REVIEW ARTICLE

Nanogel: Types, Methods of Preparation, Limitation, Evaluation and Application - A Systematic Review

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ABSTRACT

Nanogels combine the characteristics of nanomaterials with hydrogels. To meet the expanding demands from various areas, a sizable number of nanogels have been designed and manufactured using the emulsion solvent diffusion nano precipitated method, emulsion evaporation of the solvent method, reverse micellar method and modified diffusion emulsification method. Thermosensitive nanogel, pH-sensitive nanogel, ultrasound-sensitive magnetic response, response to multiple stimuli, chain transfer polymerization, photo-induced crosslinking polymerization and modifications for active targeting are the types of nanogels based on response towards stimuli and polysaccharide, chitosan, pullulan, hyaluronic acid, alginate, cyclodextrin, gum acacia, protein are used to prepare nanogel. Nanogels have considerable potential and novelty within the biomedical sector due to their uniformity, adjustable dimensions, little toxicity, resilience in the presence of serum, and capacity for responsive behavior with a comparatively high drug encapsulation capacity. Nanogels have considerable potential in bioactive substance delivery, organ targeting, and chemotherapy. The article highlighted the preparation, types, evaluation and applicability of nanogel as a targeted delivery system.

Keywords: Nanogel, Preparation, Limitation, Evaluation, Targeted drug delivery.

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INTRODUCTION

Nanogel is produced by physically and chemically cross-linking polymers to hydrogel at the nanoscale.[1] Nanogels are typically between 20 and 200 nm in size. Nanogels are characterized by their size, greater surface area, and hygroscopicity, in addition to their bulging and deteriorating characteristics. The controlled and prolonged release of medications is made possible by nanogels. Because of their three-dimensional architecture, they easily entrap medicines, polymers, and liquid phases in suspension using nanogels.[2] Even giant molecules can fit into the holes in nanogel. They work as drug carriers because they are designed to quickly form biomolecular interactions with physiologically active compounds, such as hydrophobic or hydrogen bonding and salt bonds.[3] Nanogel is a unique composite material that exhibits characteristics of both solids and liquids. According to the theoretical framework, the efficacy of the therapy is positively correlated with the duration of nanoparticle-skin contact after their entrapment inside a nanogel matrix.[4,5]

Types of Nanogel based on Response to Stimuli

Thermosensitive nanogel

Temperature-responsive nanogels demonstrate a phenomenon known as shrinkage-swelling behavior, whereby they undergo changes in size in response to variations in the temperature of their environment. This unique characteristic enables the controlled release of drugs in a titration manner.[6] The decrease in particle size induced by stimulation increased intracellular absorption and facilitated accumulation in the microenvironment associated with the illness.[7] These effects may have positive implications for the outcomes of therapy.[8]

pH-sensitive nanogel

The swelling-shrinking behavior of nanogel is primarily pH-dependent caused by ionizing groups in the design, which can changed through alteration in ionic behavior depending on the pH value.[9] pH of various environments such as pH between 6.5 to 7.2, lysosomes pH between 4.5 to 5.0, and endosomes pH in between 5.0 to 6.5 associated with cancer tissue, lysosome, endosome changed to physiological pH 7.4 has provided information about the different pH ranges in these bodily environments, which can be used to optimize the nanogel's preparation for that specific pH.[10, 11]

Ultrasound-sensitive nanogel

US-based drug delivery have seen substantial growth in the area of transdermal administration in the management of central nervous system-oriented ailments.[12,13] The use of acoustic waves for anticancer therapy has been motivated

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by their ability to deeply penetrate tissues and the associated advantages. The evaporation of perfluorohexane from its liquid state to a gaseous state was seen to facilitate the release of the medication when applied.[14]

Magnetic response nanogel

The induction of hyperthermia may be facilitated by using a magnetic field.[15,16] Furthermore, these nanoparticles can also be employed for magnetic targeting inside a robust magnetic field. A combination of magnetic nanoparticle and temperature-sensitive nanogel was used in a study to manufacture hybrid nanogels loaded with the medicine. The release of stimuli-responsive drugs from nanogels is facilitated by the dynamic process of shrinking and swelling, which is ensured by the action of alternating magnetic field.[17]

Response to multiple stimuli

Nanogels exhibiting dual or multi-stimuli responsiveness have garnered significant interest due to their enhanced ability to consistently sustain regulated drug release. Considerable advancements have been made in investigating combinations exhibiting sensitivities to pH and temperature.[18]

Chain transfer polymerization

Reversible addition–fragmentation chain-transfer (RAFT) is the only some of the reactions that can be manipulated by administering dithioester molecules to a polymer.[19] RAFT technology may modify the amphiphilic polymer's micelle structure by adjusting the polymer's length, structure, and characteristics e.g., poly (N-vinyl caprolactam).[20]

Photo-induced crosslinking polymerization

Irradiation causes crosslinking between molecules, which can create radicals and atoms in a polymer that, upon breaking down water molecules, forms nanogel.[21]

Modifications of nanogels for active targeting

Active targeting allows a ligand to reach the specific receptors on the cells or subcellular structures it was designed to affect. In addition, biological substances *viz* proteins, small molecules, peptides, and polysaccharides, were included in pharmaceutical nanoparticles to improve their efficacy.[22]

Types of Nanogel Based on Polymer

Polysaccharide-based nanogel

Inter-molecular electrostatic interaction that results in ionic complexes is employed to produce nanogels with oppositely charged polymers using polysaccharides such as chitosan, sodium alginate, sodium hyaluronate, chondroitin, and cyclodextrin. Physiological pH changes can be sensed and accounted for by using nanogels with this property.[23] Hydrophobic groups are used to modify hydrophilic polysaccharides. In an aqueous system nanogels are also produced using amphiphilic polymers.[24]

Chitosan-based nanogel

Due to its capacity to improve emulsion stability and hinder coalescence via steric and electrostatic mechanisms, chitosan presents a promising option for developing chitosan-based nanogels employing oil-in-water lipid emulsion technology. Notably, using chitosan obviates the need for surfactants or proteins. Chitosan nanogels could be chemically crosslinked to produce highly stable matrices. Reactions with bi-functional agents, i.e., di-isocyanate, di-epoxy compounds, dialdehyde, and glutaraldehyde, were used to create certain chitosan nanogel.[25] The fabrication of chitosan nanogels through reverse microemulsion using genipin as a crosslinking agent for biomedical applications.[26]

Pullulan-based nanogel

Nanogels based on pullulan and modified with cholesterol to provide functional groups could be a versatile tool. Different functional groups have been attached to the pullulan backbone in various studies. These include tricarboxylate, acryloyl groups, and urocanic acid.[27] The amount of cholesterol substituted for the hydrophobic moiety in the pullulan-based hydrogel nanoparticles correlated with their size and density. Self-associating hydrophilic polymers were used to create the nanogels, which are highly stable and effective at mitigating protein side effects by, among other things, suppressing aggregation and protection from enzymatic destruction.[28,29]

Hyaluronic acid-based nanogel

The polysaccharide HA generated from animals has favorable characteristics that make it suitable for developing nanogels. These traits include biocompatibility, mucoadhesion, and non-immunogenicity, which may be attributed to its specific glucuronic acid and N-acetylglucosamine composition. Additionally, it is essential to note that HA displays a high degree of bioactivity, mainly through its unique binding to specific cell receptors. CD44 (Cell surface adhesion receptor 44) is the most well-known of these receptors.[30]

Alginate-based nanogel

Alpha guluronic and beta mannuronic acid residues are found in alternate blocks in the polysaccharide known as alginate. Alginate is chemically vulnerable to oxidation, amidation, esterification, and sulfation due to highly reactive groups (OH, COOH). Solubility and lipophilicity can be controlled through chemical changes, expanding the scope of possible uses. The proteins are notoriously unstable in the stomach's acidic environment, yet alginate nanogels can protect them during oral delivery.[31]

Cyclodextrin-based nanogel

Cyclodextrins are biologically compatible cyclic structured oligosaccharides of D-glucopyranose units linked via α-1,4-glycosidic bonds.[32] The hydrophobic phenolphthalein was extremely effectively absorbed by the nanogels. [33]

Gum acacia-based nanogel

Acacia niloticais is the biological source of gum acacia or arabic gum. Microparticles and nanoparticles were created using it. The key advantages of this polysaccharide for this application are its high water solubility, biocompatibility, and inexpensive cost. Gum acacia was combined with proteins like gelatine or polysaccharides like alginate and chitosan to

generate nanogels.[34] Compared to chemical agents, Arabic gum has various binding sites with negative charges for interacting with polycationic polymers like chitosan because of its biocompatibility and biodegradability.

Protein based Nanogel

Gelatin

Gelatine, a collagen hydrolysate, has been used to prepare nanogels for various uses. Using gelatine in nanogel synthesis is beneficial in other ways as well. This type of biopolymer has been shown to be highly biocompatible. Second, it has several functions (COOH and NH2 groups) and may be easily modified because of this. Third, the tumor cells' porous endothelial junctions provide a pathway for the NGs to enter the cells. Various techniques, such as precipitation polymerization and inverse mini emulsions polymerization,[35] have obtained gelatine-based nanogels. Aldehydes, genipin, carbodiimide/ N-hydroxy succinimide, and enzymatic crosslinkers like transglutaminase are just some of the crosslinkers that have been utilized for this purpose. Uncross-linked gelatine-based nanogels were found to be unstable and aggregated with time. Nanogels were synthesized by oxidizing gum Arabic to gum arabic aldehyde and crosslinking with gelatin.[36] When the crosslinking density is reduced, gelatine-based nanogels can form triple helical structures at lower temperatures, resulting in the acquisition of thermo-responsive features by the nanogels.

Soy protein

Soy protein has an isoelectric point at around pH 4.8. Several synthetic polymers often used to manufacture nanoparticles have suboptimal protein encapsulation, insufficient dosage properties, and limited durability.[37] Because of the pyridine's toxicity and the difficulty of removing its remnants, a more thorough purification of the initial product is required. The protein-polymer ratio determines the nanogel's particle size, which ranges from 200 to 900 nm. Single intra-articular injections of nanogels loaded with proteins prolong their retention in rat stifle joints for more than 14 days. The use of an altered catalyst in the polyhydroxyethylmethacrylate-pyridine reaction has facilitated the attainment of meticulous control over the sizes of nanogels, confined inside a narrow range of 145 to 160 nm, allowing for the development of immunostimulatory self-assembly nanogel vaccines. These nanogels efficiently primed ovalbumin-specific $CD8^+$ T lymphocytes by delivering protein antigens to dendritic cells.[38]

Advantages of Nanogels

Nanogels transport more effectively because they have higher surface area and free energy. Creaming, flocculation, coalescence, and sedimentation have invisible internal mechanisms. It is available in several forms, such as creams, liquids, etc. They are non-toxic and advantageous for both human and animal use. The incorporation of hydrophilic compounds in cell cultures is enhanced. This substance can be an alternative to vesicle oriented drug delivery system.[39]

Restrictions of Nanogel[40]

The final removal of surfactants and solvents throughout preparation contributes to a significant financial burden. The potential for injury exists when the body is exposed to even minute quantities of polymers or surfactants. Furthermore, the drug-polymer interaction might lead to increased hydrophilicity of the nanogel matrix, causing the drug molecules to be permanently entrapped inside the matrix.[41]

METHODS OF NANOGEL PREPARATION

Emulsion Solvent Diffusion Method

The aqueous solution of drug is solubilized in an organic layer. Polymer and gelling agent are dissolved in water to form the drug phase, which is added drop wise to the aqueous phase has been homogenized for 30 minutes at 6000 rpm. When an emulsion is homogenized into a nanodroplet by a homogenizer, an oil/ water emulsion is created.[42] To create nanogel, triethanolamine is added to the oil in water emulsion and continuously stirred for an hour at 8000 rotations per minute.[43]

Nano Precipitated Method

When the organic phase contained both medication and polymer reacted with the surfactant aqueous layer, the polymer precipitated out. After the removal of the excess solvent, polymeric nanoparticles are left out.[44] Gelling agent and necessary amounts of nanoparticle dispersion are added after the particles have been moistened. The pH is stabilized by using triethanolamine.[45]

Evaporation of the Solvent Method

During two hours of treatment, the drug-polymer mixture is injected into the designated area of the aqueous phase. This process is accompanied by continuous stirring at 1000 rpm, facilitated by a magnetic stirrer.[46] The nanosponges obtained as a consequence are further subjected to filtration, followed by a drying process in a hot air oven maintained at a temperature of 40°C for 24 hours.[47] Finally, the dried nanosponges are carefully transferred into vials for storage. To achieve a homogeneous dispersion, it is recommended to immerse the polymer in water for 2 hours before the initiation of gel formation.[48,49] Subsequently, the polymer should be subjected to agitation at a rotational speed of 6000 rpm. The pH is modified with the use of a pH-adjusting agent. Subsequently, the aqueous dispersion is combined with the optimized nanosponge suspension and permeation enhancers.[50,51]

Reverse Micellar Method

A polymer, medication, and surfactant are dissolved in an organic solvent. After adding the cross-linking agent, it must be incorporated over an extended period of time during the night.[52] After the nanoparticles have been purified, the solvent is evaporated, creating a desiccated bulk.[53] It was created by dissolving the gelling component in water. When nanoparticles and an aqueous phase containing a gelling agent are combined, nanogel is formed. The application of a neutralizing substance modifies the pH.[54]

Modified Diffusion Emulsification Method

A polymer containing the solvent is mixed with the medication in a precisely calculated ratio. The organic phase is created when the drug-polymer mixture is continuously agitated in the aqueous phase at a rotating speed of 5000 to 10,000 rpm.[55] A syringe fitted with a needle is used to add the organic phase at a rate of 0.5 mL per minute to the aqueous stabilizer solution. After being agitated for six minutes at a rotational speed ranging from (10000–25000) rpm, the suspension is next subjected to sonication for five to ten minutes (Figure 1).[56,57]

Application of Nanogel in Drug Delivery and Disease Control

El-Sattar *et al.,* developed nanogel delivery system using pH regulation. In this manuscript, monitoring pH has been recognized as a crucial diagnostic component throughout the therapeutic procedure. A pH-sensitive nanogel made of polyethylene glycol and poly (maleic anhydride) copolymers (50:50 ratio) was cross-linked using gamma irradiation procedures at a dosage of 5 kiloGray. A new nanogel formulation was tested as dual inhibitor of vascular endothelial and epidermal growth factor receptor tyrosine kinase enzymes. Then the formulation was tested against human liver cancer (HEP-G2), human epithelial lung cancer (A549), human breast cancer cell line (MCF-7), and human colon cancer (HCT-116) for anticancer proliferation. Finally the developed formulation proved as a promising carrier for the anticancer molecule.[58]

Yao *et al.,* developed 5-fluorouracil and photosensitizer indocyanine green were loaded into large amounts of the thermosensitive poly-N-isopropylacrylamide nanogel particles. The formulation showed good activity against the human cervical Henrietta Lacks cancer cell line. Therefore, there is a good chance that this temperature-responsive nanogel platform will find widespread use in the treatment of cancer. [59]

Aminoleslami *et al.,* synthesized a protonation and thermo-sensitive polymeric nanogel using N-vinylcaprolactam and acrylic acid monomers with triethylene glycol dimethacrylate with anticancer doxorubicin. The formulations were examined by different characterization techniques. The characterization process proved the development of formulation. The formulation showed good release of doxorubicin with proper anticancer properties.[60]

Fujii *et al.,* established the role of ribonucleic acid interference and targeted gene silencing process as good anticancer therapy techniques. In the work nanogel formulation was developed using small interfering vascular endothelial growth factor and small interfering ribonucleic acid using cholesterol-bearing cycloamylose with spermine group to target the tumor cells. Then the formulation showed good renal carcinoma activity.[61]

Wu *et al.,* developed biologically reduced heparin nanogel formed by reaction with cystamine bis acrylamide polymer. Then antitumor drug doxorubicin was loaded into the formulation which showed good tumor-targeted anticancer activity.[62]

Chen *et al.,* developed temperature and pH-sensitive self-assembled micellar paclitaxel nanogel using a combination of methoxy polyethyleneglycol 2000 and isopropylideneglycerol for the administration of anticancer drug. The drug release pattern showed 70 hours at pH 5.0, 10% at pH 7.4 and 10% at pH 9.0 from the structure. The nanogel showed good anticancer activity.[63]

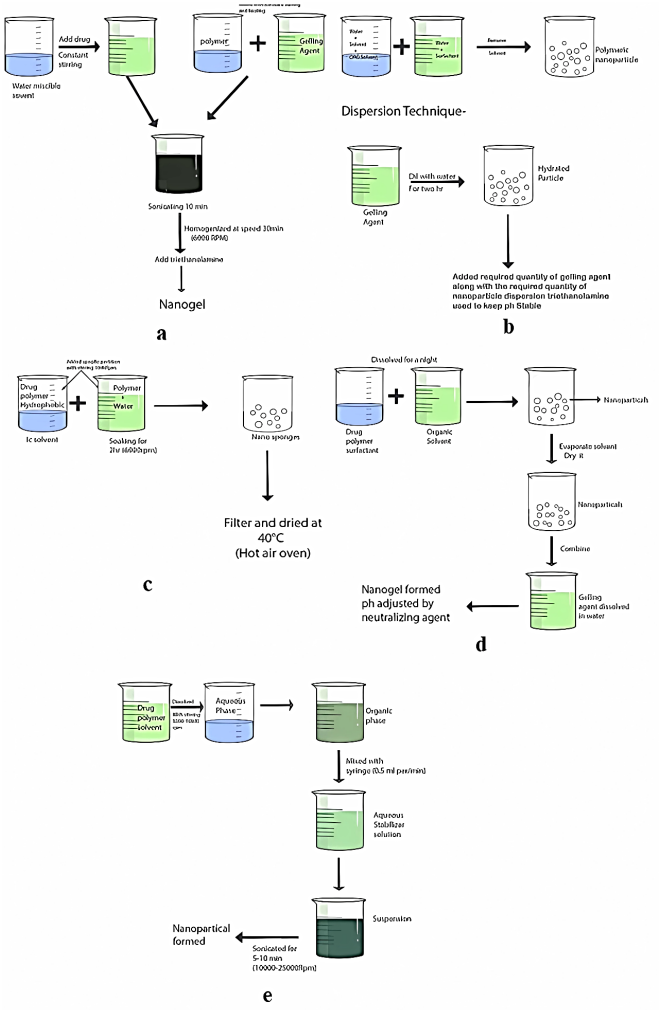

Figure 1: Methods of nanogel formation (a) Emulsification diffusion method (b) Nanoprecipitation method (c) Solvent evaporation method (d) Reverse micellar method (e) Modified diffusion emulsification method.

Su *et al.,* developed a protonation and thermocontrolled multifunctional nanogel using poly N-isopropyl acrylamide-co-acrylic acid nanogels. Doxorubicin was electrostatically adsorbed on the negatively charged nanogel at pH 7.4. The surface of the formulation was coated with fluorescent bovine serum albumin-encapsulated gold nanoclusters, which were then functionalized with the tumor-targeting peptide iRGD. The formulation showed improved anticancer activity. [64]

Pedrosa *et al.,* developed a crosslinked hyaluronic acid nanogel using 1,4-bis(3-[2-pyridyldithio]propionamido] butane crosslinking agent. Then the formulation was loaded with curcumin and simvastatin to assess the drug loading efficiency.[65]

Yang *et al.,* developed hybrid nanogel using artificial

polypeptide and cadmium selenium-zinc sulfur quantum dots. Both hydrophobic and hydrophilic drugs are simultaneously loaded in the quantum dot-polypeptide nanogel. Nanogel showed good cell toxicity against both human cervical Henrietta Lacks cancer cell line cells and mouse fibroblast cells.[66]

Yang and Zhao developed a glutathione-sensitive poly[methacrylic acid- co-poly(ethylene glycol) methyl ether methacrylate nanogel. The formulation was synthesized using poly(methacrylic acid-co-N,N-bis(acryloyl)cystamine copolymerized with polyethylene glycol methyl ether methacrylate was initially achieved by varying the length of Poly(ethylene glycol) methyl ether methacrylate. Then N, N-bis(acryloyl)cystamine was added to give PMAA-co-PEGMA glutathione-sensitive properties. The nanogel crosslinked with iron (III) to create a double-cross-linked $PMAA_{BACy}$/Fe(III)-co-PEGMA950 vehicle. The final carrier showed efficient release of anticancer drug.[67]

Bagde *et al.,* developed antioxidant quercetin and titanium dioxide-loaded nanogel for melanoma treatment. Here quercetin nanocrystals were homogenized with titanium dioxide to develop the final formulation. The nanogel formulation with 0.08 and 0.12% of quercetin showed good particle size of 249.65 and 352.48 nm, respectively. The zeta potentials of both formulations were -14.7 mV with near about 90% drug content values, respectively. The final rod-shaped crystals showed less than 400 nm-sized particles. The bioactivity profile of the formulations showed good activity against cancer and its associated inflammatory markers.[68]

Afzal *et al.,* developed a chia seed oil and resveratrol-loaded chia seed oil emulsified nanogel formulation. The best formulation showed 98.21 µg/cm^2/h of permeability (Figure 2). Topical application of nanogel on arthritis targets showed a marked decrease in inflammatory markers such as tumor necrosis factor-alpha, interleukin-6, interleukin-1 and cyclooxygenase-2 (Figure 3). These data confirmed the anti-inflammatory effects of the nanogel.[69]

Panonnummal *et al.,* developed an anticancer drug methotrexate-loaded chitin nanogel targeting psoriasis. In this work, chitin microgel, and methotrexate were incubated, and centrifuged followed by sonicating to obtain nanorange particles. Then rhodamine-123 dye was entrapped into the formulation using a centrifugation process. The methotrexate-loaded chitin nanogel showed a spherical shape with 196 nm particle size as well as good swelling and drug release pattern in an acidic medium. Elevated transdermal release showed good permeability of the formulation with good characteristics in the imiquimod (IMQ) induced psoriasis model.[70]

Panonnummal *et al.,* developed a chitin nanogel loaded with clobetasol for the treatment of psoriasis. The formulation was prepared by interacting clobetasol and chitin nanogel. Then the formulation was loaded with rhodamine 123 dye for fluorescent observation. The clobetasol-loaded chitin nanogel showed 132 nm particle size as well as good drug release pattern in an acidic medium. The formulation showed observable toxicities against human epidermal keratinocytes and monocyte cells with greater inhibitions against cyclooxygenase and

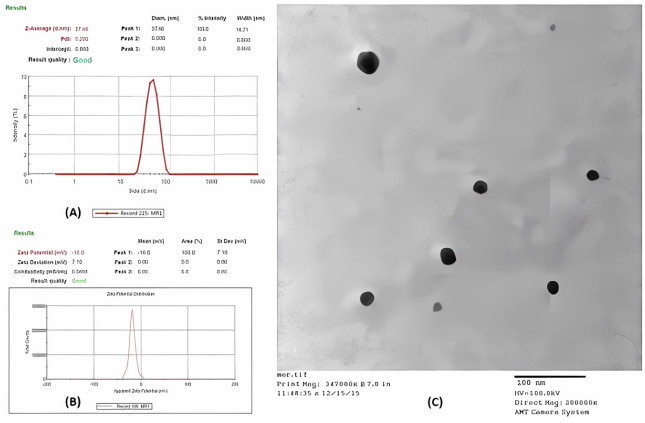

Figure 2: (A) Figure represents Particle Size Distribution; (B) TEM data; (C) Zeta Potential values.

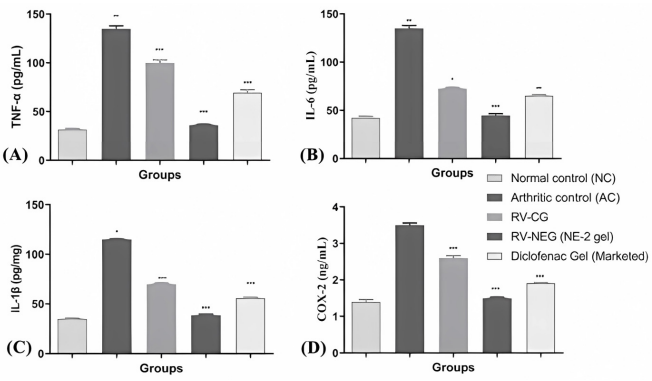

Figure 3: Examining the effects of various arthritic therapy groups on pro-inflammatory mediators in comparison to arthritic controls allows for the assessment of arthritis. (A) TNF-level. (B) Interleukin-6 concentration (C) Interleukin-1beta and (D) Cyclooxygenase-2 concentrations in joint tissue homogenized solution.

lipooxygenase enzymes. Furthermore, elevated transdermal release through stratum corneum and loosened epidermal layers showed good permeability of the formulation with good characteristics in the imiquimod (IMQ) induced psoriasis model.[71]

Wei *et al.,* developed curcumin nanogel as an antitumor agent with greater cellular uptake, and stability. The formulation was developed in different steps. First cholesteryl chloroformate reacted with 2,2′-(ethylenedioxy)-bis-ethylamine to obtain cholesteryl-amine linker. Then sodium hyaluronate reacted with a cholesteryl-amine linker to develop cholesteryl amine hyaluronic acid, which was further reacted with curcumin to form the final nanogel. The formulation showed good stability with optimized programmed cell death behavior and minimized cellular expression of nuclear factor kappa beta, tumor necrosis factor-alpha and cyclooxygenase-2 inflammatory responses.[72]

Yurdasiper *et al.,* developed a naproxen-loaded poly (N-isopropyl acrylamide) nanogel as a cyclooxygenase 2 enzyme modulator. The poly (N-isopropyl acrylamide) nanogel was prepared by the reaction of N-isopropyl acrylamide,

butyryl acetate, and N, N-methylene bisacrylamide in potassium persulfate solution. Then naproxen was added into the nanogel formulation. The formulation showed a two-fold increase in release of drug molecules from the epidermis with a decreased rate of inflammation.[73]

Khurana *et al.,* developed meloxicam nanogel using solid lipid nanoparticle process for efficient delivery through skin. The nanogel was developed upon reaction between carbopol 940 and meloxicam-solid lipid nanoparticle in triethanolamine solution. Then the formulation was characterized by entrapment efficiency, *in-vitro* skin occlusivity, and pharmacodynamic studies. The solid lipid nanoparticle gel showed good viscosity and elastic properties. Other interaction studies stated that the solid lipid nanoparticle nanogel and stratum corneum, increased the permeability of meloxicam through the dermal layer. This formulation showed good inflammatory inhibition and skin non-irritancy behaviour.[74]

DISCUSSION

Nanogels have distinctive and encouraging properties within the biomedical field because to their notable capability for drug encapsulation, uniformity, adjustable size, straightforward production, little toxicity, serum stability, and responsiveness to stimuli. This review outlined the methods of nanogel preparation with modifying shape and topology. Nanogel was prepared using different techniques such as emulsion solvent diffusion, nano precipitated method, emulsion evaporation of the solvent method, reverse micellar method and modified diffusion emulsification method. Thermosensitive nanogel, pH-sensitive nanogel, ultrasound-sensitive magnetic response, response to multiple stimuli, chain transfer polymerization, photo-induced crosslinking polymerization and modifications for active targeting are the types of nanogels based on response towards stimuli and polysaccharide, chitosan, pullulan, hyaluronic acid, alginate, cyclodextrin, gum acacia, protein are used to prepare nanogel. pH-sensitive nanogel made of polyethylene glycol and poly (maleic anhydride) copolymers (50:50 ratio) was cross-linked using gamma irradiation with anticancer properties, in another experiment 5-fluorouracil and photosensitizer indocyanine green were incorporated into large amounts of the thermosensitive acrylamide nanogel particles for the delivery of 5-fluorouracil, protonation and thermo controlled polymeric nanogel using copolymerizing N-vinyl caprolactam and acrylic acid monomers with anticancer doxorubicin, a dual temperature and protonation responsive self-assembled micellar nanogel using a combination of methoxy polyethyleneglycol 2000 and isopropylidene glycerol. Paclitaxel was loaded into nanogel using artificial polypeptide and cadmium selenium-zinc sulfur quantum dots. Both hydrophobic and hydrophilic drugs simultaneously loaded in the quantum dot-polypeptide nanogel with anticancer potential, antioxidant quercetin and titanium dioxide loaded nanogel for melanoma treatment. Here quercetin nanocrystals were homogenized with titanium dioxide to develop the final formulation with anticancer potential, chia seed oil and resveratrol loaded chia seed oil emulsified nanogel formulation with anti-inflammatory properties, methotrexate loaded chitin nanogel showed optimum release of anticancer drug. The characteristics of nanogels are contingent upon the constituent materials, whether they are synthetic or natural, as well as external factors such as protonation states, temperature, ionic behavior, or the inclusion of hydrophilic residues. The exceptional stability, biodegradability, biocompatibility, extensive surface area, and efficient manufacturing process of nanogels have resulted in their increased utilization as pharmaceutical drug carriers. This review has examined the many aspects pertaining to nanogel and their utilization in the field of biomedicine, including intracellular transportation of genetic material, targeted delivery of certain proteins, and the strategy of drug delivery. Due to the existing availability of clinical research and *in-vivo* uses of nanogels as nanogels have distinctive and encouraging characteristics within the biomedical field due to their notable capacity for drug encapsulation, uniformity, adjustable size, straightforward synthesis, limited toxicity, resilience in the presence of serum, and responsiveness to stimuli.

CONCLUSION

Nanogels, being a flexible and versatile drug carrier, have numerous applications in the pharmaceutical domain. Nanogels showed promise as a new type of bio-responsive delivery method due to their advantageous properties. In the case of cancer, skin illnesses, diabetes, etc., nanogel may transform the natural product into the most effective medication. The transdermal delivery of pharmaceuticals using these cross-linked nanogels has great potential, as it has been shown to increase patient compliance while causing fewer adverse effects. Nanogels have a higher penetration capability and greater bioavailability of the medicine. It can be concluded that nanogels are promising dosage form in targeted drug delivery that facilitate efficacy but minimizes toxicity or damage to adjacent organs.

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