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Review Article

A REVIEW OF NANOGELS AS NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

The term "nanogel" refers to highly cross-linked hydrogels with a size between 20 and 200 nm. Due to their tiny size, they have higher penetration and greater drug-loading capacity. They release the medication using mechanisms such as photochemical internalization, volume transition, pH responsiveness, thermo sensitive, and photo isomerization. They can be categorized according to whether they respond to stimuli or not as well as the kind of links that are present in the gel structure's network chains. Using photolithography, modified pollutants, and emulsions, one can create nanogel. Reverse microemulsion polymerization, inverse mini-emulsion polymerization, and the free radical cross-linking polymerization method are all examples of polymerization. Cancer, diabetes, inflammation, and bone regeneration are just a few conditions that can be treated with nanogels. The cutting-edge medication delivery technology for both hydrophilic and hydrophobic drugs is nanogels. This article focuses on the historical data regarding herbal nanogels, which have high patient compliance, delivery rate, and efficacy when used to treat various illnesses. The topic of stimulus-responsive nanogels, including pH-and temperature-responsive systems, is also covered.

Keywords: Nanogels, Gel structures, Volume transition, Photoisomerization, and Photolithography.

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INTRODUCTION

A novel drug delivery system, also known as a targeted drug delivery system, is a way to administer medication to a patient while simultaneously lowering the relative concentration of the drug in the patient's remaining tissues. Novel concepts about the regulation of pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition, and pharmacological efficacy were sparked [1].

Types of novel drug delivery systems: [1]

The following are the most typical kinds of new drug delivery systems:

1. Liposomes
2. Nanoparticles
3. Microspheres
4. Nanogels
5. Dendrimers
6. Niosomes
7. Micelles
8. Nanocarbon tubes.

This review mainly focuses on nanogels and their formulation and recent advances in nanogels.

Gel A gel is a cross-linked network of polymers swelled in a liquid media. The U.S.P. defines gels as a semisolid system made up of a dispersion composed of either big organic molecules or small inorganic particles that are encased and interpenetrated by a liquid. A natural or artificial polymer creates a three-dimensional matrix inside a dispersion medium or hydrophilic liquid to produce a gel [2].

CLASSIFICATION OF GELS

1. Inorganic hydrogels are two-phase, such as bentonite magma and aluminum hydroxide gel.
2. Organic gels are single-phase systems containing gelling agents such as carbomer and tragacanth and those with an organic liquid, like Pasties.
3. Water-soluble components such as organic hydrogels, natural and synthetic gums, and inorganic hydrogels are included in hydrogels. For instance, hydrophilic colloids like silica, bentonite, tragacanth, pectin, sodium alginate, and sodium carboxymethylcellulose.
4. Organo gels include hydrocarbons, vegetable, and animal fats, greases derived from soap, and hydrophilic Organo gels [3].

Highly cross-linked nano-sized hydrogel systems that can be made from co-polymerized monomers or ionic or non-ionic monomers are known as nanogels. Nanogels range in size from 20 to 200 nm. Numerous ligands employed for targeted drug delivery, stimulus-responsive drug release, or the creation of composite materials can be incorporated by chemical changes. Their well-known excellent properties fueled the desire for nanogels as a delivery system. They have outstanding thermodynamic stability, high solubilization potential, low viscosity, and the ability to withstand aggressive sterilization methods. Nanogels may trap drugs and biological substances. As a result, they can be used extensively in transporting genes and proteins. Some nanogels are hydrophilic, which inhibits the ability of hydrophobic medicines to be effectively encapsulated. Encapsulation of anticancer medications that are hydrophobic in nature presented this problem [4].

HISTORY

The first nanogels were created by the promising research team of Kabanov *et al*. They employed the nanogels to carry oligonucleotides and created a chemical crosslink utilizing the polymers poly (ethylene glycol) (PEG) and polyethylene mine (PEI). Since the early creation of hydrogels by the pioneer Erle and Lim in 1960, there has been a significant advancement in producing hydrogen-based products on the market. Nanogels have emerged as the preferred material for various biomedical applications, including targeted drug administration, due to their flexibility to be tailored to desired qualities. Nanogels are the top contenders, holding great promise for applications such as tissue engineering, targeted drug delivery, biosensors, imaging, gene delivery, and stimulus-responsive bioactive carriers due to their distinctive nanostructure, compositions, and three-dimensional framework [5].

Hydrogels are converted to nanogels for imaging

Since the development of hydrogels, it has been crucial to understanding how hydrogels degrade *in vivo* to create efficient drug delivery methods. The ideal scenario for determining what happens to the hydrogels' by-products is non-invasive imaging of the hydrogels that have been implanted. Mice were subcutaneously injected with gelatin hydrogels

cross-linked with lysine diisocyanate ethyl ester. The degradation of the hydrogel and its interactions with the tissue were observed using magnetic resonance imaging (MRI), optical imaging, and PET. The research used MRI images as well on both day and day 35. Nanogel systems have longer blood circulation duration due to their excellent stability. They are more specific than the commonly used contrast agents (gold and silver nanoparticles). Due to the methods used in their production and their small size, nanogels get over these restrictions. Another research team's intriguing investigation revealed a nanogel made of PEGMA and N-(2 amino ethyl) methacrylate. A chelator called DTPA's isothiocyanate derivative was used to insert Gd [5].

What is nanotechnology

Nanotechnology uses science, engineering, and technology at the nanoscale, or between 1 and 100 nanometers. Richard Feynman was a physicist and the pioneer of nanotechnology. Nanoscience and nanotechnology, which study and use very small objects, apply to all other scientific disciplines, including chemistry, biology, physics, materials science, and engineering (Fig.2) [6].

Table 1: Advantages and disadvantages of nanogel [20]

Advantages	Disadvantages
1. Both hydrophilic and hydrophobic drugs can be formulated in nanogels formulation without any leakage of medication from the solution	1. Many a times, there is very substantial intraction between the drug or active agent and the polymer, which reduces the hydrophilic nature of the nanogels, causing the structure to be wrecked, entrapping of the drug molecule
2. Administration of nanogels can be through various routes such as parental mucosal, and topical	2. Restrained drug loading competency of nanogels and suboptimum standardization of drug discharge
3. Nanogels can be controlled for sustained drug release from the formulation by adding a polymeric network. Polymeric networks also contain the particle size of the formulation	3. Unpropitious effects can be seen in the formulation of nanogels due to the presence of surface active agents or monomers

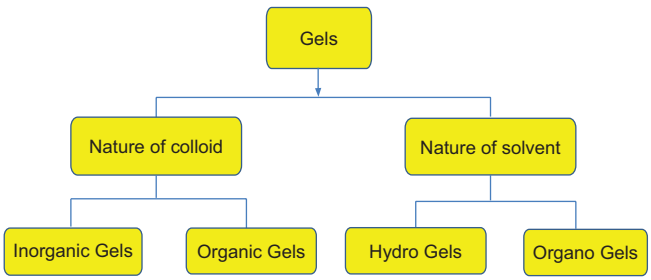

Fig. 1: General Classification of Gels [2]

Fig. 2: Nanotechnology

What is nanogel

Nanogels are nanosized particles made of physically or chemically connected polymer networks that inflate when exposed to a suitable solvent. Cross-linked PEIs and PEG bi-functional networks for the transport of polynucleotides were the first materials to be referred to as "nanogels" (PEG) (Fig.3) [3].

Polymeric properties to prepare nanogels?

Various naturally occurring polymers, manufactured polymers, or both can be found in nanogels. By adjusting the chemical makeup of

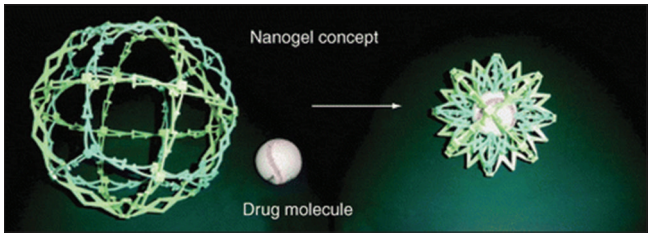

Fig. 3: Nanogel concept [7]

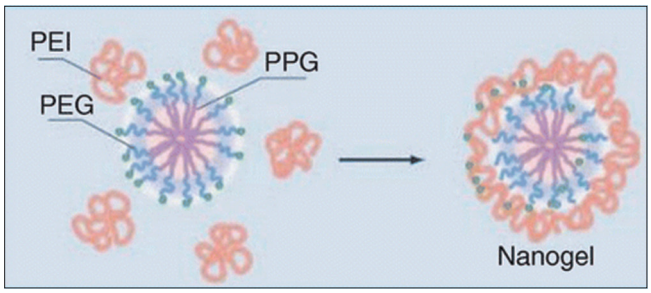

Fig. 4: Therapeutic delivery [10]

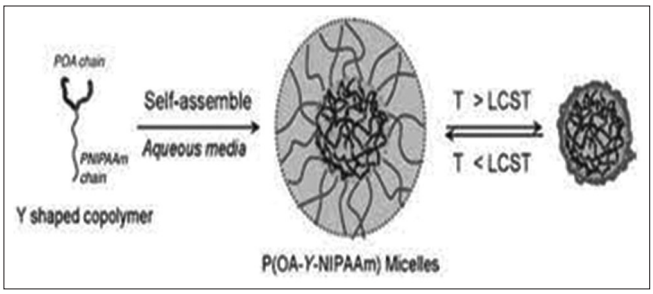

Fig. 5: Y-shaped copolymer self-assembly to give micelle structures [11]

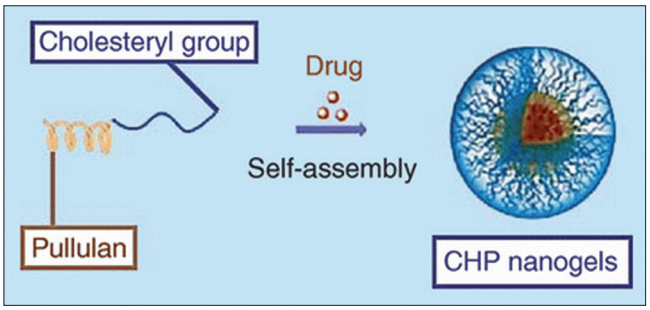

Fig. 6: Therapeutic delivery [10]

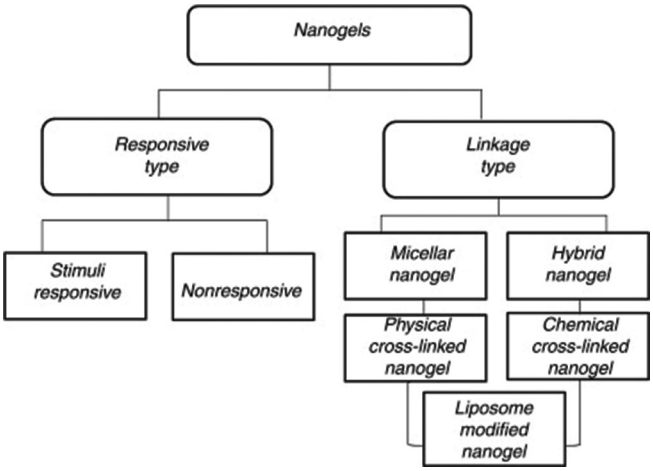

Fig. 7: General classification of nanogels [1]

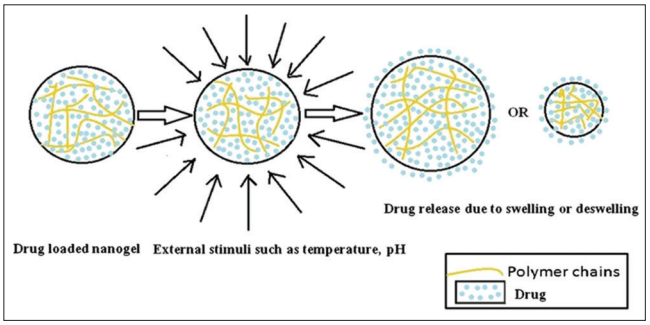

Fig. 8: Diagrammatic representation mechanism of drug release from nanogels [12]

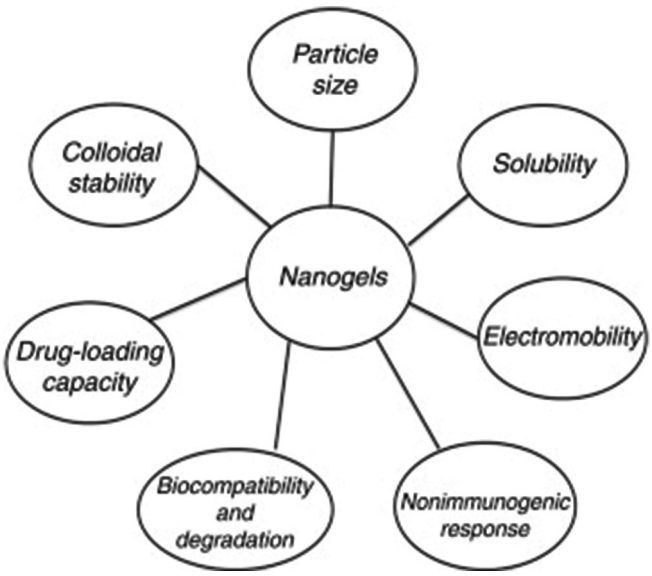

Fig. 9: Nanogels: A new dawn in antimicrobial chemotherapy [13]

the nanogels, it is possible to fine-tune their properties, including size, charge, porosity, amphiphilicity, softness, and degradability [8].

Examples of polymers that are suitable to prepare nanogels?

In addition to, synthetic materials such as poly(N-isopropyl acrylamide), poly (N-isopropyl acrylamide-co-acrylic acid), and PEG-b-poly (methacrylic acid), natural polymers such as albumin, pollutant, hyaluronic acid, methacrylate chondroitin sulfate, and

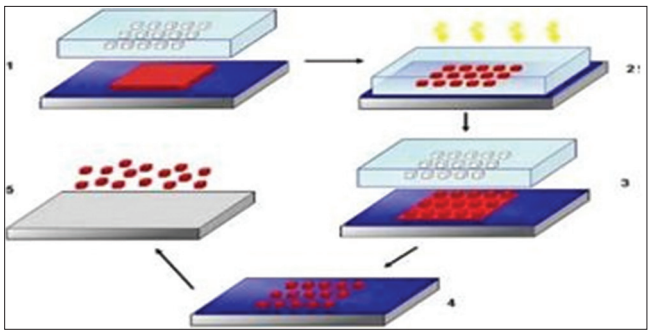

Fig. 10: Schematic diagram of five steps involved in photolithography [14]

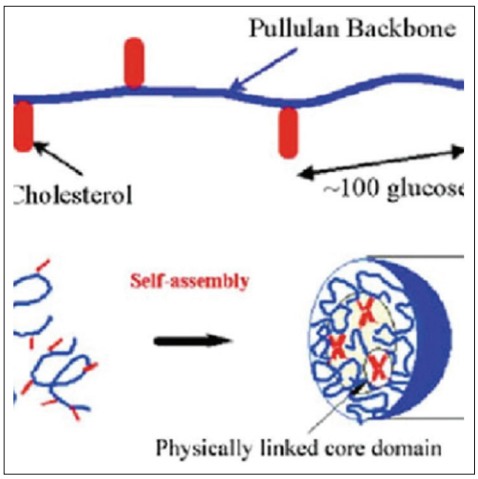

Fig. 11: Schematic representation of cholesterol-modified pullulan-based nanogel preparation by physical self-assembly [15]

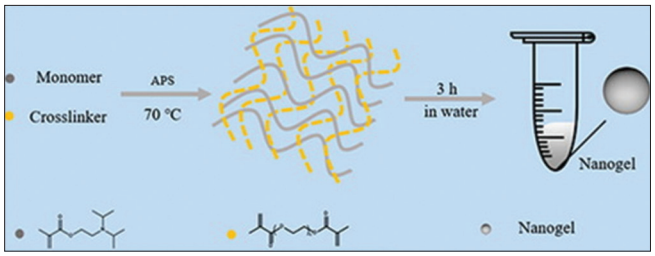

Fig. 12: Effect of environmental factors on the emulsion polymerization of nanogel [16]

chitosan are also used. Frequently referred to as the raw components for them (Fig.4) [9].

Classification of nanogels

The two main classifications of nanogel are responsive type (non-responsive and stimulus-responsive nanogels) and linkage type. Physically cross-linked, liposome's-modified, micelle type, hybrid type, and chemically cross-linked nanogel are the further subtypes of the linkage type nanogel [1].

BASED ON HOW THEY REACT TO A CERTAIN STIMULUS

Stimuli-responsive nanogels

The magnitude of the swelling or deswelling of the nanogels depends on environmental factors like temperature, pH, magnetic field, and ionic strength. The phrase "stimuli-responsive nanogels" refers to nanogels that will modify their activity in response to changes in environmental elements, which function as stimuli [4].

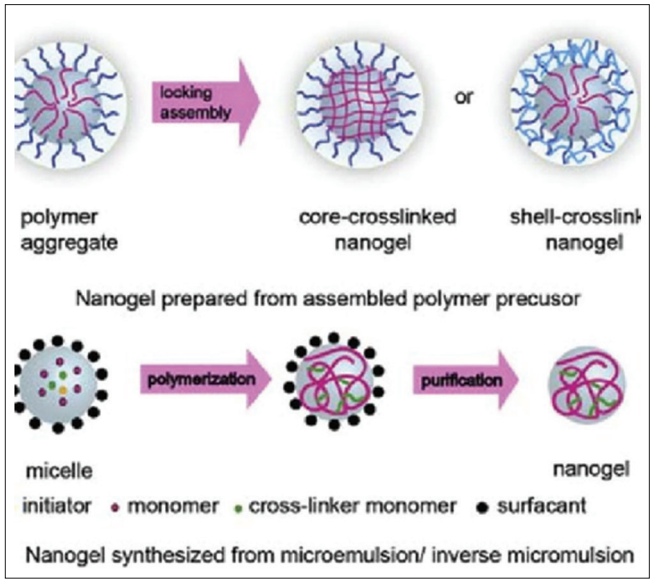

Fig. 13: Methods of nanogel synthesis: the polymer precursor method and the emulsion method [17]

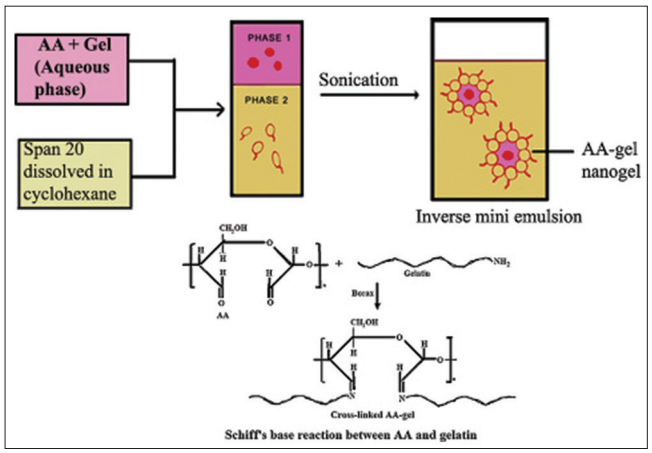

Fig. 14: Nanogels based on alginic aldehyde and gelatin by inverse miniemulsion technique [18]

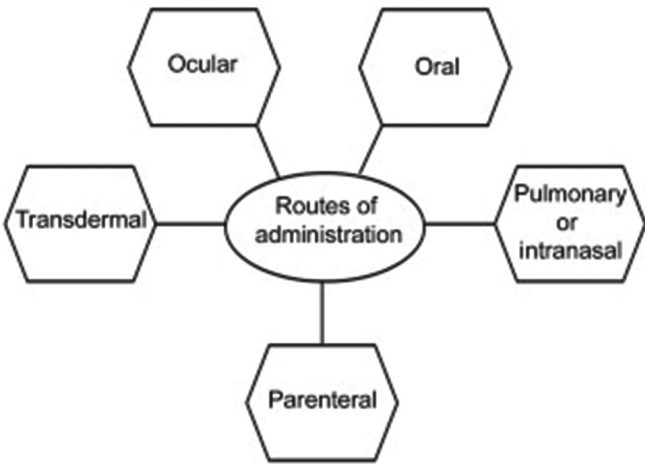

Fig. 15: Routes of administration [13]

Non-responsive nanogels

Non-responsive nanogels absorb water when they touch it, which causes the nanogel to swell.

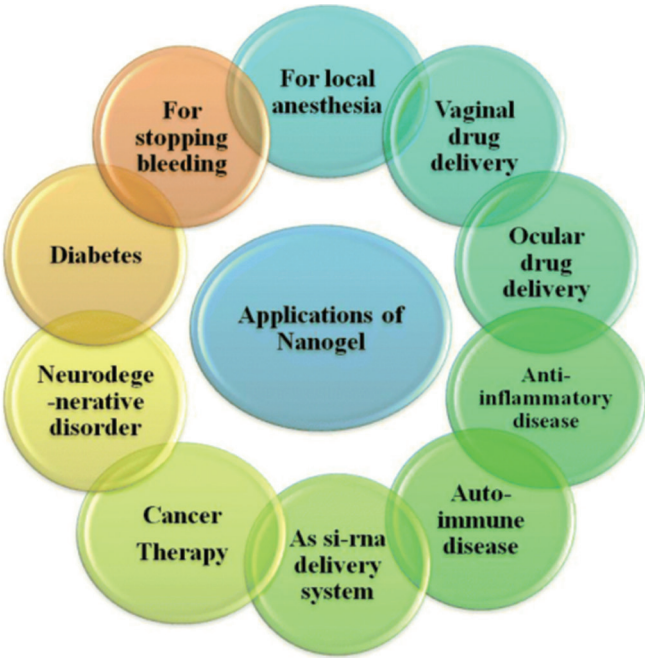

Fig. 16: Schematic representation of the application of nanogels [12]

Multi-responsive nanogels are nanogels that respond to a variety of environmental stimuli [4].

DEPENDING ON THE KIND OF LINKS FOUND IN THE POLYMERIC GEL STRUCTURE'S NETWORK CHAINS

Micellar nanogels

In an aqueous solution, graft copolymers or supramolecular self-assembly of hydrophilic and hydrophobic building blocks can form micellar nanogels. A hydrophilic shell (corona), consisting of polymer blocks, surrounds a hydrophobic core in micellar nanogels, supporting the entire micelle. By physically entrapping pharmaceuticals or biological macromolecules inside the shell's borders, this conformation serves as a drug delivery method by creating enough room to hold those substances. To shield the hydrophobic core that is transporting the medicine to its target cells, the hydrophilic shell of the micelle interacts with the aqueous medium by creating hydrogen bonds as it enters the body. This procedure guards against hydrolysis or degradation of the medication molecules caused by enzymes (Fig.5) [4].

Hybrid Nanogels

A nanogel is one in which a nanogel's particles are spread in an organic or inorganic media. The procedures used to create nanogels in an aqueous media included self-assembly and aggregation of amphiphilic polymers, including pullulan-PNIPAM, hydrophobized polysaccharides, and hydrophobized Pullulan. Investigations focused on cholesteryl pullulan (CHP) nanogels that contain cholesterol. These CHP molecules, composed of a pullulan backbone and cholesterol branches, self-aggregate to create stable monodisperse nanogels, with hydrophobic regions acting as physical cross-linking sites). Researchers discovered that CHP nanogels had the unusual capacity to coat solid surfaces such as liposomes, particles, and even living cells in addition to complexing with molecules including deoxyribonucleic acid, proteins, and different medicines. Kuroda and colleagues, hybrid nanogels are important as insulin and anti-cancer medication delivery methods (Fig.6) [4].

Physically cross-linked nanogels

Also known as pseudo gels, physically cross-linked nanogels are strongly influenced by the properties of the polymer used in their production,

including the polymer's composition, temperature, concentration, type of cross-linking agent, and the medium's ionic strength. These nanogels are created by weak linkages such as van der Waals forces, hydrogen bonds, and electrostatic interactions. These techniques involve several processes, including the association of amphiphilic building blocks, self-assembly, the aggregation of polymeric chains, and the complexation of polymeric chains with dipolar charges [4].

Chemically cross-linked nanogels

Cross-linked nanogels are connected by networks of potent covalent bonds and other irreversible chemical linkages. The functional groups in the molecules that make up the nanogel network significantly impact the bond's strength. This kind of nanogels is created by cross-linking polymeric chains at predetermined locations known as the cross-linking points chosen by the multifunctional cross-linking agent.

For example, using an eco-friendly chemical process, a nanogel with a cross-linking of 0–200 nm was created by cross-linking polymeric chains with pendant thiol groups [4].

Liposome modified nanogels

These nanogels have a high degree of responsiveness to pH and temperature because poly (N-isopropyl-acrylamide) co-polymeric groups are incorporated into the liposomes. Additionally, under a pH of <5.5, succinate poly (glycidol) s is infused into liposomes to produce nanogels that efficiently carry calcine to the cytoplasm of target cells (Fig.7) [4].

NANOGELS' DRUG RELEASE MECHANISM

Three types of drug release mechanisms from nanogels are controlled by diffusion, swelling, or degradation of the matrix. In the diffusion-controlled release mechanism, the drug is dispersed in the polymer matrix of the nanogel and diffuses down the concentration gradient. The loading or release capacity of nano-gels has been studied comprehensively about the sensitive properties of polymer systems, such as temperature, pH, volume transition, and light-responsive behavior, as mentioned below (Fig.8) [4].

1. PH-sensitive system
2. Volume transition and thermosensitive mechanism
3. Photochemical internalization and photo-isomerization diffusion
4. Diffusion
5. Degradation of nano-gel
6. ph. –responsive mechanism [4].

PROPERTIES OF NANOGELS

Biocompatibility and degradability

Polymers, whether synthetic or natural, make up nanogel. The nano gel can be made using chitosan, ethyl cellulose, methylcellulose, and different polysaccharide-based polymers such as dextran, pullulan, and dextrin. These polymers are naturally hydrophilic, biodegradable, stable, and non-toxic [4].

Swelling property in aqueous media: Nanogels can pour in an aqueous medium due to their small size and soft nature. The composition of nanogels comprises the polymer chains' chemical makeup, the degree of cross-linking, and, in the case of Polyelectrolyte Gels, the charge density. Swelling only occurs when there is an imbalance between the osmotic pressure produced by the medium ions and the swelling pressure of the polymer's network [4].

Higher drug loading capacity

Nanogels are anticipated to have a higher loading capacity than conventional dosage forms, just like any other nano-delivery technology. This is mostly caused by the formulation's ability to swell, which allows it to absorb massive amounts of water. As a result, after integration and loading, the water will offer a cargo volume large enough to hold salts and biological molecules [4].

Permeability and particle size

The unique feature of nano-delivery systems is their capacity to dramatically increase permeability with minor particle size, surface charge, and hydrophobicity adjustments. Even though nanoparticles can pass through tissues, damaged endothelium, and occasionally a specific transport system by diffusion, they have trouble crossing the blood–brain barrier (BBB). Therefore, nanogels were created with a diameter of 20–200 nm. It can traverse the BBB while avoiding fast clearance mechanisms because of its tiny size [4].

Non-immunologic response

The mononuclear phagocyte system quickly eliminates any substance that enters systemic circulation through opsonization and phagocytosis. Opsonization is simply labeling foreign substances so that phagocytes can see them. Opsonins bind to the surfaces of nanoparticles and make it easier for phagocytes to adhere. A few techniques are used to assist nanoparticles in avoiding detection and staying in the bloodstream longer. They are all based on reducing protein binding. Hydrophilic polymers, for instance, can operate as a barrier that prevents or delays binding with opsonins, making them invisible to the immune system and its defenses [4].

Colloidal stability

The colloidal stability of nanoparticles is always threatened by their propensity to aggregate when handled. Formulators frequently modify the surface charge to prevent the development of aggregates in the bloodstream and further difficulties. It can be done by raising the zeta potential (which must be at least 30 mV), which causes stronger repulsive interactions between the particles and electrostatically stabilizes them. In other methods, a surface modification like PEG is added to create steric effects and hydration forces, resulting in a stable nanosuspension. When compared based on stability, polymeric micellar nanogel systems and surfactant micelles show higher strength, lower critical micelle concentrations, lower dissociation rates, and longer retention of loaded medicines. They also have a lot of water in them (Fig 9) [4].

SYNTHESIS/METHODS OF NANOGELS

Photolithographic techniques

To create 3D hydrogel particles and nanogels for drug delivery, photolithographic techniques, photochemical reactions for activation, and subsequent reactions have been investigated. The surface of stamps or replica molds is given special qualities, allowing the molded gels to release the included agents. Such gels are often microfabricated using poly (dimethyl siloxane) (PDMS) stamps, which shape, remove, and stack gels into three-dimensional structures. The release or adherence of molded gels to a substrate is improved through surface modification. Self-assembled monolayers with ethylene glycol (EG) termination or adsorbed monolayers of bovine serum albumin are typically used to modify PDMS stamps (Fig. 10) [4].

Modified pullulan technique

Pullulan nanogel, which has been hydrophobized and self-assembled, is an example of this. Pullulans are changed in phases; first, hydrophobic 1-hexadecane thiol and, subsequently, methacrylate are utilized. The result is an amphiphilic substance that, when added to water, begins to self-assemble through interactions between alkyl chains that interact hydrophobically. Cholesterol-based pullulan nanogel is another illustration. Pullulan was changed to 1.4 cholesterol in this case, and the nanogel was created by simply reacting cholesterol isocyanate with pyridine and dimethyl sulfoxide. This mixture was freeze-dried, and after forming nanogel in the aqueous phase, it further established a complex with W-9 peptide, an antagonist of tumor necrosis factor-α and receptor activator of NF-κB, to produce osteological abnormality. The CHP reaction and glycidyl methacrylate made CHP contain methacrylic. 6.2/100 glucose units was the degree of replacement (CHPMA6). In water self-assembly, CHPMA6 created nanogel (Fig.11) [4].

Emulsion polymerization technique

Using the emulsion polymerization method, l-proline functionalized (poly [methyl methacrylate]) nanogel with a range of catalyst

functionalization (0.5–15 wt. %) and cross-linking densities (0–50 wt. %) was created. Mechanical churning produces monomer droplets during the emulsion polymerization process (Fig. 12) [4].

Reverse microemulsion polymerization technique

Polyacrylic acid (PAA) nanogels with lithium loading were created using a reverse microemulsion polymerization process. A magnetic stirrer was used to stir the 3.43 g and 2.62 g of span 80 in the oil phase of 100 mL (about 3.38 oz) of hexane. 500 mL (approximately 16.91 oz) of acrylic acid was mixed with 1.5 mL (about 0.05 oz) of 10% (w/w) Lio in water to create the aqueous phase. To the aqueous phase, add 40 l (approximately 10.57 gal) of 20% (w/v) N, N, N,' N'-Tetramethylene-diamine, 500 l (about 132.09 gals) of 2% (w/v) potassium persulfate, and 214 l approximately 56.53 gals) of 5% (w/v) N, N'-Methylene acrylamide suspension. The aqueous phase was added drop by drop into the oil phase to create the microemulsion. The emulsion was put into a 60°C water bath, agitated at 400 rpm with a magnetic stirrer, and left there for the next day. Decanted supernatant pellets were gathered, too. Thermodynamically, the microemulsion is stable (Fig. 13) [4].

Inverse mini emulsion polymerization technique

Fluorescent coloring Activators produced electron transfer atom transfer radical polymerization of oligo (ethylene oxide) monomethyl ether methacrylate (OEO300MA) by inverse mini-emulsion polymerization of water/cyclohexane at room temperature was used to create rhodamine B, or fluorescein tagged nanogels. To manage the polymerization and create functional HO-POEO300MA nanogels, an ATRP initiator that contains hydroxyl was used. ACRLPEO-GRGDS was used as a co-monomer during the polymerization to create cell adhesive nanogels. When using an O/W mini-emulsion approach, strong shear stress is applied using ultrasonication or a high-pressure homogenizer to create monomer droplets. Kinetic stability exists in Mini emulsions (Fig. 14) [4].

ROUTES OF NANOGEL ADMINISTRATION

Limitations of nanogels

- The only restrictions on employing nanogels are as follows
- Even though the manufacturing method is not extremely expensive, the surfactant and solvent must be removed at the end of the preparation phase
- Any lingering polymer or surfactant traces could negatively affect the body [4] (Fig. 15).

Applications of nanogels

Local anesthetics (LA)

One of the medication classes that causes analgesia and relieves pain is LA. LA have analgesic effects because they block nerve impulses in nerve cell membranes by closing voltage-gated Na+ channels. The degree of numbness brought on by a certain concentration of a local anesthetic depends on the way and the strength of the nerve stimulation and its resting membrane potential. According to their chemistry, LA are clinically divided into amino esters and amino amide. The high toxicity of LA because of overdosing has stimulated research into developing controlled-release medication delivery methods. LA can be more effectively administered locally if incorporated into drug delivery systems like nanogels [4].

Cancer treatment

Using a biodegradable nanogel to minimize the toxicity of 5'-triphosphorylated ribavirin was made by cross-linking polyethyleneimine and PEG/Pluronic. Acetylated chondroitin sulfate was utilized to create a doxorubicin-loaded self-organizing nanogel used to treat cancer Nanogel containing glycol chitosan grafted with 3-dimethyl aminopropyl groups and pH-responsive to doxorubicin absorption increased. Pullulan/folate-pheophorbide, a self-quenching polysaccharide, is utilized to reduce the toxicity of pheophorbide. Fludarabine's activity is increased, and its toxicity is decreased by a cross-linked, branching polyethyleneimine and PEG network known as Polyplex nanogel. Heparin Pluronic-based self-assembling nanogel delivers the Ranse enzyme for cellular internalization. Recombinant murine interlinking-12 sustained tumor immunotherapy uses pullulan sustained release nanogels containing cholesterol which prolongs blood circulation and boosts tumor delivery [4].

Autoimmune disease

The ability of the medication delivery system to specifically inhibit the immune cells that regulate the autoimmunity response provides the foundation for treating autoimmune illnesses. Since nanogels can enhance the immunosuppression effect by targeting the antigen-presenting cells that contribute to disease and enabling systemic accumulations of the loaded drug, the incorporation of immunosuppressant drugs into nanogel delivery systems has been extensively studied for this purpose. By loading liposomes with a diacrylate-ended copolymer of poly (lactic acid-co-EG), a nanogel system of mycophenolic acid complexed with non-methylated -cyclodextrin was created and tested for the treatment of systemic lupus erythematosus, an autoimmune disorder. By subjecting the nanogel system to ultraviolet light, it was possible to cross-link the acrylate monomers and gel the particles into a stable mixture [4].

Neurodegenerative disease

Since there is currently no known therapy for neurodegenerative diseases like Alzheimer's and Parkinson's, oligonucleotides were the subject of numerous studies when they demonstrated the potential to be utilized as diagnostic or therapeutic tools for these conditions. The inability of oligonucleotides to cross the blood-brain barrier, their quick elimination by renal excretion, and their instability against metabolism have all considerably hampered their use in treating neurodegenerative illness. Oligonucleotides were added to nanogel delivery devices to improve their performance. Angels' unique characteristics facilitate their transport to the central nervous system by enabling oligonucleotides to pass the blood-brain barrier. The crosslinking of PEG with polyethyleneimine to create an oligonucleotide nanogel was discovered to have the ability to encapsulate negatively charged medicinal particles and form a stable polyelectrolyte complex in an aqueous solution. Adding insulin or transferrin to the surface improves transit efficiency [4].

Anti-inflammatory

As topical delivery systems for non-steroidal anti-inflammatory medicines, nanogels have been used in dermatology and cosmetology to treat allergic contact dermatitis, psoriatic plaque, and other skin conditions. Since they can get beyond the main drawback of topical delivery systems, namely, the brief interaction period between active medicines and the application site [4].

Vaccine delivery

The foundation of vaccination is activating an antigen-specific immune response. Polymeric nanogels are being used as an innovative, alternative method of vaccine delivery to improve the potency and effectiveness of vaccines. The ability of the nanogel network to shield vaccine antigens from enzymatic degradation distinguishes nanogels from conventional vaccinations. Using surface-modified nanogels with coupled antibodies and other ligands can dramatically increase the target specificity of the vaccine delivery [4].

Transdermal drug delivery

Compared to other administration methods, transdermal skips the first pass effect, boosts medication effectiveness, offers constant state drug concentration in plasma, and enhances patient compliance. Several strategies were considered to increase the drug's penetration into the site of action. Using nanogels to topically transport active pharmacological components to the stratum corneum is a promising strategy. Transdermal distribution of the medication was investigated as an alternative. It demonstrated improved stability and permeability because oral administration of cyclofenil generates a few side effects, such as ulcers and stomach hemorrhage [4].

Bone regeneration

Biodegradable cell scaffolds should gradually release lithium and other medications locally for optimal bone repair. Lithium can enhance bone growth; hence, it is used to make lithium nanogels by microprocessing. Lithium and other medications must release gradually and locally for biodegradable cell scaffolds to regenerate bones successfully. Lithium can enhance bone growth; hence it has been created as lithium nanogels for the controlled release of lithium into bone tissue. These nanogels are made by micro-emulsion polymerizing PAA [4].

Antibacterial and antimicrobial activity

Infections are harder to treat due to resistance to traditional antibiotic delivery methods. A rapid and targeted response is needed to treat a microbial disease, achievable by nanogel delivery methods. Using the mini-emulsion process, dextran crosslinked polyacrylamide nanogels (polysaccharide-based nanogels) were created and loaded with zinc nitrate (zinc ions) as an antibacterial agent. Methacrylate hyaluronic acid was the crosslinking agent employed. This nanogel's goal was to combat methicillin-resistant *Staphylococcus aureus* strains [4].

People with diabetes

To cure diabetes, which is becoming increasingly common in the world's population, innovative treatments is being examined. An injectable nanogel network with a network of dipolar nanoparticles has been developed that is sensitive to changes in blood glucose levels and releases precise insulin doses in response. These nanoparticles generate an adhesive gel matrix that keeps its integrity and adapts to pH fluctuations. The nano gel network will transport insulin and other enzymes required to convert glucose into gluconic acid using dextran. When there is hyperglycemia, the easily soluble glucose molecules pass through the nanogel network and start turning into gluconic acid, lowering the medium's pH. In turn, this will encourage the secretion of insulin. Although this method is quite effective for treating diabetes, further research must be done before this nanogel may be used in human trials [4].

Ophthalmology

A solution evaporation or emulsification process was used to create an eye drop that contains dexamethasone utilizing a 2-hydroxypropyl-cyclodextrin (CD) medium that has CD nanogel for sustained release. Pilocarpine was encapsulated in pH-sensitive polyvinylpyrrolidone-poly [acrylic acid] (PVP/Pac) nanogels that were created by radiation-induced polymerization of acrylic acid (Aa) in an aqueous solution of polyvinylpyrrolidone (PVP) acting as a template. This improved pilocarpine's bioavailability and stability and maintained an adequate concentration of the drug at the site of action at a sufficient level for a long time (Fig. 16)[4].

HERBAL DRUG FORMULATIONS

Nano-capsules

Natural medicinal treatments known as herbal nanocapsules are composed of nanoshells made from a pure polymer. Drugs are delivered to a specific area using these nanocapsules in a controlled and targeted manner. Natural nanocapsules are made of poly-e-caprolactone, poly(lactide), and poly(lactide-co-glycolide). Due to their small size, high surface area to the east ratio, and nanoparticle medication therapies improving the pharmacokinetics and biodistribution of therapeutic substances, nanocapsules are utilized in natural medicinal pharmaceuticals [19].

Nano-tablets

In impoverished nations, people can use herbal water pills with nanoparticles to cleanse their water for safe drinking. This tablet, placed inside a water container and can purify water for up to 6 months, was made with Brahmi (Bacopa Monnier) extract on a tiny ceramic disc loaded with silver or copper nanoparticles. Nano tablets containing herbal drugs are used to deliver medication in a regulated and targeted manner. Ayurvedic Bhasma's coated nano tablets' potential anticancer properties are being researched. The formulations of the term "Bhasma" incorporate nanoparticles. The fact that India possesses a 5000-year-old medical system astonished many specialists. The Bhasma has have long been employed in Ayurveda as a nanotechnology for treating several ailments. (Immune modulation) "Rasayana" Ayurvedic Bhasma's frequently have the qualities "Yogavati" (drug carrying capacity and focused drug delivery) and "Agni" (anti-aging property). Hydrogel nanoparticles called herbal nanogels, whose sizes range from 10 to 100 nm, are better at regulating and concentrating medication release. It reduces fat in the abdomen, arms, legs, thighs, and double chin and is the fastest and safest way to lose weight without having any negative effects. This nanogel reaches a great depth Enter the skin, functioning immediately to remove stored fat [19].

Nanoemulsions

Both the composition and the method of preparation impact the properties of nanoemulsions. These nanoemulsions can be employed for cleaning, cancer therapy, and drug delivery to cells. About 20 years ago, the first nanoemulsions were created, primarily for the creation of nanoparticles. Nowadays, pharmaceuticals and cosmetics are the two main industries using nanoemulsions. Numerous applications for a nanoemulsions emulsions with a diameter of 20–200 nm are multiple. They are safe, do not irritate the skin, and can be employed in transdermal delivery systems. They boost the drug's solubility and bioavailability as a result [19].

Nano paste and nano pure (nano-air purification)

An herbal nano paste made of *Aloe Vera* is currently being studied as a potential osteoporosis therapy. This nano paste strengthens the bones after surgery and has a long-lasting effect due to the nanoparticles' sequential and continual stimulation of the surrounding bone cells. Long-term air quality, availability, and viability of air resources can all be improved by nanotechnology, for instance, by better filtration that allows for more air reuse, recycling, and purification using herbal formulations [19].

Herbal medicaments as nanogels

Dermal dosing systems have proven more efficient than conventional methods because they bypass the drug's first-pass metabolic action and match patient desire with drug release. No alternative administration method can circumvent the limited absorption of the medication through the skin. Nanogels are being researched in this field to achieve the best skin penetration while including other features, like drug release reaction to external stimuli, pH, and other parameters. For instance, curcumin-loaded chitosan nanogels dramatically enhanced curcumin absorption and exhibited excellent skin penetration [19].

Herbal nanogels for oral usage

For many therapeutic procedures, oral administration is the preferred form of delivery. On the other hand, oral dosage has certain drawbacks, including poor bioavailability, gastrointestinal degradation, and first-pass metabolism. Despite the great market potential for oral administration, the unfavorable side effects of oral medications limit their use to a select few chronic illnesses. Nanogels have achieved considerable advancements in the formulation of buccal natural fauna due to their non-poisonous characteristics, good medication release, or better systemic release. For many medicinal medications, oral administration is the preferred way of delivery [19].

Nanogels

One of the most well-known nanotechnologies approaches for effective medication administration both within and outside the body and topical therapy is nanogels. Nanogels have properties that enable them to deliver substances to the target area, including chemical agents such as diclofenac, dyes, proteins, oligonucleotides, RNA, and quantum dots. Because of its controlled drug release at the target site and reduced drug molecule toxicity, it has been found to increase drug bioavailability. The harmonious interaction of each herbal medicine's essential components determines its effectiveness. Herbaceous maximum drugs have high systemic clearance

and low absorption because they contain insoluble materials. The nanogel formulations of these drugs overcome these limitations [19].

ADVANTAGES AND DISADVANTAGES OF NANOGELS

Table 1.

CONCLUSION

Nanogels have been shown to significantly progress this sector as a new and improved method for detecting and treating various ailments. Nanogels can effectively deliver biologically active compounds, especially biopharmaceuticals, due to their wide range of characteristics. This has led to several therapeutic uses, including the controlled distribution of active pharmaceutical ingredients using nanogels. As carriers or chaperones, they can also treat conditions like diabetes, cancer, and neurological diseases. These uses of nanogels have been facilitated by their special qualities, such as their tailoring capabilities and simplicity in encapsulating medicines. In addition, they can reduce drug side effects and therapeutic doses, enhancing the effectiveness of therapeutic agents, raising their energy, and providing a greater advantage for the patient. Nanogels are preferable in that they can simplify this delivery system while also doing away with the drawbacks of earlier approaches. Applications in drug and gene delivery, smart imaging modalities, responsive materials, and multivalency as therapeutic strategies emphasize the enormous promise of functional nanogels as distinct polymeric platforms for biomedicine.

AUTHORS CONTRIBUTION

Maheswari Karanam wrote the paper, lakshmi devi Gottemukkula review the manuscript, and all the authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

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