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# DEVELOPMENT AND APPLICATION OF NANOGELS IN DRUG DELIVERY

**[1]Nikhil Mahadev Kause, [2]Dr. Prasad G. Ghugarkar.**
**[1]Student, [2]Professor**
**PHARMACY**
**Dr. NJ. Paulbudhe College of Pharmacy, Ahmednagar.**

**Abstract**

Nanogels are produced through the dispersion of hydrogel using both physical and chemical cross-linking polymers on a nanoscale. These nanogels exhibit a distinctive blend of solid and liquid properties. It is postulated that prolonged contact between nanoparticles and the skin, when trapped within a nanogel, enhances the effectiveness of treatment. This review is based on the techniques for preparing, assessing, applications, advantages, and limitations of nanogel formulations as discussed in articles from reputable sources such as Scopus, PubMed, Medline, Google Scholar, and others.

Various methods, including Emulsion Solvent Diffusion, Nano-precipitation, Emulsion Solvent Evaporation, Reverse Micellar, and Modified Emulsification-Diffusion, are employed to create nanogels. These nanogels undergo evaluation and characterization based on physical attributes, pH, spreadability, particle size distribution, homogeneity, drug content, FTIR, SEM, viscosity, in-vitro drug release, and stability. Importantly, they exhibit no creaming, flocculation, coalescence, or sedimentation, which are inherent issues in the manufacturing process.

Nanogels are classified into five major types based on their responsiveness to stimuli. Notably, smaller particle sizes offer larger surface areas, resulting in increased activity. This makes nanogels valuable for enhancing the efficacy and potency of medicines. In summary, nanogels represent an efficient pathway for drug delivery with targeted precision. They hold significant promise in the field of pharmaceutical drug design and development, as they can reduce adverse effects and toxicity by limiting their impact on adjacent organs.

**Keywords:** Nanogel, Preparation, Evaluation, Advantages, Applications

## Introduction

The nanogel, a product of dispersing hydrogel through physical and chemical cross-linking polymers at the nanoscale, typically falls within the 20-200 nm size range [1]. Beyond their adaptable size, nanogels possess notable attributes such as a high surface area, substantial water content, and the ability to swell and degrade. They offer a platform for the controlled and sustained release of pharmaceuticals. The three-dimensional structure of nanogels simplifies the entrapment of pharmaceuticals, polymers, and liquid phases [2]. Notably, nanogels have cavities spacious enough to accommodate even large molecules, and they serve as effective drug carriers due to their ability to readily form biomolecular interactions, including salt bonds and hydrophobic or hydrogen bonding with physiologically active substances [3]. The remarkable aspect of nanogels lies in their unique blend of solid and liquid characteristics. There is a hypothesis that prolonged contact of nanoparticles with the skin, once encapsulated within a nanogel, could enhance the effectiveness of treatment [4].

Nanogels, a subclass of hydrogels, preserve the water-rich nature and the ability to shrink and swell, characteristic of hydrogels. Their three-dimensional framework allows them to encapsulate both hydrophobic and hydrophilic drugs within their internal network, safeguarding them against hydrolysis and enzymatic breakdown during storage or circulation. Moreover, surface modifications can extend the circulation duration of nanogels and imbue them with multifunctionality and targeting capabilities [5].

**Nanogels preparation techniques:**

Nanogel preparation methods can be categorized into two groups: chemical crosslinking and physical self-assembly, which are distinguished by the specific nanogel structures and building components involved [6].

**1. Emulsion Solvent Diffusion**

The medication was dissolved in a water-miscible solvent with continuous stirring in the organic phase. Simultaneously, the polymer and gelling agent were dissolved in water through continuous stirring and heating. The drug phase was then subjected to sonication in an ultra-bath Sonicator for 10 minutes. As the drug phase was added drop by drop, the aqueous phase was homogenized at high speed for 30 minutes at 6000rpm. A homogenizer transformed the emulsion into nanodroplets, forming an O/W emulsion. Following an hour of homogenization at 8000 rpm, triethanolamine was introduced while the mixture was continuously stirred to produce the nanogel [7].

**2. Nano-precipitated:**

The polymer precipitates when the organic phase, containing the drug and polymer dissolved in organic solvents, is mixed with the aqueous phase, composed of water and a surfactant. After removing the solvent, polymeric nanoparticles remain. A dispersion technique is employed to create the gel. To induce swelling, a gelling agent is mixed with water for a duration of two hours. Once the particles are hydrated, the gelling agent is added, along with the necessary amount of nanoparticle dispersion. Triethanolamine is utilized to maintain a stable pH [8].

**3. Emulsion Solvent evaporation:**

Over a span of 2 hours, the dispersion phase, which contains the drug and polymer dissolved in a water-immiscible solvent, was gradually introduced into a specific part of the aqueous phase while being stirred at 1000 rpm using a magnetic stirrer. The resulting nano sponges were separated through filtration, dried in a hot air oven at 40 degrees Celsius for 24 hours, and subsequently stored in vials. To ensure a uniform dispersion, the polymer was soaked in water for 2 hours before gel formation and agitated at 6000 rpm with a magnetic stirrer. The pH was adjusted by incorporating a pH modifier, and the aqueous dispersion was infused with the optimized nano sponge suspension and permeation enhancers [9].

**4. Reverse micellar:**

An organic solvent was used to dissolve surfactant, along with an extra polymer and medication. Mixing in the cross-linking agent took an entire night after its addition. Following the purification of nanoparticles in a buffer, the subsequent step involved evaporating the solvent, resulting in a dry bulk material. The gelling agent was created by dissolving it in water. Nanogel formation occurred when these produced nanoparticles were combined with an aqueous phase containing a gelling agent. The pH was regulated by the introduction of a neutralizing agent [10].

**5. Modified emulsification - diffusion:**

A measured amount of the medication was mixed with a polymer in the presence of a solvent. This drug-polymer blend was dissolved in an aqueous phase while continuously stirring at a speed ranging from 5000 to 10000 rpm, forming the organic phase. Using a syringe equipped with a needle, the organic phase was slowly injected into the aqueous stabilizer solution at a rate of 0.5 ml/min. After agitation for 6 minutes at speeds ranging from 10,000 to 25,000 rpm, the resulting suspension was sonicated for 5-10 minutes. To encourage the organic solvent's diffusion into the continuous phase, double-filtered water was gradually added to the dispersion while continuously stirring for 1 hour [11].

**Evaluation of nanogels** [12]

**Physical appearances:** The nanogel base was visually assessed for the color and appearance of any particles it contained.

**Homogeneity**: Visual assessment was conducted to evaluate the homogeneity of the nanogel formulation. The samples were examined for aggregates and overall appearance.

**Particle size and PDI:** The measurement of particle size, polydispersity index, and particle dispersion can be performed. The average sizes of the nanogels were determined using a Malvern Master Sizer 2000 MS and a Zeta sizer.

**pH range:** The pH of the nanogel formulation was assessed using a digital pH meter. A portion of the formulation was mixed with a specified volume of sterile water in a beaker, and the nanogel's pH was determined by immersing an electrode into the solution.

**Drug content:** The medication concentration in the final product was analyzed using high-performance liquid chromatography and a scanning UV spectrophotometer.

**Spread ability:** We utilized two slides, each with a 5 cm2 area, to assess this specific property of the nanogel. Within the central region of the two slides, we placed 0.5g of the formulation for a duration of 1 minute. Subsequently, we compared the diameters of several nanogel circles.

**Infrared spectroscopy:** Infrared (IR) spectra of the nanogel were obtained using an FT-IR spectrophotometer within the range of 4000-400 cm-1.

**Scanning Electron Microscopy:** The surface morphology of the nanogel formulation was examined using scanning electron microscopy at magnifications of X30, X500, X1000, and X3000, with a 20kV electron beam. To observe the samples under the scanning electron microscope, a droplet of nanoparticulate dispersion was deposited onto an aluminum metal plate and then subjected to vacuum drying to create a dry film.

**Viscosity:** In order to determine the viscosity of the nanogel formulation, we passed it through a Brookfield Rheometer equipped with spindle no. 64, operating at 10 rpm. The instrument was placed in a temperature-controlled water bath at 25 degrees Celsius maintained by a thermostat. Following the viscosity measurement, the mixture was transferred to a temperature-regulated beaker, and we recorded the values after allowing the spindle to move freely within the nanogels.

**Drug release analysis (in-vitro):** In order to study the in vitro drug release, the formulation was subjected to testing using a Franz diffusion cell. A dialysis membrane was positioned within the center of the donor-receptor chamber of the Franz diffusion cell, and the formulation was applied on top of it. The setup was maintained at a constant temperature of 30 degrees Celsius, with continuous stirring achieved by a magnetic field. The objective was to assess the percentage of medication released from the nanogel.

**Stability test:** The stability of the nanogel was assessed following the accelerated testing guidelines outlined by ICH recommendations. Over a period of three months, the stability of the topical nanogel was examined by placing it in an environmental stability room set at 25 ± 2°C and 60 ± 5% relative humidity. The formulation was stored in sealed amber glass vials within the stability chamber. After the three-month duration, assessments were conducted to evaluate uniformity, drug content, and in-vitro drug release.

**Classification of nanogel:**

Nanogels are categorized into the following groups based on their responsiveness to stimuli-

**Thermo-responsive:** One of the most fascinating types of smart drug delivery systems is thermo-responsive nanogels. These nanogels display a shrinkage-swelling behavior in reaction to alterations in temperature, making them capable of controlled drug release. Additionally, the reduction in particle size when stimulated may enhance their intracellular absorption and accumulation in disease-related areas, contributing positively to treatment outcomes [13] [14][15].

**pH-Responsive:** The ionizable groups within the nanogel system play a central role in its pH-responsive swelling and shrinking behavior, as they can change their structure through ionization or deionization in response to the pH level. Research has provided evidence by comparing the pH of tumor tissue microenvironments (ranging from pH 6.5 to 7.2) and the pH of tumor cell lysosomes and endosomes (pH 4.5 to 5.0 and pH 5.0 to 6.5, respectively) with the physiological pH of 7.4 in the bloodstream and normal tissues [16] [17] [18].

**Ultrasound-Responsive:** Ultrasound (US)-based drug delivery systems are widely adopted for transdermal delivery and the management of central nervous system (CNS) diseases [33][34]. Leveraging the advantages of acoustic waves, an ultrasound-responsive drug delivery system was introduced for anticancer treatment. In this system, the ultrasound agent perfluoro hexane (PFH) transitioned from a liquid to a gas state upon application, facilitating controlled drug release [19].

**Magnetic-Responsive:** Hyperthermia can be induced using magnetic nanoparticles (MNPs) when exposed to an alternating magnetic field (AMF) [20][21]. MNPs are also employed in magnetic targeting under the influence of a strong magnetic field. As a result, a combination of magnetic nanoparticles (MNPs) and temperature-sensitive nanogels was employed to create hybrid nanogels loaded with the chemical medication DOX. The 3D network structure of nanogels allows for the co-encapsulation of both MNPs and chemical drugs. The alternating magnetic field (AMF) plays a pivotal role in triggering drug release from nanogels due to their responsive swelling and shrinking behavior [22].

**Multistimuli-Responsive:** Nanogels exhibiting dual- or multi-stimuli responsiveness have garnered significant attention due to their enhanced capability to maintain controlled drug release [23][24][25]. Substantial advancements have been achieved in the investigation of dual-sensitivity combinations such as pH-temperature responsiveness and other multi-responsive systems.

**Modification of nanogels for facilitated**

**targeting:**

Enhancing drug accumulation in the disease site can be further achieved through active targeting by modifying the surface of the nanogel [26]. This complements the passive targeting abilities achieved by altering the nanogel's size, shape, or surface properties. Active delivery is facilitated by incorporating ligands that can bind to specific receptors on cells or subcellular structures. Additionally, the surfaces of nanoparticles (NPs) were modified with biological ligands, including small molecules, proteins, peptides, and polysaccharides, as an additional step [27].

**Small molecule conjugation:** Folic acid has become a compelling candidate for targeted anticancer therapy because of its capacity to selectively interact with cells that overexpress folate receptors (FRs). Ovarian cancer tissues exhibit high levels of FR expression, whereas normal human tissues rarely express FRs. This distinct differential expression of FRs in ovarian cancer and other tumor tissues holds promise as a valuable biomarker for tumor diagnosis and therapy [28].

Peptide conjugation: Recent research has focused extensively on the exploration of active targeting using specific peptide ligands for both therapeutic and diagnostic purposes. For instance, the tumor-targeting peptide LyP-1 has demonstrated a strong interaction with the p32 protein found in various tumor cells, indicating the potential to enhance tumor targeting by attaching this peptide to nanoparticles. Our previous studies have shown that treatment with these modified nanoparticles can lead to enhanced therapeutic outcomes in the context of photo-thermotherapy, photo-chemotherapy, and photo-immunotherapy [29][30].

**Antibody conjugation:** Nanogels modified with antibodies exhibit a heightened affinity for binding sites, enabling them to achieve superior targeting and precision when compared to receptors present on the surface of tumor cells [31]. Besides their role as ligands, antibodies have been employed as therapeutic agents in the context of cancer treatment. For example, antibody-dependent cell-mediated cytotoxicity has been demonstrated to inhibit cellular signaling pathways associated with tumor growth and initiation [32].

**Biomembrane Camouflaged:** When nanoparticles are exposed to a biological environment, they invariably develop a protein corona on their surface. Some studies have indicated that this protein corona can diminish the effectiveness of tumor-targeting ligands [33]. While in vivo corona formation may reduce the targeting capacity of ligands, recent research suggests that this reduction can be mitigated. Although the protein corona formed on ligand-modified nanoparticles is believed to enhance targeting, the exact mechanisms remain unclear [34].

In recent investigations, a novel approach to targeted delivery using nanomedicine has been developed, where drug delivery systems (DDSs) are "hidden" within a membrane to mimic the appearance and behavior of biological membranes. These concealed DDSs have demonstrated superior penetration through physiological barriers, more precise accumulation, extended circulation time, and improved drug efficacy in comparison to traditional ligand-modified delivery systems [35][36].

**Advantages:**

Nanogels offer several advantages over other dosage forms [37], including:

- Greater surface area and free energy, making them more efficient for transportation.

- Absence of issues like creaming, flocculation, coalescence, and sedimentation, which are often associated with other processes.

- Versatility in terms of available forms, such as foams, creams, liquids, and sprays.

- Non-toxic and non-irritating properties.

- Potential for oral administration when containing biocompatible surfactants.

- Suitable for both human and veterinary applications.

- Enhanced uptake of hydrophilic substances in cell cultures.

- The ability to replace traditional delivery systems like liposomes, vesicles, and lamellar liquid crystalline phases.

**Limitations** [38][39]:

- The costly process of surfactant and solvent removal upon completion of preparation.

- The potential for harm when even small amounts of polymers or surfactants are present in the body.

- Limited medication loading capacity and inadequate control over drug release.

- The possibility of the nanogel matrix becoming more hydrophilic due to drug-polymer interactions, resulting in the permanent entrapment of drug molecules within the matrix.

**Applications:**

Nanogels are effective for the delivery of various types of drugs. These systems primarily consist of synthetic polymers or natural biopolymers with crosslinked structures, forming the basis of nanogel systems. Their porous 3D network allows for the incorporation of small molecules or biomacromolecules. Utilizing polymeric nanogels as drug carriers offers several advantages, including the ability to finely control medication dosage in response to environmental stimuli, masking the unpleasant odors associated with pharmaceuticals, enhancing therapeutic effectiveness, and reducing undesirable side effects [40].

We have selected nanogel formulations for the following reasons:

**1. Delivery of small molecules:**

Nanogels hold significant promise as drug delivery systems (DDSs) due to their water solubility, biocompatibility, biodegradability, as well as their ability to encapsulate drugs with stability and provide intelligent release mechanisms. Current research in nanogels is aimed at enhancing the stability of protein-based medicines for more precise and effective delivery to tumor sites [41][42]. Their ability to respond to environmental stimuli by swelling and collapsing allows for efficient drug entrapment and controlled release.

**2. Delivery of macromolecules:**

Biological macromolecules possess distinctive characteristics such as large molecular weight, complex structure, and vital biological functions. However, these characteristics can pose challenges in terms of controlling the stability and permeability of biomacromolecules [43]. Nanogels, composed of nanoscale hydrogels, exhibit exceptional drug-loading capacity, stability, and hydrophilicity, making them promising candidates for effective macromolecule carriers [44].

**Protein Delivery:**

Proteins require pharmaceutical modification for therapeutic use due to their well-known instability, limited permeability, vulnerability to enzymatic degradation, and short half-lives. One way to control drug release and prolong drug retention is by encapsulating proteins in various polymers [45]. Nanogels were specifically designed for the delivery of insulin, with both natural (such as chitosan, dextran, and alginate) and synthetic polymers proving to be biocompatible, permeable, and responsive to glucose levels. The remarkable advantages of these oral nanogels have demonstrated significant effects in managing hypoglycemia. Oral insulin administration has shown improved patient compliance compared to insulin injections, even in the presence of epithelial barriers in the gastrointestinal system [46][47].

**Nucleic Acid Delivery:**

Certain genetic disorders can be specifically addressed through gene therapy, which involves administering therapeutic DNA or RNA sequences. Small interfering RNA (siRNA) has become a crucial therapeutic approach for gene-related disorders due to its potent ability to silence genes and selectively block gene expression [48]. However, siRNAs have limitations, including poor transfection rates and short half-lives due to rapid enzymatic degradation [49]. This is because siRNAs are hydrophilic, negatively charged molecules that cannot easily cross cell membranes. When dealing with nucleic acids, potential solutions to these challenges include incorporating cholesterol into naked siRNA, loading it into liposomes, or attaching it to polymer nanoparticles [50].

**3. In Combination Chemotherapy:**

Enhanced therapeutic outcomes can be achieved by simultaneously administering multiple chemotherapeutic drugs, a strategy known as combination chemotherapy [51]. This approach frequently requires the use of suitable nanocarriers to deliver the pharmaceuticals specifically to the disease site. When compared to conventional single-drug chemotherapy, there are advantages to adopting a combination approach. Firstly, the lower dosage of medication used in combination therapy can reduce the toxicity and adverse effects of the chemotherapeutic agents. Secondly, since chemotherapeutic drugs operate through diverse mechanisms, multiple therapeutic targets can be engaged simultaneously, potentially slowing the development of drug resistance [52]..

**4. Phototherapy for Cancer Treatment:**

Phototherapies have been extensively employed to treat skin disorders, including lupus, and malignancies since the early 20th century [53][54]. Currently, two prominent phototherapies are in use: photodynamic therapy (PDT) and photothermal therapy (PTT). In PTT, photon energy is harnessed to directly heat tumors, while PDT utilizes photosensitizers (PSs) to generate cytotoxic reactive oxygen species, leading to the death of cancer cells [55]. Phototherapies offer advantages such as non-invasiveness, high selectivity, and minimal side effects, setting them apart from radiation and chemotherapy as effective treatment options [56][57].

**Photothermal Therapy for Cancer:**

Photothermal therapy (PTT) has emerged as a groundbreaking approach to eliminate various cancer types, thanks to its simplicity, minimally invasive nature, and low systemic toxicity [58]. In PTT, near-infrared (NIR) light is absorbed, converted into heat by a photothermal agent, and utilized to destroy cancer cells. Notably, research indicates that combining PTT with chemotherapy can enhance the effectiveness of cancer treatment [59][60]. This combination leads to improved drug uptake by cells, enhanced drug release, and superior therapeutic outcomes in hyperthermic conditions. Additionally, chemo-photothermal combination therapy offers the advantage of increased cellular membrane permeability [61][62].

**Photodynamic Therapy for Cancer:**

Its ability to induce localized cancer cell death has positioned photodynamic therapy (PDT) as a promising anti-tumor strategy [63]. The primary mechanism by which PDT triggers apoptosis and death in tumor cells involves the use of light at specific wavelengths to activate photosensitizers (PSs). This activation leads to energy transfer from activated PSs to molecular oxygen, generating highly toxic reactive oxygen species (ROS), particularly singlet oxygen [64][65]. However, the clinical utility of PDT is limited, especially in hypoxic solid tumors, as most PDT processes rely on oxygen, which is continuously consumed during PDT [66]. Furthermore, the effectiveness of PDT is constrained because the laser can only penetrate a limited depth into the tumor [67]. To achieve synergistic anticancer effects, PDT and chemotherapy can be combined, with nanogels serving as a versatile delivery platform for combination chemo-photodynamic therapy [68].

**CONCLUSION:**

The utilization of nanogels has proven to be a valuable approach in enhancing the effectiveness and potency of drug delivery, primarily due to their smaller particle size, resulting in a larger surface area and increased activity. The inherent hydrogel properties of nanogels enable them to absorb significant amounts of water, thus boosting their drug loading capacity, imparting tissue-like characteristics, and rendering them flexible. Their nanoscale dimensions facilitate deeper tissue penetration, evasion of the reticuloendothelial system, and the provision of site-specific drug delivery, among other benefits.

In summary, nanogels represent a more efficient pathway for drug delivery with a focus on targeted drug delivery. They hold great promise in the evolving field of pharmaceutical drug design and development by minimizing adverse effects and toxicity, thereby reducing their impact on adjacent organs.

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