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REVIEW ARTICLE

A Review: Nanogel Recent Drug Delivery

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ABSTRACT

Nanogel drug delivery has remained as one of the most challenging task for pharmaceutical scientists at this 21st century. From the three decades ocular drug delivery research accelerated advanced towards developing a novel, safe, patient compliance formulation and drug delivery techniques which may suppress these barriers maintain drug level in tissues. Nanogel have shown a great potential for the delivery of large number of drugs to different organs of the body owing to their high biocompatibility, high drug loading capacity, great bioavailability, good permeation capacity and tissue mimicking properties. Due to high water retention capacity, that makes them ideal capable of incorporation of bulky drugs, such as- proteins, peptides, and macromolecules. All these properties of nanogels make them able to carry number of drugs to vast number. Nanogels have shown potential in many fields including chemotherapy, diagnosis, organ targeting, gene delivery and many others. The main areas of the target for the nanogels include tumors of brain, liver, skin, etc. Other uses of the nanogels are in the diabetes, Inflammation, wound healing, local anesthesia etc. This review concentrates over the targeting potential of nanogels in different organ for various conditions.

KEYWORDS

Gels, Nanoparticle, Polymers, Control and Sustained Release, Bioavailability

INTRODUCTION

Nanogels may be defined as nano-sized hydrogel systems which are highly cross-linked systems in nature involving polymer systems which are either co-polymerized or monomers. Sudden outbreak in the field of nanotechnology has introduced the need for developing.[1] Nanogel systems which have 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.[2]

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Nanogels are swollen in nano - sized networks composed of hydrophilic or amphiphilic polymer chains, which can be ionic or non-ionic. Nanogels are developed as a carrier for drug which can be designed to spontaneously absorb biologically active molecules through formation of salt bonds, hydrogen bonds or hydrophobic interactions.[3] 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 reduce the chances of activation of immune cells upon administration of drugs inside the body.[4] The pores in nanogels can be filled with small molecules or macromolecules and usually the size of nanogels in one to hundreds nanometers in diameter. The nanogel contains the some

properties like swelling, degradation and chemical functionality, that can be controlled.[5] 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 (physicochemical) properties. Current studies at the clinical level shows promising value of nanogel.[6] Nanogels have revolutionized the field of gene therapy, as delivery of gene has now become possible within cellular organelles for gene silencing therapy systems.[7]

Advantages of Nanogels

1. It can be applied to both hydrophobic & hydrophilic drugs and charged solutes.
2. It provides protection from biodegradation of drug inside the body.
3. Low amount drug is required as well as quantity of doses is reduced.
4. Improves the bioavailability of the drug molecule and reduce the toxicity of the drugs.
5. Good for specific target and transport characteristics.
6. These are able to cross blood brain barrier as well as physiological barrier like skin.
7. Permeation capabilities are good due to extremely small in size.
8. Target or site specific delivery to be achieved.
9. Helps in enhancing oral and brain bioavailability of low molecular weight drugs and biomacromolecules.

Disadvantages of Nanogels

1. Solvent and surfactant is not easily removed at the end of preparation, so it may be some more expensive.

2. Sometimes, traces of surfactants can cause toxicity.[1, 8]

Classification of Nanogels

Generally, nanogels are classified in to following three types-

1. Based upon the polymer

Chitosan based nanogel

Poly (vinyl - alcohol) based nanogel

Alginate - based nanogel

Poly (vinyl - pyrrolidone) based nanogel

Poly - N - Isopropylacrylamide-based nanogel

2. Based on their responsive behavior

Stimuli - responsive

Non - responsive

3. Based on their linkages present in the network chain of gel structure

Physical cross linked gels

Chemically cross linked gels

Liposome modified nanogels

Hybrid nanogel

1) Based upon the Polymer

Chitosan based nanogel - Chitosan, α (1 - 4) - 2 amino – 2 - deoxy β – D - glucan, is a deacetylated form of chitin, an abundant polysaccharide present in crustacean shells. Even though the discovery of chitosan dates back from 19th century, it has only been over the last two decades that this polymer has received attention as a material for biomedical and drug delivery applications.[9] The accumulated information about the physicochemical and biological properties of chitosan led to the recognition of this polymer as a promising material for drug delivery and more specifically for the delivery of macromolecules.[10] From a technical point of view, it is extremely important that chitosan is hydro-soluble and positively charged. These properties enable this polymer to interact with negatively charged polymers, and even with certain polyanions upon contact in aqueous environment. These interactive forces and the resulting so-gel transition stages have been exploited for nano - encapsulation purposes.[11] On the other hand; chitosan has the special possibility of adhering to the mucosal surfaces within the body, a property leading to the attention to this polymer in mucosal drug

delivery. The potential of chitosan for this specific application has been further enforced by the demonstrated capacity of chitosan to open tight junctions between epithelial cells though well organized epithelia. The interesting biocompatibility and low toxicity. Many articles on the potential of chitosan for pharmaceutical applications have been published. Therefore our purpose is to focus on the specific feature and application of the chitosan-based nanoparticulate systems prepared and characterized to date for delivery of macromolecular compounds such as peptides, proteins, antigens, oligonucleotides, and genes.[12,13]

Poly (vinyl – alcohol) based nanogel - Poly vinyl – alcohol (PVA) plays vital role for nanogel studies. It has the crosslinking characteristics which have been carried out using physical and chemical methods. Physical methods such as e.g. (freezing / thawing) methods and chemical methods such as (eg: crosslinking agents, electron beam, γ-irradiation). Even though crosslinking method is difficult but it is useful for various applications in medical and pharmaceuticals fields.[14] In the late 1990s, PVA nanoparticles (NPs) were prepared with the aim of protein/peptide drug delivery using a water-in-oil emulsion/cyclic freezing-thawing procedure. In this study, the emulsion was kept frozen at -20^{0}C followed by a thawing phase at ambient temperature and no emulsifier involved. The average diameter of PVA nanoparticles obtained was 675.5± 42.7 nm with a skewed or log normalized size distribution. Bovine serum albumin (BSA) was loaded in this study in nanogels with a notable loading efficiency of 96.2 ± 3.8 % and a diffusion controlled release trend. In another study, three separate production methods, including salting-out, emulsification, diffusion and nanoprecipitation, have been used by Galindo-Rodriguez et al, as a comparative scale-up production evaluation to reach PVA - based NPs loaded with ibuprofen. The pilot-scale stirring rates of 790- 200 rpm led to mean sizes range from 174 to 557 nm for salting-out and 230 to 565 nm for emulsification diffusion.[15]

Unlike structured composites involving PVA has been interested in the field of nanogel. Biodegradable polymers having short polylactone chains grafted to PVA or change sulfobutyl- PVA were prepared and used as a novel class of water soluble comb - like polymers. These types of polymers directly undergoes and assembling to produce the nanogel a stable complexes with a number of protein such as human serum albumin, tetanus toxoid and cytochrom C.[16]

Alginate- based nanogel - A new drug carrier made up of sodium alginate by Rajaonarivony in 1993.[17] These prepared alginate nanoparticles with a wide range of particle sizes (250 – 850 nm), by using the sodium alginate and calcium chloride and followed by poly – lysine. In this study the concentration of both polymer and opposite ion solutions were less than those regularly used for gel formation. Now a day the numbers of studies involving alginate- based nanoparticles are increasing, using the therapeutic agents such as insulin, antitubercular and antifungal drugs, and prominent increases in the field of gene delivery. The antitubercular chemotherapy is increases the bioavailability by using the alginate nanoparticles and of all drug encapsulated in alginate nanoparticles were significantly higher than those with free drugs.[17,18]

Poly (vinyl pyrrolidone) - based nanogel - Baharali et al., have described a procedure for preparation of PVP - based hydrogel NPs with final diameter less than 100 nm, using the aqueous cores of reverse micellar droplets as nanoreactors.[19] These reverse micellar are highly monodispersed, the droplet sizes can be well - controlled and size can be modulated by controlling the size of the reverse micellar droplets.[20]

Poly – N – Isopropylacrylamide (PNIPAM) Based Nanogel - Covalently crosslinking are formed by the PNIPAM – c – allylamine nanoparticles network. These are the more stable and stated that the more bioavailability. Thermo responsive core – shell PNIPAM nanoparticles via seeding and feeding precipitation

polymerization is described by Gan & Lyon, they describe the kinetic and thermodynamic behavior between the core and shell of polymers.[21]

2. Based on their Responsive Behavior

Nanogels are more commonly classified in two major categories-

Stimuli Responsive - Stimuli responsive microgels swell or de - swell upon exposure to environmental changes such as temperature, pH, magnetic field and ionic strength. Multi-responsive microgels are responsive to more than one environmental stimuli.

Non - Responsive Behavior - In the case of non-responsive microgels, they simply swell as a result of absorbing water.[22]

3. *Based on their Linkages Present in the Network chain of Gel Structure*

Based on their linkage it have a capacity like to form a gel structure, polymeric gels (including nanogel) and these are divided as follows:

Physical Crossed Linked Gel - These types of gels are also known as pseudo gels. They are formed by weaker linkages through Vander Waals forces, hydrogen bonding, hydrophobic or electron static interactions. It is very sensitive gels and depends on polymer composition, temperature, ionic strength or the medium concentration of polymer and the cross – linking agent. A nanogel can easily formed by the combination of amphiphilic block copolymers and complexation of oppositely charged polymeric chains.

Chemically Cross Linked Gel - These types of gels are permanently linkages through the covalent bonds. It has the properties like cross - linked gel system and depends on the functional group present in the gel networks. Different types of chemical linking have the properties of synthesized different types of nanogels. By the polymerization of vinyl monomers in the presence of multifunctional cross - linkers the hydrophilic polymers and hydrophilic-hydrophobic copolymers are obtained. These types of cross - linking points allow altering the total physicochemical properties of the gel system.

Liposome Modified Nanogels - When liposomes are mixed with the succinylated Poly (glycol)s; these liposomes can be efficiently deliver calcein to the cytoplasm by fusion the chain below pH 5.5. Liposomes which are the thermo and pH responsive nanogel like as poly (N - isopropylacrylamide) are being investigated for transdermal drug delivery.[23]

Hybrid Nanogels - When the nanogel particles dispersed in organic and inorganic matrices is known as hybrid nanogels. These types of nanogel formation takes place in an aqueous medium by self assembly or aggregation of polymer amphiphiles, such as pullullan – PNIPAM, hydrophobized polysaccharides, and hydrophobized pullan.[24]

Hybrid nanogel has the ability to form complexes with various proteins, drugs and DNA, and it is even possible to coat surface of liposomes and solid surface including cells. These types of hybrid nanogel are formed physical cross linkings and capable to deliver the insulin and anti-cancer drugs more effectively.[25,26]

Route of Administration

The nanogels are administered by the following routes-

a) Oral route

b) Pulmonary route

c) Topical route

d) Parenteral route

e) Intra ocular route

f) Nasal route[22]

Properties of Nanogels

There are following properties of nanogels-

1. Biocompatibility and Degradability - Nanogel based drug delivery system is highly biocompatible and biodegradable; due to this characteristics it is highly promising field now a days.

2. Swelling Property in Aqueous Media **-** The most beneficial feature of Nanogels is their rapid swelling/de - swelling characteristics.

3. Higher Drug Loading Capacity **-** Drug loading capacity of nanogels depends on the functional group present in the polymeric unit. These functional groups have a tremendous effect on drug carrying and drug - releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications. These pendent functional groups of polymeric chains contribute toward establishing hydrogen bonding or Vander Waals forces of interactions within the gel network and thus facilitate the drug - carrying efficiency. Moreover, the presence of functional groups at interface with drug/protein molecules is also responsible for higher loading.

4. Particle Size **-** Nanogels typically range in size of 20 – 200 nm in diameter and hence are effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticuloendothelial system. Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB).

5. Solubility **-** Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.

6. Electromobility **-** Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating biomacromolecules.

7. Colloidal Stability **-** Nanogels or polymeric micellar nanogel system have better stability over the surfactant micelle concentrations, slower rate of dissociation, and longer retention of loaded drugs.

8. Non Immunologic Response - This type of drug delivery system usually does not produce any immunological responses.

9. Others **-** Both type of drugs (hydrophilic, hydrophobic drugs and charged solutes) can be given through nanogel. Such properties of nanogel are significantly influenced by temperature, presence of hydrophilic/ hydrophobic groups in the polymeric networks, the cross - linking density of the gels, surfactant concentration, and type of cross - links present in the polymer networks.[22]

Synthesis of Nanogels

The nanogel are synthesized by following techniques-

1) Synthesis of Nanogel by Free Radical Polymerization (FRP) **-** The monomers present in the compound play a vital role, which may be hydrophilic or water soluble monomers either difunctional or multifunctional cross - linkers have been mostly used. Different methods by this free radical polymerization are as follows -

a. Dispersion Polymerization **-** In this 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 micro - sized particles of PHEMA were also prepared by dispersion polymerization in the presence of PEO – b - poly (1, 1, 2, 2- tetrahydroperfluorodecyl acrylate) di - block copolymer as a stabilizer in supercritical CO_2 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 applications.[26,27]

b. Inverse (mini) Emulsion Polymerization **-** This type of polymerization is also known as w/o polymerization in which aqueous droplets (including water - soluble monomers) stably dispersed in an oil soluble surfactant in a continuous organic medium. By the help of mechanical stirring for inverse emulsion and by sonification the stable dispersion of polymerization is formed. By addition of radical initiators, polymerization occurs within the aqueous droplets producing colloidal particles.[26]

c. Inverse Micro - emulsion 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 and thermodynamically stable. This process also has same disperse and continuous phase like as inverse mini - emulsion but producing stable hydrophilic and water soluble colloidal nanoparticles having a diameter of less than 50-100 nm. This technique was invented for the synthesis of stable nanogels.[19,28]

d. Precipitation Polymerization - Initially, this type of polymerization takes place in the homogenous mixtures. If the polymers are not swellable in the medium then the use of crosslinker is necessary to crosslink the polymer chains for separation of particles. The present crosslinked often has an irregular shape with a high polydispersity. By using the precipitation polymerization synthesize nanospheres by using poly (methacrylic acid – g – ethylene glycol) (P (MAA – g - EG)), delivery of proteins. They also disclosed that the increasing the cross – linker concentration during polymerization decreased the equilibrium swelling of the nanospheres.[26]

e. Heterogeneous Controlled/ Living Radical Polymerization: Now a days, controlled radical polymerization (CRP) has been explored as a tool to preparation of well controlled polymer protein/peptide biconjugates. There are many methods of CRP have been developed; however, the most successful technique includes Atom transfer radical polymerization (ATRP), Stable free radical polymerization (SFRP), and Reversible addition fragmentation chain transfer (RAFT) polymerization.[29,30]

2) Photolithographic Technique –

Photolithography has been explored to fabricate 3D hydrogel particles and microgel or nanogel rings for drug delivery. The photolithographic method requires the development of techniques for surface treatment of stamps or new materials for replica molds, to permit the release of molded gels from stamps or replica molds. Photolithography technique consists of five steps. In the first step, the UV cross - linkable polymer, which possesses low surface energy, as a substrate is released on the pre - baked photo resist - coated water. The second step involves molding the polymer into patterns on the silicon wafer by pressing the quartz template onto the polymer and exposed it to the intense UV light.

In the third step, the particles with a thin residual interconnecting film layer are uncovered by removing the quartz template. Subsequently, this residual thin layer is removed by a plasma containing oxygen that oxidizes it. In the last step, the fabricated particles are directly collected by dissolution of the substrate in water of buffer.[22,24,26,27]

The step of photolithographic is shown in figure –

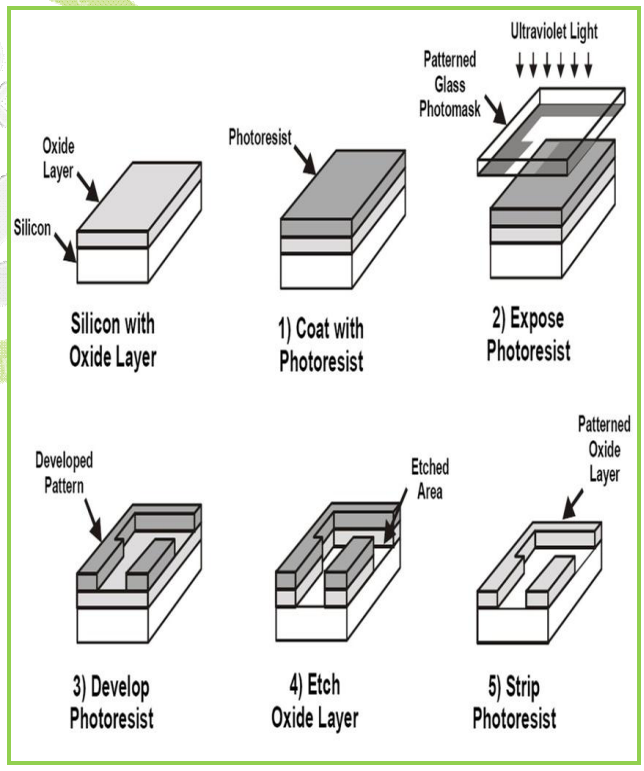

Figure 1: Schematic Representation of five steps involved in Photolithography Technique

3) 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 this process, cells were suspended in

a hydrogel precursor solution consisting of either methacrylated hyaluronic acid (MeHA) or PEGDA or a photo - initiator in water. The resulting mixture was deposited on to plasma - cleaned hydrophilic PDMS patterns and then photo - crosslinked 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.[22]

4) Fabrication of Bipolymers - Naturally occurring polymers (eg. Chitosan, hyaluronan and dextran) are based on biopolymers. Many methods have been developed for the preparation of microgels of these biopolymers.

They can be classified in to four categories -

1. Water in oil (W/O) heterogeneous emulsion
2. Aqueous homogeneous gelation
3. Spray drying method
4. Chemical cross - linking of dextran.

5) Reverse Micellar Method - Reverse micellar method is 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. The resulting micellar droplets have a submicron size ranged from 10-100 nm in diameter.

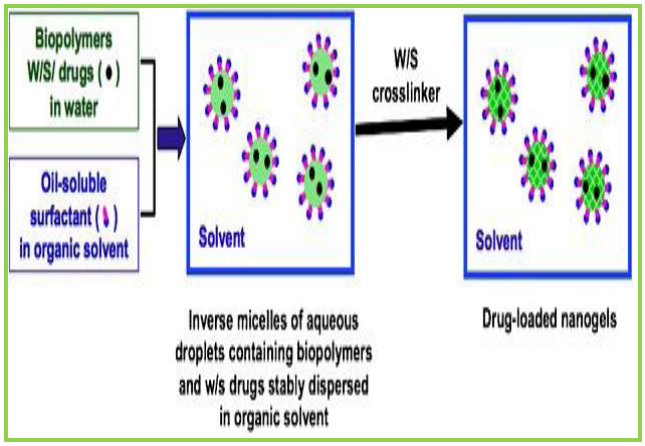

Figure 2: Diagram of the Reverse Micellar Method for the synthesis of nanogels

6) Membrane Emulsification Method - In the membrane emulsification method, the dispersed phase is passed through the membrane (i.e. glass or ceramic). In which the membrane contains uniform pore size. On the surface of membrane the emulsion droplets are formed under the specific condition and afterwards the continuous phase which is flowing across the membrane, these formed emulsion droplets or microgels are recovered. The formation microgel emulsion takes place in the different form such as, water in oil (w/o), oil in water (o/w), oil in water in oil (o/w/o), 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 transmembrane.[22,31]

7) Holocene Methodologies for Nanogel Synthesis - There are two Holocene techniques for the synthesis of the nanogels.

a) Novel Pullulan Chemistry Modification - When mixture of cholesterol isocynate in dimethyl sulfoxide and pyridine then synthesis of cholesterol based pullulan nanogel takes place. This preparation was freeze dried and in aqueous form it forms a nanogel which was complexed with W – 9 peptide for drugs delivery for the osteological disorders, here pullulan was substituted with 1.4 cholesterol moieties per 100 anhydrous glucoside units. Pullulan is known as good protein carrier so, that it is used in the nanogel drug delivery.[32,33]

b) Novel Photochemical Approach - This technology has the advantage to gene delivery. By this technique we produce the ferric oxide nanoparticles nanogel for MRI application by coating oxide with N - (2 - aminoethyl) methylacrylamide and N,N - methylene bis acrylamide treated with U.V radiation at 388 nm for 10 minutes and recovering the product after washing with water.[34] Like this way diacrylated pluronic and glycidyl methylacrylated chitooligosaccharide were loaded with plasmid DNA at different ratio's and were photo irradiated with long wave length UV light at 365 nm, the photo initiator was igracure added to the mixture for cross - linking.[35]

8) Chemical Modification - Acetylation of chondriotin sulfate can easily release doxorubicin in HeLa cells over a three week period for the anticancer purposes. From this we can understood chemical modification of polymers controlled the release of drugs from the nanogels.[36] By using quaternary group to form the nanogel complexes by consisting of poly 2 - (N,N - diethylaminoethyl) methacrylate increases SiRNA binding capacity which provides the treatment of cancer and gene delivery.[37]

9) Reversible Addition Fragmentation Transfer (RAFT) Process - Reversible Addition Fragmentation Transfer (RAFT) process adopted a single step of synthesis for PEGylated poly (N, N - dimethylaminomethyl) methacrylate nanogel utilizing an amphiphilic macro RAFT agent tri - thiocarbonate with hydrophobic dodecyl chain supporting polymerization rather than two step process, which produced 500-800 nm size. By this method only in one step reduced the radii of nanogel i.e. 10 nm.

Procedure to obtain Nanogel by RAFT method:

1. Dodecanethanoil and tetrabutyal ammonium bromide mixed and N2 passed at 10^0C temperature.
2. Then carbon di - sulfide and acetone added drop wise.
3. After then, chloroform and sodium hydroxide added.
4. 30 minutes later yellow precipitate obtained.
5. The precipitate are dissolves in isopropanol and crystallized in hexane, Raft agent obtained.
6. PEG reacted with RAFT in dichloroethane.
7. Polymerization in polymer with aqueous dispersion with RAFT agent to obtain nanogel.[38,39]

Drug Loading Techniques in Nanogels

Nanogels are widely used as carriers of therapeutic agents. A successful nanodelivery system should have a high drug - loading capacity, thereby reducing the required amount of carrier. There are following techniques are used for the drug loading in nanogels.

a) Co - valent Conjugation - In the biological agents by using covalent conjugation can achieved nanogels. e.g. Acrylic groups are modified with enzymes and copolymerized with acrylamide either in inverse micro emulsion or dilute aqueous solution to obtained nanosized hydrogel.[22,26]

b) Physical Entrapment - Physical entrapment was employed for incorporation of proteins in cholesterol - modified pullulan nanogels and SiRNA in HA nanogels. In nonpolar domains by addition of hydrophobic molecules, formed a hydrophobic chain which is present in selected nanogels. e.g. in the cholesterol – modified pullulan the prostaglandin E2 is easily solubilized another e.g. N - hexyl carbamoyl – 5 - Fluorocil (HCFU) was non - covalently incorporated in cross linked nanogels of N - isopropylacrylamide (NIPAAM) and N – vinylpyrrolidone 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%).[26,40]

c) Self Assembly - The self-assembly process, defined as the autonomous organization of components into structurally well - defined aggregates. The self assembly process has following advantages -

1 - Versatile & facile.

2 - It is cost-effective.

3 - Minima thermodynamics in which resulting in stable & robust structures.

Molecular self - assembly is characterized by diffusion followed by specific association of molecules through non - covalent interactions, including electrostatic and/or hydrophobic associations. Individually, such interactions are weak, but dominate the structural and conformational behavior of the assembly due to the large number of interactions involved. While

oppositely charged polysaccharides associate readily as a result of electrostatic attractions, interactions among neutral polysaccharides tend to be weaker or nonexistent, a modification with chemical entities able to trigger assembly being necessary.

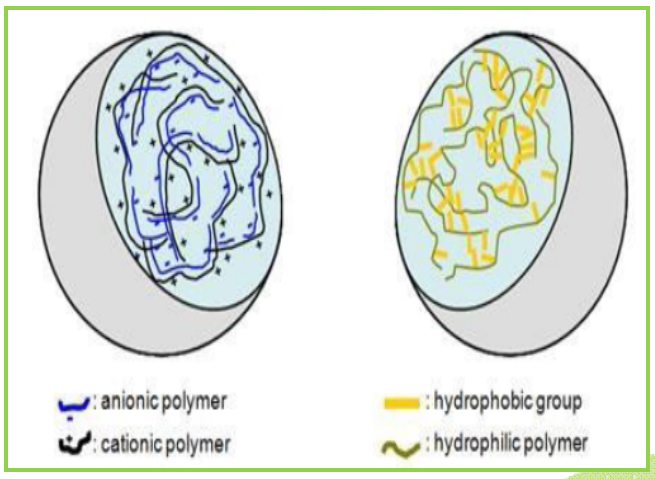

Figure 3: Schematic Representation of Intermolecular interactions driving self assembly process that includes - (a) Electrostatic interaction, (b) Hydrophobic association

A convenient strategy consists on linking hydrophobic grafts to e.g., a highly water - soluble polysaccharide, inducing the formation of nanoparticles via hydrophobic interactions. This kind of amphiphilic polymers can be used by three methods.

1 - Hydrophilic chains grafted to a hydrophobic backbone (grafted polymer).

2 - Hydrophobic chains grafted to a hydrophilic backbone.

3 - 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.[22,26,41,42]

Mechanism of Drug Release from Nanogels

The drug can be released from the nanogel by following mechanism -

1) Diffusion Mechanism **-** Doxorubicin follows the diffusional release and which is stable hydrogel nanoparticles based on pluronic block copolymer. This release mechanism is simple and has been successfully employed in various nanomedicines, such as polymeric micelles that have already reached a clinical stage.

2) Photochemical Interaction and Polymerization **-** 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.
2. Acidification of the media by decreasing pH from 7.4 to 5.5.[43,44]

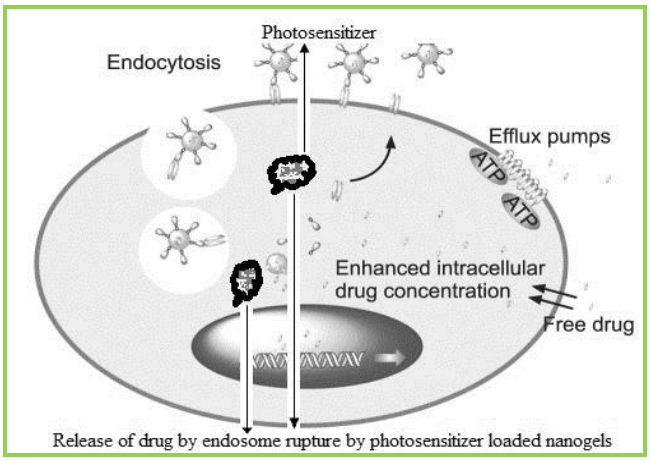

Figure 4: Schematic Representation of Drug Release due to Endosomal rupture caused by Photosensitizers loaded

3) *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. 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.[45,46,26]

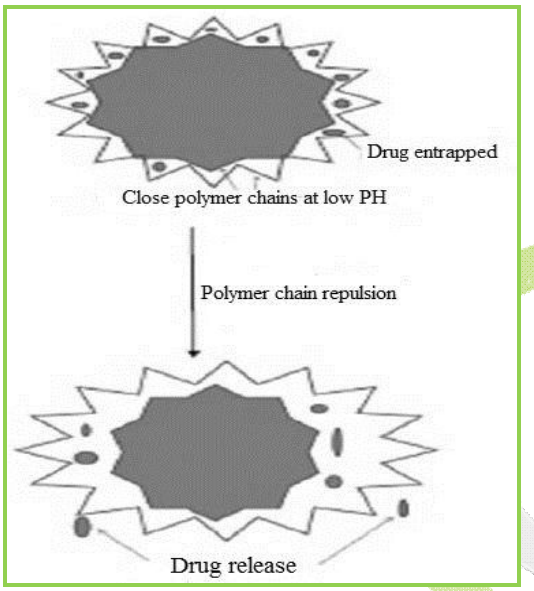

Figure 5: Schematic Representation of Drug Release from Nanogel due to pH Responsive Mechanism

4) 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. e.g. 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 complexes and explain cellular accumulation of drug delivered with nanogel.[26, 43]

5) Thermosensitive and Volume Transition Mechanism - The polymer which has thermosensitive characteristics like as poly (N - isopropylacrylamide) leads to initially shrinkage in gel volume and efflux of indomethacin drug due to maintenance of temperature above lower critical solution temperature. The superficial modification of polyethyleneimine nanogels by pluronic, it has the thermoresponsive characteristics with regard to size and successfully used a gene delivery systems. By the physical destruction of cellular network, it is expand up to 1 μm in nanogel size by thermally triggered volume of nanogels of poly alkylene oxides.[47,48,49]

Evaluation of Nanogels

There are following parameters used for the evaluation of nanogels.

1 - Measurement of Particle Size - The mean size and polydispersity index of the size distribution of the selected nanogels were determined by using Malvern Mastersizer 2000 MS (Malvern Instruments UK). The mean particle size and size distribution were recorded.[50,51]

2 - Determination of Zeta Potential- The zeta potential of the selected formulation was measured by Beckman coulter (Bekman Coulter Delsa^{TM} Nano common).[52]

3 - Total Drug Content (TDC) - A 0.5 gm. of the prepared nanogel was diluted with 10 ml of ethyl acetate and filtered with a 0.45 μm whatman filter paper. Total drug content was determined by UV spectrophotometer at 274 nm by using following formula.[51]

$$TDC = \frac{\text{Total amount of Nanogel} \times \text{Amount of drug in 0.5 gm. nanogel}}{\text{Amount of nanogel in gm W initial drug} - \text{W free drug}}$$

4 - Differential Scanning Calorimetry - DSC was performed by Mettler-Toledo DSC 821e (Columbus) instrument. DSC scan for aceclofenac was recorded at heating rate of 10°C/min in temperature range 30° - 300°C. The degree of crystallinity of nanodispersion was also analyzed by DSC.[53]

5 - Entrapment Efficiency - A small portion of the nanodispersion was centrifuged at 10,000 rpm for 1 hr using Microcentrifuge. The supernatant was removed and amount of unincorporated drug was measured by taking the

absorbance of appropriately diluted supernatant solution at 274 nm using UV spectrophotometer, against blank/control nanodispersion. Entrapment efficiency was calculated by using following formula -[54]

$$\text{Entrapment Efficiency (\%)} = \frac{\text{W (weight) initial drug} - \text{W (weight) free drug}}{\text{W (weight) initial drug}} \times 100$$

6 - In vitro Drug Diffusion Studies - Dialysis membrane diffusion technique was used to study in vitro diffusion of drug from the prepared nanogel formulations. The receptor medium was used on the freshly prepared phosphate buffer pH 7.5. Dialysis membrane previously soaked overnight in the receptor medium was on the Franz's Diffusion cell assembly. 0.5 g of formulation was placed in the donor compartment and the assembly was kept on the multi station diffusion study apparatus at $37^0C \pm 2^0C$ stirred at 700 RPM. Aliquots of 0.5 ml were withdrawn at pre-determined time intervals (0.5, 1, 2, 3, 4, 5, 6, 8, and 24 hrs) and immediately replaced by same volume of the fresh medium. The aliquots were suitably diluted with the dissolution medium and analyzed by UV - Vis spectrometer at 254 nm. The data obtained from the in vitro diffusion studies were fitted to various kinetic equations to find out the mechanism of drug release from the nanogels.[51,55]

Application of Nanogels

Nanogel based drug delivery formulations improve the effectiveness and safety of certain anti-cancer drugs and many other drugs, due to their chemical composition, which have been confirmed from In vivo study in animal models.

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

2 - Nanogel as NSAIDS - Carbopol and Hydroxypropylmethyl cellulose (HPMC) with the desired viscosity used to prepare the nanogels. Same like another polymer chitosan and poly-(Lactide – co - glycolic acid) used to prepare bilayered nanoparticles and surface was modified with oleic acid. e.g. Two anti - inflammatory drugs spantide II and 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.

3 - Nanogel as an Autoimmune Disease - Nanogels were fabricated by remotely loading liposomes with mycophenolic acid (MPA) solubilized within cyclodextrin, oligomers of lactic acid - poly(ethylene glycol) that were terminated with an acrylate end group and Irgacure 2959 photoinitiator. Particles were then exposed to ultraviolet light to induce photopolymerization of the PEG oligomers. The Nanogels are attractive because of their intrinsic abilities to enable greater systemic accumulations of their cargo and to bind more immune cells in vivo than free fluorescent tracer, and permits high localized concentrations of (mycophenolic acid) MPA. This type of new drug delivery system increases the patient compliance and delays the onset of kidney damage, a common complication of lupus.[22,56]

4 - Nanogel in Stop Bleeding - A protein molecules which is in solution has been used for the formation of nanogel, has been used to stop bleeding, even in severe cases. The proteins have mechanism of self - assemble on the nanoscale in to a biodegradable gel.[22,26]

5 - Nanogel in Opthalmic - Polyvinyl pyrollidone (PVP) – poly acrylic acid (PAA_c) 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.[57]

6 - Nanogel in Gene Delivery - Controlled delivery of plasmid DNA by using the polymer Di – acrylated pluronic 127 and glycidyl methacrylated chitoolgosaccharides and making photocrosslinking 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 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.[33,39,57]

Current Status and Future Perspective of Nanogels

The recombinant murine interleukin - 12 (IL-12) encapsulated in cholesteryl pullulan (CHP) nanogels, via incubation at room temperature and injected in mice with subcutaneous fibrosarcoma leads delayed release and retardation the growth of tumor.[58]

Recently the new development of controlled diabetes by optical sensitive insulin loaded silver nanoparticle nanogel of poly (4 - vinyl phenyl boronic acid – co – 2 - (dimethylamino) ethyl acrylate) have been designed.[59]

Now a days nanogel is conjugated with antibiotics for the specific drug delivery and conducted at the single cell level.[26, 57]

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

CONCLUSION

Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. Future design and development of effective nanogel based drug delivery systems for in vivo applications requires a high degree of control over properties. Nanogels appear to be excellent candidates for brain delivery. 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. This will be especially important for the targeting of cancer cells, thereby reducing non - specific uptake into healthy cells.

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