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Nanogel as a Pharmaceutical Carrier – Review Article

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Review Article

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Abstract: A nanoparticle which is composed of a hydrogel with a cross linked hydrophilic polymer network is known as "Nanogel". The term 'nanogels' defined as the nanosized particles formed by physically or chemically cross-linked polymer networks that is swell in a good solvent. The term "nanogel" was first introduced to define cross-linked bifunctional networks of a polyion and a nonionic polymer for delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG) or PEG-cl-PEI). Sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systems which proven their potential to deliver drugs in controlled, sustained and targetable manner. With the emerging field of polymer sciences 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, current status, clinical trial status, and future perspective of nanogels have been summarized.
Keywords: Nanoparticle, Nanogel, Nanotechnology, polymer.

INTRODUCTION

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 *-*effective function at nanometer scale. This technique mainly focuses on the radiacal improvements in the current therapeutic and diagnostic procedures.

Development of novel nano-sized particulate drug delivery systems (DDS) have shown the 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 have overcome the challenges by enhancing absorption of drugs, reducing toxicity of drugs, controlled release of doses and reducing biodegradation. It has also reduces 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 functionalised 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, nanoemulsions, nanocrystals, nanodiamonds, carbon nanotubes, nanosuspensions and nanogels have been introduced as an advanced DDS in which nanogels have been introduced in the market due to its maximum advantages over other DDS techniques [1-3]. A nanoparticle which 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 which are made up of flexible hydrophilic or amphiphilic polymer networks. These polymer networks can be anionic or ionic. They behaves as a carrier molecule for drugs and 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 class of biomolecules by optimizing the molecular composition, size and morphology, to ensure the controlled release of drug molecule in vivo. When nanogels dispersed in the aqueous media, their swollen networks become soft and are able to 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 is able to 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 [2-6].

Nanogels, during the first decade of its development, have been proved to be a potential structure for systemic drug release, designing of multifunctional nanocarriers like theranostics and controlled drug release at the target site.

Due to the large surface area and adjustable sixe of nanogels, these molecules are able to incorporate different molecules.

Benefits of Nanogel Drug Delivery Approach

- It provides protection from biodegradation of drugs inside the body.
- Physical properties like size of nanogels can be easily adjusted and maintained according to the desired delivery molecule.
- Low amount drug is required as well as quantity of doses is reduced.
- Improves the bioavailability of the drug molecule and reduce 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 are able to cross blood barin barrier as well as physiological barrier like skin.

Drawbacks of Nanogels

- 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 in the one to hundreds nanometers in diameter. The nanogel contains the some properties like as swelling, degradation and chemical functionality can be controlled [7,8]. Not, only for drug delivery the nanogels is investigated from a longer period of time for making miscellaneous agents like quantum dots, dyes and other diagnostic agents[9,10]. The major significance of nanogels has been arisen due to specific delivery system expectation, wide variety of polymer systems and the ease of change of the physical-chemical properties. Current studies at the clinical level shown promising value of nanogel [11,12]. Nanogels are used in the field of gene therapy, since delivery of gene now become possible within cellular organelles for gene silencing the system [13]. In nanogel, by using varying solvent quality & branching the volume fraction can be altered variability to maintain a three dimensional structure [14].

Routes of administration

- Oral,
- Pulmonary
- Nasal
- Parenteral
- Intra-ocular
- Topical

Drug loading technique in nanogels

Nanogel drugs delivery systems can be successful technique by a high drug loading capacity and by reducing the amount of carriers. Various methods are as follows:

Covalent Conjugation

In the biological agents by using covalent conjugation can achieved nanogels. For egg; Acrylic groups are modified with enzymes and copolymerized with acrylamide either in inverse microemulsion or dilute aqueous solution to obtain nanosized hydrogel. Physical Entrapment In cholesterol – modified pullulan nanogels proteins was incorporated by physical entrapment and SiRNA in HA nanogels [14]. In nonpolar domains by addition of hydrophobic molecules formed a hydrophobic chain which is present in selected nanogels. Eg; in the cholesterol – modified pullulan the prostaglandin E2 is easily solubilized. Another eg; N – hexyl carbamoyl – 5 – fluorocil (HCFU) was noncovalently incorporated in cross – linked nanogels of N – isopropylacrylamide (NIPAAM) & N – vinylpyrrolidone (VP) copolymers. Doxorubicin was also loaded in amphiphilic cross – linked nanogels based on pluronic F127 Due to the hydrophobic interaction in the most of the cases the loading of drug molecules with the nanogel result in relatively low degrees (not more than 10%).

Self-Assembly

When the autonomous organizations of components are aggregates in to structurally well – define then it is known as self-assembly.

It has advantage such as,

- Minima thermodynamics in which resulting in stable & robust structures.
- Versatile & facile,
- It is cost – effective.

Many molecules are self – assembly is characterized by diffusion followed by specific association of molecules through non – covalent interaction, hydrophobic associations or including electrostatics. Due to large number of interaction involved it has weak and dominates the structural and conformational behavior of the assembly [15].

While oppositely charged polysaccharides associates readily as a result of electrostatic attractions [16]. Interactions with neutral polysaccharides lead to be weaker or non – existent, by the modification with chemical it is able to trigger assembly being necessary. The polysaccharides which are highly water soluble, inducing the formation of nanoparticles via hydrophobic interactions. This kind of amphiphilic polymer can be used by three methods.

- Hydrophilic chains grafted to a hydrophobic backbone (grafted polymer).
- Hydrophobic chains grafted to a hydrophilic backbone.
- Or, with alternating hydrophilic & hydrophobic segments (block polymers).

Amphiphilic polymers when contact with aqueous environment then spontaneously form self – aggregated nanoparticle via intra or intermolecular association between the hydrophobic moieties, primarily to minimize the interfacial free energy. The important feature, from the physicochemical point of view is that the hydrophobic portion aggregates in the internal core and the hydrophilic region to the polar or aqueous medium. The concentration above which the polymeric chains are aggregates is known as critical micelle concentration or critical aggregates concentration.

Mechanism of drug release from nanogels

Thermosensitive & Volume Transition Mechanism

The polymer which has thermosensitive characteristics like as poly (N – isopropyl acrylamide) leads to initially shrinkages in gel volume and efflux of indomethacin drug due to maintenance of temperature above lower critical solution temperature (LST) [17]. In the rats the polymer (N – isopropyl acrylamide – co – acrylamide) with 5 – fluorouracil is advantageous due to low temperature & release at body temperature [18]. The superficial modification of polyethylene mine nanogels by pluronic, it has the thermoresponsive characteristics with regard to size and successfully used a gene delivery systems [19]. By the physical destruction of cellular network, it is expand up to 1 µm in nanogel size by thermally trigerred volume of nanogels of poly alkylene oxides [20].

By the modification of temperature of nanogels like as poly (N – isopropyl acrylamide) and chitosan in which the lower critical solution temperature could be modified by changing ratio of polymers and used in the hyperthermic cancer treatments [21].

Photochemical Internalization & photo isomerization

Singlet oxygen & reactive oxygen is produced by the excitation of photosensitizers loaded nanogels & cause oxidation of cellular compartment walls such as endosomal barrier walls which effects release of therapeutics in to cytoplasm easily, otherwise hindered by intracellular compartment [22].

By using photoregulation in the azobenzene the Cis – trans isomerization can see in which azo dextran loaded nanogel with aspirin as model drug exhibited that E – configuration of azo group lead to better release profile of drug than Z – configuration at 365 nm radiation [23].

Diffusion Mechanism

Doxorubicin follows the diffusional release and which is stable hydrogel nanoparticles based on puronic block copolymer. Various nanomedicine are follows this mechanism & simple procedure, such as polymeric micelles that have already reached a clinical stage.

PH responsive Mechanism

In the acidic skin PH the reactive oxygen species scavenging the on & off 8catalytic activity by the platinum nanoparticles containing nanogel and for the reason of protonation of crosslinked poly (2 – (N, N – diethylamino) methacrylate) core and PEG [11]. when there is exit low PH the polymers methacrylic acid – ethyl acrylate are insoluble 3D structures, again by increasing the PH ranges acidic groups ionizes due to the polymeric chains repulsions begins and lead to a particular release profile of procaine hydrochloride [14].

The control the release kinetics mechanism shown by the drug temozolidine due to swelling action of PH sensitive polyacryrlic acid chains [24]. But the release of doxorubicin was significantly increased due to PH sensitive of glycol chitosan nanoparticles, & to grafting of diethylaminopropyl groups [25].

Displacement by Ions present in the Environment

Maximum research work is developing nanogel that can release biological agents in response to environmental cues at the specific site of action. Eg Water soluble polymers like as POEOMA nanogels are biodegraded in aqueous in the presence of glutathione tripeptide, which is commonly found in cells.

Cationic nanogels when triggered with negatively charged drug in cell – membrane from complelexes and explain cellular accumulation of drug delivered with nanogel [26].

Application of Nanogels

Nanogel in Opthalmic

Polyvinyl pyrrolidone – poly (acrylic acid) (PVP/PAAc) nanogel is Ph sensitive and prepared by γ – radiation – induced polymerization. It is used to encapsulate pilocarpine in order to maintain an adequate concentration of the pilocarpine at the site of action for prolonged of time [27].

Nanogel in Stopping Bleeding

A protein molecules which is in solutuion & been used for formation of nanogel has been used to stop bleeding, even in severe gashes. The proteins have mechanism of self – assemble on the nanoscale in to a biodegradable gel [28].

Nanogel as NSAIDS

Carbopol and Hydroxypropylmethyl cellulose (HPMC) with the desired viscosity used to prepare the nanogels. Same like another polymer chitosan & poly – (Lactide – co – glycolic acid) used to prepare bilayered nanoparticles and 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 [29].

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 photo initiator. After it is exposed to ultraviolet light to produce photo polymerization 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 types of drug delivery system there will increase patient compliance & delays the onset of kidney damage and common complication of lupus [30].

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 amino propyl group & used Doxorubicin uptake accelerated [25].

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) grxafted poly (l – lysine) these all are used in the traumatic cell death due to physical stress and good source for loading anticancer drugs [20].

Poly (N – isopropyl acrylamide – co – acrylamide) is a insitu gelatinized thermosensitive nanogel used for drug loading capacity of low molecular weight of 5 – Flourouracil was higher than that of macromolecules, bovine serum albumin [20]. Poly (N – isopropylacrylamide) and chitosan is a thermosensitive magnetically modalized nanogel & used in hyperthermia cancer treatment and targeted drug deliverey [21].

Hydroxypropyl cellulose – poly (acrylic acid) and cholesterol bearing pullulan modified with amino group is a nanogel quantum dot hybrid PH and temperature responsive cadmium II ions quantum dots which is used for probe for imaging[9], optical PH sensing, cell imaging and drug loading of temozolomide [24].

Based on Sustained Release Cholesterol bearing pullulan nanogels is controlled by sustained release nanogel and used for recombinant murine interleukine–12 sustained tumour immunotherapy [31]. Reducible heparin with disulfide linkages nanogel is used for internalization of heparin for apoptoric death of melanoma cells [32].

Based upon the Self Assembly Heparin pluronic which is a self-assembling nanogel and used in RNase an enzyme delivery internalized in cells [33]. Polymer with cross linked poly (2 – (N, N – diethylamino) methacrylate) core & PEG is a quarternized, amine and size dependent nanogel which is used for efficient SiRNA delivery [34]. Acetylated chondroitin sulfate is self-organizing nanogel and used for Doxorubicin loaded [35]. Acrylate group modified cholesterol bearing pullulan is nanosized cationic

hydrogel which is used enhancing oral and brain Bioavailability of oligo nucleotides [36].

Based on Gene Delivery Controlled delivery of plasmid DNA by using the polymer Di – acrylated pluronic 127 and glycidyl methacrylate chitoolgosaccharides and making Photo crosslinking nanogel[37]. Potential in gene therapy by using the polymer poly (2 – (N, N – diethylaminoethyl) methacrylate) PEGlyted macroRAFT agent for making one step PEGlylated cationic nanogel [38].

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 [27]. 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 alzehimer's disease by inhibiting aggregation of amyloid β – protein by using cholesterol bearing amino group modified for making artificial chaperone nanogel [31].

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 [39]. Assisted protein refolding of carbonic anhydrase and citrate synthase during GdmCL denaturation by using cholesterol bearing pullan for making self-assembled artificial molecular chaperone [40].

Clinical Trail Status of Nanogels

Cholesteryl pullulan (CHP) nanogels have shown tremendous potential in delivering peptides. The CHP-HER-2 vaccine was administered to nine patients biweekly dosing of 300µg with booster doses. The vaccine was well tolerated with some skin sensitivity at site of subcutaneous injection. All the patients showed CD4+ and CD8+ T- cell response suggesting better therapeutic activity [41,42]. CHP angels have further proved their prospects for clinical trials by reducing cytotoxicity of nervous system cells by showing increase in binding capacity to Aβ oligomer in treating Alzheimer's disorder, it has also been clinically investigated for bone loss disorder and it proved its worth by reducing the dosage of W9 peptide by only two times a day than tedious eight time dosage of drug which was clinically impossible [43]. Recent prospects in diabetes management by optical sensitive insulin loaded silver nanoparticle nanogel of poly (4-vinylphenylboronic acid-co-2-(dimethylamine) ethyl acrylate) have been designed opening new era in the field of clinical trials 50. Development of antibiotic conjugated angels and their in-vivo application have given promising approach tow

Current status and future perspective of angels

The recombinant murine interleukin – 12 (IL – 12) encapsulated in CHP angels, via incubation at room temperature and injected in mice with subcutaneous fibro sarcoma leads delayed release & retardation the growth of tumor [44].

Nanogels have been primarily used for cancer therapy. Cholesteryl pullulan angel has shown in clinical trials for delivery of peptidase. The cholesteryl – HER – 2 vaccine was administered to nine patients with 300 µg with booster doses twice a week. From this shown that skin sensitivity at the site of S.C injection & CD4+ & CD8+ T- cell shows the better therapeutic efficacy [35]. Cholesterol pullulan angels show the reduce the toxicity to the nervous system cells and increase the binding capacity to AB oligomer in treating Alzheimer's disease [40, 45].

Recently the new development of controlled diabetes by optical sensitive insulin loaded silver nanoparticle nanogel of poly (4 – vinyl phenyl boronic acid – co – 2 – (dimethylamine) ethyl acrylate) has been designed [45]. Now a day's nanogel is conjugated with antibiotics for the specific drug delivery and conducted at the single cell level [27].

In future the mechanism of blood brain barrier and cytosolic destination over and endosomal or nuclear are necessary to study for the specific and targeting drug delivery.

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