AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

An Overview Of Nanogel In Pharmaceutical Science

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ABSTRACT

The term "nanogel" describes hydrogel nanoparticles composed of cross-linked hydrophilic polymer networks. This review highlights the various types, applications, and evaluation strategies for nanogels, which are emerging as a highly promising platform for drug delivery. Nanogels demonstrate significant potential in areas such as chemotherapy, diagnostics, targeted organ delivery, and the administration of bioactive compounds. While conventional macroscopic gels react to environmental stimuli relatively slowly and often face challenges like poor pharmacokinetics, limited in vivo stability, and potential toxicity, nanogels and other nanoscale carriers are helping to overcome these limitations. These nanoparticles can selectively swell or collapse in response to external pH changes, offering precise control over drug release. Nanogel formulations represent a convergence of advanced technology and herbal therapeutics, providing innovative delivery systems for herbal drugs due to their high encapsulation efficiency, uniformity, low toxicity, and enhanced stability. This article primarily reviews general strategies and recent advancements in the field. Nanogels are notable for their uniform size, tunable dimensions, minimal toxicity, stability in serum, and responsive behavior, along with high drug-loading capacity. Additionally, current biomedical applications and ongoing clinical trials involving nanogels are briefly summarized. The discussion focuses on different types of nanogels, their synthesis methods, and mechanisms of drug release. Overall, nanogels have gained significant attention as versatile drug delivery systems, particularly for site-specific and controlled release of therapeutic agents.

Keywords: Nanogel, Pharmaceutical Science

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Received 22 October 2025, Accepted 05 October 2025

Please cite this article as: Gatkal SA *et al*., An Overview Of Nanogel In Pharmaceutical Science . American Journal of PharmTech Research 2025.

INTRODUCTION

Nanogels are nanosized particles formed through physical or chemical crosslinking of polymers. The concept was first introduced using cross-linked bifunctional networks composed of a polyion and a non-ionic polymer for the delivery of polynucleotides. While nanogels have been applied in areas such as sensing, diagnostics, and bioengineering, their most significant impact lies in drug delivery.

Compared to macroscopic drug delivery systems, nanogels and other nanoscale carriers offer several advantages, particularly in controlled drug release. This property is especially valuable in cancer therapy, where the size of the carrier allows it to target tumors through the enhanced permeability and retention (EPR) effect. Targeting can be further enhanced by conjugating ligands or antibodies to the nanocarrier surface, enabling it to recognize disease-specific features such as overexpressed proteins or enzymes.

Nanogels consist of porous networks that can encapsulate small molecules or macromolecules. They exhibit swelling and degradation properties, possess a flexible size range, large surface area, and high water content. These characteristics allow nanogels to deliver biologically active agents in a controlled and sustained manner. Structurally, they exist as three-dimensional networks capable of entrapping drugs, polymers, and dispersed liquid phases. The availability of diverse polymer systems and the ease of modifying their properties make nanogel formulations highly advantageous.

Nanogels are considered next-generation drug delivery systems, owing to their high drug encapsulation efficiency, versatility in drug loading, uniform particle size, tunable dimensions, straightforward preparation, minimal toxicity, serum stability, and responsiveness to external stimuli. Unlike macroscopic gels that respond slowly to environmental changes, the nanoscale size of nanogels enables rapid responses. For instance, Tanaka et al. demonstrated that the time required for a spherical gel to swell or shrink is proportional to the square of its radius, highlighting how nanosizing improves responsiveness.

Nanoparticles have been extensively studied over the past three decades to improve organ-specific drug targeting and bioavailability across biological membranes. In ophthalmology, nanoparticles have shown effectiveness in prolonging drug action. The nanogel network can incorporate drugs, proteins, and DNA while providing a large surface area for multivalent bioconjugation. Encapsulation occurs through interactions such as salt bridges, hydrogen bonding, and hydrophilic-hydrophobic forces within the polymer chains. The chemical framework of nanogels can be tailored to control water uptake, mechanical strength, and biocompatibility.

Nanogels are also considered smart materials because they respond rapidly to external stimuli such as pH, temperature, ionic strength, light, and magnetic fields, leading to changes in volume, hydrophilicity, refractive index, and water absorption. Functionalization techniques, such as ATRP or surface modification, can make nanogels responsive to specific stimuli. This property makes them suitable as carriers in medical diagnostics, biosensing, bioimaging, and tissue engineering.

An effective drug delivery system (DDS) should possess key features, including: suitable particle size for enhanced permeability and retention, non-covalent drug encapsulation, prevention of premature release, stimulus-triggered release, tunable kinetics, minimal toxicity, and reproducible preparation. Figure 1 illustrates the mechanism of stimuli-triggered drug release from nanogels.

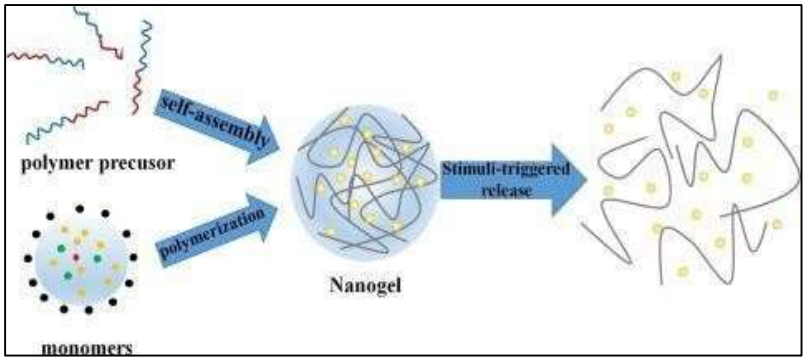

Figure 1: Nanogel

Ideal Features of Nanogel Drug Delivery Systems

An effective nanogel drug delivery carrier typically possesses several key characteristics, including: a small particle size (10–200 nm), biodegradability and/or biocompatibility, prolonged circulation in the bloodstream, high drug or enzyme loading capacity, and protection of therapeutic molecules from the body's immune system. The multifunctional properties of nanogels can be fine-tuned by adjusting cross-linking density, introducing specific chemical functional groups, and incorporating surface-active or stimuli-responsive components.

Nanogel macromolecular chains contain rings and loops, so careful consideration of the polymer composition and polymerization conditions is essential. A challenge in nanogel synthesis is **macrogelation** (or critical gelation), which can lead to the formation of microgels or bulk hydrogels instead of nanosized particles. This issue can be mitigated by selecting a solvent with a solubility parameter compatible with the desired nanogel or by using a chain transfer agent to control macrogelation and favor nanogel formation.

Advantages of Nanogels

- Highly biocompatible due to their high water content, minimizing immunological responses.

- Small particle size allows drug delivery to tiny capillaries and deep tissue penetration via transcellular or paracellular pathways.
- Enhanced bioavailability of encapsulated drugs.
- Improved dispersion within tissue macrophages.
- Protection against physical and chemical degradation, which is particularly beneficial for sensitive herbal extracts or plant-derived actives that may otherwise degrade in acidic environments or undergo rapid liver metabolism.
- Minimal immune response.
- Reduced uptake by the reticuloendothelial system.
- Drug release can be controlled through cross-linking density.
- Excellent tissue permeation due to nanoscale size.
- Suitable for both hydrophilic and hydrophobic drugs, as well as charged solutes.
- Efficient transport characteristics.

Disadvantages of Nanogels

- Production can be costly, especially when removing solvents and surfactants at the end of the process.
- Residual surfactants or monomers may cause adverse effects.
- Some particles may remain in the micrometer size range.
- Scaling up production is challenging due to particle size and weight considerations.
- Limited drug-loading capacity and suboptimal control over drug release.
- Physicochemical and structural changes at the nanoscale can lead to unexpected material interactions, potentially causing toxicological effects.

Classification of Nanogels

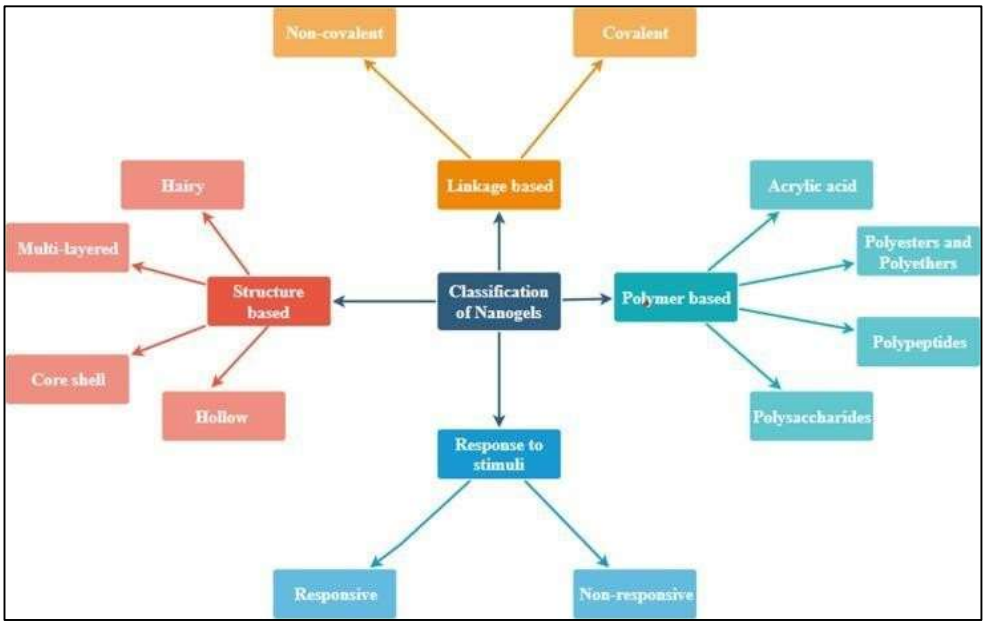

Figure 2: Types of nanogel

Nanogels can be categorized into various types based on their composition, cross-linking methods, and functional properties (illustrated in Figure 2).

Classification of Nanogels

Nanogels can be categorized based on several factors, including polymeric composition, structure, type of linkage, and responsiveness to external stimuli. The main classifications reported in the literature are as follows:

1. Polymer-Based Classification

Nanogels can be classified according to the polymers that form their framework. For example, polyether- and polyester-based nanogels are commonly used in pharmaceutical applications due to their biodegradability and biocompatibility. These polymers have covalent bonds in ether (R–O–R) or ester (R–C–O–O–R) groups. Nanogels can also be prepared using oppositely charged polymers (e.g., chitosan, sodium alginate, sodium hyaluronate, chondroitin, cyclodextrin) that form ionic complexes through electrostatic interactions. Such nanogels can respond to physiological pH changes. Hydrophilic polysaccharides can be modified with hydrophobic groups, and amphiphilic polymers can also be used to prepare nanogels in aqueous systems.

2. Linkage-Based Classification

Depending on the type of linkages in the polymer network, nanogels are divided into:

- **Non-covalent linkage nanogels** (physically cross-linked), formed via hydrogen bonding, hydrophobic interactions, van der Waals forces, or electrostatic interactions.

- **Covalent linkage nanogels**, which are chemically cross-linked networks offering greater stability.

3. Structure-Based Classification

Nanogels are often spherical, but modifications in synthesis can produce different shapes and characteristics. For instance, hollow nanogels contain a central cavity and can be made using materials like gold, cellulose derivatives, or gel dioxide, with the core removed by pH adjustment.

4. Stimuli-Responsive Nanogels

Stimuli-responsive nanogels respond to tumor microenvironment conditions such as low pH, elevated temperature, or high glutathione (GSH) levels. This targeted responsiveness reduces systemic drug doses, minimizes toxicity to healthy tissues, and ensures drug release only at the desired site. Chemical modifications can be introduced to make nanogels sensitive to specific disease-related stimuli.

Ideal Characteristics of Nanogels

- **High Water Content / Swellability:** Nanogels rapidly swell and shrink due to the hydrophilic functional groups in their polymers.
- **Softness:** Softness is crucial for biodistribution and can be tuned by adjusting the nanogel structure.
- **Colloidal Stability:** Surface charges prevent aggregation in the bloodstream. Zeta potential adjustment and polyethylene glycol (PEG) coating can enhance stability through steric and hydration effects.
- **Biocompatibility and Biodegradability:** Nanogels are synthesized from natural or synthetic polymers (e.g., chitosan, polyacrylic acid, methyl cellulose, sodium alginate, dextran, pullulan, cyclodextrin), which are generally nontoxic, hydrophilic, and biodegradable.
- **Particle Size:** Typically, 20–200 nm, allowing nanogels to avoid rapid renal clearance while evading uptake by the reticuloendothelial system. Small size enables penetration across barriers such as the blood-brain barrier (BBB).
- **High Drug Loading Capacity:** Functional groups in the polymer network facilitate hydrogen bonding or van der Waals interactions with drugs, enhancing encapsulation and enabling targeted delivery.
- **Solubility:** Nanogels can solubilize both hydrophilic and hydrophobic agents in their core or polymer network. For example, cholesterol-modified pullulan nanogels can encapsulate prostaglandin E2, and amphiphilic Pluronic F127-based nanogels can carry doxorubicin.

- **Electromobility:** Nanogels are prepared under mild conditions, preserving sensitive biomacromolecules.
- **Colloidal Stability:** Nanogels show superior stability over conventional micelles, with slower dissociation and prolonged drug retention.
- **Non-Immunogenic:** They generally do not trigger immune responses.

History of Nanogels and Nanotechnology

While Richard Feynman popularized the concept of manipulating matter at the nanoscale, the use of nanosized materials predates him. John Utynam patented glass containing gold nanoparticles in 1449, and Paracelsus (Theophrastus von Hohenheim) used gold nanoparticles for medical treatments in the 16th century. Richard Zsigmondy introduced the concept of nanometers and won the Nobel Prize in Chemistry in 1925 for studying colloidal particles like gold. Norio Taniguchi coined the term "nanotechnology" in 1974 to describe precise processing of materials at the nanoscale. Subsequent innovations, including the scanning tunneling microscope (STM), fullerenes, and carbon nanotubes, further advanced nanoscience. In the U.S., initiatives in 1991 and 2001 promoted nanotechnology awareness. One common method for producing nanogels involves high-pressure homogenization to reduce larger particles into nanosized carriers in the presence of suitable surfactants.

Applications of Nanogels

Nanogels are widely applied in drug delivery, diagnostics, biosensing, bioimaging, and tissue engineering (illustrated in Fig. 18.3). Their nanoscale size, biocompatibility, and stimuli-responsive properties make them versatile platforms for a variety of biomedical applications.

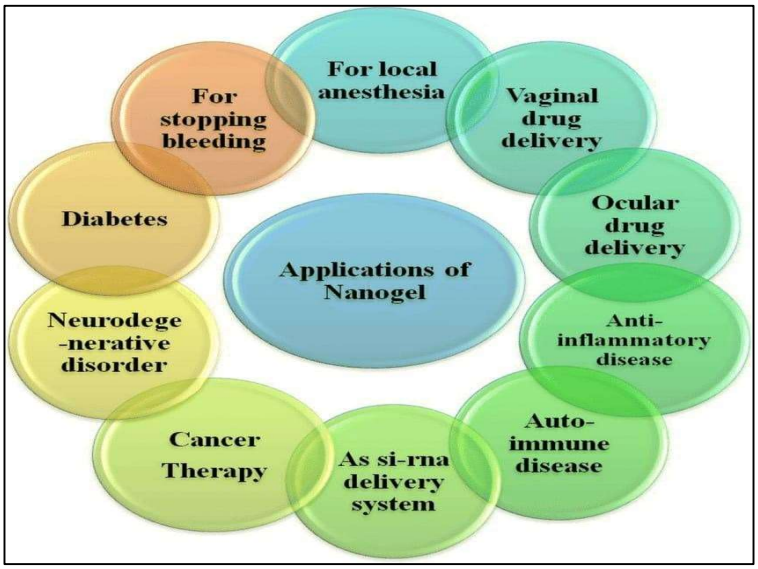

Figure 3. Application of nanogels

Design and Biomedical Applications of Nanogels

The development of hydrogels has attracted considerable attention in biomedical engineering, pharmaceutical sciences, and biomaterials research due to their tunable chemical composition, three-dimensional (3D) network structure, favorable mechanical properties, high water content, and biocompatibility. These characteristics make hydrogels, and in particular nanogels, highly versatile for various therapeutic applications [16].

Ophthalmic Applications

pH-sensitive nanogels composed of polyvinyl pyrrolidone (PVP) and poly(acrylic acid) (PAAc) have been prepared via γ-radiation-induced polymerization of acrylic acid in an aqueous PVP solution. These nanogels have been used to encapsulate pilocarpine, ensuring prolonged maintenance of therapeutic drug concentrations at the site of action in the eye [14].

Tumor Therapy

Conventional chemotherapeutics are often limited by poor solubility, narrow therapeutic windows, and cytotoxicity to healthy tissues. Nanogels provide an effective alternative as anticancer drug carriers. Their porous network structure allows high drug loading, protects drugs from premature degradation, and minimizes systemic exposure, making them highly suitable for targeted tumor therapy [17].

Protein Delivery

Therapeutically relevant proteins, increasingly used for treating malignant, viral, and autoimmune diseases, face challenges such as instability, short shelf-life, and rapid clearance. Nanogels can encapsulate proteins non-covalently, preserving their activity while improving circulation time.

Two main strategies exist for protein encapsulation in nanogels:

1. **Diffusion method:** Proteins are loaded into pre-formed nanogels via specific interactions. Strong interactions may denature proteins, while weak interactions reduce encapsulation efficiency.
2. **In-situ encapsulation:** Proteins are incorporated during nanogel formation, resulting in high encapsulation efficiency and uniform distribution. Mild preparation conditions are essential to maintain protein activity [17].

Vaginal Drug Delivery

Nanogels have been used for vaginal delivery of antibacterial and antiviral drugs. They help reduce infections, irritation, and other reproductive tract issues. However, certain vaginal nanogels are contraindicated during menstruation and pregnancy. For example, Tenofovir-loaded nanogels have been studied for HIV prevention. Gelatin nanoparticles of Tenofovir were prepared using a two-

step desolvation method, and HPMC K15M was incorporated as a bioadhesive and gelling agent [1].

Diabetes Management

Injectable glucose-responsive nanonetworks have been developed for insulin delivery. These systems consist of oppositely charged nanoparticles that self-assemble into a stable gel, preventing nanoparticle diffusion in the body. In vivo studies in diabetic rats demonstrated that insulin-loaded nanogels reduced blood glucose levels by 51% for approximately 2 hours and maintained more stable glucose levels compared with free insulin [1].

Manufacturing Methods of Nanogels

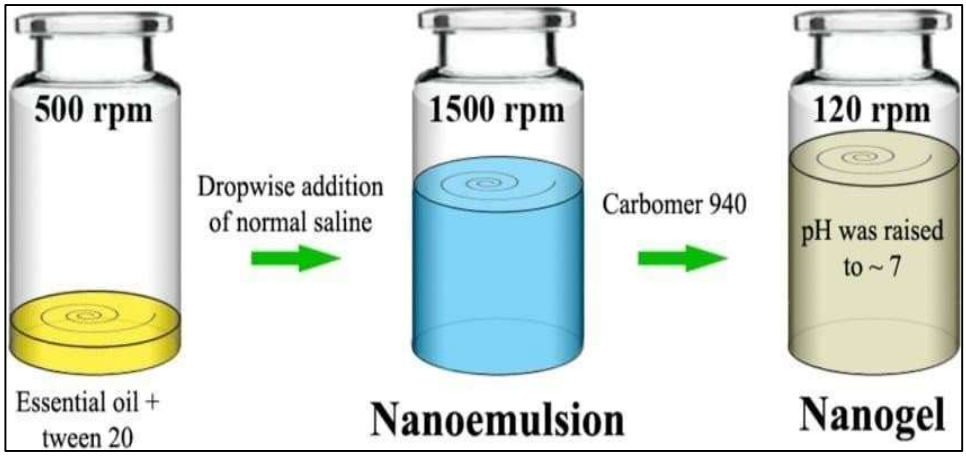

Figure 4. Manufacturing of nanogel from nano emulsion

Nanogels can be prepared via various techniques, including methods derived from nanoemulsion technology, which allow precise control over particle size, drug loading, and stability. Figure 4 illustrates the process of nanogel preparation from nanoemulsions.

Methods of Nanogel Preparation

1. Emulsion Solvent Diffusion Method

In this method, the drug is first solubilized in an organic phase, while the polymer and gelling agent are dissolved in water to form the drug-containing phase. This aqueous phase is added dropwise to a pre-homogenized aqueous solution and stirred at 6000 rpm for 30 minutes to form an oil-in-water emulsion. The emulsion is further processed using a homogenizer to produce nanodroplets. Subsequently, triethanolamine is added to the emulsion and stirred continuously at 8000 rpm for one hour, resulting in the formation of nanogels [18]. Figure 5 illustrates the process.

2. Modified Diffusion Emulsification Method

In this technique, the drug is mixed with a polymer in a solvent at a precise ratio to form the organic phase. The organic phase is slowly added to an aqueous stabilizer solution using a syringe

at a rate of 0.5 mL/min while continuously stirring at 5000–10,000 rpm. The resulting mixture is agitated further for 6 minutes at 10,000–25,000 rpm and then subjected to sonication for 5–10 minutes to achieve uniform nanogel formation [18].

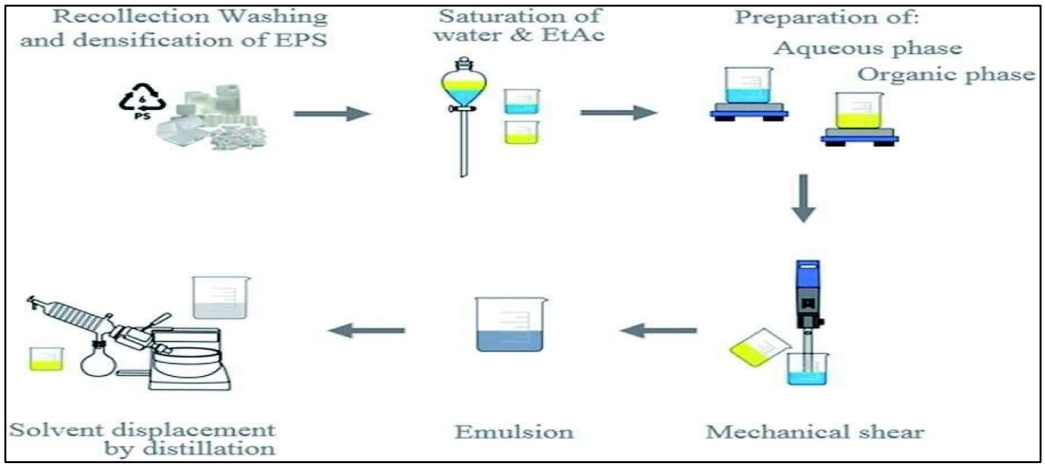

Figure 5. Emulsion solvent diffusion method

Nano-Precipitation Method

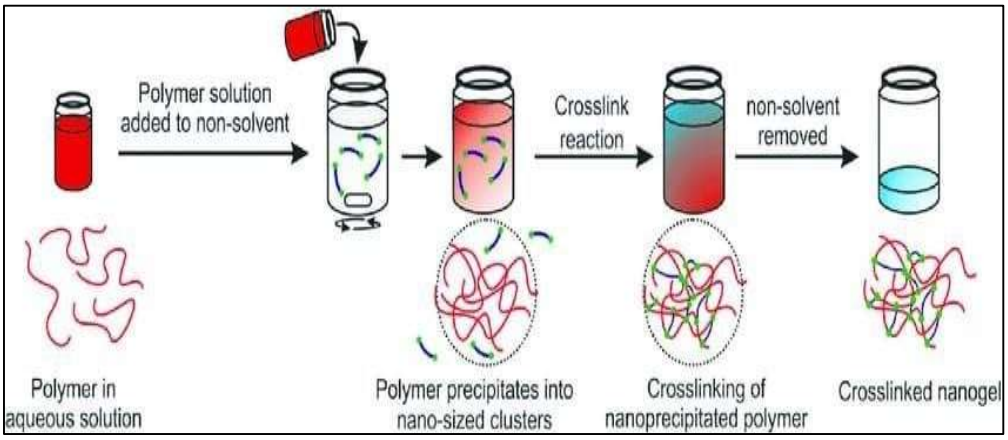

Figure 6. Nano precipitated method

In this approach, the organic phase containing the drug and polymer is introduced into an aqueous solution with a surfactant. Upon contact, the polymer precipitates out as nanoparticles. After removing the excess solvent, the resulting polymeric nanoparticles remain. A gelling agent along with the appropriate amount of nanoparticle dispersion is then added, and the pH is adjusted using triethanolamine to stabilize the nanogel [18]. Figure 18.6 illustrates this method.

Evaporation of Solvent Method

In this method, the drug-polymer mixture is added to the aqueous phase and stirred continuously at 1000 rpm using a magnetic stirrer for approximately two hours. The resulting nanosponges are then filtered and dried in a hot air oven at 40°C for 24 hours. Once dried, the nanosponges are transferred into vials for storage.

To ensure uniform dispersion, the polymer is first immersed in water for two hours before gel formation and then agitated at 6000 rpm. The pH is adjusted using an appropriate agent, and the aqueous polymer dispersion is mixed with the optimized nanosponge suspension along with permeation enhancers. Figure 7 illustrates this preparation method [18].

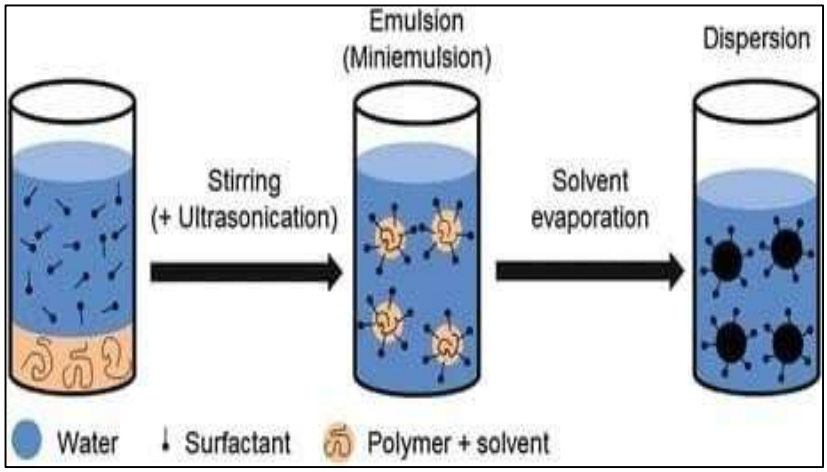

Figure 7. Evaporation of the solvent method

Reverse Micellar Method

In the reverse micellar approach, the **polymer, drug, and surfactant** are initially dissolved in an **organic solvent**. A **cross-linking agent** is then added gradually, typically over an extended period (e.g., overnight), to allow the formation of nanoparticles. After purification, the **organic solvent is removed**, resulting in a dried bulk of nanoparticles.

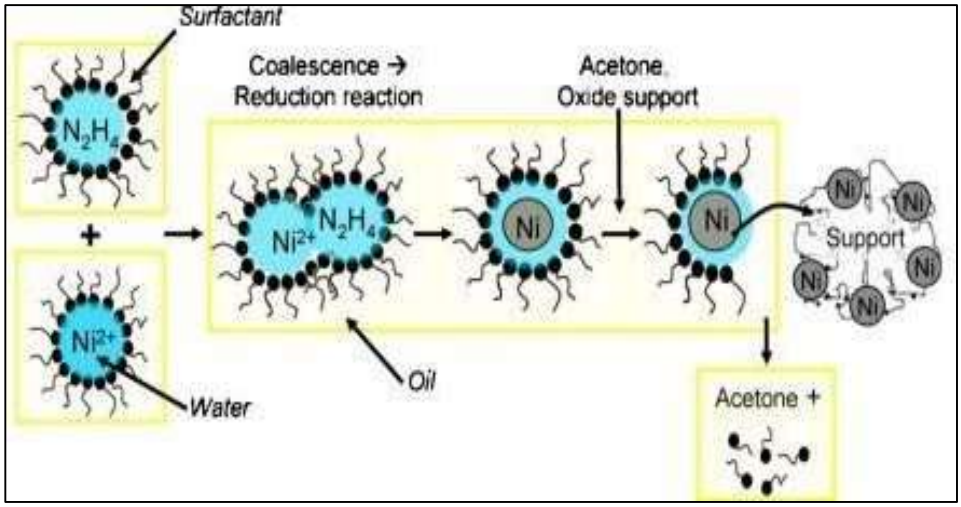

Figure 8. Reverse micellar method

The dried nanoparticles are subsequently dispersed in an aqueous solution containing a gelling agent to form the nanogel. The pH of the resulting nanogel can be adjusted by adding a suitable neutralizing agent. Figure 18.8 illustrates this method [18].

Composition of excipients for preparation of nanogel:

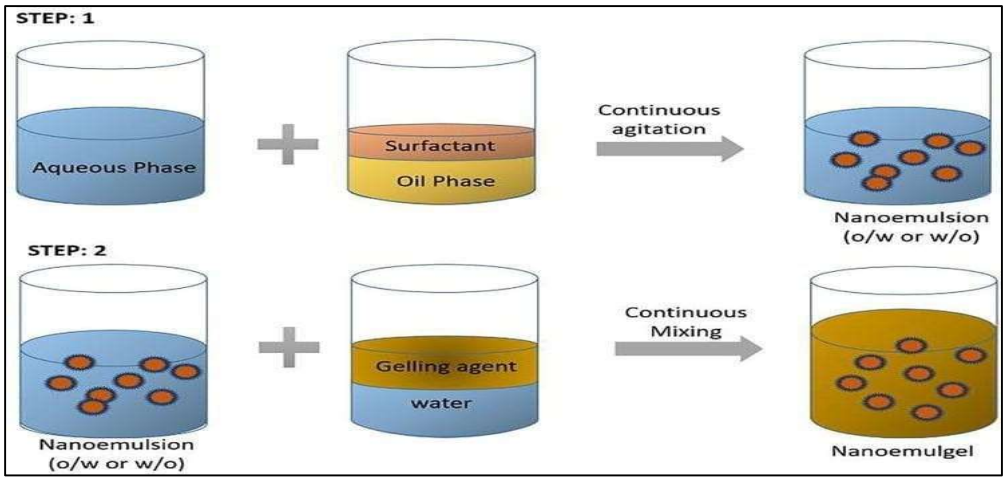

Figure 9. Preparation of nanogel by using various excipients

Figure 9, describes the preparation of nanogel by using various excipients.

Nanoemulsion Formulation

1. Screening of Oils

The solubility of ropinirole was assessed in various oils including Capryol 90, Sefsol-218, triacetin, isopropyl myristate, castor oil, and olive oil. An excess amount of the drug was added to 2 mL of each oil in 5 mL vials and mixed using a vortex mixer. Samples were incubated at 25±1°C for 72 hours in an isothermal shaker to reach equilibrium. After centrifugation at 3,000 rpm for 15 minutes, the supernatant was filtered (0.22 µm) and analyzed using HPLC to determine drug solubility.

2. Screening of Surfactants

Five surfactants—Labrasol, Cremophor EL, Tween 20, Tween 60, and Tween 80—were evaluated. A 15% (w/v) aqueous solution of each surfactant (2.5 mL) was mixed with 4 µL of oil. If a clear single-phase solution was formed, additional oil was added incrementally until the solution became cloudy.

3. Screening of Cosurfactants

Tween 20 was combined with cosurfactants such as ethanol, isopropyl alcohol, n-butanol, PEG 400, Carbitol, and propylene glycol at a 1:1 Smix ratio. Pseudoternary phase diagrams were constructed using twelve different oil-to-Smix ratios (e.g., 1:9 to 9:1) to delineate phase boundaries and identify optimal nanoemulsion formulations [19].

Nanogel Formulation

Nanogels are synthesized from natural or synthetic polymers. Common biopolymers include chitosan, ethyl cellulose, methyl cellulose, and polysaccharide derivatives like dextran, pullulan,

and dextrin. Methods for nanogel preparation include heterogeneous atom polymerization, inverse emulsion, W/O heterogeneous emulsion, precipitation polymerization, controlled/living radical polymerization, and dispersion polymerization [20].

Evaluation of Nanogels

1. Particle Size Measurement

Mean particle size and polydispersity index were determined using a Malvern MasterSizer 2000 (Malvern Instruments, UK).

2. Zeta Potential

Zeta potential of nanogels was measured with a Beckman Coulter Delsa™ Nano analyzer.

3. Entrapment Efficiency

Nanogel dispersions were centrifuged at 10,000 rpm for 1 hour. The supernatant was analyzed at 274 nm using a UV spectrophotometer to determine the unincorporated drug. Entrapment efficiency (%) was calculated from the drug content in the nanogel versus total drug added.

4. In Vitro Drug Diffusion Studies

Drug release was studied using a dialysis membrane (MWCO >12,000) in a Franz diffusion cell with phosphate buffer (pH 7.5) as the receptor medium. 0.5 g of nanogel was placed in the donor compartment, stirred at 700 rpm, and maintained at 37±2°C. Aliquots (0.5 mL) were withdrawn at predetermined intervals (0.5–24 h) and replaced with fresh buffer. Samples were analyzed by UV-Vis spectroscopy at 274 nm. Release data were fitted to kinetic models to determine the release mechanism.

5. Experimental Design and Optimization

A 3^2 factorial design was employed to optimize nanogel formulations. Independent variables included polymer combination ratio (1:1) and stabilizer concentration (% w/v). Dependent variables were particle size, % drug content, and % in vitro drug release at 8 hours. Optimization and statistical analysis were performed using Design Expert software, resulting in polynomial equations to predict optimal formulations [21].

Table 1: Marketed Examples of Nanogel

Sr.no	Product name	Application
1	Skin perfect brightening nanogel	It brightens the skin and gives complete hydration. It repairs, tones, and protects the skin
2	Oxalginnanogel	It gives deeper action and quicker penetration
3	Aqua Multi Effect Nano Gel Cream	It's a moisturizing gel that gives complete hydration for a long time. It also works as anti-wrinkle cream
4	Augen Nanogel Eye-care Gel	It is an eye care gel with deep penetration properties
5	Revivagenix Pro Collagen Nano Gel	It is an anti-wrinkle cream, gives complete hydration to the skin for longer time

6	Sane care nanogel	Reduces accumulated fats on the abdomen, arms, legs, thighs.
7	HA nanogel	Excellent alternative to regular toothpaste. Reducing risk of decay and also reduced bad breath [1].

Drug Release Mechanism of Nanogels

Thermo-Sensitive and Volume Transition Mechanism

Thermo-sensitive nanogels release drugs in response to temperature changes, leveraging polymers that exhibit a lower critical solution temperature (LCST). Below the LCST, the polymer chains are hydrated and swollen, retaining the drug inside the gel network. When the temperature rises above the LCST, the polymer undergoes volume shrinkage, expelling water and triggering drug release.

Example Polymers: Poly(N-isopropylacrylamide) (PNIPAM) and its copolymers, such as N-isopropylacrylamide–co–acrylamide, are commonly used due to their sharp phase transition around body temperature.

Applications:

- **Indomethacin Delivery:** Initial shrinkage at elevated temperature facilitates the controlled efflux of indomethacin.
- **5-Fluorouracil Delivery in Rats:** Temperature-dependent release improves drug availability at the target site.
- **Gene Delivery Systems:** Pluronic-modified polyethyleneimine nanogels expand in response to heat, physically disrupting cellular networks and enhancing gene transport.

By adjusting the polymer ratios, the LCST can be fine-tuned for applications like hyperthermic cancer therapy, enabling selective drug release in heated tumor tissues. Nanogels such as PNIPAM–chitosan combinations are particularly suitable for these applications due to their biocompatibility and temperature responsiveness.

Figure 10 (not shown) schematically represents the temperature-triggered volume transition and subsequent drug release mechanism.

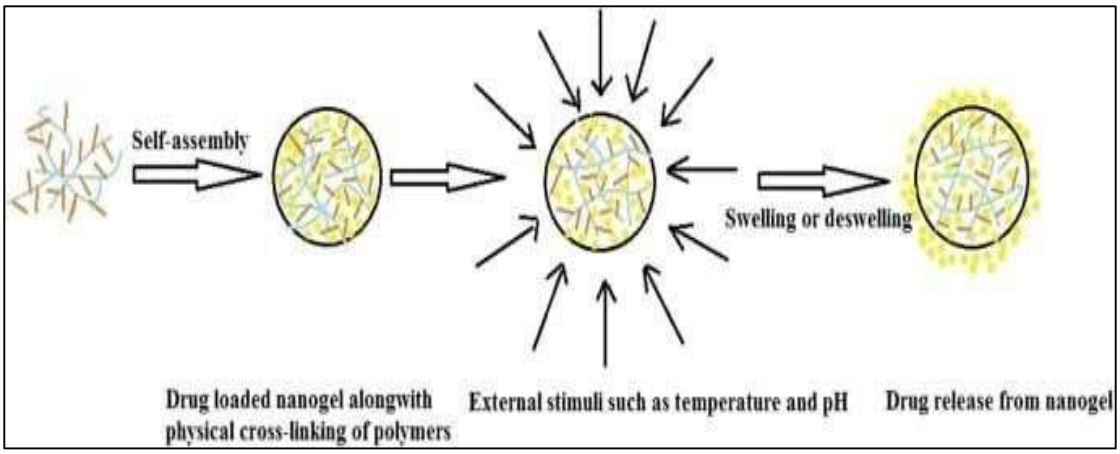

Figure 10: Drug release from nanogel

Drug Release Mechanisms of Nanogels

In addition to thermo-sensitive release, nanogels can release drugs through several other mechanisms depending on the environment, external stimuli, or chemical triggers:

1. Photochemical Internalization and Photo-Isomerization

- **Photochemical Internalization (PCI):** Nanogels loaded with photosensitizers generate singlet oxygen and reactive oxygen species (ROS) upon light exposure. These ROS oxidize cellular barriers, such as endosomal membranes, allowing the encapsulated drug to escape into the cytoplasm.
- **Photo-Isomerization:** Light can trigger cis-trans isomerization in photosensitive nanogels. For example, azobenzene-dextran nanogels loaded with aspirin showed that the E-configuration of azobenzene released drugs more efficiently than the Z-configuration under 360 nm light exposure.

2. Diffusion Mechanism

Drugs such as doxorubicin are released from nanogels via passive diffusion through the polymer network. This mechanism is widely used in many nano-medicines due to its simplicity and predictable kinetics.

3. pH-Sensitive Mechanism

- Nanogels respond to changes in environmental pH:
- Polymers like polyacrylic acid or methacrylic acid-ethyl acrylate form insoluble 3D networks at low pH.
- When pH rises, acidic groups ionize, leading to polymer swelling and drug release.
- Example: pH-sensitive glycol chitosan nanoparticles grafted with diethylaminopropyl groups showed enhanced doxorubicin release in higher pH environments.

4. Ion-Induced Displacement

- Drug release can be triggered by ions present in the environment.
- Cationic nanogels can complex with negatively charged drugs, facilitating cellular uptake and release.
- Biodegradable polymers, like POEOMA nanogels, degrade in aqueous environments in the presence of intracellular agents such as glutathione, releasing the therapeutic payload at the target site.

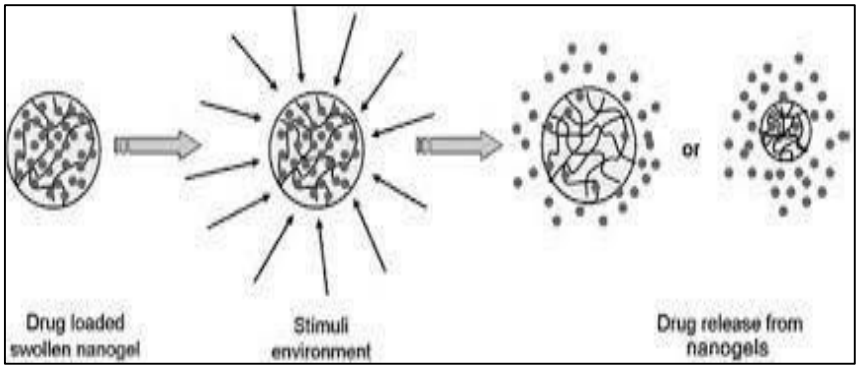

Figure 11: Drug release model from Nanogel

Figure 11 (not shown) illustrates these nanogel drug release models, highlighting the versatility of nanogels for controlled and targeted drug delivery.

Clinical Trial Status of Nanogels

- **Cholesteryl Pullulan (CHP) Nanogels**:

  CHP nanogels have shown promise for peptide delivery, particularly in cancer immunotherapy. In clinical studies, the CHP-HER-2 vaccine was administered in 300 µg doses every two weeks, with booster doses in between. Patients experienced minimal skin sensitivity at the injection site, and immune responses were confirmed via CD4+ and CD8+ T-cell activation, demonstrating effective immunogenicity.

- **Diabetes Management**:

  Recently, optically sensitive insulin-loaded nanogels composed of poly(4-vinylphenylboronic acid-co-2-(dimethylamine) ethyl acrylate) with silver nanoparticles were developed for controlled insulin release, marking progress toward clinical applications in diabetes.

- **Antibiotic Delivery**:

  Nanogels conjugated with antibiotics have been studied for targeted delivery in vivo, showing potential to address infection-related challenges at the cellular level.

Current Status and Future Prospects

- **Cancer Therapy**:
  Nanogels, especially CHP-based, have primarily been explored for cancer immunotherapy, demonstrating efficacy in peptide delivery with minimal adverse effects.
- **Alzheimer's Disease**:
  Cholesteryl pullulan nanogels have shown the ability to reduce neurotoxicity while enhancing binding to amyloid-beta (Aβ) oligomers, suggesting potential in neurodegenerative disease treatment.
- **Diabetes**:
  Optically responsive insulin-loaded nanogels allow controlled, stimuli-responsive insulin release, improving glycemic management.
- **Targeted Antibiotic Delivery**:
  Nanogels conjugated with antibiotics are being developed for precise cellular targeting, increasing therapeutic efficacy while minimizing systemic side effects.
- **Future Directions**:
  Research should focus on understanding mechanisms of blood-brain barrier penetration, endosomal escape, and nuclear or cytosolic targeting for highly specific drug delivery.

CONCLUSION

Nanogels are versatile and promising drug delivery systems due to their, High biocompatibility. Tunable physical and chemical properties. Ability to encapsulate both small molecules and biomacromolecules. Stimuli-responsive and targeted delivery capabilities They have demonstrated potential in cancer therapy, dermatology, diabetes, and neurodegenerative diseases. By overcoming limitations of conventional therapeutics, such as poor stability and nonspecific effects, nanogels represent a next-generation, bio-responsive drug delivery platform. Future in vivo studies and clinical evaluations are expected to expand their therapeutic applications significantly.

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