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NANO GELS : AN INNOVATIVE CONCEPT FOR BOOSTING THERAPEUTIC PROFILE

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Abstract

Nanogels are hydrogel nanoparticle consist of a network of cross-linked hydrophilic polymers.Nanogels are cross-linked polymeric nanoparticles that enlarge when exposed to particular solvent. Cross-linked networks comprising of a poly ion, a nonionic polymer (cross-linked polyethyleneimine) and poly ethylene glycol are used for polynucleotide delivery . The remarkable expansion in the field of nanotechnology has prompted the need to develop Nanogel systems that have shown their potential to distribute medications in a continuous, regulated, and targetable manner.while clinical trials progress , it is practically impossible to avoid designing of sophisticated nano-systems that can be employed for therapy because of the rapidly expanding domain of polymeric sciences .This comprehensive study seeks to present exhaustive examples of novel Nanogel technologies, drug loading strategies, and drug release mechanisms. Moreover, a summary of the current state of Nanogels, the stage of clinical trials, and potential future applications has been included.

Key words : Nanogels, nanotechnology, nanoparticles, polymers, drug delivery system , drug release mechanism , stability.

I. INTRODUCTION

Nanogels are ingenious drug delivery systems that helps to identify numerous challenges including both traditional and current methods of treatment, such as nonspecific side effects and poor stability.The term "nanogel" refers to extensively cross-linked hydrogels having size around 20 to 200 nm[1].Nanogels can be taken in a number of ways, including oral, parenteral, nasal, intravenous means etc.Despite of their small size, they have a higher penetration capability and better drug loading capacity.They release the medication through mechanisms such as photochemical internalisation, volume transition, pH responsiveness, thermosensitivity, and photoisomerization. Nanogels can be categorised according to whether they respond to stimuli or not as well as the type linkages that are present in the network chains on gel structure.

The need for nanogels as a delivery mechanism is fueled by their well-known excellent properties. They possess superior thermodynamic stability, high solubilization potential, low viscosity, and the ability to withstand aggressive sterilising techniques[2]. Drugs and biological substances can be entrapped within nanogels. So that , they may be used extensively in the conveyance of genes and proteins.Some nanogels are hydrophilic, which inhibits the encapsulation ability of hydrophobic substances. Encapsulation of anticancer medications that are hydrophobic in nature faces this problem. Optimized structural engineering was used to enable high encapsulation of such hydrophobic drugs. Thus, nanogels offered a novel method of drug administration for medicines that were not only poorly soluble but also unstable & boosting the potential of their cellular absorption compared to the free drug.

They are perceived as promising carriers for the delivery and cellular uptake of proteins, peptides, and other biological compounds because they depict a relatively high affinity to aqueous solutions, an outstanding

stability, inertness in the systemic circulation as well as the internal fluids, and appropriateness for molecular incorporation in bulk.

ADVANTAGES

- The biodegradation of drugs within the body is protected.
- According to the desired delivery molecule , physical properties such as nanogels can be adjusted.[3]
- Very less amount of drug is required and the dosing frequency can be reduced.
- Absorption capacity of drugs can be increased.
- Drug toxicity can be reduced.
- Side effects can be reduced and applied trans dermally.
- Nanogels can cross blood-brain barrier and physiological barriers such as the skin.[4]

DIS ADVANTAGES

- At the end of the process, expensive techniques are required to remove solvents and surfactants.
- Side effects occur if any traces of polymers or surfactant remain in the body .[5]

II. MACHANISM OF DRUG RELEASE

- p^H responsive mechanism

p^H ofthe surrounding environment highly influence drug release. The release is mostly accomplished in a designated area of the body since the majority of the drug release will take place based on the particular pH of that area.p^H sensitive functional group present on the polymers which used in the synthesis of nanogels deionizes in the polymeric network is the main mechanism.Deprotonation induces the polymer to inflate, become more porous, and leads to a rise in osmotic pressure, all of which induce the electrostatically bonded molecules to release from the formulation.[2]

- Thermosensitive and volume transition mechanism

Certain nanogels react at a certain temperature known as volume phase transition temparature, which indicates thatnanogels shows a temperature-dependent change in volume based on that temparature. When the surrounding environment is below VPTT, the polymer turns hydrated and quenched, leading it to enlarge and release the entrapped drug. In the past, as thermoresponsive nanogels are used to shatter the cellular network when they swelled and increased volume. In order to reduce the critical solution temperature, certain modifications were made to thermosensitive drug-containing nanogels by modifying the polymer ratio. A remarkable example is the biocompatible magnetic feild targetability of poly (N-isopropylacrylamide) and chitosan nanogel , which is currently used in hyperthermic cancer therapy.[6]

- Photochemical internalization and photoisomerization

When exposed to light, nanogels shows photoisomerization . It is a process in which bonds of limitted rotation are subjected to certain conformational alterations. A excellent examples are a molecules with a double bond; when exposed to light, they often isomerize from a trans orientation to a cis orientation. The oxidation of the cellular compartment walls that results from the excitation of photosensitizer-loaded nanogel can have a significant impact on the release of therapeutic medicines into the cytoplasm. Studies on the release of aspirin-loaded azodextran nanogel were performed for its detection . The study demonstrated that the creation of the E-configuration of the azo group results from the cis-trans isomerization of azobenzene by photoregulation. Aspirin's release profile is improved as compared to the former Z-configuration.[7]

- Diffusion Mechanism

Through the diffusion of stable copolymer block hydrogel nanoparticles releases Doxorubicin . This technique and uncomplicated procedures are applied across several Nano-medicines formulations.

- Displacement caused by the ions present in the environment

The majority of scientists are focused on developing Nanogels that can deliver biological agents at the site of impact when excited by the environment. In aqueous environments, water-soluble polymers as POEOMA Nanogels are biodegradable in the presence of glutathione tripe-tide, which is found within the cells. Cationic Nanogels produce complexes in the cell membrane when stimulated with a negatively charged drug, which accounts for the cellular accumulation of drug delivered using Nanogel.[8]

III. CLASSIFICATION OF NANOGELS

Nanogels are classified on the basis of their behaviour towards specific stimuli and the type of linkages present in the network chains of polymeric gel structure.

- According to the behaviour towards particular stimuli

1. Non-responsive nanogels
   Non-responsive nanogels absorb water when they come into contact with it, that induces the nanogel to swell.
2. Stimuli-responsive nanogels
   The amount of the swelling or deswelling of the nanogels is determined by environmental factors such as temperature, pH, magnetic field, and ionic strength. The phrase "stimuli-responsive nanogels" refers to nanogels that will alter their activity in response to changes in any of these environmental factors, which act as stimuli. Multi-responsive nanogels are those that respond to a variety of environmental stimuli.[9]

- Depending on the kind of linkages found in the polymeric network

1. Nanogels with physical cross-linking

The parameters of the polymer employed in their formation, such as the polymer's composition, temperature, concentration, kind of cross-linking agent, and the ionic strength of the medium, have a significant impact on the Pseudogels, also referred to as physically cross-linked nanogels.. These types of nanogels are created by weak linkages such as van der Waals forces, hydrogen bonds, or hydrophobic and electrostatic interactions. Several simple and easy processes may be used to efficiently manufacture physically crosslinked nanogels. These techniques includes a number of different processes, including the association of amphiphilic blocks, self-assembly, the aggregation of polymeric chains, and the complexation of oppositely charged polymeric chains.

- Nanogels – Liposome modified

Liposome modified nanogels, which are stimuli-responsive and physically cross-linked nanogels, are being considered as transdermal drug delivery systems due to their special characteristics . These nanogels have a high degree of responsiveness to pH and temperature because poly (N-isopropyl-acrylamide) co-polymeric groups are incorporated into the liposomes. Additionally, under a pH of less than 5.5, succinylated poly(glycidol)s are infused into liposomes to produce nanogels that efficiently carry calcein to the cytoplasm of target tissues.[10]

- Micellar nanogels

Micellar nanogels are created via graft copolymers or supramolecular self-assembly of hydrophilic and hydrophobic building components in an aqueous solution. A hydrophilic shell comprised of polymer blocks surrounds a hydrophobic core in micellar nanogels, stabilising the entire micelle. By physically entrapping pharmaceuticals or biological macromolecules inside the shell's boundaries, this conformation serves as a drug delivery method by enabling adequate area to retain those substances.In order to shield the hydrophobic core that delivering the medicine to its target cells, the hydrophilic shell of the micelle interacts with the aqueous medium by creating hydrogen bonds as it enters the body. By using this method, the medication molecules are shielded from hydrolysis or enzyme degradation.

- Hybrid nanogels

A hybrid nanogel is one in which a nanogel's particles are spread in an organic or inorganic medium. The procedures employed to create nanogels in an aqueous media included self-assembly and aggregation of amphiphilic polymers including pullulan-PNIPAM, hydrophobized polysaccharides, and hydrophobized Pullulan. Investigations focused on pullulan (CHP) nanogels that contain cholesterol are already done. These CHP molecules, which are composed of a pullulan backbone and cholesterol branches, self-aggregate to create stable monodispersde nanogels, with hydrophobic regions acting as physical crosslinking sites. It was discovered that CHP nanogels has the rare capacity to coat solid surfaces like liposomes, particles, and even living cells in addition to complexing with molecules including DNA, proteins, and different medicines. Hybrid nanogels are important as insulin and anti-cancer drug delivery systems.

2. Chemically cross-linked nanogels

These are constructed by networks of intense covalent bonds and other irreversible chemical linkages, as compared to physically cross-linked nanogels, which are joined by weak forces. The kind of functional groups found in the molecules that make up the nanogel network has a significant impact on how strong the bond is. This kind of nanogels are created by cross-linking polymeric chains at predetermined sites known as the cross-linking sites, which are chosen by the multifunctional cross-linking agent which is present in molecule .

The development of nanogels with a variety of features for a number of purposes is made possible by the use of various polymers and chemical linking techniques.Additionally, depending on the kind of cross-linking agent used to create the polymer and the arrangement of the cross-linking regions, the physiochemical characteristics of the nanogel can be altered. Chemically cross-linked nanogels are often created by polymerizing hydrophilic polymers or amphiphilic copolymers, which are made from vinyl monomers.

For example, a nanogel with a size range of 20 to 200 nm was synthesized by crosslinking polymeric chains with pendant thiol groups using an eco-friendly chemical process.

IV. METHODS OF PREPARATION OF NANOGELS

1. Photolithographic techniques

An attempt to generate 3D hydrogel particles and nanogels for drug administration, the photochemical reaction for activation and subsequent reaction have been examined. In this method, stamps or replica moulds are treated to give the surface specific properties that allow the moulded gels to release the embedded agents. Such gels are often microfabricated using poly (dimethylsiloxane) (PDMS) imprints, which are employed to mould, release, and stack gels into 3 dimensional structures. The release or adherence of moulded gels to a substrate is improved via surface modification. Self-assembled monolayers (SAMs) with an ethylene glycol (EG) termination or adsorbed monolayers of bovine serum albumin are often used to alter PDMS stamps (BSA)[11]

2. Modified pullulan technique

Pullulan nanogel that has been self assembled and hydrophobized is an example of this kind. Pullulans are transformed in phases; primarily,methacrylates and subsequentlyhydrophobic 1-hexadecanethiol are utilised. The outcome is an amphiphilic substance that begins to self-assemble when water is added due to interactions between alkyl chains that are hydrophobic.

Cholesterol-based pullulan nanogel is another example. In this case, pullulan was replaced to 1.4 cholesterol, and the nanogel is generated by simply reacting cholesterol isocynate with pyridine and dimethyl sulfoxide. When this combination was freeze dried, it leads to the formation of nanogel in the aqueous phase, which then formed a compound with W-9 peptide, TNF-alpha and RANKL antagonist , to deliver medications for osteological dysfunction.[12]

The reaction of cholesteryl pullulan (CHP) with glycidyl methacrylate produces cholesteryl pullulan (CHP) containing methacrylol. 6.2 per 100 glucose units (CHPMA6) was the degree of substitution . In water self-assembly, CHPMA6 forms nanogel.

3. Emulsion polymerization technique

By using the emulsion polymerization method, l-proline functionalized PMMA [poly (methyl methacrylate)] nanogels with a variety of catalyst functionalization (0.5-15 wt%) and cross linking densities (0-50 wt%) were formulated . Mechanical stirring produces monomer droplets during the emulsion polymerization process.[13]

4. Reverse microemulsion polymerization technique

Polyacrylic acid (PAA) nanogels loaded with lithium loadin were created using a reverse microemulsion polymerization process.A magnetic stirrer was used to blend the 3.43 g and 2.62 g of span 80 with 100 ml of hexane as the oil phase . 500 ml of acrylic acid were mixed with 1.5 ml of 10% (w/w) LiOH in water to create the aqueous phase. To the aqueous phase, add 40 l of 20% (w/v) N, N, N', N'- Tetramethylene-diamine (TEMED), 500 l of 2% (w/v) potassium persulfate, and 214 l of 5% (w/v) N, N'-Methylenebisacrylamide (MBA) suspension.[14]

Aqueous phase was added drop by drop into the oil phase to create the microemulsion. Emulsion wastransferred into a 60°C water bath and stirred at 400 rpm with a magnetic stirrer while being left at room temperature for the night. Pellets were collected after decanting the supernatent . Thermodynamically, microemulsions are stable.

5. Inverse miniemulsion polymerization technique

Activators generated electron transfer atom transfer radical polymerization (AGET ATRP) of oligo (ethylene oxide) monomethyl ether methacrylate (OEO300MA) by inverse mini-emulsion polymerization of water/cyclohexane at room temperature was used to create fluorescent dye rhodamine B or fluorescein tagged nanogels. In order to fabricate active HO-POEO300MA nanogels, polymerization was regulated using hydroxyl containing ATRP initiator . During the polymerization,cell adhesive nanogels are synthesised using ACRLPEO-GRGDS as a co- monomer . By using an O/W mini-emulsion concept, intense shear stress is applied using ultrasonication or a high pressure homogenizer to fabricate monomer droplets. Miniemulsions are thermally sable.[13]

6. Free radical crosslinking polymerization technique

Vinyl containing floresent pre polymer was used to create photocrosslinked biodegradable photoluminescent polymeric (PBPLPs) nanogel for drug delivery and cell imaging. The synthesis of PBPLPs nanogel brought a new era to fabricate nanomaterials in theranostic nanomedicine for drug delivery and cell imaging.[15]

V. NANOGELS – APPLICATIONS

1. Local anaesthetics

Local anaesthetics coming under an important pharmacological classes that causes analgesia and relieves pain . The analgesic action of local anaesthetics is because of the hindrance of the nerve impulses in the nerve cell membrane by shutting the voltage-gated Na+ channels . The extent of numbness brought by a certain local anaesthetics concentration depends on the manner and strength of nerve stimulation as well as its resting membrane potential. Clinically, local anaesthetics are divided into two groups based on their chemical components: amino esters and amino amide. The severe toxicity of local anaesthetics caused by overdosing has generated interest in developing controlled release drug delivery devices for them.[16] Local anaesthetics can be more effectively administered locally if they are formulated into drug delivery systems like nanogels.Procaine hydrochloride, an amino ester local anaesthetic, was loaded into a methacrylic acid ethyl acrylate nanogel via hydrogen bonds and hydrophobic interactions, and at high pH,shows more drug delivery. The strategy of release is based on the deprotonation of the acid on the nanogel, which elevates osmotic pressure and enables the system to expand, increasing porosity and facilitating the release of procaine hydrochloride.[17]

2. Cancer therapy

Using a biodegradable nanogel to minimise the toxicity of 5'- triphosphorylated ribavirin was made by cross-linking polyethyleneimine and PEG/pluronic. Acetylated chondroitin sulphate was utilised to create a doxorubicine-loaded self-organizing nanogel for cancer therapy. The absorption of doxorubicine in a nanogel containing glycol chitosan that had been grafted with 3-diethylaminopropyl groups was increased by pH

responsiveness. Pullulan/folate-based self-quenching polysaccharide is utilised to reduce the toxicity of pheophorbide.[18] PEG [Polyplex nanogel] and polyethyleneimine generates a cross-linked, branching network that is utilised to increase fludarabine's activity while reducing its toxicity. Heparin pluronic self-assembled nanogel is employed to transport the RNaseA enzyme for cellular internalisation. Recombinant murine onterlikine-12 sustained tumour immunotherapy uses cholesterol-containing pullulan sustained release nanogels. Reducible heparin with disulfide linkage nanogel is utilised to internalise heparin for melanoma cell apoptosis. Doxorubicin-loaded acetylated hyaluronic acid nanogel utilised for targeted cancer therapy. Hydroxypropylcellulose-poly (acrylic acid) quantum dots with cadmium (II) ions that are pH and temperature sensitive are employed in cell imaging. 5-fluorouracil is delivered in-situ using a gelatinized thermosensitive nanogel made of poly (Nisopropylacrylamide-co-acrylamide). Pullulan with modified amino groups that contains cholesterol is employed in a quantum dot hybrid nanogel for bioimaging. Nanoparticles typically have a diameter of close to 100 nm, are neutral, and have hydrophilic surfaces, all of which prolong blood circulation and boost tumour delivery.[19]

3. Autoimmune disease

The efficiency of the drug delivery system to prominently inhibit the immune cells that regulate the autoimmune response provides the foundation for treating autoimmune disorders. Since nanogels can enhance the immunosuppression effect by targeting the antigen-presenting cells that contribute to disease and facilitates systemic accumulations of the loaded drug, the incorporation of immunosuppressant drugs into nanogel delivery systems has been extensively studied for this purpose. By loading liposomes with a diacrylate ended copolymer of poly (lactic acid-co-ethyleneglycol), a nanogel system containing mycophenolic acid compexed with non-methylated -cyclodextrin was designed and evaluated for the treatment of , an autoimmune disorder like systemic lupus erythematosus. By exposing the nanogel system to UV light, it is possible to cross-link acrylated monomers and gelatin th particles into a stable mixture.[20]

4. Neurodegenerative disease

Since there is currently no known therapy for neurodegenerative illnesses like Alzheimer's and Parkinson's, oligonucleotides were the subject of several research when they shows the potential to be used as diagnostic aid or therapeutic tools for these conditions. The difficulty of oligonucleotides to cross the blood brain barrier, their quick elimination by renal excretion, and their instability against metabolism have all considerably hampered their use in the treatment of neurodegenerative disorders . Oligonucleotides were added into nanogel delivery devices to improve their performance. By enabling oligonucleotides to pass the blood–brain barrier, nanogels' unique characteristics facilitate their transport to the central nervous system.[19] By entrapping negatively charged drug particles in an oligonucleotide nanogel created by crosslinking poly (ethylene glycol) and polyethylenimin, it was discovered that the nanogel could create a stable polyelectrolyte complex in aqueous dispersion. Increased transporting efficiency is the result of surface modification with insulin or transferrin.

5. Anti- inflammatory

As topical delivery systems for non-steroidal anti-inflammatory drugs (NSAIDs), nanogels have found applications in dermatology and cosmetology for the treatment of allergic contact dermatitis, psoriatic plaque, and other skin conditions. Since they can surpass the major limitations of topical delivery systems, namely the relatively brief interaction period between active medicines and the application site, nanogels are perfect for this application. This is accomplished by keeping water in the gel matrix and creating a homogeneous nanogel dispersion. Through the use of a poly-(lactide-co-glycolic acid) and chitosan nanogel, the simultaneous topical delivery of two anti-inflammatory medicines, Spantid II and ketoprofen, was successfully accomplished. Oleic acid was applied to modify surfaces. The ability of this nanogel technology to penetrate deeply to the layers of skin makes it useful for treating a number of inflammatory conditions.

6. Vaccine drug delivery

The foundation of vaccination is the activation of an antigen-specific immune response. Polymeric nanogels are being used as an innovative, alternative method of vaccine delivery to improve the potency and effectiveness of vaccines. The ability of the nanogel network to shield vaccine antigens from enzymatic degradation is

advantageof nanogels over conventional vaccinations. Using surface-modified nanogels with coupled antibodies and other ligands can significantly increase the target specificity of the vaccine delivery.[21]

7. Transdermal drug delivery

In comparison to other routes, the transdermal dermal mode of administration has the advantages of eliminating the first pass effect, increasing medication effectiveness, providing constant state drug concentration in plasma, and improving patient compliance. To increase the drug's penetration into the site of action, a number of strategies were taken into consideration. Using nanogels ,the topical delivery of active pharmaceutical components to the stratum corneum is a promising strategy. Transdermal delivery of the medication was explored as an alternative because oral administration of aceclofenac has a variety of negative side effects, such as ulcers and stomach haemorrhage, and it demonstrated improved stability and permeability. A dispersion of aceclofenac was created using the emulsion solvent diffusion method and added to a gel matrix to create a nanogel for the trans dermal delivery of drug for the treatment of arthritis.[22]

8. Bone regeneration

Biodegradable cell scaffolds should release lithium and other medications gradually and locally for effective bone regeneration. Lithium can enhance bone growth, hence it's been formulated as lithium nanogels for the controlled release of lithium into bone tissue. These nanogels are made by micro-emulsion polymerization of polyacrylic acid.

9. Antibacterial and anti-microbial activity

Due to resistance to antibiotics conventional delivery systems,it is very difficult to treat infectious diseases. A rapid and targeted approach is needed to treat a microbial infection, which is made achievable by nanogel delivery methods. By using the mini-emulsion process, dextran crosslinked polyacrylamide nanogels (polysaccharide based nanogels) were created and loaded with zinc nitrate (zinc ions) as an antibacterial agent. Methacrylated hyaluronic acid was employed as the crosslinking agent . Th intention of these nanogels was to target methicillin-resistant staphylococcus aureus strains.[23]

10. Diabetes

In order to cure diabetes, innovative treatment approches are being examined.An injectable nanogel network withf dipolar nanoparticles has been developed ,that is sensitive to changes in blood glucose levels and releases exact doses of insulin in response. These nanoparticles generate an adhesive gel matrix that keeps its integrity and responds to pH fluctuations. The nanogel network will transport insulin and other enzymes required for the conversion of glucose into gluconic acid by using dextran. When there is hyperglycemia, the easily soluble glucose molecules pass through the nanogel network and start the process of turning into gluconic acid, which drops the pH of the medium. In turn, this will encourage the secretion of insulin. Although this strategy shows great potential for the treatment of diabetes, additional work needs to be done before this nanogel is ready for human trials.[24]

11. Ophthalmology

Dexamethasone-containing eye drops were developed using an emulsification or solvent evaporation process with 2-hydroxypropyl—cyclodextrin (HP CD) medium that contains CD nanogel for sustained release. Pilocarpine was encapsulated in pH-sensitive polyvinylpyrrolidone-poly [acrylic acid] (PVP/PAAc) nanogels ,that are synthesized by radiation-induced polymerization of acrylic acid (AAc) in an aqueous solution of polyvinylpyrrolidone (PVP) acting as a template. This improved bioavailability ,stability of pilocarpine and maintained an adequate concentration of the drug at the site for a long period of time .[25]

VI. CONCLUSION

Nanogels have been discovered to significantly progress the nano sector for the detection and treatment of a variety of ailments. Nanogels can deliver biologically active compounds, especially biopharmaceuticals, effectively due to their wide range of characteristics.

This has led to a number of therapeutic uses, including the controlled delivery of active pharmaceutical ingredients. As a carrier or facilitator, they can also be utilised to treat conditions like diabetes, cancer, and neurological diseases. These uses of nanogels have been promoted by their special qualities, such as their customizing capabilities and simplicity in encapsulating medicines. Additionally, they can reduce drug side effects and therapeutic doses,helps to enhancing the effectiveness of therapeutic agents and raising their level of effectiveness to the patients .

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