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Review Article

An Overview of Nanogel –Novel Drug Delivery System

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A B S T R A C T

Nanogels are innovative drug delivery system that can play an integral part in pointing out many issues related to old and modern courses of treatment such as nonspecific effects and poor stability. Biomedical and pharmaceutical applications of Nanogels have been explored for tissue regeneration, wound healing, surgical device, implantation, and peroral, rectal, vaginal, ocular, and transdermal drug delivery. Nanogels are proficiently internalized by the target cells, avoid accumulating in nontarget tissues thereby lower the therapeutic dosage and minimize harmful side effects. Nanogels may be defined as highly cross linked nano-sized hydrogels ranges from 20-200 nm. They can be administered through various routes, including oral, pulmonary, nasal, parenteral, intra-ocular etc. They have a high degree of drug loading capacity and it shows better permeation capabilities due to smaller size. Nanogels are the novel drug delivery systems for both hydrophilic and hydrophobic drugs.

Keywords: Nanogel, Novel Drug Delivery, Mechanism

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INTRODUCTION

Nanogels may be defined as highly cross linked nano-sized hydrogel systems that are either co-polymerized or monomers which can be ionic or non-ionic. The size of Nanogels ranges from 20-200 nm. Nanogels are known to exhibit great qualities that contribute to the drive towards it as a delivery system[1].They include remarkable thermodynamic stability, elevated capacity of solublilization, relatively low viscosity, and capability of undergoing vigorous sterilization technique[3].Nanogels may entrap drugs and biological molecules. Therefore, they can be vastly employed in protein and gene delivery. The particle size and surface properties can be manipulated to avoid rapid clearance by Phagocytic cells, allowing both passive and active drug targeting. Controlled and sustained drug release at the target site, improving the therapeutic efficacy and reducing side effects[4].

Drug loading is relatively high and may be achieved without chemical reactions; this is an important factor for preserving the drug activity. Ability to reach the smallest capillary vessels, due to their tiny volume, and to penetrate the tissues either through the paracellular or the transcellular pathways. Highly biocompatible and biodegradable. Nanogel dispersions have a larger surface area which is important for *in vivo* applications. Nanogels have sizable drug loading capacity, low buoyant density and high dispersion stability in aqueous media. Nanogels show promise as a suitable nanomedicine carrier as compared to other nanoparticles especially in terms of drug loading[5].

PROPERTIES OF NANOGELS

Biocompatibility and Degradability-

Nanogel is madeup of either natural or synthetic polymers. They are highly biocompatible and biodegradable thereby avoiding its accumulation in the organs. Chitosan, ethyl cellulose, methyl cellulose 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 in nature[6].

Swelling Property in Aqueous Media

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

The structure of Nanogels:

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

Environmental parameters which 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, temperature is a trigger of swelling in case of thermo responsive gels[7].

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 large quantity of water. Thus, upon incorporation and loading the water will provide cargo space sufficient to contain salts and biomaterial. 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 hydrophilic vehicle. Covalent attachment of bioactive molecules which leads to the formation dense drug-loaded core[8].

Controlled self-assembly-which is generally for polyelectrolyte-based Nanogel. The high loading efficiency is attributed to 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 nanodelivery systems is that a tiny manipulation in particle size, surface charge and hydrophobicity can remarkably improve permeability. In spite of the fact that 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 Blood Brain Barrier (BBB). So, in order to overcome such 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[9]

Colloidal Stability

Nanogels or polymeric micellar Nanogel systems have better stability over the surfactant micelles and exhibit lower critical micelle concentrations, slower rates of dissociation, and longer retention of loaded drugs.

Non-Immunologic Response

Any agent that enters systemic circulation 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 bloodstream. All of which are 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 immune system and its defenses[7].

ADVANTAGES OF NANOGELS

- High biocompatibility, which makes Nanogels a very promising approach to drug delivery systems.
- High biodegradability, which is crucial to avoid accumulation of Nanogel material in the bodily organs, thereby leading to toxicity and adverse effects.
- Nanogels are inert in the blood stream and the internal aqueous environment, meaning that they do not induce any immunological responses in the body.
- Extremely small size, which induces a number of effects such as:
- Enhanced permeation capability.
- Avoidance of rapid renal exclusion. Escaping renal clearance leads to prolonged serum half-life[8].
- Avoidance of clearance by phagocytic cells and the uptake by reticuloendothelial system, which permits both passive and active drug targeting.
- Capability to cross the Blood Brain Barrier.
- Enhanced penetration of endothelium in pathological sites like solid tumors, inflammation tissue and infracted areas. Since Tumor tissues have a high capillary permeability, more nanoparticles permeate into the tumor tissue and accumulate there, which increases the amount of drug delivered and the selectivity of the drug delivery.
- Improved ability to access areas that is not accessible by hydrogels, upon intravenous administration.
- Safe delivery of drug carrying Nanogel particles into the cytoplasm of target cells, therefore making them ideal for intracellular drug delivery.
- Rapid responsiveness to environmental changes such as pH and temperature[9].

CLASSIFICATION OF NANOGELS

Based On Their Behavior Towards A 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.

Based On the Type of Linkages Present In the Network Chains of Polymeric Gel Structure

PHYSICAL CROSS-LINKED GELS

Physical gels or pseudo gels are formed by weaker linkages through either

- Van der Waals forces,
- Hydrophobic, electrostatic interactions, or
- Hydrogen bonding. A few simple methods are available to obtain physical gels.

These systems are sensitive and this sensitivity depends on polymer composition, temperature, ionic strength of the medium, concentrations of the polymer and of the cross-linking agent. The association of amphiphilic block copolymers and complexation of oppositely charged polymeric chains results in the formation of micro- and Nanogels in only a few minutes. Physical gels can also be formed by the aggregation and/or self-assembly of polymeric chains[10].

Liposome Modified Nanogels

Kono *et al.*,have disclosed liposomes bearing succinylated poly(glycidol)s; these liposomes undergo chain fusion below pH 5.5 that has been shown to efficiently deliver calcein to the cytoplasm. Liposomes anchored by or modified with poly(*N* isopropylacrylamide)-based copolymeric groups are suitable for thermo- and pH-responsive Nanogels, which are being investigated for transdermal drug delivery[12].

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[11]. 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 in order 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.

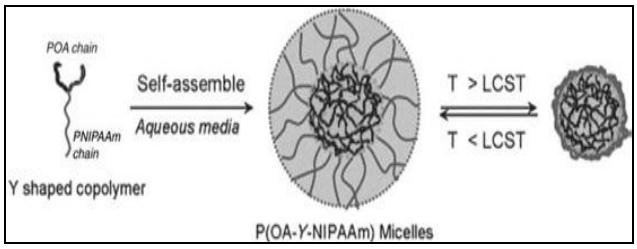

Figure 1 : *Y*-shaped copolymer self-assembly to give micelle structures.

HYBRID NANOGELS

When particles of a Nanogel are dispersed in 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 aqueous medium. Specifically, cholesterol-bearing pullulan (CHP) Nanogels were investigated[13]. 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[15].

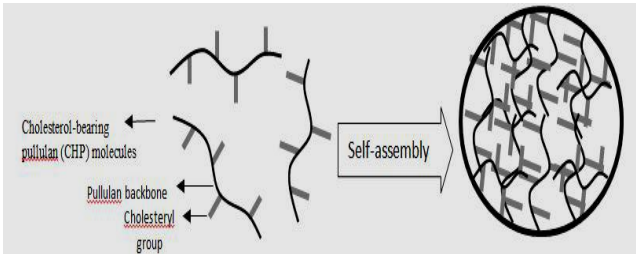

Figure 2: Self-assembly of CHP molecules to form CHP Nanogel

DRUG RELEASE MECHANISM OF THE NANOGELS

pH Responsive Mechanism

As the name indicates, drug release responds to pH changes in the surrounding environment. In other words, the release of drug can take place in different physiological environments that acquire different pH values. The most release will take place in the appropriate pH which means that the release is mainly achieved in a targeted area of the body that possesses that pH. This mechanism is based on the fact that polymers employed in the synthesis of a Nanogel contain pH sensitive functional groups that deionize in the polymeric network. The deprotonation results in increase in osmotic pressure, swelling and porosity of the polymer which triggers the release of the electrostatically bound molecules[12].

Thermosensitive and Volume Transition Mechanism

Some Nanogels are reactive to a specific temperature known as volume phase transition temperature (VPTT) which means they display a change in volume according to the temperature. If the surrounding medium is below VPTT, the polymer becomes quenched and hydrated which makes it swell and release the drug loaded. Above VPTT the opposite occurs and the Nanogel shrinks abruptly and the content flows out. Previously, the thermoresponsive Nanogels used to rupture cellular network when they expand and increase in volume. So, some alterations were applied on thermosensitive drug-containing Nanogels like changing the polymers ratio to achieve lower critical solution temperature. A good example is the biocompatible magnetic field targetibility of poly (N-isopropylacrylamide) and chitosan Nanogel which is quiet employed in hyperthermic cancer treatmen[14]t.

Photochemical Internalization and Photoisomerization

Photoisomerization refers to a process in which a bond of restricted rotation undergoes some conformational changes due to exposure to light. Double bond containing molecules are good example; they isomerize usually from a trans orientation to cis orientation upon light irradiation. When photosensitizers loaded Nanogel are excited, they produce two species of oxygen (singlet and reactive) which can result in oxidation in the cellular compartment walls that highly influence the release of therapeutic agents into the cytoplasm.Azodextran Nanogel loaded with aspirin was a subject of release studies. The observations showed that Cis-trans isomerization of azobenzene by photoregulation causes the formation of E-configuration ofazo group. These results in better release profile of aspirin compared to the previous Z-configuration[15].

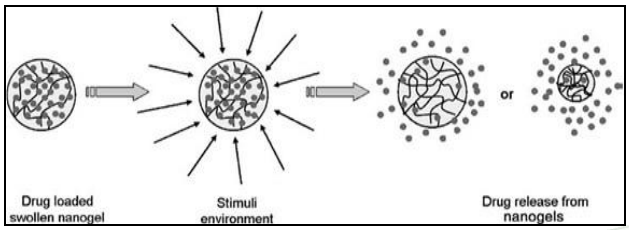

Figure 3 : Drug release model from Nanogel

SYNTHESIS OF NANOGELS

Photolithographic Techniques

Photolithographic techniques, photochemical reaction for activation and subsequent reaction have been explored in strive of producing 3D hydrogel particles and Nanogels for drug delivery. In this method, stamps or replica molds are treated to give the surface specific properties that allow the molded gels to release the incorporated agents.Microfabrication of such gels follow the general strategy where poly (dimethylsiloxane) (PDMS) stamps are utilized to mold, release, and stack gels into 3 dimensional structures. Surface modification enhances the release or adhesion of molded gels to a substrate. The most known techniques to modify PDMS stamps are usually achieved by hexa (ethylene glycol)-terminated self-assembled monolayers (SAMs), or by adsorbed monolayers of bovine serum albumin (BSA)[16].

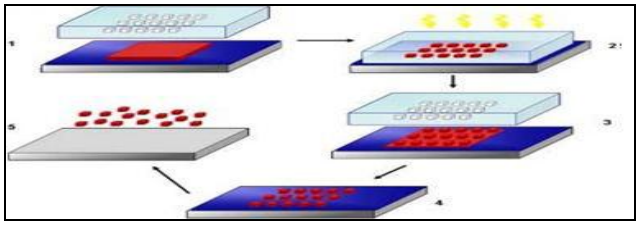

Figure 4: Schematic diagram of five steps involved in photolithography

MICROMOLDING METHOD

The methods are similar to photolithographic techniques. However, they can minimize the need to use costly lithographic equipment and clean room facilities. In the process, cells were suspended in a hydrogel precursor solution consisting of either methacrylated hyaluronic acid (MeHA) or PEGDA or a photoinitiator in water. The resulting mixture was deposited onto plasma-cleaned hydrophilic PDMS patterns and then photocross linked via exposure to UV light. The resulting cell-laden microgels were removed, hydrated, and then harvested. They were also molded into various shapes including square prisms, disks, and strings[17].

Water-In-Oil (W/O) Heterogeneous Emulsion Methods

W/O emulsion methods involve generally two steps: emulsification of aqueous droplets of water soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and cross linking of biopolymers with water-soluble cross linkers[18].

Inverse (mini) emulsion method

- A W/O emulsion is formed from a mixture consisting of aqueous biopolymer droplets and a continuous oil phase using either a homogenizer or a high-speed mechanical stirrer.
- Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents. then crosslinked microgel particles are prepared as dispersion in organic solvent purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization. the size of the prepared microgel particles can be controlled by amount of surfactants and crosslinking agents as well as stirring speed during the formation of inverse emulsion.

Reverse Micellar Method

Similar to the inverse (mini) emulsion method, the reverse micellar method also involves a W/O dispersion; however, a relatively large amount of oil-soluble surfactants is used to form a thermodynamically stable micellar solution consisting of aqueous droplets dispersed in the continuous oil phase[19] .The resulting micellar droplets have a submicron size ranged from tens to hundreds of nanometers in diameter. Tumor targeted CS based Nanogels were prepared in inverse microemulsion of hexane containing Aerosol OT as a stabilizer in the presence of doxorubicin (Dox)-modified Dex. Aqueous glutaraldehyde was used to crosslink CS. The resulting Dox-encapsulating CS-based Nanogels have a diameter of around 100nm.

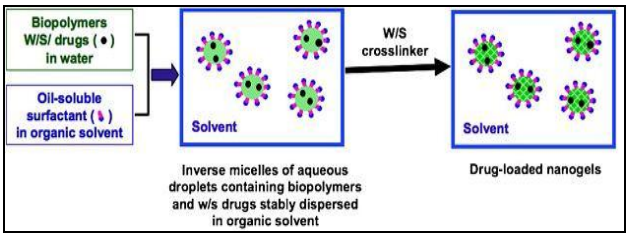

Figure 5: Reverse Micellar method for the preparation of Nanogels

Membrane Emulsification

In the membrane emulsification technique, the to-bedispersed phase is passed through the membrane (glass or ceramic), which possesses uniform pore size. Under certain conditions the emulsion droplets or microgels with specific morphology are formed on the surface of the membrane and afterwards, with a continuous phase that is

flowing across the membrane, these fabricated emulsion droplets or microgels are recovered.These fabricated emulsion droplets can be in different emulsion formation such as water-inoil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water (W/O/W). The size of the formed droplet is controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane[20]

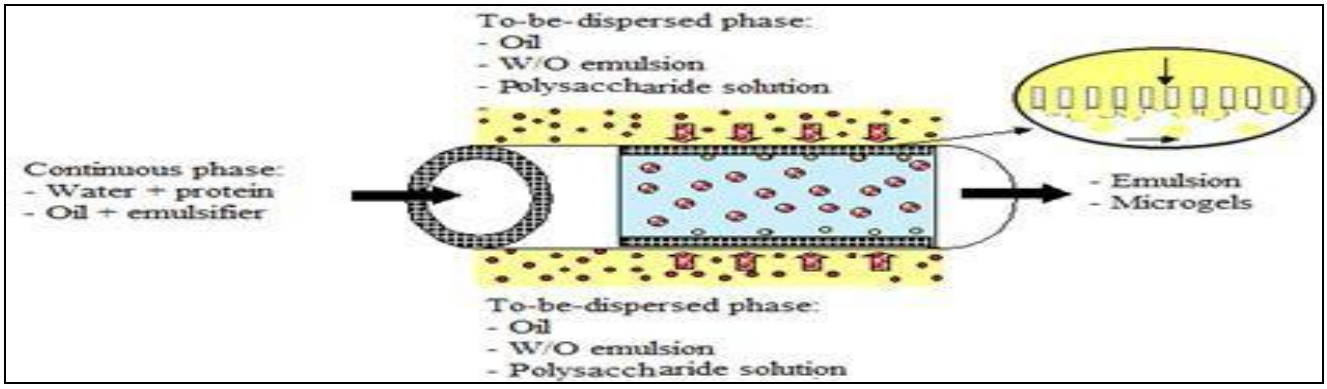

Figure 6: Schematic diagram of the membrane emulsification technique

CARBODIIMIDE COUPLING

Novel Pullulan Chemistry Modification

Synthesis of cholesterol based pullulan Nanogel (CHP) was done by reacting mixture of cholesterol isocynate in dimethyl sulfoxide and pyridine. Pullulan was substituted with 1.4 cholesterol moieties per 100 anhydrous glucoside units. The preparation was freeze dried and in aqueous phase it formed Nanogel which was complexed with W-9 peptide for delivery in osteological disorders. The capacity of pullulan has been known to act as good protein carrier hence was used in Nanogel formulation for drug delivery.

Further CHP has been modified with acrylate group and their thiol group was modified with polyethylene glycol by adopting Michael addition reaction, this allowed reduction in mesh size to 40 nm encapsulating 96% interleukin-12. These nanosystems have also been investigated by modifying cholesterol units by 1.1 units of cholesteryl group per 100 glucose units of parent pullulan shown significant interaction with Aβ oligomer and monomer for alzhiemer's disease treatment enhancing microglia and cortical cell viability[22]. More recently pullulan have been used in folate receptor targeted system in which folate was substituted to pullulan by 1.6 glucose units. Further Coupling of pullulan and photosensitizer (pheo-A) was done with carbodimide to produce the conjugate which was converted to Nanogel by dialysis in DMSO against deionised water, investigated for photodynamic therapy and were successfully localized at tumor cells to cause cell death by photo destruction[21].

Heterogeneous Free Radical Polymerization

Various heterogeneous polymerization reactions of hydrophilic or water-soluble monomers in the presence of either difunctional or multifunctional crosslinkers have been mostly utilized to prepare well-defined synthetic microgels. They includeprecipitation, inverse (mini) emulsion, inverse micro emulsion, and dispersion polymerization utilizing an uncontrolled free radical polymerization process.

Precipitation Polymerization

Precipitation polymerization involves the formation of homogeneous mixture at its initial stage and the occurrence of initiation and polymerization in the homogeneous solution. As the formed polymers are not swellable but soluble in the medium, the use of crosslinker is necessary to crosslink polymer chains for the isolation of particles. As a consequence, the resulting crosslinked particles often have an irregular shape with high polydispersity. Peppas *et al.*,synthesized narrow size distribution poly (methacrylic acid-*g*-ethylene glycol) (P (MAA-*g*-EG)) nanospheres through precipitation polymerization for the oral delivery of proteins. They obtained better control over particle size and particle size distribution by controlling monomer concentration in water. They also revealed that increasing the cross-linker concentration during polymerization decreased the equilibrium swelling of the nanospheres .

Inverse (Mini) Emulsion Polymerization

Inverse (mini) emulsion polymerization is a W/O polymerization process that contains aqueous droplets (including water-soluble monomers) stably dispersed with the aid of oilsoluble surfactants in a continuous organic medium. Stable dispersions are formed by mechanical stirring for inverse emulsion process and by sonification for inverse miniemulsion**n** polymerization. Upon addition of radical initiators, polymerization occurs within the aqueous droplets producing colloidal particles[23.]

Inverse Microemulsion Polymerization

While inverse (mini) emulsion polymerization forms kinetically stable macroemulsions at, below, or around the critical micellar concentration (CMC), inverse microemulsion polymerization produces thermodynamically stable microemulsions upon further addition of emulsifier above the critical threshold. This process also involves aqueous droplets, stably dispersed with the aid of a large amount of oil-soluble surfactants in a continuous organic medium; polymerization occurs within the aqueous droplets, producing stable hydrophilic and water-soluble colloidal nanoparticles having a diameter of less than 50–100nm. Inverse microemulsion polymerization was explored for the synthesis of well-defined Nanogels. Poly(vinylpyrrolidone)- based

Nanogels incorporated with Dex as a water-soluble macromolecular carbohydrate drug were prepared.

Dispersion Polymerization

In the process, most ingredients including monomers, polymeric stabilizers, and initiators are soluble in an organic solvent as a continuous phase. At the onset, polymerization occurs in a homogeneous reaction mixture; however, the formed polymers become insoluble in the continuous medium, ultimately leading to the formation of stable dispersion of polymeric particles with an aid of colloidal stabilizers Hydrophilic monodisperse micron-sized particles of PHEMA were also prepared by dispersion polymerization in the presence of PEO-b-poly (1,1,2,2-tetrahydroperfluorodecyl acrylate) diblock copolymer as a stabilizer in supercritical carbon dioxide, and methacryloyl-terminated PMMA in a 55/45 (wt/wt) mixture of 2-butanol/tolune. Drugs and magnetic nanoparticles were either physically incorporated or chemically attached to microgels. The resulting microgels were effective as drug delivery carriers and for DNA application.

Heterogeneous Controlled/Living Radical Polymerization

Recently, CRP has been explored as a tool to preparation of well controlled polymer–protein/peptide bioconjugates. Various methods for CRP have been developed; however, the most successful techniques include atom transfer radical polymerization (ATRP), stable free radical polymerization (SFRP), and reversible addition fragmentation chain transfer (RAFT) polymerization[23].

MECHANISM OF DRUG RELEASE FROM NANOGELS

Diffusion

The diffusional release of doxorubicin from stable hydrogel nanoparticles based on pluronic block copolymer (Missirlis *et al.*, 2006). This release mechanism is simple and has been successfully employed in various nanomedicines, such as polymeric micelles that have already reached a clinical stage[24].

Nanogel Degradation

The degradation of these Nanogels was shown to trigger the release of encapsulated molecules including rhodamine 6G, a fluorescent dye, and Doxorubicin, an anticancer drug, as well as facilitate the removal of empty vehicles. Example: The release of Doxorubicin was significantly increased due to glycol chitosan nanoparticles sensitivity to pH stimuli due to grafting of diethylaminopropyl group. Significant mesh size alteration has been seen in dietylaminoethyl methyacrylate cationic Nanogel for release of medium size molecules by virtue of pH sensitivity[25].

Displacement By Ions Present In The Environment

There is an increased interest in developing Nanogels that can release biological agents in response to environmental cues at the targeted site of action. For example: disulfide cross-linked POEOMA Nanogels biodegraded into water-soluble polymers in the presence of a glutathione tripeptide, which is commonly found in cells.Cell membrane-triggered release of negatively charged drugs from complexes with cationic Nanogels was also proposed to explain cellular accumulation of an NTPs drug delivered with Nanogels[27].

OTHERS

Photochemical Internalization and Photoisomerisation

Excitation of photosensitizers loaded Nanogels leads to production of singlet oxygen and reactive oxygen species which cause oxidation of cellular compartment walls such as endosomal barrier walls which effects release of therapeutics into cytoplasm. Polyelectrolyte hydrogels that incorporate biological agents via electrostatic bonds allow for release of biological agents in response to environmental changes. For instance, hydrogels of cross-linked PEG and PAA were shown to release an oppositely charged protein upon 1) addition of calcium ions that reacted with carboxylate groups of PAA and displaced the protein or 2) acidification of the media by decreasing pH from 7.4 to 5.5.A similar mechanism was proposed for release of oligonucleotides from PEG-*cl*-PEI Nanogels. In this case, electrostatically bound oligonucleotides are believed to be displaced by negatively charged cellular components[28].

APPLICATIONS OF NANOGELS

Local Anesthetics (LA)

Local anesthetics are one of the classes of drugs that induce analgesia and eliminate pain[28]The analgesic effect of local anesthetics is due to the blockage of the nerve impulses in nerve cell membrane by shutting the voltage gated Na+ channels. The manner and the intensity of nerve stimulation as well as its resting membrane potential will determine the degree of numbness induced by a specific concentration of a local anesthetic. Local anesthetics are clinically classified into two classes, depending on their chemistry: amino esters and amino amide. Over dosage of local anesthetics leads to their high toxicity, which has sparked the interest in formulating controlled release drug delivery systems of them. Incorporating local anesthetics into drug delivery systems like Nanogels can improve their regional administration[30]. A delivery system of procaine hydrochloride, which is an amino ester local anesthetic, loaded into methacrylic acid ethyl acrylate Nanogel via hydrophobic and hydrogen bonds exhibited a high release rate at high pH. The mechanism of release is based on the deprotonation of the acid on the Nanogel which leads to an increase in the osmotic pressure and the swelling of the whole system, which increases the porosity, thus promoting the release of the procaine hydrochloride.

Cancer Treatment

Biodegradable Nanogel prepared by cross linking of polyethyleneimine and PEG/pluronic used for 5'-triphosphorylated ribavirin reduced toxicity. Doxorubicine loaded self-organizing Nanogel formulated by acetylated chondroitin sulphate used for cancer treatment. pH responsive doxorubicine uptake accelerated Nanogel containing glycol chitosan, which was grafted with 3-diethylaminopropyl groups. Self-quenching polysaccharide based pullulan folate-pheophorbide used in minimal toxicity of pheophorbide.Cross linked branched network of polyethyleneimine and PEG Polyplex Nanogel used for elevated activity and reduced

toxicity of fludarabine. Self-assembled Nanogel composed of heparin pluronic used to deliver RNAas enzyme to internalize in cell[32].

Cholesterol bearing pullulan sustained release Nanogels used in recombinant murine onterlikine-12 sustained tumor immunotherapy. Reducible heparin with disulfide linkage Nanogel used in internalization of heparin for apoptotic death of melanoma cells. Specific targeting Nanogel of doxorubicin loaded acetylated hyaluronic acid used in cancer treatment.pH and temperature responsive cadmium (II) ions quantum dots, made of Hydroxypropylcellulose – poly

(acrylic acid) used in cell imaging. *In-situ* Poly (Nisopropylacrylamide- co-acrylamide) gelatinized thermosensitive Nanogel used to deliver 5-fluorouracil. Cholesterol bearing pullulan with modified amino group, quantum dot hybrid Nanogel used for bioimaging. Generally, nanoparticles possess an average diameter of nearly 100 nm, neutrality and surface hydrophilicity which results in a prolonged blood circulation and an increased level of tumor delivery.

Autoimmune Disease

The treatment of autoimmune disorders is based on the ability of the drug delivery system to selectively disable the immune cells that mediate the autoimmunity response. The incorporation of immunosuppressant drugs into Nanogel delivery systems have been extensively studied for this purpose since Nanogels can improve the immunosuppression effect by targeting the antigen presenting cells that contribute to disease and enabling systemic accumulations of the loaded drug. A Nanogel system of mycophenolic acid compexed with non-methylated β- cyclodextrin was formulated by loading of liposome's with a diacrylate terminated copolymer of poly (lactic acid-co-ethyleneglycol) and tested for the treatment of systemic lupus

erythematosus, an autoimmune disease. The cross linking between acrylated monomers and the gelation of the particles into a stable mix was achieved by exposing the Nanogel system to ultraviolet radiation.

Neurodegenerative Disease

Currently, neurodegenerative disorders like Alzheimer's & Parkinson's disease have no known cure, therefore, when oligonucleotides showed a potential to be used as a diagnostic or therapeutic tool for these diseases, they became the focus of many studies. So far, the application of oligonucleotides in the treatment of neurodegenerative disease is significantly hindered by their instability against metabolism, their inability to penetrate the blood brain barrier, and their rapid clearance by renal excretion. To enhance the performance of oligonucleotides, they were incorporated into Nanogel delivery systems. The novel properties of Nanogels allow oligonucleotides to cross the blood brain barrier, thereby aiding their delivery into the central nervous system. A Nanogel of oligonucleotide, which was formulated by cross linking poly (ethylene glycol) and polyethylenimin, was found to have the ability to form a stable aqueous dispersion of polyelectrolyte complex by encapsulating negatively charged particles of the drug. Modifying the surface with insulin or transferrin, results in enhanced transport efficacy.

Anti-Inflammatory

Nanogels have found an application dermatology and cosmetology as topical delivery systems of non-steroidal anti-inflammatory drugs (NSAIDs) and for the treatment of allergic contact dermatitis and psoriatic plaque. Nanogels are ideal for this application since they can overcome the major limitation of topical delivery systems, which is the relatively short contact time between active drugs and the application site. This is done by retaining water into the gel matrix and forming a uniform a dispersion of the Nanogel. The simultaneous topical delivery of two anti-inflammatory drugs, Spantid II and ketoprofen was successfully achieved through a Nanogel of poly-(lactide-co-glycolic acid) and chitosan. Oleic acid was used for surface modification. A variety of inflammatory disorders can be treated using this Nanogel system as it can effectively permeate to deep layers of the skin[30].

Vaccine Delivery

Vaccination is based on the induction of an immune response that antigen-specific. In order to enhance the potency and the performance of vaccines, polymeric Nanogels are being utilized as novel, alternative means of vaccine delivery. The advantage of Nanogels over conventional vaccines lies in the ability of the Nanogel network to protect vaccine antigens from enzymatic degradation. Target specificity of the vaccine delivery can be significantly enhanced by using surface modified Nanogels with attached antibodies and other ligands[25].

Transdermal Drug Delivery

Transdermal route of administration has advantages over other routes in that it bypasses first pass effect, improves the efficiency of drugs, provides steady state drug concentration in plasma and increases patient compliance. A variety of approaches were considered to enhance the penetration of drug into site of action. A promising approach is the use of Nanogels for topical delivery of active pharmaceutical ingredients to the stratum corneum. As the oral administration of aceclofenac causes a number of side effects like ulcers and gastric bleeding, transdermal delivery of the drug, was studied as an alternative, and showed better stability and permeability. Through the emulsion solvent diffusion method, a dispersion of aceclofenac was formed and incorporated into a gel matrix to formulate a Nanogel for the transdermal delivery of the drug[29].

Bone Regeneration

For the successful regeneration of bones, biodegradable cell scaffolds should release lithium as well as other medicament slowly and locally. Bone growth can be increased by lithium, hence, lithium Nanogels, synthesized by micro-emulsion polymerization of polyacrylic acid and incorporated into the biodegradable polyhydroxybutyrate matrix, are formulated for the controlled release of lithium into bone tissue.

Antibacterial and Anti-Microbial Activity

Infections are becoming increasingly difficult to cure due to resistance to conventional delivery systems of antibiotics. In order to treat a microbial infection, a quick and localized action is required, which is possible in Nanogel delivery systems. Dextran cross linked

polyacrylamide Nanogels (polysaccharide based Nanogels) loaded with zinc nitrate (zinc ions) as antibacterial agent were prepared by mini-emulsion method. The crosslinking agent used was methacrylated hyaluronic acid. The purpose of this Nanogel was to target the methicillin-resistant strains of staphylococcus aureus.

Diabetics

As diabetes becomes more and more prevalent in the world's population, revolutionized approaches are being considered for its treatment. An injectable Nanogel network that is sensitive to changes of glucose levels in the blood and releases specific amounts of insulin accordingly has been formulated, containing a network of oppositely charged nanoparticles. These nanoparticles attract each other, forming a gel matrix that remains intact and responds to changes in pH. By utilizing dextran, the Nanogel network will carry insulin and other enzymes necessary for the conversion of glucose into gluconic acid. Under conditions of hyperglycemia, glucose molecules, being easily diffusible through the Nanogel, pass the gel network and trigger the conversion process of glucose into gluconic acid, thereby decreasing the pH of the medium. This will, in turn, stimulate the release of insulin. Even though this approach is very promising for the treatment of diabetes, it is still new and needs some work to be done before this Nanogel is suitable for human trials[30].

Ophthalmology

Dexamethasone containing eye drop was prepared by solvent evaporation or emulsification method using 2-hydroxypropyl-γ-clclodextrin (HP γ CD) medium containing γ- CD Nanogel for sustain release. pH-sensitive polyvinylpyrrolidone-poly [acrylic acid] (PVP/PAAc) Nanogels, formulated by γ radiation-induced polymerization of acrylic acid (AAc) in an aqueous solution of polyvinylpyrrolidone (PVP) acting as a template, were used to encapsulate pilocarpine, thus enhancing the bioavailability as well as the stability of pilocarpine and maintaining an adequate concentration of the drug at the site of action for prolonged period of time.

CONCLUSION

Nanogel are novel drug delivery and innovative drug delivery that can play vital role in diagnosis and treatment of wide rase of disese. Nanogels have versatile properties that make them capable of efficient delivery of biologically active molecules, particularly biopharmaceuticals. They can also be used as a carrier, or chaperone, to treat diabetes, cancer, neurodegenerative disease, etc.It is widely used in pharmaceutical field. One future goal of research in this area should be the improved design of microgels/Nanogels with specific targeting residues to enable highly selective uptake into particular cells.

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