical properties offer them distinct advantages over other types of nanomaterials for biomedical applications. Nanogels not only protect the cargo from degradation and elimination but also participate actively in the delivery process due to their characteristic properties like stimuli-responsive behavior, softness, and swelling to help achieve a controlled, triggered response at the target site. The versatility of their architecture allows for the incorporation 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 their gel-like behavior. This multifunctionality and stability are hard to find in other types of nanoparticulate systems; especially the ability to incorporate entities with very different physical properties within the same carrier. Inorganic nanomaterials have distinct material properties like optical activity, electrical conductivity, and magnetic properties that make them suitable for in vivo diagnostic and imaging applications, but they suffer from limitations of poor colloidal stability, low aqueous solubility, and rapid elimination by the mononuclear phagocytic system (MPS). Polymeric nanogels can be used as carriers for such imaging probes by imparting stability and increasing their utility. This lead to the evolution of a new class of agents termed ‘nanohybrids’ which are nanogels incorporating inorganic materials. Such nanohybrids can contain a wide variety of diagnostic and imaging agents for different types of medical conditions. Nanogels prevent biomolecules like enzymes and genetic material from degradation while their macromolecular properties help increase the circulation half-lives of small molecules, and serve as a highly convenient platform for combination delivery of therapeutic molecules. They can be targeted specifically to the site of interest by conjugation

with a targeting ligand or due to the passive targeting that is a characteristic feature of their nanoscale size. Despite such diversity in their applications, nanogels are not yet a part of clinical use. Many comprehensive and more specialized review articles on the synthesis and application of nanogels were recently published. For that reason, in the present paper, we attempted to briefly consider characteristic features of nanogels and to demonstrate representative examples for major directions in their applications in the biomedical field. We also highlight some of the key hurdles that need to be overcome to make nanogels a part of routine clinical practice.

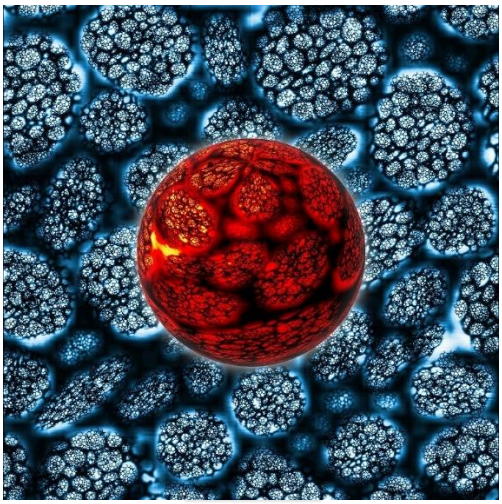

Figure No. 1: Nanogel

Nanotechnology, a relatively novel technique, offers a broad scope for a smart drug delivery and drug manufacturing (nanomedicine) approach involving the design, synthesis, and characterization of materials or molecules and devices that have an effective function at the nanometer scale. This technique mainly focuses on the radical improvements in the current therapeutic and diagnostic procedures. The development of novel nano-sized particulate drug delivery systems (DDS) has shown a profound impact on disease prevention, diagnosis, and treatment as reported after the researches in academic laboratories and pharmaceutical companies all over the world. This technique has overcome the challenges by enhancing the absorption of drugs, reducing the toxicity of drugs, controlled the release of doses, and reducing biodegradation. It has also reduced the chances of activation of immune cells upon administration of drugs inside the body. The application of nanotechnology to medicine has enabled the development of functionalized nanoparticles that, acting as carriers, can be loaded with drugs or genetic material to be released with a controlled mechanism in specific districts of the organism. Various nanotechnological techniques like protein-based

nanoparticles, lipid-based nanoparticles, nano-emulsions, nanocrystals, nano-diamonds, carbon nanotubes, nanosuspensions, and nanogels have been introduced as an advanced DDS in which nanogels have been introduced in the market due to their maximum advantages over other DDS techniques. A nanoparticle that is composed of a hydrogel with a cross-linked hydrophilic polymer network is known as "Nanogel". Nanogels (nanosized hydrogels) are physically or chemically cross-linked, swollen small particles that are made up of flexible hydrophilic or amphiphilic polymer networks. These polymer networks can be anionic or ionic. They behave as a carrier molecule for drugs and are designed in which a way that they can easily absorb biologically active compounds by the formation of biomolecular interactions like salt bonds, hydrophobic or hydrogen bonding.

They are designed in such a way that these nanogels can easily encapsulate diverse classes of biomolecules by optimizing the molecular composition, size, and morphology, to ensure the controlled release of drug molecules *in-vivo*. When nanogels are dispersed in the aqueous media, their swollen networks become soft and can encapsulate a required volume of water. Desired biological or drug molecules can be loaded into the nanogels by allowing the formation of spontaneous interactions between the polymer matrix and the agents; resulting in the formation of highly dispersed hydrophilic particles. This resulting structure can provide physical protection to the desired loaded biomolecule from degradation. Therefore, nanogels are a kind of versatile structure for both drug encapsulation and drug-controlled release on the target site. Nanogels, during the first decade of their development, have been proved to be a potential structure for systemic drug release, designing of multifunctional nanocarriers like controlled drug release at the target site. Due to the large surface area and adjustable size of nanogels, these molecules can incorporate different molecules.

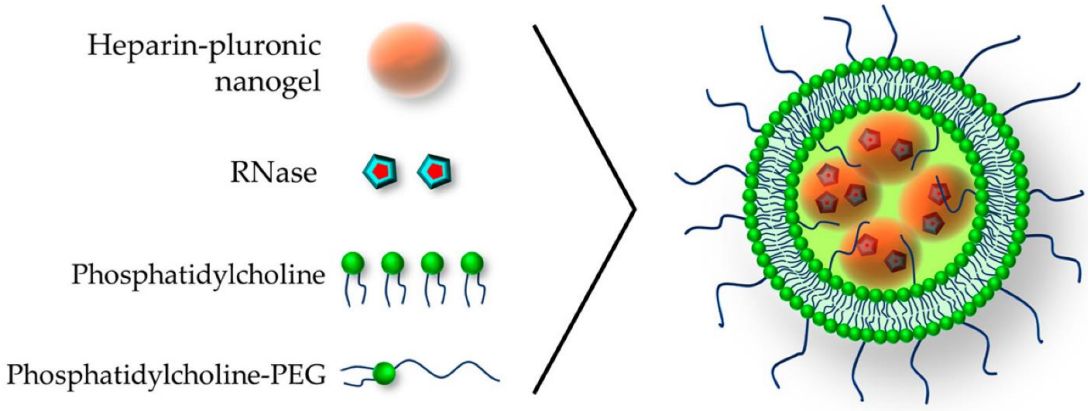

Figure No. 2: Nano Particle

Classification of Nanogels [11-15]

Nanogels are classified according to two bases:

Based on their behavior towards specific stimuli

Non-responsive nanogels: When non-responsive nanogels come in contact with water, they absorb it, resulting in swelling of the nanogel.

Stimuli-responsive nanogels: Environmental conditions, such as temperature, pH, magnetic field, and ionic strength, control whether swelling will occur or not and the extent of swelling or deswelling of the nanogels. Any changes in any of these environmental factors, which act as stimuli, will lead to alteration in the behavior of the nanogels as a response, hence the term stimuli-responsive nanogels. Nanogels that are responsive to more than one environmental stimulus are termed multi-responsive nanogels.

Based on the type of linkages present in the network chains of polymeric gel structure

Physically cross-linked nanogels:

Physically cross-linked nanogels, which are also called pseudo gels, depend greatly on the characteristics of the polymer used in their products including polymer composition, temperature, the concentration of the polymer, type of cross-linking agent, and the ionic strength of the medium. Weak linkages like van der Waals forces, hydrogen bonding or hydrophobic, electrostatic interactions are the forces that form this type of nanogels. Physically crosslinked nanogels can be produced within a short time via several simple methods. These methods involve a variety of processes such as an association of amphiphilic blocks, self-assembly, aggregation of polymeric chains as well as complexation of oppositely charged polymeric chains.

Liposome Modified Nanogels

Liposome-modified nanogels are physically cross-linked, stimuli-responsive nanogels, which are being studied as transdermal drug delivery devices, due to their unique properties. These nanogels involve the incorporation of poly [N-isopropyl-acrylamide] co-polymeric groups into the liposomes, resulting in a high degree of responsiveness to both pH and temperature. In addition, Succinylated poly[glycidol]s are infused into the liposomes, under pH of less

than 5.5, to create nanogels that effectively and efficiently deliver Calcein to the cytoplasm of target cells.

Micellar Nanogels

Micellar nanogels are produced by supramolecular self-assembly of both hydrophilic and hydrophobic blocks or by graft copolymers in an aqueous solution. Micellar nanogels consist of a hydrophilic shell (corona), made of polymer blocks, surrounding a hydrophobic core, and stabilizing the whole micelle. The purpose of this conformation is to provide sufficient space to contain drugs or biological macromolecules just by physically entrapping these particles inside the borders of the shell, thereby acting as a drug delivery system. As the micelle enters the body, the hydrophilic shell interacts with the aqueous media by forming hydrogen bonds to protect the hydrophobic core that is carrying the drug to its target cells. This process protects the drug molecules from being hydrolyzed or degraded by enzymes.

Hybrid Nanogels

When particles of a nanogel are dispersed in an organic or inorganic medium, it is known as a Hybrid nanogel. Self-assembly and aggregation of amphiphilic polymers, such as pullulan-PNIPAM, hydrophobized polysaccharides, and hydrophobized Pullulan, were the processes used for the formation of nanogels in an aqueous medium. Specifically, cholesterol-bearing pullulan (CHP) nanogels were investigated. These are stable monodispersed nanogels formed by the self-aggregation of CHP molecules (formed of pullulan backbone and cholesterol branches) with hydrophobic groups providing physical crosslinking points CHP nanogels were found to have the unique abilities to not only complex with molecules like DNA, proteins, and various drugs but also to coat solid surfaces like liposomes, particles, and even cells. Hybrid nanogels have significance, particularly, as drug delivery systems for insulin and anticancer drugs.

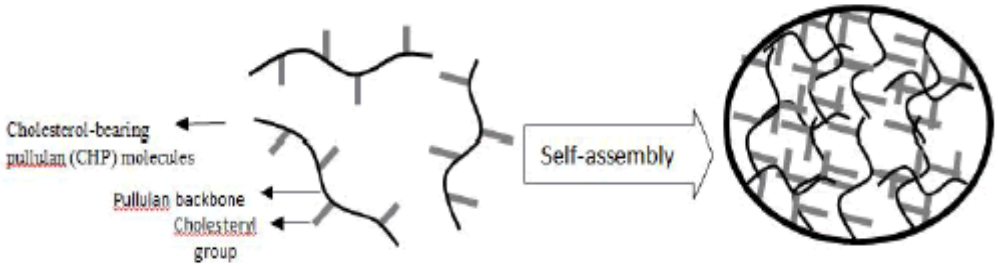

Figure No. 3: Self-assembly of CHP molecules to form CHP nanogel

Chemically cross-linked nanogels:

Where physically cross-linked nanogels are linked by weak forces, chemically cross-linked nanogels are formed by networks of strong covalent bonds and other permanent chemical linkages. The strength of the linkage is highly dependent on the type of functional groups present in the molecules of the nanogel network.

To synthesize this type of nanogels, polymeric chains are cross-linked at specific points, called the cross-linking points, which are determined by the multifunctional crosslinking agent present. Using different polymers and different chemical linking strategies leads to the production of nanogels with a variety of properties for several applications. In addition, the physicochemical properties of the nanogel can be modified depending on the type of cross-linking agent used to produce the polymer and the position of cross-linking points. Hydrophilic polymers or amphiphilic copolymers, produced by polymerization of vinyl monomers, are usually used to produce chemically cross-linked nanogels.

For example, a nanogel ranging in size from 20 to 200 nm, in which polymeric chains containing pendant thiol groups were crosslinked by an environment-friendly chemical method, was produced.

PROPERTIES OF NANOGELS[16-20]

Biocompatibility and degradability:

Nanogel is made up of either natural or synthetic polymers. They are highly biocompatible and biodegradable thereby avoiding their accumulation in the organs. Chitosan, ethylcellulose, methylcellulose, and various polysaccharide-based polymers like dextran, pullulan, and dextrin can be used to prepare the nanogel. Polysaccharides are mostly carbohydrate-based polymers, formed of repeating monosaccharide units linked by glycosidic bonds. These polymers are stable, non-toxic, hydrophilic, and biodegradable.

Swelling property in aqueous media:

Due to the fact that Nanogels are very small, soft materials, they can swell the presence of an aqueous medium. It is considered to be the fundamental property influencing the mechanism of action followed by this delivery system. It depends on:

S**tructure of Nanogels:** This includes the chain's chemical nature as well as cross-linking degree and in the case of polyelectrolyte gels; the charge density.

•parameters that are related to the variables of the aqueous medium. For instance, in polyelectrolyte gels pH as well as ionic strength and ions' chemical nature are influential factors. Likewise, the temperature is a trigger of swelling in the case of thermoresponsive gels.

Providing appropriate circumstances allows rapid swelling/deswelling. Regardless of the trigger, swelling takes place only when the osmotic pressure is exerted by medium ions and the polymer's network swelling pressure is imbalanced.

Higher drug loading capacity:

Just like any other nano delivery system, nanogels are expected to have greater loading capacity compared to conventional dosage forms. This is mainly due to the swelling property which allows the formulation to absorb a large quantity of water. Thus, upon incorporation and loading, the water will provide cargo space sufficient to contain salts and biomaterials.

Loading takes place through three methods:

Physical entrapment: it can refer to the linkage between hydrophilic chains and hydrophobic regions of the polymer or to dissolving hydrophobic molecules in the hydrophilic vehicle.

The covalent attachment of bioactive molecules leads to the formation of a dense drug-loaded core.

Controlled self-assembly: which is generally for polyelectrolyte-based nanogel. The high loading efficiency is attributed to an interaction between oppositely charged electrolytes. Other factors also contribute to the high loading capacity, such as the composition, molecular weight, the possible interactions between the drug and the employed polymer, and the different functional groups in each polymeric unit.

Permeability and particle size:

What distinguishes nano delivery systems is that a tiny manipulation in particle size, surface charge, and hydrophobicity can remarkably improve permeability. Even though nanoparticles are capable of permeation by diffusion through tissues or compromised areas of endothelium

and in some cases through a particular transport system, they created a challenge crossing the Blood Barrier (BBB). So, to overcome such a dilemma, nanogels were formulated in a way where they possess a diameter of 20-200 nm. It's small enough to cross (BBB) and in the same time avoid rapid clearance mechanisms.

Non-immunologic response:

Any agent that enters the systemic is rapidly eliminated by the Mononuclear Phagocyte System through opsonization and phagocytosis. Opsonization is nothing but marking foreign agents and make them visible to phagocytes. Opsonins bind on the surface of nanoparticles and facilitate the attachment of phagocytes. Few methods are adopted to help nanoparticles flee recognition and remain longer in the bloodstream. All of which is based on minimizing protein binding. For example, hydrophilic polymers can act as a shield that hinders or delays binding with opsonins rendering them unnoticeable by the immune system and its defenses.

Colloidal stability:

When handling nanoparticles, there is always a propensity of aggregation that compromises the colloidal stability. Formulators tend to alter the surface charge to avoid the formation of aggregates in the bloodstream and further complications. It can be achieved through increasing zeta potential (minimum of ± 30 mV) that results in larger repulsive forces between particles that electrostatically stabilize them. Other techniques involve the incorporation of a surface modifier like PEG that produces steric effects and hydration forces to give a stable nanosuspension. If we compare polymeric micellar nanogel systems and surfactant micelles on basis of stability we will find that the former exhibits better stability lower critical micelle concentrations, decrease in dissociation rates, and longer retention of loaded drugs. They also have a high water content that assure good dispersion stability.

Benefits of Nanogel Drug Delivery Approach

- It protects biodegradation of drugs inside the body.
- Physical properties like the size of nanogels can be easily adjusted and maintained according to the desired delivery molecule.
- Low amount of drug is required as well as quantity of doses is reduced.
- Improves the bioavailability of the drug molecule and reduces the toxicity of the drugs.

•Drugs-loaded nanogels can be delivered inside the body with no adverse or side effects as well as can be applied topically.

• These can cross the blood-brain barrier as well as a physiological barrier like skin.

DRAWBACKS OF NANOGELS [21-25]

• It requires expensive techniques to completely remove the solvent sand surfactants at the end of the process.

• Sometimes, traces of surfactants can cause toxicity.

The pores in nanogels can be filled with small molecules or macromolecules and usually, the size of nanogels is one to hundreds of nanometers in diameter. The nanogel contains some properties like swelling, degradation, and chemical functionality that can be controlled. Not, only for drug delivery, the nanogels are investigated for a longer period for making miscellaneous agents like quantum dots, dyes, and other diagnostic agents. The major significance of nanogels has been arisen due to specific delivery system expectations, a wide variety of polymer systems, and the ease of change of the physical-chemical properties. Current studies at the clinical level have shown promising value of nanogel. Nanogels are used in the field of gene therapy since delivery of genes has now become possible within cellular organelles for gene silencing the system. In nanogel, by using varying solvent quality & branching the volume fraction can be altered variability to maintain a three-dimensional structure.

EVALUATION PARAMETERS [26-30]

Appearance: The prepared gel bases were inspected visually for clarity, colour, and presence of any particles.

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Measurement of particle size of the formulation.

The mean size of the selected nanogels was determined by using Malvern Master sizer 2000 MS. The mean particle size was recorded.

PH measurement

The pH measurement was carried out by using calibrated digital type pH meter by dipping the glass electrode and the reference electrode completely into the gel system to cover the electrodes.

Drug content

For the estimation of the drug in gel, Diclofenac sodium was extracted from 1 gm of a gel formulation with 50 ml of phosphate buffer 6.8, and the mixture was filtered through a membrane filter (pore size 0.45 µm). From this, 2 ml was pipette out and made up to 10 ml. The absorbance of the sample was determined spectrophotometrically at 276 nm. The concentration of Diclofenac sodium was estimated from the calibration curve.

In-vitro release studies

The drug release from the formulation was determined by using the apparatus known as Franz Diffusion Cell, which consists of a cylindrical glass tube that was opened at both ends. 1 gm of gel equivalent to 10 mg of Diclofenac sodium was spread uniformly on the surface of the cellophane membrane (previously soaked in the medium for 24 hrs) and was fixed to the one end of the tube. The whole assembly was fixed in such a way that the lower end of the tube containing gel was just touched (1-2 mm deep) the surface of the diffusion medium i.e. 100 ml of pH 6.8 phosphate buffer contained in a 100 ml beaker. The assembly was placed on the thermostatic hot plate with a magnetic stirrer and maintained at temperature 37°±2° the contents were stirred using a magnetic bar at 100 rpm for a period of 24 hrs, 5 ml of samples were withdrawn at different time intervals. This 5 ml was diluted up to 10 ml of fresh phosphate buffer (pH 6.8) and samples were analyze at 276 nm in UV-Vis spectrometer for diclofenac sodium.

Skin irritation test: An irritation test was performed on human volunteers. For each gel, four volunteers were selected and 1.0 g of formulated gel was applied on an area of 2 square inches to the back of the hand. The volunteers were observed for lesions or irritation.

Spreadability

Spreadability is determined by the apparatus suggested by Mutimer. By this method, spreadability is measured based on “Slip” and “Drag”. A ground glass slide is fixed on this block. A sample of 0.1 g of nanogel under study is placed on this ground slide. The gel is

fixed on the beach formula was pressed between two slides and a 1 kg weight is placed on the top of two slides and left for about 5 min to expel air and to provide a uniform film of the nanogel between two slides. Excess of the gel is scraped from the edges. The top plate is then subjected to pull the weight. With help of string attaches to the hook and the time required by the top slide to cover the distance is noted.

APPLICATION OF NANOGELS[31-45]

Nanogel in Ophthalmic

Polyvinyl pyrrolidone – poly (acrylic acid) (PVP/PAAc) nanogel is Ph sensitive and prepared by γ – radiation-induced polymerization. It is used to encapsulate pilocarpine to maintain an adequate concentration of the pilocarpine at the site of action for a prolonged time.

Nanogel in Stopping Bleeding

A protein molecule that is in solution & been used for the formation of nanogel has been used to stop bleeding, even in severe gashes. The proteins have a mechanism of self – assemble on the nanoscale into a biodegradable gel.

Nanogel as NSAIDs

Carbopol and Hydroxypropylmethylcellulose (HPMC) with the desired viscosity were used to prepare the nanogels. Same like another polymer chitosan & poly – (Lactide – co – glycolic acid) used to prepare layered nanoparticles and the surface was modified with oleic acid. For eg. Two anti-inflammatory drugs spantide II & ketoprofen drugs are effective against allergic contact dermatitis and psoriatic plaque were prepared in nanogel and applied topically. The results show that nanogel increases the absorption through percutaneous of these two drugs deeper skin layers for the treatment of various skin inflammatory disorders.

Nano gel in Autoimmune Diseases

Cyclodextrin easily solubilized the loading liposomes with mycophenolic acid, oligomers of lactic acid – poly (ethylene glycol) that were terminated with an acrylate end group and Irgacure 2959 photoinitiator. After it is exposed to ultraviolet light to produce photopolymerization of the PEG oligomers. Nano gel is having greater systemic accumulation due to their intrinsic abilities and bind to immune cells in vivo than free

fluorescent tracer and permit high localized concentration of mycophenolic acid. By this type of drug delivery system, there will increase patient compliance & delays the onset of kid.

Nanogel in Cancer

Nanogel in cancer is used for the specific targeted drug delivery with low toxicities with high therapeutic efficacy.

Based on the Mechanism of Action

PH responsive mechanism Glycol chitosan grafted with 3 – diethyl aminopropyl group & used Doxorubicin uptake accelerated.

Thermosensitive & Volume Transition Mechanism Pluronic polyethylene mine / DNA complex which are used in thermoresponsive endosomal rupture by nanogel and drug release. Crosslinking of oligo (L –lactic acid) – poly (ethylene oxide) – poly (propylene oxide) – poly (ethylene oxide) – poly (lactic acid) grafted poly (l – lysine) these all are used in the traumatic cell death due to physical stress and a good source for loading anticancer drugs.

Poly (N – isopropyl acrylamide – co – acrylamide) is an institute gelatinized thermosensitive nanogel used for drug loading capacity of low molecular weight of 5 – Fluorouracil was higher than that of macromolecules, bovine serum albumin. Poly (N – isopropyl acrylamide) and chitosan is a thermosensitive magnetically modularized nanogel & used in hyperthermia cancer treatment and targeted drug delivery.

Hydroxypropyl cellulose – poly (acrylic acid) and cholesterol-bearing pullulan modified with an amino group is a nanogel quantum dot hybrid PH and temperature-responsive cadmium II ions quantum dots which is used for a probe for imaging, optical PH sensing, cell imaging, and drug loading of temozolomide.

Based on Sustained Release Cholesterol bearing pullulan nanogels is controlled by sustained release nanogel and used for recombinant murine interleukine–12 sustained tumor immunotherapy. Reducible heparin with disulfide linkages nanogel is used for internalization of heparin for apoptotic death of melanoma cells.

Based upon the Self Assembly Heparin pluronic which is a self-assembling nanogel and used in RNase an enzyme delivery is internalized in cells. Polymer with cross-linked poly (2 – (N, N – diethylamino) methacrylate) core & PEG is a quartered, amine, and size-dependent

nanogel which is used for efficient siRNA delivery. Acetylated chondroitin sulfate is a self-organizing nanogel and used for Doxorubicin loaded. Acrylate group modified cholesterol bearing pullulan is a nanosized cationic hydrogel that is used to enhance oral and brain Bioavailability of oligonucleotides.

Based on Gene Delivery Controlled delivery of plasmid DNA by using the polymer Di – acrylate pluronic 127 and glycidyl methacrylate chitooligosaccharides and making Photo crosslinking nanogel. Potential in gene therapy by using the polymer poly (2 – (N, N – diethylaminoethyl) methacrylate) PEGlyted macroRAFT agent for making one step PEGlylated cationic nanogel.

Used in Endosomal escape of SiRNA by using the polymer Dextran hydroxyl ethyl methacrylate – co – (2 – methacryloyloxy) – ethyl) trimethyl ammonium chloride for making nanogels with photochemical internalization. siRNA delivery to HCT – 116 cells by using the polymer thiol functionalized hyaluronic acid for making specific target and degradable nanogel. Based on Protein Treatment of Alzheime's disease by inhibiting aggregation of amyloid β – protein by using cholesterol bearing amino group modified for making artificial chaperone nanogel.

Based on the Enzymes α – chymotrypsin immobilized on aminated nanogel by using methyl acrylic acid and N, N– methylene – bis – (acrylamide) for making super magnetic nanogel functionalized with carboxyl group. Assisted protein refolding of carbonic anhydrase and citrate synthase during GdmCL denaturation by using cholesterol bearing pullan for making self-assembled artificial molecular chaperone.

Current status and future perspective of gels

Recombinant murine interleukin – 12 (IL – 12) encapsulated in CHP angels, via incubation at room temperature and injected in mice with subcutaneous fibrosarcoma leads to delayed-release & retardation of the growth of tumor. Nanogels have been primarily used for cancer therapy. Cholesteryl pullulan angel has been shown in clinical trials for the delivery of peptidase. The cholesteryl – HER – 2 vaccines were administered to nine patients with 300 µg with booster doses twice a week. This shown that skin sensitivity at the site of S.C injection & CD4+ & CD8+ T- cell shows better therapeutic efficacy. Cholesterol pullulan angels show to reduce the toxicity to the nervous system cells and increase the binding capacity to AB oligomer in treating Alzheimer"s disease. Recently the new development of

controlled diabetes by optical sensitive insulin loaded silver nanoparticle nanogel of poly (4 – vinyl phenylboronic acid – co – 2 – (dimethylamine) ethyl acrylate) has been designed. Nowadays nanogel is conjugated with antibiotics for specific drug delivery and conducted at the single-cell level. In the future, the mechanism of the blood-brain barrier and cytosolic destination over and endosomal or nuclear are necessary to study for the specific and targeting drug delivery.

CONCLUSION

Nanogel is one of the fascinating fields of analysis in approaching the future, which may help deliver the drug in a controlled manner with minimizing the aspect result of typical nanogel. It has versatile advantages and properties that make them competent for economical delivery for biologically active molecules, significantly bio-pharmaceuticals. They will even be used as a carrier or chaperoned to treat inheritable diseases such as cancer, neurodegenerative sickness etc. Nanogel seems to be a wonderful candidate for the treatment of varied diseases.

REFERENCES

1. Rolland JP, Maynor BW, Euliss LE, Exner AE, Denison GM, DeSimone JM. Direct fabrication and harvesting of monodisperse, shape-specific nanobiomaterials. J Am Chem Soc. 2005; 127:10096– 10100. [PubMed: 16011375]
2. Kersey FR, Merkel TJ, Perry JL, Napier ME, DeSimone JM. Effect of aspect ratio and deformability on nanoparticle extravasation through nanopores. Langmuir. 2012; 28:8773–8781. [PubMed: 22612428]
3. Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew Chem Int Ed. 2009; 48:5418–5429.
4. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nat Rev Drug Discov. 2014; 13:813–827. [PubMed: 25287120]
5. Zha L, Banik B, Alexis F. Stimulus responsive nanogels for drug delivery. Soft Matter. 2011; 7:5908–5916.
6. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013; 12:991–1003. [PubMed: 24150417]
7. Motornov M, Roiter Y, Tokarev I, Minko S. Stimuli-responsive nanoparticles, nanogels and capsules for integrated multifunctional intelligent systems. Prog Polym Sci. 2010; 35:174–211.
8. Stuart MAC, Huck WT, Genzer J, Müller M, Ober C, Stamm M, et al. Emerging applications of stimuli-responsive polymer materials. Nat Mater. 2010; 9:101–113. [PubMed: 20094081]
9. Oh JK, Drumright R, Siegwart DJ, Matyjaszewski K. The development of microgels/nanogels for drug delivery applications. Prog Polym Sci. 2008; 33:448–477.
10. Ayame H, Morimoto N, Akiyoshi K. Self-assembled cationic nanogels for intracellular protein delivery. Bioconjug Chem. 2008; 19:882–890. [PubMed: 18336000]
11. Raemdonck K, Demeester J, De Smedt S. Advanced nanogel engineering for drug delivery. Soft Matter. 2009; 5:707–715.
12. Karanth H, Murthy RS. Nanotechnology in brain targeting. Int J Pharm Sci Nanotechnol. 2008;1(1):10-24.
13. Vinogradov SV. Nanogels in the race for drug delivery. Nanomedicine. 2010 Feb 11;5(2):165-8. 3. Jain N, Jain R, Thakur N, Gupta BP, Jain DK, Banveer J, Jain S. Nanotechnology: a safe and effective drug delivery system. Asian J. Pharm. Clin. Res. 2010;3(3).

14. Raemdonck K, Demeester J, De Smedt S. Advanced nanogel engineering for drug delivery. Soft Matter. 2009;5(4):707-15.
15. Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angewandte Chemie International Edition. 2009 Jul 13;48(30):5418-29.
16. Dorwal D. Nanogels as novel and versatile pharmaceuticals. Int J Pharm Pharm Sci. 2012;4(3):67-74.
17. Nahas E, Fakhry G, Shereen et al. Effect of various penetration enhancers on diclofenac sodium. Asian J Pharm. 2011;5:33.
18. Kumar JA, Pullakanda N, Prabu SL, et al. Transdermal Drug Delivery System: An Overview, International J. of Pharm. Sciences Review and Research. 2010;3(2):49
19. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. European Journal of Pharma Science. 2001;14(2):101-14.
20. Dinda SC. Advances in Pharmaceutical Techonology. School of Pharmaceutical Education and Research. 2011;69-82.
21. Phatak A, Jorwekar P, Chaudhari P. Nanosuspension a promising nanocarrier as a drug delivery system. Research J Pharm Dosage Forms and Tech. 2011;3:176.
22. The Merck Index, 13th edition. 2001;6909.
23. Williams AC, Barry BW. "Penetration Enhancers". Advanced Drug Delivery Reviews, 2004;56;603-18.
24. Wu W, Aiello M, Zhou T, Berliner A, Banerjee P, Zhou S. In-situ immobilization of quantum dots in polysaccharide-based nanogels for integration of optical pH-sensing, tumor cell imaging, and drug delivery. Biomaterials, 2010; 31(11): 3023-31.
25. Oh NM, Oh KT, Baik HJ, Lee BR, Lee AH, Youn YS, Lee ES. A self-organized 3- diethylaminopropyl-bearing glycol chitosan nanogel for tumor acidic pH targeting: in vitro evaluation. Colloids and surfaces B: Biointerfaces. 2010 Jun 15;78(1):120-6.
26. Vinogradov SV, Batrakova EV, Kabanov AV. Nanogels for oligonucleotide delivery to the brain. Bioconjugate chemistry, 2004; 15(1): 50-60.
27. Abd El-Rehim HA, Swilem AE, Klingner A, Hegazy E-SA, Hamed AA. Developing the Potential Ophthalmic Applications of Pilocarpine Entrapped Into Polyvinylpyrrolidone– Poly (acrylic acid) Nanogel Dispersions Prepared By γ Radiation. Biomacromolecules, 2013; 14(3): 688- 98.
28. http:en.Wikepedia.org/wiki/Nanogels, (Aceessed 19th june, 2013.
29. Shah PP, Desai PR, Patel AR, Singh MS. Skin permeating nanogel for the cutaneous co- delivery of two anti-inflammatory drugs. Biomaterials, 2012; 33(5): 1607-17.
30. Look M, Stern E, Wang QA, DiPlacido LD, Kashgarian M, Craft J, Fahmy TM. Nanogel-based delivery of mycophenolic acid ameliorates systemic lupus erythematosus in mice. The Journal of clinical investigation. 2013 Apr 1;123(4):1741.
31. Ikeda K, Okada T, Sawada S-i, Akiyoshi K, Matsuzaki K. Inhibition of the formation of amyloid β-protein fibrils using biocompatible nanogels as artificial chaperones. FEBS letters. 2006; 580(28): 6587-95.
32. Bae KH, Mok H, Park TG. Synthesis, characterization, and intracellular delivery of reducible heparin nanogels for apoptotic cell death. Biomaterials, 2008; 29(23): 3376-83.
33. Choi JH, Jang JY, Joung YK, Kwon MH, Park KD. Intracellular delivery and anti-cancer effect of self-assembled heparin-Pluronic nanogels with RNase A. Journal of Controlled Release, 2010; 147(3): 420-7.
34. Tamura A, Oishi M, Nagasaki Y. Efficient siRNA delivery based on PEGylated and partially quaternized polyamine nanogels: enhanced gene silencing activity by the cooperative effect of tertiary and quaternary amino groups in the core. Journal of controlled release, 2010; 146(3): 378-87.
35. Park W, Park S-j, Na K. Potential of selforganizing nanogel with acetylated chondroitin sulfate as an anti-cancer drug carrier. Colloids and Surfaces B: Biointerfaces, 2010; 79(2): 501-8.
36. Vinogradov SV, Bronich TK, Kabanov AV. Nanosized cationic hydrogels for drug delivery: preparation, properties and interactions with cells. Advanced drug delivery reviews, 2002; 54(1): 135- 47.
37. Patnaik S, Sharma AK, Garg B, Gandhi R, Gupta K. Photoregulation of drug release in azo-dextran nanogels. International journal of pharmaceutics, 2007; 342(1): 184-93.
38. Yan L, Tao W. One-step synthesis of pegylated cationic nanogels of poly (N, N′- dimethylaminoethyl methacrylate) in aqueous solution via self-stabilizing micelles using an amphiphilic macroRAFT agent. Polymer, 2010; 51(10): 2161-7.

39. Hong J, Xu D, Gong P, Ma H, Dong L, Yao S. Conjugation of enzyme on superparamagnetic nanogels covered with carboxyl groups. Journal of Chromatography B, 2007; 850(1): 499-506.
40. Nomura Y, Ikeda M, Yamaguchi N, Aoyama Y, Akiyoshi K. Protein refolding assisted by self- assembled nanogels as novel artificial molecular chaperone. FEBS letters, 2003; 553(3): 271-6.
41. Kitano S, Kageyama S, Nagata Y, Miyahara Y, Hiasa A, Naota H, Okumura S, Imai H, Shiraishi T, Masuya M, Nishikawa M. HER2-specific T-cell immune responses in patients vaccinated with truncated HER2 protein complexed with nanogels of cholesteryl pullulan. Clinical Cancer Research. 2006 Dec 15;12(24):7397-405.
42. Kageyama S, Kitano S, Hirayama M, Nagata Y, Imai H, Shiraishi T, Akiyoshi K, Scott AM, Murphy R, Hoffman EW, Old LJ. Humoral immune responses in patients vaccinated with 1– 146 HER2 protein complexed with cholesteryl pullulan nanogel. Cancer science. 2008 Mar 1;99(3):601-7.
43. Alles N, Soysa NS, Hussain MA, Tomomatsu N, Saito H, Baron R, Morimoto N, Aoki K, Akiyoshi K, Ohya K. Polysaccharide nanogel delivery of a TNF-α and RANKL antagonist peptide allows systemic prevention of bone loss. European Journal of Pharmaceutical Sciences. 2009 May 12; 37(2): 83-8.
44. Nukolova NV, Oberoi HS, Cohen SM, Kabanov AV, Bronich TK. Folate-decorated nanogels for targeted therapy of ovarian cancer. Biomaterials, 2011; 32(23): 5417-26.
45. Wu W, Mitra N, Yan EC, Zhou S. Multifunctional hybrid nanogel for integration of optical glucose sensing and self-regulated insulin release at physiological pH. Acs Nano. 2010 Jul 12;4(8):4831-9.