A REVIEW ON NANOGEL: RECENT APPROACHES AS TARGETED DRUG DELIVERY

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Abstract

Nanogel is developed by dispersing hydrogel by physical and chemical cross-linking polymer at the nanoscale size. Nanogel has a unique combination of solid and liquid characteristics. It is hypothesized that the longer the nanoparticles remain in contact with the skin after being entrapped in a nanogel, the more effective the treatment will be. The present review was based on the techniques of preparation, evaluation, applications, advantages, and limitations of nanogel formulations as described in the articles from various reputed platforms i.e., Scopus, PubMed, Medline, Google Scholar etc. Nanogels are prepared by using various techniques i.e., Emulsion Solvent Diffusion, Nano-precipitated, Emulsion Solvent evaporation, Reverse micellar and Modified emulsification – diffusion. Nanogels are evaluated and characterized in terms of their physical appearances, pH, spread ability, particle size distribution, homogeneity. drug content, FTIR, SEM, viscosity, in-vitro drug release and stability. They do not show creaming, flocculation, coalescence & sedimentation that are inherent in the process. Based on behaviour of nanogels towards stimuli, nanogels are classified in major 5 types as described. As the smaller the particle size, the greater the surface area, and thus the greater the activity, nanogels have been useful in delivering the better action or potency of the medicine. In conclusion, nanogels are more efficient drug delivery pathway with targeted drug delivery. It is highly promising in new era of pharmaceutical drug design and development as it lowers the adverse effects/ toxicity by minimising its reach to adjacent organs.

Keywords: nanogel, preparation, evaluation, advantages, applications

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INTRODUCTION

Nanogel is developed by dispersing hydrogel by physical and chemical cross-linking polymer at the nanoscale size [1]. Nanogels typically have a size in the 20-200 nm range. In addition to their malleable size, high surface area, and high-water content, nanogels also exhibit bulging and degrading features. Nanogels allow for the controlled and sustained release of medicines. Nanogels' three-dimensional architecture made it simple to entrap pharmaceuticals, polymers, and liquid phases in suspension [2]. Nanogel holes are large enough to hold even large molecules. They take on the role of drug carriers, functioning as such because they are constructed to readily create biomolecular interactions such as salt bonds and hydrophobic or hydrogen bonding with physiologically active substances [3]. Nanogel has a unique combination of solid and liquid characteristics. It is hypothesized that the longer the nanoparticles remain in contact with the skin after being entrapped in a nanogel, the more effective the treatment will be [4].

The highly hydrated nature and shrinking-swelling capabilities of hydrogels are maintained in nanogels, which are a type of hydrogel. Because of their three-dimensional structure, they may encapsulate both hydrophobic and hydrophilic medicines within their internal network, shielding them from hydrolysis and enzymatic degradation whether in storage or circulation. Additionally, surface modification can increase the nanogels' circulation time and make them multifunctional and targeted [5].

Nanogel preparation techniques

The techniques of nanogel preparation can be broken down into two categories, chemical crosslinking and physical self-assembly, based on the distinct nanogel architectures and constituent building blocks [6].

1. Emulsion Solvent Diffusion

Using a water-miscible solvent and constant stirring (organic phase), the exact amount of the medication was dissolved. Polymer and gelling agent were dissolved in water using continuous stirring and heating, and the drug phase was then sonicated in an ultra-bath Sonicator for 10 minutes. The aqueous phase was homogenized at high speed for 30 minutes at 6000rpm while the drug phase was added drop by drop. A homogenizer turned the emulsion into a nanodroplet, creating the O/W emulsion. After homogenizing the O/W emulsion for an hour at 8000 rpm, triethanolamine was added while the mixture was being stirred constantly to create nanogel [7].

2. Nano-precipitated

Precipitation of the polymer occurs upon combining the organic phase, in which the drug and polymer have been solubilized in organic solvents, with the aqueous phase, which consists of water and surfactant. After the solvent was removed, polymeric nanoparticles were left behind. The dispersion technique was used to make the gel. For swelling, a gelling agent is diluted with water for two hours. After the particles were hydrated, the gelling agent was added along with the required quantity of nanoparticle dispersion. Triethanol-amine was used to keep the pH stable [8].

3. Emulsion Solvent evaporation

Over the course of 2 hours, the dispersion phase containing the drug and polymer in a water-immiscible solvent was introduced to a specific portion of the aqueous phase while being stirred at a speed of 1000 rpm by a magnetic stirrer. The resultant nano sponges were filtered out, dried in a hot air oven at 40 degrees Celsius for 24 hours, and then placed in vials for storage. Soaking the polymer in water for 2 hours prior to gel formation and then agitating it at 6000 rpm with a magnetic stirrer should yield a uniform dispersion. The pH was adjusted by adding a pH adjuster. Aqueous dispersion was then infused with the optimized nano sponge suspension and permeation enhancers [9].

4. Reverse micellar

Surfactant dissolved in an organic solvent with an additional polymer and medication. It took all night to mix in the cross-linking agent after it had been added. After the nanoparticles in the buffer have been purified, the next step is for the solvent to evaporate, leaving behind a dry bulk. Gelling agent was made by dissolving it in water. Nanogel was formed when the produced nanoparticles were combined with an aqueous phase containing a gelling agent. The pH was adjusted by the addition of a neutralizing agent [10].

5. Modified emulsification - diffusion

A measured quantity of the medication was blended with a polymer containing the solvent. The drug-polymer mixture is dissolved in the aqueous phase while being continuously stirred at a speed of 5000-10000 rpm, making up the organic phase. The organic phase was injected into the aqueous stabilizer solution using a syringe fitted with a needle at a rate of 0.5 ml/min. The resultant suspension was sonicated for 5-10 minutes after

being agitated for 6 minutes at 10,000-25,000 rpm. In order to stimulate diffusion of the organic solvent into a continuous phase, double-filtered water was added progressively to the dispersion while stirring continuously for 1 hour [11].

Evaluation of nanogels [12]

❖ **Physical appearances**

The colour, and appearance of any particles in the nanogel bases were visually evaluated.

❖ **Homogeneity**

The nanogel formulation's homogeneity was evaluated visually. The aggregates and overall appearance of the samples were evaluated.

❖ **Particle size and PDI**

The particle size, polydispersity index, and particle dispersion can be measured. Nanogels' average sizes were recorded after being measured using a Malvern Master Sizer 2000 MS and Zeta sizer.

❖ **pH range**

The nanogel formulation's pH was checked with digital pH meter. A fraction of the formulation was transferred to a beaker containing the measured amount of sterile water. The pH of the nanogel was measured by dipping an electrode into the solution.

❖ **Drug content**

High-performance liquid chromatography and a scanning UV spectrophotometer were used to determine the medication concentration in the final product.

❖ **Spread ability**

Two slides, each 5 cm2 in area, were used to measure this nanogel characteristic. In the middle of two slides, we set aside the 0.5g of the formulation for 1 minute. We compared the diameters of nanogel circles of several sizes.

❖ **Infrared spectroscopy**

Nanogel's infrared (IR) spectra were collected using an FT-IR spectrophotometer between 4000-400 cm-1.

❖ **Scanning Electron Microscopy**

Scanning electron microscopy at X30, X500, X1000, and X3000 magnifications with a 20kV electron beam was used to assess the surface morphology of the nanogel formulation. In order to observe samples under a scanning electron microscope, a droplet of nanoparticulate dispersion was placed on an aluminum metal plate and dried under vacuum to form a dry film.

❖ **Viscosity**

To calculate the nanogel formulation's viscosity, we ran it through a Brookfield Rheometer set to 10 rpm on spindle no. 64. The component was immersed in a bath of circulating water kept at 25 degrees Celsius by means of a thermostat. After calculating the viscosity, the mixture was poured into a thermostatically-controlled beaker. We recorded the values after letting the spindle move freely in the nanogel.

❖ **Drug release analysis (in-vitro)**

To examine the drug release in vitro, the formulation was tested in a Franz diffusion cell. A dialysis membrane was placed in the center of the Franz diffusion cell's donor-receptor chamber and the formulation was put on top. It was kept at a comfortable 30 degrees Celsius. The magnetic field was used to continuously stir the assembly in question. It was determined what percentage of the medication was freed from the nanogel.

❖ **Stability test**

The nanogel's stability was tested at an accelerated rate in accordance with ICH recommendations. Over the course of three months, the stability of topical nanogel was studied by keeping it in an environmental stability room set at 25 2°C and 60 5% RH. Amber glass vials were used to store the formulation inside the stability chamber after being sealed. After three months, the uniformity, drug content, and in-vitro drug release were evaluated.

Classification of nanogel

Based on behaviour of nanogels towards stimuli, they are classified as below-

Thermo-responsive

Among the most alluring intelligently responsive DDSs are thermo-responsive nanogels. Temperature-responsive nanogels exhibit shrinkage-swelling behavior in response to changes in their surrounding temperature, allowing for titratable drug release. Stimulated reduction in particle size may also improve intracellular absorption efficiency and accumulate in the disease-related microenvironment, both of which are beneficial to treatment results [13] [14][15].

pH-Responsive

The ionizing groups in the nanogel system are primarily responsible for its pH-dependent swelling-shrinking activity because they can deform by ionization or deionization depending on the pH value. There is evidence from studies comparing the pH of tumor tissue micro-environments (pH 6.5-7.2) and tumor cell

lysosomes and endosomes (pH 4.5-5.0 and pH 5.0-6.5, respectively) to the physiological pH of 7.4 in the blood circulation and normal tissues [16] [17] [18].

Ultrasound-Responsive

Drug delivery systems that utilise ultrasound (US) are popular for transdermal administration and the treatment of CNS diseases [33][34]. Based on the benefits of acoustic wave's deep penetration, a US-responsive delivery system was also introduced for anticancer therapy. The US agent perfluoro hexane (PFH) evaporated from liquid to gas upon application, aiding the induced drug release [19].

Magnetic-Responsive

Hyperthermia can be achieved by magnetic nanoparticles (MNPs) in the presence of an alternating magnetic field (AMF) [20][21], in addition to their use in magnetic-targeting in a strong magnetic field. Therefore, magnetic nanoparticles (MNPs) and temperature-sensitive nanogels were utilized in the construction of hybrid nanogels loaded with the chemical medication DOX. Because of their 3D network structure, nanogels can be used to co-encapsulate MNPs and chemical medicines. AMF ensures stimuli-drug release from nanogels because of their shrinking-swelling nature [22].

Multistimuli-Responsive

Since nanogels with dual- or multi-stimuli responsiveness can more reliably sustain the controlled drug release, they have gained considerable interest [23][24][25]. Significant progress has been made in the study of pH-temperature dual-sensitivity combinations and other multiresponsiveness combinations.

Modification of nanogels for facilitated targeting

Active targeting via modification of the nanogel's surface can further enhance drug accumulation in the disease location [26] in addition to the passive targeting capabilities offered by alterations in nanogel size, shape, or surface property. Using ligands that bind to specific receptors on cells or subcellular structures allows for targeted, active delivery. As an added step, NPs' surfaces were modified with biological ligands like small molecules, proteins, peptides, and polysaccharides [27].

➢ **Small molecule conjugation**

Folic acid has emerged as a promising target for anticancer targeted therapy due to its ability to selectively interact with cells that overexpress folate receptors (FRs). FRs are highly expressed in ovarian cancer tissues but are rarely expressed in normal human tissues. For tumor diagnosis and therapy, FR's differential expression in ovarian cancer and other tumor tissues makes it a promising biomarker [28].

➢ **Peptide conjugation**

Active targeting with certain peptide ligands has been studied intensively in recent years for use in treatment and diagnostics. The tumor-homing peptide LyP-1, for example, was found to interact preciously with the p32 protein of a variety of tumor cells, suggesting that it would be possible to improve tumor targeting by conjugating this peptide with nanoparticles. Treatment with these modified nanoparticles has also been shown to improve therapeutic outcomes in our prior work using photo-thermotherapy, photo-chemotherapy, and photo-immunotherapy [29][30].

➢ **Antibody conjugation**

Antibody-modified nanogels demonstrate a stronger affinity for binding sites, allowing them to achieve higher targeting and precision, in comparison to receptors on the surface of tumor cells [31]. In addition to their use as ligands, antibodies have also been put to use as therapeutic agents in cancer treatment. Antibody-dependent cell-mediated cytotoxicity for instance, has been shown to suppress cellular signalling pathways involved in tumor development and initiation [32].

➢ **Biomembrane Camouflaged**

Exposure of nanoparticles to a biological environment always results in the formation of a protein corona on their surface. Protein corona has been shown to dampen the potency of tumor-targeting ligands in some investigations [33]. While in vivo corona formation can reduce the targeting potential of ligands, some recent investigations have shown that this reduction can be mitigated. The protein corona that forms on the ligand-modified nanoparticle is thought to improve targeting, but it is not known how [34].

In recent research, a novel approach to targeted delivery using nanomedicine that is hidden by bio membranes has been devised. DDSs that have been "hidden" within a membrane mimic the look and behaviour of biological membranes [35]. They showed greater penetration through physiological barriers, more precise accumulation, longer circulation time, and increased drug efficacy compared to traditional ligand-modified delivery systems [36].

Advantages

Nanogels have several advantages over other dosage forms [37] that includes as below –

- Nanogel has a greater surface area & free energy that make them more efficient to transport.
- They do not show creaming, flocculation, coalescence & sedimentation that are inherent in the process.
- It comes in a variety of forms, including foams, creams, liquids, and sprays.
- They are non-poisonous & non-irritant.
- If it contains biocompatible surfactants then it can be taken by mouth.
- It is better for human and veterinary uses.
- It improves the uptake of hydrophilic substances in cell cultures.
- It can be used to replace liposomes, vesicles, and lamellar liquid crystalline phases.

Limitations [38][39]

- Removing the surfactant and solvent at the conclusion of preparation is an expensive step.
- The presence of even small amounts of polymers or surfactants in the body has the potential to cause harm.
- Third, insufficient medication loading capacity and poor control over drug release.
- Fourth, the nanogel matrix may become more hydrophilic as a result of the drug-polymer interaction, permanently trapping the drug molecules within the matrix.

Applications

It is effective in delivery of following types of drugs-

Synthetic polymers or natural biopolymers with crosslinked structures make up the bulk of nanogel systems. Small molecules or biomacromolecules can be incorporated into nanogels thanks to the porous 3D network. The use of polymeric nanogels as drug carriers has many benefits, including the ability to artificially regulate medication dosage in response to environmental stimuli, protection from the unpleasant odour of pharmaceuticals, increased therapeutic efficacy, and decreased unwanted effects [40].

These are following mentioned reasons why we have chosen the formulation of nanogel-

1. Delivery of small molecules

Because to their water solubility, biocompatibility, and biodegradability as well as their encapsulation stability and intelligent release, nanogels show considerable promise as DDSs. Nanogel research now focuses on stabilising protein medicines for more precise therapeutic delivery to tumours [41] [42]. Changes in swelling and collapsing in response to environmental stimuli could easily accomplish drug entrapment and controlled release.

2. Delivery of macromolecules

Large molecular weight, complex structure, and biological functions distinguish biological macromolecules from chemical medications; yet, these features also make it difficult to control bio-macromolecule stability and permeability [43]. Nanogels, which are made up of nanoscale hydrogels, have an outstanding drug-loading capacity, stability, and hydrophilicity, and hence have the potential to be good carriers [44].

Protein delivery

Proteins need to be pharmaceutically changed for therapeutic use since they are notoriously unstable, poorly permeable, easily degraded by enzymes, and have short half-lives. Controlling drug release and extending drug retention duration can be achieved through encapsulation in various polymers [45]. Nanogels were developed to administer insulin, and both natural (e.g., chitosan, dextran, alginate) and synthetic polymers proved to be bio-compatible, permeable, and responsive to glucose. These oral nanogels' exceptional benefits have allowed for significant effects on hypoglycemia. Oral insulin administration was found to increase patient compliance compared to insulin injection [70], despite the presence of epithelial barriers in the gastrointestinal system [46][47].

Nucleic acid delivery

Certain hereditary illnesses can be treated in very specific ways by administering therapeutic DNA or RNA sequences, a process known as gene therapy. Due to their potent capacity to silence genes and effectively and selectively block gene expression [48], small interfering RNA (siRNA) applications have become an essential therapeutic for gene-related disorders. However, siRNAs are limited in their usefulness due to features like their poor transfection rates and short half-lives due to rapid enzymatic destruction [49]. This is because, as nucleic acids, siRNAs are negatively charged hydrophilic molecules that cannot permeate the cell membrane. When treating nucleic acids, adding cholesterol to bare siRNA, loading it into liposomes, or joining it to polymer nanoparticles are all potential solutions to these issues [50].

3. In combinational chemotherapy

Improved therapeutic benefits can be achieved through the coadministration of numerous chemo-therapeutic medicines in a process known as combination chemotherapy [51]. This process often involves the use of appropriate nanocarriers to

deliver pharmaceuticals in proportion to the disease site. When compared to standard, single-drug chemotherapy, there are benefits to using a combination approach. First, the lower dose of the medicine used in combinational therapy compared to single administration can help reduce the toxicity and unwanted effects of the chemotherapeutic agents. Second, because chemotherapeutic medicines work in different ways, many therapeutic targets would be stimulated at once, which would slow the spread of drug resistance [52].

4. Photo chemotherapy

Phototherapies have been used extensively to treat skin illnesses (including lupus) and malignancies [53][54] since the turn of the 20th century. Both photodynamic therapy (PDT) and photothermal therapy are considered to be valid phototherapies at the present time (PTT). Whereas photothermal therapy (PTT) makes use of photon energy to directly heat tumours, photodynamic therapy (PDT) makes use of photosensitizers (PSs) to generate cytotoxic reactive oxygen species and trigger cancer cell death [55]. Non-invasiveness, great selectivity, and few side effects are only a few of the ways in which phototherapies excel over radiation and chemotherapy [56][57].

Photothermal chemotherapy

PTT has developed as a revolutionary way to eradicate numerous types of cancer due to its simplicity, minimum nature, and low systemic toxicity [58]. In PTT, NIR light is absorbed, transformed to heat via a photothermal agent, and then used to kill cancer cells. Most importantly, research shows that PTT and chemotherapy together can boost the effectiveness of cancer treatment [59][60]. Effective medication uptake by cells, increased drug release, and better therapeutic outcomes were all brought about by hyperthermic circumstances. Increased cellular membrane permeability is another benefit of chemo-photothermal combination therapy [61][62].

Photodynamic chemotherapy

Its ability to induce cancer cell death on a regional scale has made it a promising antitumor strategy [63]. The primary mechanism by which PDT induces tumour cell apoptosis and death is the use of light at appropriate wavelengths to activate PSs, whereupon energy is transferred from activated PSs to molecular oxygen, resulting in the production of highly toxic reactive oxygen species (ROS), particularly singlet oxygen [64][65]. The clinical utility of PDT is severely constrained, especially in hypoxic solid tumours, since most PDT processes are oxygen-dependent and oxygen is continuously consumed during PDT [66]. PDT is less effective because the laser can only reach a small depth into the tumour [67]. In order to achieve synergistic anticancer effects, PDT and chemotherapy can be used together. Combination chemo-photodynamic therapy has made use of nanogels as a multipurpose delivery platform [68].

CONCLUSION

As the smaller the particle size, the greater the surface area, and thus the greater the activity, nanogels have been useful in delivering the better action or potency of the medicine. Hydrogel properties allow nanogels to accommodate a massive quantity of water, which in turn increases their drug loading capacities, imparts tissue-like properties, and makes them flexible; nanometric particle size allows nanogels to enter deeper tissues, escape invasion by the reticuloendothelial system, provide site-specific delivery, etc.

In conclusion, nanogels are more efficient drug delivery pathway with targeted drug delivery. It is highly promising in new era of pharmaceutical drug design and development as it lowers the adverse effects/ toxicity by minimising its reach to adjacent organs.

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Nil.

CONFLICT OF INTEREST

Authors have been declared for ‘none’ conflict of interest.

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