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REVIEW ARTICLE

Nanogels as Next Generation Drug Delivery Systems

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Abstract

Nanogels are the innovative drug delivery systems which plays an integral part in pointing out many issues related to old and modern courses of treatment, such as nonspecific effects and poor stability. Nanogels are the highly cross linked nanosized hydrogels ranges from 20-200 nm. These can also be administered through various routes, including oral, pulmonary, nasal, parenteral, intraocular etc. Nanogels have high degree of drug loading capacity and it also shows better permeation capabilities due to a smaller size. These are also release the drug by pH responsive, thermosensitive, volume transition, photochemical internalization and photo-isomerization mechanism. With emerging field of polymer sciences it has now become an inevitable to prepare smart nanosystems which can prove effective for treatment as well as clinical trials progress. The present review provides the comprehensive illustrations on novel applications, drug loading technique, mechanism of the drug release from nanogels. Further, current status, clinical trial status, and future perspective of the nanogels have been summarized.

Keywords: *Nanogel*, *Thermo-sensitive*, *Photoisomerization*, *Stimuli responsive*, *Vaccine delivery.*

Introduction

Nanogels defined as nanosized particles formed by the physically or chemically crosslinked polymer networks that swells in a good solvent. The term "nanogel" (NanoGel™) was first introduced to define cross-linked bifunctional networks of the polyionic and nonionic polymer for the delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly ethylene glycol (PEG) or PEG-cl-PEI). Nanogels and other advanced nano-delivery systems are used for several years for the effective delivery of drugs [1].

A Sudden outbreak in the field of nanotechnology have been introduced the need for developing nanogel systems which proven their potential that deliver drugs in controlled, sustained and targetable manner. With the emerging field of polymer sciences which has been now become an inevitable to prepare smart nano-systems which can alsoprove an effective for treatment as well as the clinical trials progress. The size of nanogels ranges from 20-200 nm [2].

Nanogels can escape renal clearance and exhibit prolonged serum half-life period due to their size. Chemical modifications can be made to help incorporating plenty of ligands which can be used for the targeted drug delivery, stimulus responsive drug release or preparation of composite materials [3]. Nanogels are known to be exhibit great qualities which contribute to drive towards it as a delivery system. These include remarkable thermodynamic stability, elevated capacity of the solubilization, relatively low viscosity, and the capability of undergoing vigorous sterilization techniques [4].

Nanogels may entrap drugs and the biological molecules. Therefore, they are vastly employed in protein and gene delivery. Some nanogels possess a hydrophilic nature which limits good encapsulation property of hydrophobic drugs. Thereby, nanogels provided a new means of drug delivery for poorly soluble drugs by either swelling or by shrinking, which doesn't only improve their solubility and stability but increasing the opportunity of their cellular uptake than the free drug [3].

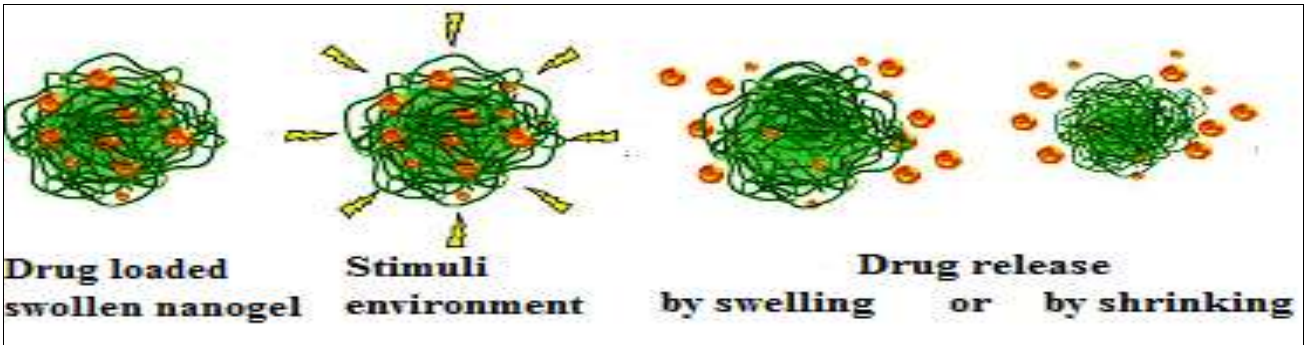

Figure 1: Drug loaded nanogel

Advantages [5-8]

- High biodegradability, which is a crucial to avoid the accumulation of nanogel material in the bodily organs, thereby leading to toxicity and adverse effects.
- High biocompatibility, which makes nanogels are very promising approach to drug delivery systems.
- Extremely small size, which can induces a number of effects.
- Nanogels are inert in the blood stream and in the internal aqueous environment, meaning that they do not induce any immunological responses in the body.
- Nanogels are suitable to administer both hydrophilic and hydrophobic drugs, as well as charged solutes and other diagnostic agents.
- Drug loading in nanogels is relatively high when compared to other nanocarriers and drug delivery systems.
- Nanogels are prepared to be capable of releasing drug in a controlled and sustained pattern at the target site, thereby enhancing the therapeutic efficacy of the drug and avoiding its adverse reactions.
- Nanogels can be formulated in the form of polymeric micellar nanogel systems that exhibit slower rates of dissociation, better stability over the surfactant micelles, lower critical micelle concentrations, and, most importantly, longer retention of loaded drugs.
- Bio-macromolecules as well as delicate compounds with low or high molecular weights can be successfully and efficiently encapsulated in the nanogels for the purpose of prolonging the activity of these molecules in the biological environment.

Properties of Nanogels

Biocompatability and Degradability

Nanogel is made up of either natural or synthetic polymers. They are highly biocompatible and biodegradable thereby avoiding its accumulation in organs. Chitosan, ethyl cellulose, methyl cellulose and various polysaccharide-based polymers like the dextran, pullulan and the dextrin can be used to prepare the nanogel [5].

Permeability and Particle Size

Tiny manipulation in the particle size, surface charge and hydrophobicity can be remarkably improving permeability of nanosystems. In spite of the fact these nanoparticles are capable of the permeation by diffusion through tissues or compromised areas of the endothelium and in other some cases through a particular transport system, they created a challenge crossing blood brain barrier (BBB) [6]. So, in order to overcome such dilemma, nanogels were formulated in a way where the size of these systems small enough to cross BBB and in same time avoid rapid clearance mechanisms [8].

Higher Drug Loading Capacity

Just like any of the other nanodelivery system, nanogels are expected to have the greater loading capacity compared to the conventional dosage forms.

This is mainly due to swelling property which allows the formulation to absorb a large quantity of water. Thus, upon the incorporation and loading of the water will provide the cargo space sufficient to contain salts and biomaterials [1].

Loading Takes Place through Three Methods

- Physical entrapment

- Covalent attachment
- Controlled self-assembly

Colloidal Stability

When handling nanoparticle, there is always a propensity of aggregation that compromises the colloidal stability. Formulators are tends to alter surface charge to avoid formation of aggregates in bloodstream and further complications. It can be achieved by increasing zeta potential (minimum of ± 30 mV) that results in the larger repulsive forces between particles that electro statically stabilize them.

Other techniques involve the incorporation of surface modifier like PEG that can produce steric effects and hydration forces to give a stable nanosuspension[7]. If we compare polymeric micellar nanogel systems and surfactant micelles on basis of the stability we will find that the former exhibits better

stability lower critical micelle concentrations, decrease in the dissociation rates, and longer retention of loaded drugs. They can also have a high water content that assure good dispersion stability [9, 10].

Swelling Property in Aqueous Media

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

- The structure of nanogels: includes the polymer chain's chemical nature as well as the cross-linking degree and in case of the 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. Temperature is a trigger of swelling in cases of thermoresponsive gels [2].

Providing appropriate circumstances allows rapid swelling/deswelling. Regardless of the trigger, swelling takes place only when the osmotic pressure exerted by medium ions and the polymers network swelling pressure are imbalanced [8].

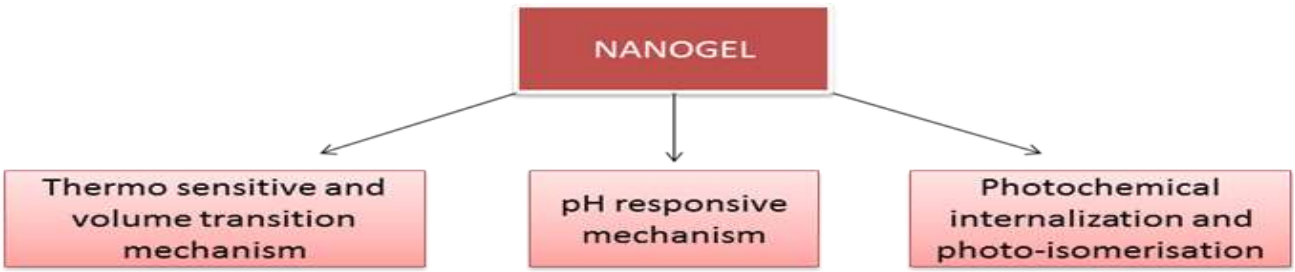

Figure 2: Drug release mechanism of nanogels

There are multiple mechanisms to which release of the drug or the biomolecule is attributed to including: simple diffusion, degradation of the nanogel structure, pH and temperature changes, counterion displacement or due to induced external energy source [2].

Thermo-Sensitive 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 the volume according to temperature. If surrounding medium is below VPTT, the polymer becomes quenched and hydrated which makes it swell and release the loaded drug. Above VPTT that opposite occurs and the nanogel shrinks abruptly and the content flows out [11]. Previously, the thermo-responsive nanogels used to rupture cellular network when they expand and increase in the volume. So, some of the alterations were applied on thermo-sensitive drug containing nanogels like changing of polymers ratio to achieve lower critical solution temperature. One of good example is the biocompatible magnetic field targetibility of poly (N-isopropylacrylamide) and chitosan nanogel which is quiet employed in hyperthermic cancer treatment.

Limitations

It is expensive to remove the surfactant and the solvent at the end of preparation process although the manufacturing process itself is not very pricey. Adverse effects may occur if any traces of polymers or surfactant remain in the body [10].

PH Responsive Mechanism

As of the name indicates, drug release responds to pH changes in surrounding environment. In other words, the release of drug can be take place in different physiological environments which acquire different pH values. The most release will take place in appropriate pH which means that the release is mainly by 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 [2, 5].

Photochemical Internalization and Photoisomerization

Photoisomerization refers to a process in which a bond of restricted rotation undergoes some conformational changes due to the exposure of light. Double bond containing molecules which are good example; these isomerize usually from a transorientation to cis orientation upon light irradiation [12]. When photosensitizers loaded nanogel are excited, they produce two species of the oxygen (singlet and reactive) which can be a result in oxidation in the cellular compartment walls that highly influence the release of therapeutic agents into the cytoplasm [1].

Azodextran-nanogel loaded with aspirin was a subject of release studies. The observations showed that cis-trans isomerization of azobenzene by photo regulation cause the formation of E-configuration ofazo group. This result in better release profile of aspirin compared to the previous Z-configuration [1, 12, 13].

Classification of Nanogels

Based on Their Behavior Towards Specific Stimuli:

- Nonresponsive nanogels
- Stimuli responsive nanogels [9]

Based on the Type of Linkages Present in the Network Chains of Polymeric Gel Structure:

- Chemically cross linked nanogels [9]
- Physically cross linked nanogels [1-3]
- Liposome modified nanogels **[**14]
- Micellar-nanogels
- Hybrid nanogels **[**9]

These are stable monodispersed nanogels formed by self-aggregation of the CHP molecules (formed of pullulan backbone and cholesterol branches) with hydrophobic groups providing physical crosslinking points (Figure 3). Different types of nanogels with examples are given in Table 1.

Table 1: Different types of nanogels with examples [15, 16]

S. No.	Type of nanogel	Drug	Disease	Activity
1	PAMA-DMMA nanogels	Doxorubicin	Cancer	Increase in the release rate as the pH value decreased. Higher cytotoxicity at pH 6.8 in cell-viability studies
2	PCEC nanoparticles in Pluronic hydrogels	Lidocaine	Local anesthesia	Produced long-lasting infiltration anesthesia of about 360 min
3	Cholesterol bearing pullulannanogels	Recombinant murine interleukine-12	Tumor immunotherapy	Sustained release nanogel
4	Poly(N-isopropylacrylamide) and chitosan		Hyperthermia cancer treatment and targeted drug delivery	Thermosensitive magnetically modalized
5	Cross-linked branched network of polyethyleneimine and PEG	Fludarabine	Cancer	Elevated activity and reduced cytotoxicity

	Polylexnanogel			
6	Biocompatible nanogel of cholesterol-bearing pullulan	As artificial chaperone	Treatment of Alzheimer's disease	Inhibited aggregation of amyloid ß-protein
7	DNA nanogel with photocross-linking	Genetic material	Gene therapy	Controlled delivery of plasmid DNA

Preparation Methods of Nanogels

Modified Pullulan Technique

The example that can be given for this category is selfassemble dhydrophobized pullulan nanogel. The pullulans are modified in two stages; initially methacrylates are used, then with hydrophobic 1-hexadecanethiol. The end product is an amphiphilic material that upon addition of water starts to assemble itself by hydrophobic interaction among alkyl chains [17]. Another example is Cholesterol based pullulannanogel. Here, pullulan was substituted with cholesterol and the nanogel is fabricated by simply reacting cholesterol isocynate in dimethyl sulfoxide and pyridine. This mixture was freeze dried and in aqueous phase it formed nanogel which further formed a complex with W-9 peptide, a TNF-alpha and RANKL antagonist for delivery of osteological disorder [18]. Cholesterylpullulan (CHP) bearing methacrylol was formulated by the reaction of CHP with glycidyl methacrylate. The degree of substitution was 6.2 per 100 glucose unit (CHPMA6). CHPMA6 formed nanogel in water self-assembly [19].

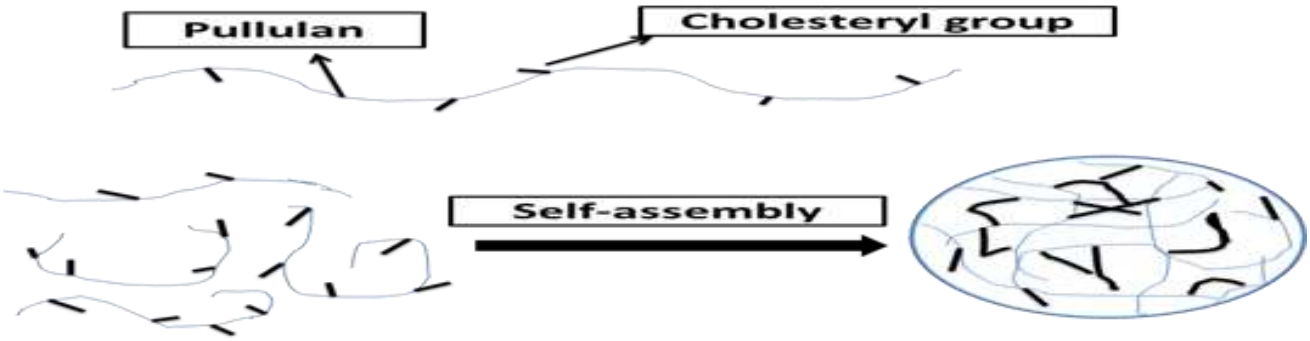

Figure 3: Self-assembly of CHP molecules to form CHP nanogel

Reverse Microemulsion Polymerization Technique

Lithium loaded polyacrylic acid (PAA) nanogels were formulated by reverse micro emulsion polymerization technique.2.62 g span 80 was added to 100 ml hexane that is oil phase and kept for stirring using magnetic stirrer. Aqueous phase was prepared by adding 1.5 ml of 10% (w/w) LiOH in water to 500 µl acrylic acid. Add 214 µl of 5% (w/v) N, N'-Methylenebisacrylamide (MBA) suspension, 500 µl of 2% (w/v) potassium persulfate and 40 µl of 20% (w/v) N, N, N', N'Tetramethylene-diamine (TEMED) to an aqueous phase [20].

Microemulsion was formed by addition of an aqueous phase drop wise into an oil phase. Emulsion was transferred to 60°C water bath and the stirred at an 400 rpm using the magnetic stirrer, kept overnight at a room temperature. Supernatant were decanted and the pellets were collected. Microemulsion is thermodynamically stable [20].

Free Radical Cross Linking Polymersization Technique

Photocrosslinked biodegradable photoluminescent polymers (PBPLPs) nanogel was prepared by the free radical crosslinking of a vinyl-containing florescent prepolymer for the drug delivery and cell imaging. Development of a PBPLPs nanogelwhich shows a new era to develop nanobiomaterials in nanomedicine for drug delivery and cell imaging [21].

Photolithographic Technique

Photolithographic techniques, photochemical reaction for activation and subsequent reaction which have 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 also allow the molded gels to release the incorporated agents [15].

Microfabrication of such gels follow a general strategy where poly (dimethylsiloxane) (PDMS) stamps are utilized to mold, release, and which stack gels into 3 dimensional structures. Surface modification enhances the release or adhesion of the 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 the adsorbed monolayers of bovine serum albumin (BSA) [16].

Emulsion Polymerization Technique

l-proline functionalized PMMA [poly (methyl methacrylate)] nanogel with a range of catalyst functionalization (0.5-15%) and cross linking densities (0-50%) was prepared by the emulsion polymerization technique [22]. In emulsion polymerization technique monomer droplets are formed by mechanical stirring [23].

Inverse Miniemulsion Polymerisation Technique

Fluorescent dye Rhodamine B or the fluorescein labeled nanogels were prepared by the activators generated electron transfer radical polymerization (AGET ATRP) of oligo (ethylene oxide) monomethyl ether methacrylate (OEO300MA) by an inverse mini-emulsion polymerization of the water/cyclohexane at an ambient temperature.

Hydroxyl containing ATRP initiator was used to control the polymerization to produce functional HO-POEO300MA nanogels. Cell adhesive nanogels were synthesized using ACRLPEO-GRGDS as a co-monomer during the polymerization [3]. In o/w mini-emulsion technique monomer droplets are formed by applying high shear stress by ultrasonication or high pressure homogenizer. Miniemulsion is kinetically stable [21].

Applications of Nanogels

Vaccine Delivery

Vaccination is based on the induction of an immune response that is antigen-specific.

In order to enhance potency and performance of the vaccines, polymeric nanogels are being utilized as the novel, alternative means of a vaccine delivery. The advantage of nanogels over conventional vaccines lies in the ability of 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 [24].

Bone Regeneration

For a successful regeneration of the bones, where biodegradable cell scaffolds should release lithium as well as the other medicament slowly and locally. Bone growth can be increased by the lithium, hence, lithium nanogels, synthesized by a micro-emulsion polymerization of thepolyacrylic acid and is incorporated into the biodegradable polyhydroxybutyrate matrix, are formulated for the controlled release of lithium into bone tissue [21].

Anti-inflammatory

Nanogels have found an application in dermatology and incosmetology as topical delivery systems of non-steroidal anti-inflammatory drugs (NSAIDs) and for the treatment of allergic contact dermatitis and psoriatic plaque. Nanogels are being ideal for this application since they overcome major limitation of the topical delivery systems is relatively short contact time between the active drugs and the application site. This is done by the retaining water into gel matrix and forming a uniform dispersion of the nanogel.

The simultaneous topical delivery of two anti-inflammatory drugs, spantid II and ketoprofen was successfully achieved through a nanogel of the 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. Anti-TNFα agent etanercept (ETR) loaded with thermo-responsive nanogel resulted in effective delivery and showed enhanced anti-inflammatory responses [24].

Local Anesthetics (LA)

Local anesthetics are one of the classes of drugs that induce analgesia and eliminate pain.

The analgesic effect of the local anesthetics is due to the blockage of the nerve impulses in the nerve cell membrane by shutting the voltage gated Na^+ channels. The manner and intensity of the nerve stimulation as well as its resting membrane potential will determine the degree of the 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.

An over dosage of local anesthetics leads to their high toxicity, which has been sparked the interest in formulating controlled release drug delivery systems of them. Incorporating local anesthetics into the drug delivery systems like nanogels can improve their regional administration. A delivery system of a 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 a high pH.

The mechanism of release is based on 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 [5].

Cancer Treatment

Biodegradable nanogel prepared by a cross linking of the polyethyleneimine and PEG/pluronic used for 5'triphosphorylated ribavirin reduced toxicity [25]. Doxorubicine loaded self-organizing nanogel formulated by acetylated chondroitin sulphate used for the cancer treatment [26].

PH responsive doxorubicine uptake accelerated nanogel containing glycol chitosan, which was grafted with the 3-diethylaminopropyl groups [27].

Self-quenching polysaccharide based pullulan/folate-pheophorbide used in minimal toxicity of pheophorbide [28]. Cross linked branched network of a polyethyleneimine and PEG [Polyplexnanogel] used for elevated activity and reduced by the toxicity of fludarabine [29]. Self-assembled nanogel composed of heparin pluronic used to deliver the RNaseA enzyme to internalize in cell [30]. Cholesterol bearing pullulan sustained release nanogels used in recombinant murine interleukine-12 sustained tumor immunotherapy [31]. Reducible heparin with the disulfide linkage nanogel used in an internalization of heparin for apoptotic death of melanoma cells [32].

Specific targeting nanogel of a doxorubicin loaded acetylated hyaluronic acid used in cancer treatment [33]. pH and temperature responsive cadmium (II) ions quantum dots, made of hydroxypropylcellulose –poly (acrylic acid) used in the cell imaging [34]. *In-situ* poly (N-isopropylacrylamide-co-acrylamide) gelatinized thermo sensitive nanogel used to deliver the 5-fluorouracil [35].

Recently, photosensitizer agent chlorine6 has been used for the photodynamic therapy of cancer using chitosan-based nanogels [36]. Generally, the nanoparticles possess an average diameter of nearly 100 nm, neutrality and a surface hydrophilicity which results in a prolonged blood circulation and an increased level of tumor delivery [37]. Examples of drugs loaded in nanogels used as anti- cancer agents were given in Table 2.

Table 2: Drugs loaded nanogels in anti-cancer treatment

S. No	Composition of nanogel	Drugs used	Types of nanogel and method of preparation	Applicability	References
1	*In situ* immobilization of CdSe quantum dots in interior of hydroxypropyl cellulose poly(acrylic acid) (HPC-PAA)	Temozolomide	pH and temperature-responsive nanogel, Polymerization method	High drug loading, better stability, and pH-dependent sustained release. Used in cell imaging and optical pH sensing.	[38]
2	Acetylated chondroitin sulfate (CS)	Doxorubicin	Self-organizing nanogel, Dialysis method	Drug was internalized into the cytoplasm through endocytosis. Effective drug carrier for anticancer therapy.	[39]
3	N-Isopropylacrylamide (NIPAM), poly(ethylene glycol) (PEG), poly(ethylene glycol) methyl ether methacrylate (mPEGMA)	Cisplatin	pH-thermal dual-responsive nanogel, Emulsion polymerization method	Reduced side effects, Treatment of breast cancer.	[40]
4	Chitin poly (L-lactic acid)	Doxorubicin	pH-responsive composite nanogel,	Effective for the treatment of liver cancer.	[41]
5	Dextrin with formaldehyde as a cross-linker	Doxorubicin	pH-sensitive nanogel, Emulsion cross-linking method	Efficacious antitumor activity It is an important in treatment of colorectal cancer.	[42]

6	Poly(ethylene glycol)-b-poly(L-glutamic acid) (PEG-b-PGA)	AAG Doxorubicin	Polypeptide-based nanogel, Cross-linking method	Improved anticancer activity Effective cytotoxicity in a breast cancer cell panel	[43, 44]
7	PVA (polyvinyl alcohol)	Doxorubicin	Charge conversional and reduction-sensitive nanogel, Inverse nanoprecipitation	Better cell toxicity. Improved targeted intracellular drug release.	[45]

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. These nanogels by glucose-dependent swelling and shrinking mechanisms exhibited sustained release of the insulin [46].

Antibacterial and Anti-microbial Activity

Infections have been becoming increasingly difficult to cure due to the resistance to conventional delivery systems of antibiotics.

In order to treat a microbial infection, where a quick and localized action is required, which is possible in ananogel delivery systems. Dextran crosslinked 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* [47].

Ophthalmology

Dexamethasone containing eye drop was prepared by a solvent evaporation or emulsification method using 2-hydroxypropyl-γ-cyclodextrin (HP γ CD) medium containing γCD nanogel for the sustain release. pH-sensitive polyvinylpyrrolidone-poly (acrylic acid) (PVP/PAAc) nanogels, formulated by the γ radiation-induced polymerization of an acrylic acid (AAc) in an aqueous solution of polyvinylpyrrolidone (PVP) acting as a template, were used to encapsulate pilocarpine, thus the enhancing of bioavailability as well as the stability of pilocarpine and maintaining an adequate concentration of the drug at a site of action for a prolonged period of time [48, 49]. Examples of drugs loaded in nanogels for ophthalmic delivery shown in Table 3.

Table 3: Nanogels for ophthalmology

S. No	Composition of nanogel	Drugs used	Types of nanogel and method of preparation	Applicability	References
1	Cyclodextrin	Dexamethasone	Emulsion-solvent Evaporation	Enhanced ocular bioavailability. Extended drug retention at eye surface	[50]
2	*N*-Isopropyl acrylamide, 2-hydroxy-methacrylate Lactide–dextran	Tacrolimus		Sustained drug release profile Increased penetration to the cornea	[51]
3	Chitin	Fluconazole		Controlled regeneration chemistry method	[52]
4	Polyvinylpyrrolidone and acrylic acid (AAc)	Pilocarpine	γ radiation-induced Polymerization	Sustained release and improved bioavailability	[42]
5	Poly lactic-co-glycolic acid, chitosan	Levofloxacin	*In situ* nanogel	Sustained drug release Enhanced corneal retention Slow drug clearance	[53]

Auto-immune Disease

The treatment of an autoimmune disorders is based on ability of the drug delivery system to a selectively disable the immune cells that mediate an autoimmunity response. The incorporation of the immunosuppressant drugs into the nanogel delivery systems have been extensively studied for this purpose which since nanogels can improve that 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 the mycophenolic acid complexed with non-methylated ß-cyclodextrin was formulated by loading of liposomes with a diacrylate terminated copolymer of poly (lactic acid-co-ethyleneglycol) and is tested for the treatment of systemic lupus erythematosus, an autoimmune disease. Where 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 [54, 55].

Transdermal Drug Delivery

Transdermal route of an administration has many advantages of over other routes in that it bypasses first pass effect, improves the efficiency of drugs, provides steady state drug concentration in the plasma and also increases patient compliance. There are a variety of approaches which 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 an 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 [56].

Conclusion

As it is a new and improved approach to diagnosis and the treatment of a wide range of diseases, nanogels have been proved to bring about huge advancements in this field. Nanogels have been versatile properties that make them which are capable of efficient delivery of biologically active molecules, particularly biopharmaceuticals. This has given rise to a number of therapeutic applications; nanogels are used in a controlled delivery of an active drug compounds.

They can also be used as a carrier, or chaperone, to treat diabetes, cancer, neurodegenerative disease, etc. Unique properties of nanogels, like of their tailoring characteristics and easy encapsulation of therapeutics, have promoted these applications of nanogels. They can also been used to minimize the side effects of drugs and lower their therapeutic dose, resulting in improved efficacy of therapeutic agents and increased benefit to the patient.

Future Perspectives

Nanomaterials are recently used in conventional drug delivery and as diagnostic tools. Scientists from various fields investigated extensively about nanomaterials for drug delivery applications over the past three decades. Properties of small size with large surface area of these nanomaterials have improved pharmacokinetics, reduced toxicity, controlled drug release, and targeted delivery of therapeutics.

Nanogels offer combined properties of cross-linking gelling materials and nanotechnology. Nanogel technology has wide use in biomedicine, drug delivery, imaging to diagnosis and biosensing. Surface functionalization and stimulus responsiveness have added a lot to the advantages and applications of nanogels.

Instead of endosomal target, nanogels will prefer cytosolic destination, thereby nanogel based drug delivery system would target at subcellular level. For a large-scale production of nanogels, development of cost-effective methods and resolution of technological issues are required. Questions related to pharmacokinetics and pharmacodynamics needs to be answered. If these shortcomings are satisfied, nanogels can transform into efficient next-generation pharmaceuticals with enhanced clinical care in the near future.

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