NANOGEL AS A UNIQUE TREND OF NANO-DRUG DELIVERY SYSTEM

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Abstract

Nanogels are known as small (20–200 nm) swollen particles made of flexible hydrophilic polymer networks that are chemically or physically cross-linked. The nanogels network makes a promising system for ideal drug delivery due to the unique characteristics of nanogels, such as high drug loading capacity, ease of preparation, stability, adjustable size, uniformity, and minimal toxicity. Additionally, nanogel has biocompatibility, high water absorption, large surface area, and stimuli responsiveness; thus, they are utilized to improve and develop drug delivery systems and target a specific site of action to enhance drug activity and decrease potential adverse effects. Nanogels are prepared by various copolymerization methods, including photolithography, micro-molding, reverse micellar, homogeneous, and membrane emulsification. Nanogel has a high loading capacity depending on the polymer used, which reduces the number of carriers needed. Furthermore, the release of drugs can be controlled at the right time and proper place in response to specific conditions, like temperature and pH. A variety of nanogel applications were introduced to treat different diseases, including cancer, skin allergy or inflammation, and Alzheimer's disease. Moreover, nanogel can be used in gene therapy and local anesthesia. Clinical trial studies suggest the development of nanogel for co-administration of multiple drugs, increase targeting, decrease systemic cytotoxicity of cancer medicines, and increase the efficacy of many drugs. The limitations of hydrogels served as the reason to fabricate nanoparticles hydrogels (nanogels) as new advanced DDS. The swelling and deswelling of nanogel controlled the loading and release of drugs in response to certain stimuli.

Keywords: Semisolids; Nanogel; targeting drug delivery

Introduction:

Among the most critical challenges of medicine is developing treatments and gaining effective methods to combat pathologies continuously. Available medications and activated molecules are useful tools for treating different illnesses. However, their efficacy has severe restrictions due to the difficulty in administering them. As a result, huge work has been done to improve so-called 'drug delivery systems, which are instruments that can carry medications and active molecules to therapeutic target site (1).

Semisolids

Semisolids are medicinal formulations with solid and liquid properties where the therapeutic agent is dissolved or suspended. It has many types, such as cream, ointment, gel, and emulsion or pastes (2).

Cream

Semi-solidified creams made of opaque emulsion systems are homogeneous. Its rheological, quality, and characteristics are based on the kind of emulsion, whether oil in water (o/w) or water in oil (w/o) (3).

Ointment

They are homogenous semi-solid formulations for the local or transdermal transportation of active ingredients for utilization on the skin. Typically, they are dispersions or solutions in non-aqueous bases with one or more medications (4).

Pastes

They are homogeneous semi-solid formulations with high amounts (20% or more) of non-soluble powder particles dispersed in the appropriate base (3).

Emulsion

They are liquid dispersed systems composed of two immiscible phases where one is distributed in the other liquid form as globules (4).

Gel

Semisolid gels preparations consist of two interpenetrating systems. That includes colloidal particles evenly dispersed within a solvent or a dispersion medium. The gel has grouped into organogels and hydrogels (5). Hydrogels are 3D hydrophilic polymer networks swelling while conserving structural integrity in the presence of water (6). Organogels are prepared using water-insoluble oleaginous materials (3).

Nanogel

With the development of superior nanotechnologies in current years, Nanocarriers have appeared and gained interest in the biomedical field (7). Alexander and Serguei (2008) first announced the concept of nanogel (NanoGel), describing nonionic polymer and polyion cross-linked bifunctional systems for polynucleotide transport (6).

Definition of Nanogel

Nanogels (nanosized hydrogels) are small swollen particles made of flexible amphiphilic or hydrophilic polymer networks that are chemically or physically cross-linked. These polymer networks are either cationic or anionic (8). Polymers, or polymer combinations, aid in the encapsulation of small molecules, oligonucleotides, and proteins (7).

Reasons for Nanogel

To optimize hydrogel properties by reducing particle size and controlling hydrogel hurdles such as:
Their large 3D structures may result in the elution of the active ingredient through the swollen cross-linked matrix (9).

It has restricted hydrophobic drug delivery through hydrogels and non-homogenous hydrophobic drug dispersion inside hydrogels (10).
Macroscopic dimensions (which necessitate surgical implantation) (11),
For oral drug delivery systems, chitosan-based hydrogel matrices dissolve quickly in the acidic pH of the stomach (10).

These disadvantages are easily solved by the use of hydrogel nanoparticles or nanohydrogels (9).

Properties of Nanogel

Nanogel polymer networks have the dual properties of cross-linked polymer gels and dispersed colloidal particles due to their unique construction (6). These properties can be modified by external factors such as pH, temperature, or specific molecules (1).

Biocompatibility and Degradability: Nanogel is made up of either natural or synthetic polymers (12). It is based drug delivery system that is highly biocompatible and biodegradable (13) thereby avoiding its accumulation in the organs (14).

Swelling Property in Aqueous Media: Since nanogels are very small and soft materials (14), their most advantageous feature is the rapid swelling/de-swelling properties (13) in an aqueous medium (14) through solvent penetration where the system undergoes a subsequent volume increase (1).

Loading Capacity: Nanogels have a higher loading capacity than conventional dosage types (14), owing to their swelling property, which enables them to absorb a significant amount of water (12). The composition and molecular weight are two other factors that contribute to the high loading capability (12).

Colloidal Stability: Owing to their swelling property, there is always a tendency for aggregation, which hinders colloidal stability. To prevent the aggregates in the bloodstream and further problems, formulators prefer to either alter the surface charge or incorporate a surface modifier (14). Polymeric micellar nanogels in body fluids have greater stability than surfactant micelles (1).

Permeability and Particle Size: Nanogels have a diameter of 20–200 nm and thus avoid fast renal clearance (15). Hydrophobicity and surface charge have been shown to significantly increase permeability (14). Nanoparticles can permeate via diffusion, and in certain cases, through a specific transport system (12). Due to their small size, they have excellent permeation capabilities also can cross the blood-brain barrier (13).

Non-Immunologic Response: The Mononuclear Phagocyte System rapidly eliminates agents that enter the systemic circulation through phagocytosis and opsonization (12). Hydrophilic polymers, for example, can serve as a shield that prevents or delays binding with opsonins, making them undetectable by the immune system and its defenses (14).

Solubility: Hydrophobic drugs and diagnostic agents are solubilized in nanogel core or gel networks (13). Their solubility is an important consideration when designing nanoparticulate drug delivery systems (15).

Routes of Nanogel Administration:

Many routes include oral, pulmonary, nasal, parenteral, intra-ocular, and topical (8).

Advantage of Nanogel

Nanoparticle size, and the transcellular or paracellular penetration pathways into tissues and reach deeper tissues (13). These can cross body physiological barriers such as the skin (8).

Properties and particulate size can be managed to bypass phagocytic cell clearance and reticuloendothelial system uptake, that allowing the passive and active targeting of drugs (9).

High biocompatibility makes Nanogel a highly promising strategy for drug delivery systems (12) due to the absorption of high amounts of water, which makes it behave as natural tissue (9).

Highly biodegradable, essential to prevent nanogel material build-up in the body, which results in toxicity and harmful effects (14).

Nano hydrogels display rapid responses to environmental changes such as temperature and pH (12).
Have a greater loading capacity and a controlled release regulated by different polymer cross-linking densities (loading efficiency up to 50%) (4).

Limitations of Nanogel

At the end of the process, costly techniques are needed to fully extract the solvents and surfactants (8).
Some of the particle fractions are in the micrometer size (15).
If any traces of surfactants or polymers remain in the body, adverse effects can occur (14).
Due to the mean size and weight, scaling up is difficult (15). There are drawbacks in the manufacturing of nanogels since only a certain number of properties can be integrated and all nanogel properties can be only incorporated in a limited range (9).

Classification of Nanogel

The main classifications of nanogels are based on the types of linkages they possess and the responsive behavior (13).
Based on Behavior towards a Specific Stimuli

Non-Responsive Nanogels: Non-responsive nanogels absorb water when they come in contact with it, causing the nanogel to swell (12). They can serve as a drug-controlled release depot for the drug may sustain the release of the drug at the targeted site (9).

Stimuli-Responsive Nanogels: Stimuli-responsive nanogels are composed of synthetic or natural polymers that can absorb a large quantity of solvent and swell as a result (9). They swell or de-swell in response to environmental stimuli (16)like temperature, electric field, pH, ions, enzymatic substrates (9). Because of its stability, high drug loading capacity, easiness of synthesis, and the ability to change in many ways it was commonly used (7).

Multi-Responsive Nanogels: When subjected to more than one environmental change they swell or de-swell. Water absorption results in their swelling easily (16).

Based on Cross-Linking
It is based on the manner of cross-linking in the gel and polymer nanogels 3D network structure, are categorized into two main categories (9):

Physical Cross-Linking

Supramolecular particles of polymers formed by non-covalent (7). weaker linkages in physical gels (pseudo gels) are formed by either (a) van der Waals forces (b) hydrophobic, electrostatic interactions, or (c) hydrogen bonding (12). It greatly depends on polymer properties involved in its production includes the composition of the polymer, temperature, polymer concentration, cross-linking agent type, and medium's ionic strength(14).

Liposome Modified Nanogels

Liposome-modified nanogels are stimuli-responsive, physically cross-linked nanogels, because of the unique features they are being studied for transdermal application (14). It is an attractive DDS as it possesses the following advantages: permeation, targeting, controlled release, and sensing (9).

Micellar Nanogels

They can be formulated in an aqueous medium (9)by the supramolecular self-assembly of amphiphilic units or graft copolymers (12). It is composed of a hydrophilic polymer shell surrounding a hydrophobic core and stabilizes the whole micelle (13). The core of Micelles offers sufficient capacity for encapsulation of drug and bio-macromolecules. The drug molecules, in the hydrophobic core, are

protected from hydrolysis and enzymatic degradation (4).

Hybrid Nanogels

Particles of nanogel dispersed in an organic or inorganic medium formed by aggregating the polymer amphiphiles in an aqueous medium or self-assembly. Such as hydrophobized polysaccharides (16). They can form complexes with many drugs, DNA, and proteins (4). thus, used for delivering insulin and cancer medicines (14).

Chemical Cross-Linking

These forms of gels consist of strong covalent linking and other permanent chemical bond networks (14).

The types of chemical cross-linkage and functional groups in the Gel networking determine the gel properties and nature (9), which enables modification of all physicochemical characteristics of gel systems (1).

Chemical cross-linking techniques include emulsion polymerization, click chemistry cross-linking, reversible addition-fragmentation chain transfer (RAFT), and photo-induced cross-linking (7). The chemical cross-linking is sub differentiated into three types:

Photo Induced

Chemical linking induced by reactants photo-irradiation of photosensitive or particle that activated by photo-irradiation (9). It is a clean process used to purifying, removing unreacted cross-linker, and preserving the accumulation of polymer (17).

Amine Based

It is typically used in the formulation of biodegradable amino acid-based nanogels (7). Amine groups have a valuable role in preparing the nanogels because of their reactivity against carboxylic acids, activated iodides, esters iso-cyanates, etc (17). Diamine linker's potential to be modulated is responsible for the incorporation in nanogels of stimuli-responsive properties (9).

Disulfide based

Disulfide bonds are used to produce redox-sensitive nanogels coordinated by metal as a ligand, used with a hydrophilic polymer (9). It has a critical role in the stability and rigor of structural, and it can be established in proteins and natural peptides (17).

Based on Structure

The table below illustrates the common types of nanogel with different structures.

Table 1: Classification of nanogel according to their structure (18).

No.	Type	Schematic structure	Network structure	Example
1	Simple Nanogel		a) Cross-linked b) Semi-interpenetrating polymer(semi-IPN) c) Self-assembled	Artificial chaperone, cholesterol-bearing pullulan (CHP) nanogel. Quantum dot nanogel. Artificial chaperone cholesterol enzymatically synthesized glycogen (CHSEG) nanogel.
2	Hollow nanogel		Interpenetrating polymer	Stimuli sensitive/responsive nanogel.
3	Core-shell nanogels		Cross-linked	Stimuli sensitive/responsive nanogel.
4	Hairy nanogel		Cross-linked	Stimuli-responsive nanogel
5	Multilayer nanogels		Cross-linked	Stimuli sensitive/responsive nanogel
6	Functionalized nanogels		Cross-linked	Polyethyleneglycol-b-poly (methacrylic acid) [PEGb-PMA] with PEG terminal aldehyde functionality

Based on Polymer Source

1. Natural

Because of their biodegradable nature, stability, easily compatible properties, nontoxicity, and economical cost, they have wide applications for the production of nanogels. Examples of natural polymers include natural gums, collagen, proteins, peptides, cellulosic materials, etc (9).

2. Synthetic

Mostly they are spherical-shaped particles, but recent advances in synthetic strategies allow nanogels fabrication of different shapes. Some conventional synthetic polymers for nanogel preparation include poly(lactic)–poly(glycolic) and Poly(lactic acid) copolymers (9).

Aim of the study

This work was achieved to appoint the importance of nanogel drug delivery system as a novel technique with optimized and unique pharmaceutical and formulation properties. Among which, to improve stability and targeting of therapeutic agent to a specific site of action with accompanied enhanced activity and minimized adverse effects, and hence obtain smart delivery of drugs.

Preparation and Evaluation of Nanogel

Preparation of Nanogel

Physical Self-Assembly

The organization of components autonomously forms structurally well-defined aggregates (13). Via amphiphilic block copolymers, which can self-assemble into micelles (9). Interaction between drug moiety and the solvent is arisen by van der Waals forces and hydrogen bonding (19), which allows large molecules encapsulation (6) with micro-molecules and macromolecules being captured within them, such as insulin and protein-loaded (19). It's the most utilized technique because of its simplicity, which involves mixing both the polymer as a carrier and the drug to be loaded. For example, cholesterol-bearing pullulan (CHP) nanogel (9)as in the formulation of insulin hydrogels where they achieved particle sizes of 20–30 nm (16).

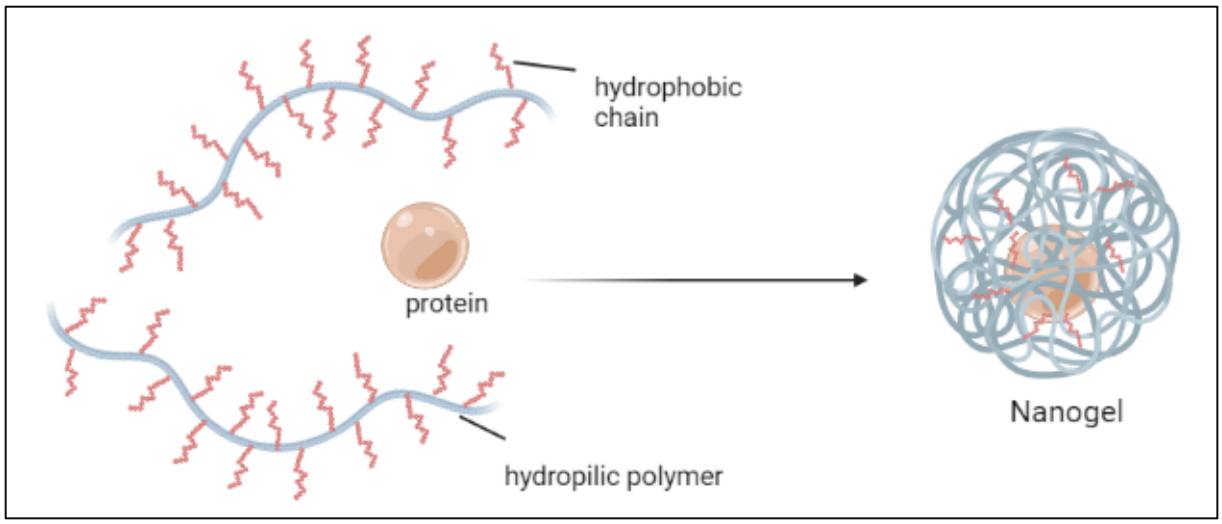

Figure 1: Physical Self-Assembly

Emulsion Polymerization Technique

This process includes a heterogeneous system that undergoes radical addition and polymerization. Which is then followed by the oil-in-water emulsification of a monomer that is hydrophobic in nature (9). Mechanical stirring results in the formation of monomer droplets (14). UV technology is used to produce a specific type of nanogel, for example, dextran nanogel (16).

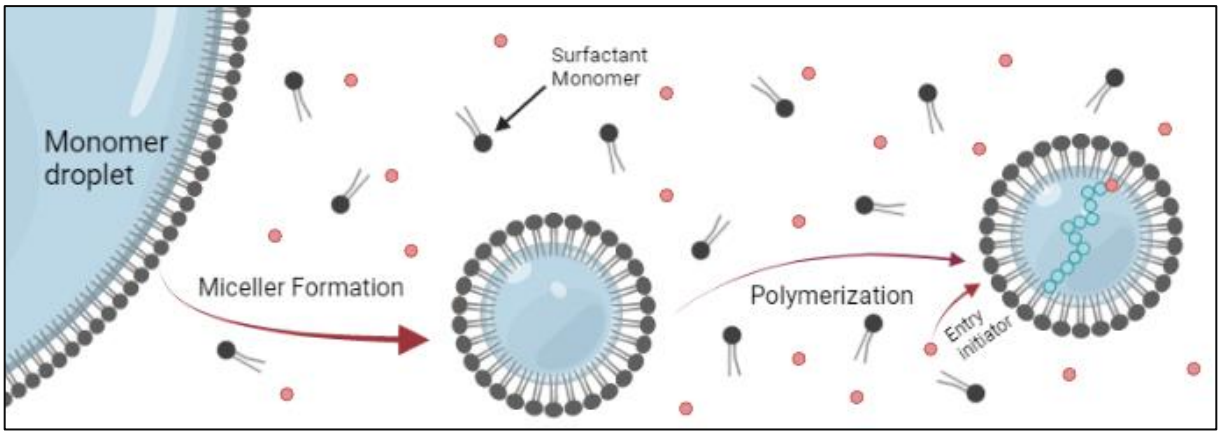

Figure 2: Emulsion Polymerization Technique

Water-in-Oil (W/O) Heterogeneous Emulsion Techniques

Methods of W/O emulsion require two steps: the first one is the emulsification of water-soluble biopolymers as aqueous droplets in continuous oil phase with the aid of oil-soluble surfactants (9), followed by cross-linking of biopolymers with water-soluble cross-linkers (12).

Inverse Emulsion Polymerization

Using a water-in-oil emulsifier, an aqueous solution that contains a hydrophilic monomer is emulsified in a continuous oil phase and polymerized using either a water-soluble or oil-soluble initiator (7). In general, inverse emulsions are thermodynamically unstable. Thermodynamic stability can be achieved by using higher concentrations of the emulsifier, the addition of co-emulsifiers, and a lesser amount of the aqueous phase (9).

Inverse Mini Emulsion Polymerization

Via a mixture of aqueous biopolymer droplets and a continuous oil phase (12), followed by oil-soluble surfactant addition, where the production of monomer droplets is carried by applying high shear stress through a high-pressure homogenizer or ultrasonication (14). In the final step, centrifugation is used to purify the nanogel (17). The miniemulsion is kinetically stable (14). An example of this method is using glutaraldehyde as a cross-linker in chitosan-based nanogels (9).

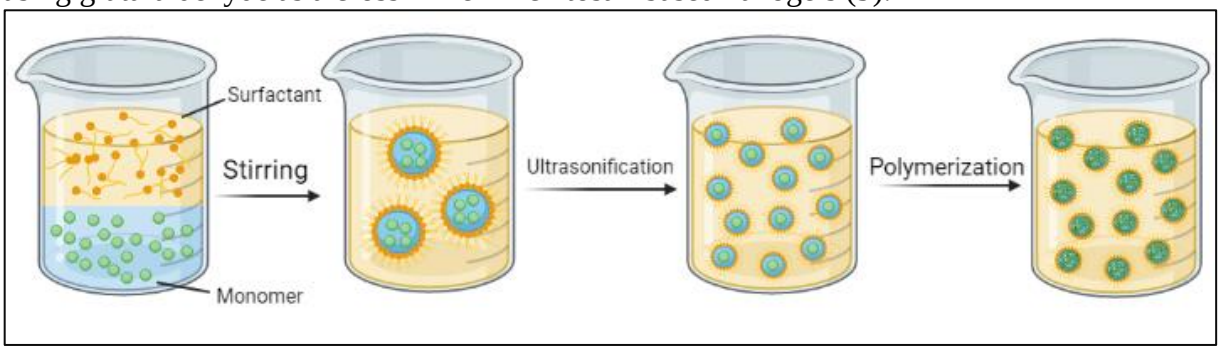

Figure 3: Inverse mini emulsion polymerization

Inverse Microemulsion Polymerization

In the absence of high shear stress, a critical concentration of surfactant is used to form monomer molecules in micelles (4). Aside from that aspect, the entire procedure is identical to that of inverse miniemulsion polymerization (9). Nanogel sizes of 10 to 150 nm are usually achievable (5), they are thermodynamically stable (14).

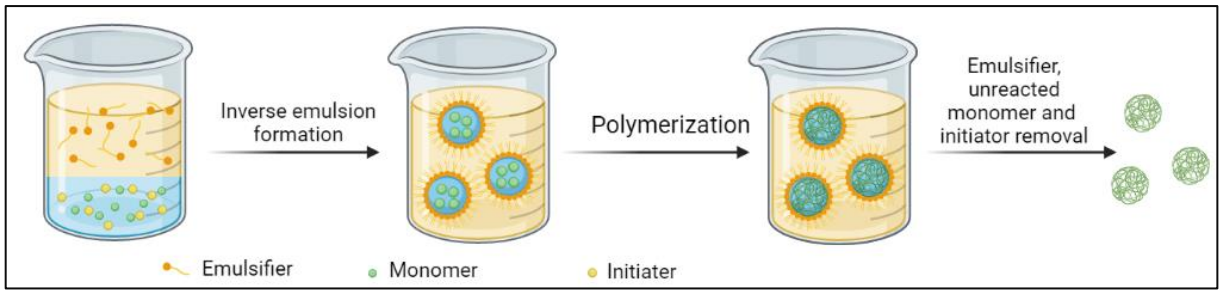

Figure 4: Inverse microemulsion polymerization

Reverse Micellar Method

The technique of this process and the inverse miniemulsion polymerization process are similar, involving a water-in-oil dispersion system (9), except for using a large amount of oil-soluble surface-active agents to produce a micellar solution that is thermodynamically stable (12). The resultant micellar droplets vary in size from 10 to 100 nanometers in diameter (13). This technique was used to formulate Chitosan-based nanogels of doxorubicin to target tumors (9).

Membrane Emulsification

A novel process in which the phase to be dispersed is passed through a membrane (glass or ceramic) (12). The membrane has a uniform pore size, producing a microgel with a specific pattern on the membrane surface, with the external phase being streamed crosswise the membrane (17)under optimized pressure. Simple o/w and w/o emulsions, multiple emulsions, and solid/o/w dispersions can be obtained (9).

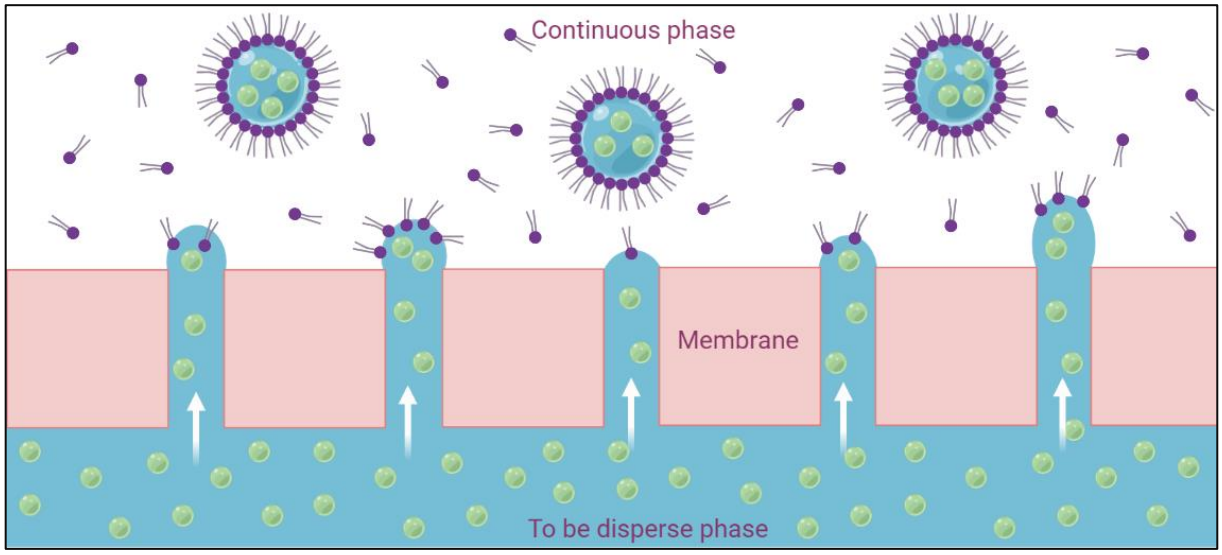

Figure 5: Membrane emulsification

Photolithographic Techniques

Photolithography has been utilized to design three-dimensional nanogel to deliver a drug (9). The polymer is molded into patterns on a silicon wafer and exposing it to intense UV light by pressing the quartz template (17).

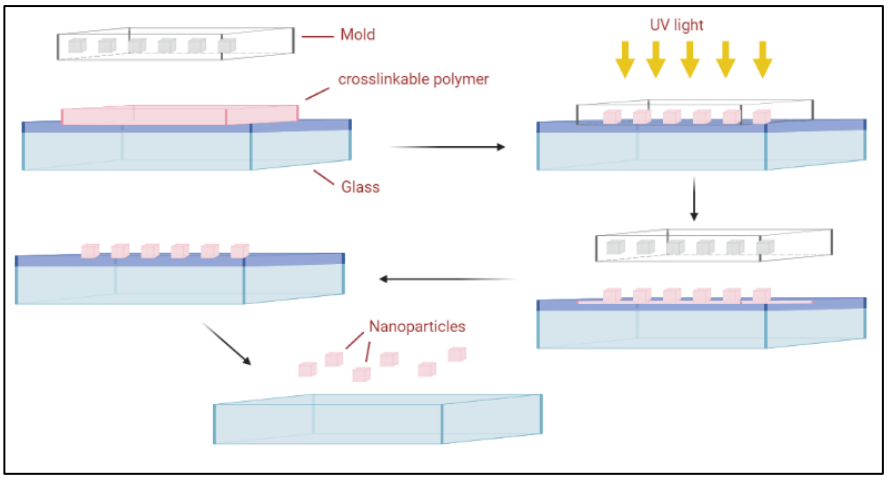

Figure 6: Photolithographic Techniques

Micromolding Method

They are a group of fabrication methods for microstructure polymers replication using molds to identify features (20), where the dimension is easily adjusted by changing the mold stamp size (9). The techniques are comparable to photolithographic techniques but also more economical (17).

Formulation of Copolymers and Biopolymers

Hyaluronic acid (HA), Chitosan (CS), and dextran are biopolymers existing naturally and based on carbohydrates. These are non-toxic, highly soluble water, biodegradable, and biocompatible (9).

Chemical Cross-Linking

Covalent chemical cross-linkages have been used for biopolymer-based nanoparticle preparation in water, such as microgels and hydrogels based on dextrans (9).

Heterogeneous Free-Radical Polymerization

Different heterogeneous reactions of the hydrophilic monomers, with aid of difunctional or multifunctional crosslinkers agents, have been mainly used for preparing synthetic well-defined microgels (12). This technique includes:

Inverse mini emulsion polymerization

Inverse microemulsion polymerization

These two methods were discussed previously.

Precipitation polymerization

It involves the first stage of initiation and polymerization in the homogeneous solution (4), then the formed mixture of polymers is not swellable but soluble in the medium (17). For the particle's isolation by crosslink polymer chains, the use of a cross-linker is essential (12).

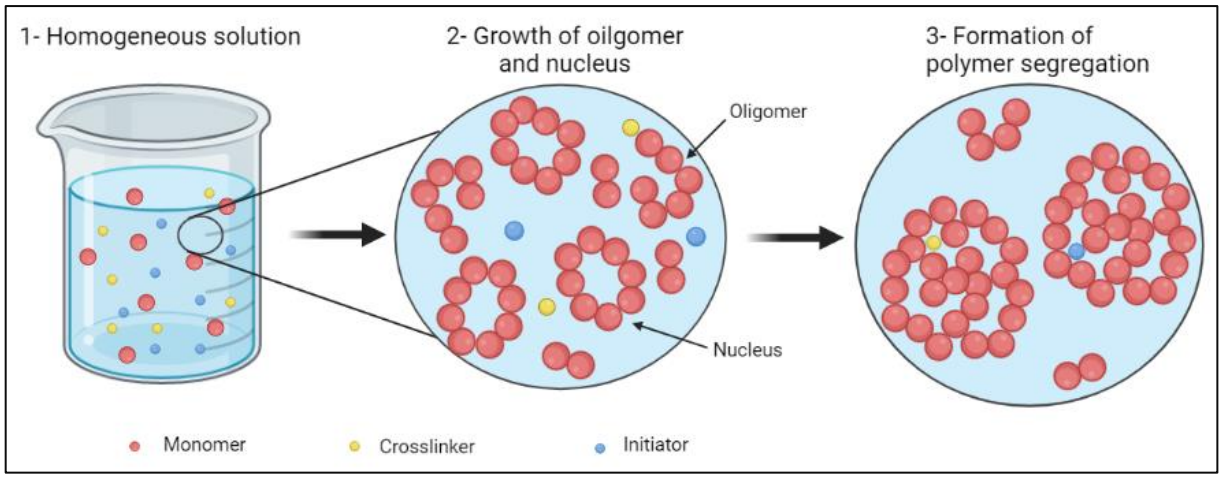

Figure 7: Precipitation polymerization

Dispersion polymerization

The majority of components, including monomers, initiators, and polymer stabilizers, are soluble as a continuous phase in an organic solvent (12). In the homogenous reaction mixture, the reaction begins with polymerization (9), leading to the production of insoluble polymers, which in the presence of colloidal stabilizers form a stable dispersion (4).

Heterogeneous Controlled/Living Radical Polymerization

Explored as a method for preparation of well-controlled bioconjugates of polymer–protein/peptide (13). In comparison to free radical polymerization, this approach minimizes the irreversible termination since it follows an alternating activation–deactivation mechanism in which the inactive but possibly active species is activated into a polymer radical (21).

Transfer of Macroscopic Gels into Nanogel

The macroscopic gel is easy to prepare and there is no limiting factor, such as size control, then undergoes a reduction in size by crushing, grinding, and use sieving, for separation of size to achieve the favored particle size distribution of nanogel. Nevertheless, it needs more energy consumption and time (9).

Drug-Loading Techniques in Nanogel

Nanogels as DDS have a high potential for drug loading and can therefore reduce the number of carriers (13). The loading capacity depends on the features of the polymer used (9).

Covalent Conjugation

Preformed nanogels can be used to achieve covalent conjugation of the biological agents (15), like in bovine serum albumin (BSA) conjugation to nanogel of disulfide cross-linked polymer (4).

Physical Entrapment

Physical entrapment is used in cholesterol-modified pullulan (CHP) nanogels for the incorporation of proteins (9). Furthermore, hydrophobic molecules can be incorporated in hydrophobic chains in non-polar domains in selective nanogels (16). For example, prostaglandin E2 can be solubilized in cholesterol-modified pullulan nanogels (15).

Self-Assembly

The auto organization of ingredients into structurally well-defined aggregates (13). It has many characteristics, including economic efficiency, versatility, and minimal thermodynamics, which lead to a stable, robust structure (8). This method is defined by diffusion followed by linking of molecules by non-covalent interactions, including electrostatic and or hydrophobic bonds (15).

Drug Release Mechanisms from Nanogel

The release of drugs can be controlled in response to an assumed condition that provides the physiological conditions at the right time and proper place (9).

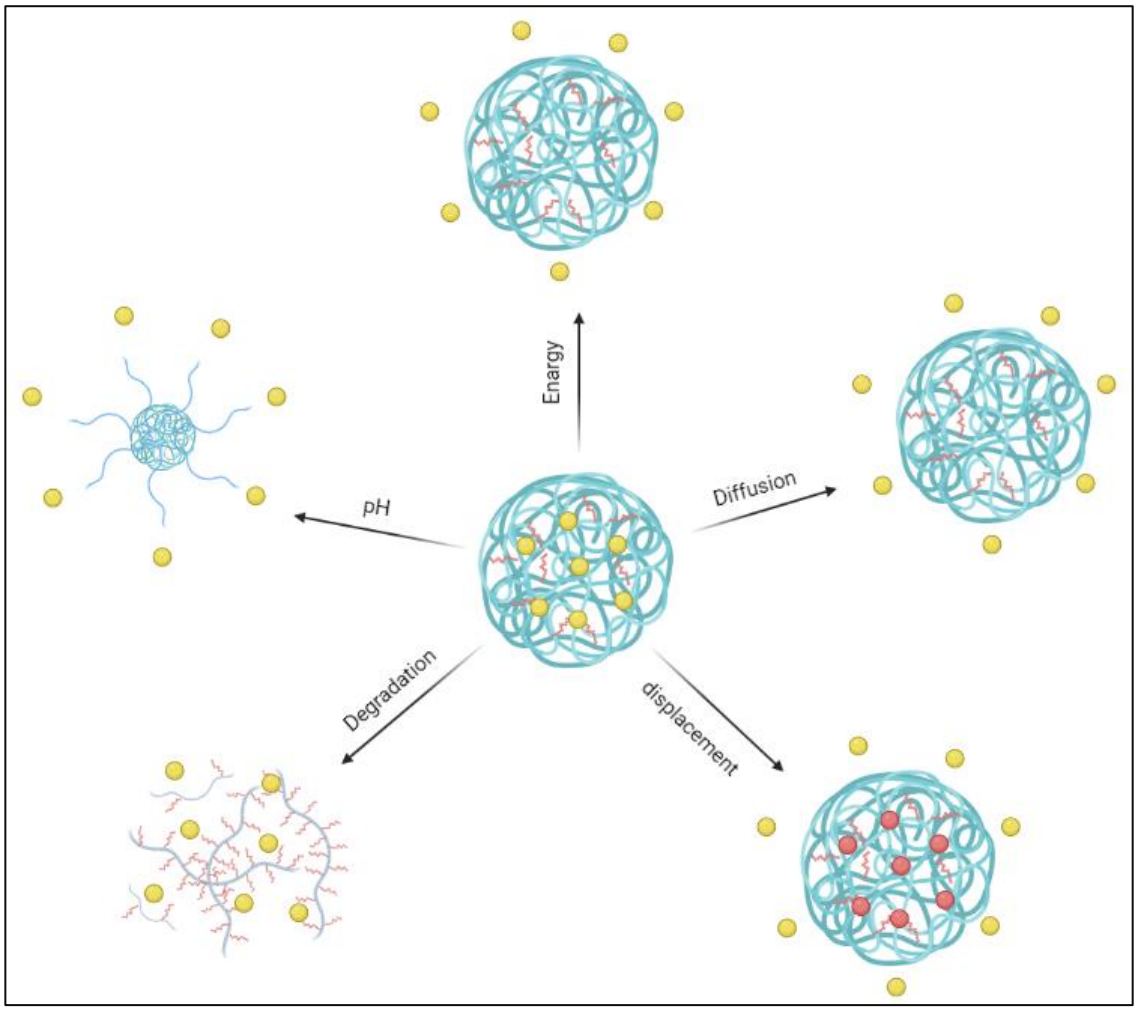

Figure 8: Different mechanisms by which drug are released from nanogel

pH-Responsive Mechanism

The release of drugs in this method depends on differences in pH in the surrounding medium (14). This method is based on the selection of polymers that contain pH-sensitive functional groups in the synthesis of a nanogel (17). Such as the release of proteins from poly(N-vinylformamide) nanogels (15).

Diffusion Mechanism

As the active agent is designed to pass through a polymer, the diffusion process tends to generate a controlled release system. The procedure is done through pores of the polymer matrix on a macroscopic scale (17). For example, the release of doxorubicin from stable puronic base copolymer nanogels (9).

Nanogel Degradation

Degradation of the nanohydrogel can cause the release of the drug that is encapsulated. The release of Rhodamine 6G is an example (15). In another study, glutathione was used to cause the breakdown of disulfide cross-linked HA nanogels and the release of siRNA (22).

Photochemical Internalization and Photoisomerization

Photo-sensitive nanogels can cis-trans isomerize, and when exposed to particular radiations, nanogels can swell or shrink in response to temperature changes, triggering drug release (23). Azodextran nanohydrogel loaded with aspirin is an example (17).

Ione Displacement

Displacement is caused by counterions found in the environment. Multivalent low-molecular cations or polyions of either charge can displace drugs having the same charge sign from electrostatic complexes with ionic nanogel, as in biomacromolecules that are negatively charged bound to nanogels can be substituted by negatively charged cellular components (22).

Thermosensitive and Volume Phase Transition Mechanism VPTT

Many nanogels respond to a certain temperature known as the VPTT, which means they exhibit a variation in volume response to temperature (12). If the medium is less than the VPTT, the nanogel become quenched and hydrated causing it to swell and release the content. The opposite when the medium above VPTT, The nanogel shrinks suddenly and the drug flows out (14).

Evaluation and Characterization of Nanogel

1. **Total Drug Content (TDC):** Nanogel diluted and filtered, then UV spectrophotometry measures the drug content.

2. **Entrapment Efficiency:** By centrifuging to remove the supernatant then the unincorporated drug is estimated by utilizing a UV spectrophotometer.
3. **Viscosity:** It is measured using a Brookfield DV-III rheometer.
4. **In Vitro Nanogel Release:** Using a modified Franz diffusion cell.
5. **Water uptake:** Using a thermal gravimetric analyzer (TGA), by measuring the difference in weight between the fully hydrated (Wh) and dried (Wd) hydrogel.
6. **Compatibility:** Using FTIR spectroscopy, any changes in the chemical structure after combination with polymers will be investigated.
7. **Transmission Electron Microscopy and Photon Correlation Spectroscopy:** Determine the shape of a nanogel, size, and distribution of particles.
8. **Sol-Gel Transition Nanogels Behavior:** By measuring the turbidity of the aqueous dispersions using a thermoregulated UV/VIS spectrometer (15).

Applications and Future Work

Applications of Nanogel

The table below illustrates some applications of nanogel as a drug delivery system.

Table 2: Applications of nanogel (6).

Type of Nanogel	Drug	Disease	Activity
PAMA-DMMA nanogels	Doxorubicin	Cancer	The release rate increased when the pH value decreased. Also, higher cytotoxicity at pH 6.8.
Chitosan-based nanogels decorated with hyaluronate	Photosensitizers like tetra-phenyl-chlorin-tetra carboxylate, tetra-phenyl-porphyrin tetra-sulfonate, and chlorin e6	Rheumatic disorders	Taken up rapidly by macrophages (<4 hours) and will accumulate in their cytoplasm and organelles.
PCEC nanoparticles in Pluronic hydrogels	Lidocaine	Local anesthesia	Long-lasting (about 360 mins) infiltration anesthesia was produced.
Chitosan and poly (lactide-co-glycolic acid) nanoparticles dispersed in Carbopol gel and HPMC	Spantide II	Allergic contact dermatitis and other skin inflammatory disorders	The potential for percutaneous delivery of Spantide II is increased by the use of nanogel.
pH-sensitive polyvinyl pyrrolidone-poly (acrylic acid) (PVP/PAAc) nanogels	Pilocarpine		The adequate concentration of pilocarpine was maintained for a prolonged time at the site of action.
Cross-linked poly (ethylene glycol) and polyethylenimine	Oligonucleotides	Neurodegenerative diseases	Transported across the BBB effectively. When the surface of the nanohydrogel is modified with insulin or transferrin
Cholesterol bearing pullulan nanogels	Recombinant murine interleukine-12	Tumor immunotheray	Sustained-release nanogel
Poly(*N*-isopropylacrylamide) and chitosan		Cancer treatment, target drug delivery, and hyperthermia	Thermosensitive magnetically modulated
Cross-linked branched polyethyleneimine network and PEG Polyplexnanogel	Fludarabine	Cancer	Reduced cytotoxicity and increased activity
Biocompatible nanogel of cholesterol-bearing pullulan	As artificial chaperone	Alzheimer's disease treatment	Inhibited the aggregation of Amyloid β-protein
DNA nanogel with photo cross-linking	Genetic material	Gene therapy	Plasmid DNA controlled delivery

Future Work

Hydrogel nanoparticles with designed internal structures can be generated in the future for more efficient drug delivery systems, such as co-administration of multiple drugs, which may provide a greater therapeutic effect than single-drug therapies (9).

The CHP-HER-2 vaccine in a clinical trial showed a response of CD4+ and CD8+ T- cell proposing better therapeutic action (13). CHP also shows decreasing in cytotoxicity of the nervous system by increasing in binding capacity to AB oligomer in treating Alzheimer's disorder (8). On ovarian carcinomas A2780 overexpression of folate-a-receptor, targeted nanogels can be used to correctly recognize the target (13).

There are prospects for development in diabetes management, antibiotic conjugated nanogels, and mechanisms for uptake not just at the BBB but also at the level of neurons and or glial cells inside the central nervous (8).

Conclusion

The limitations of hydrogels served as the reason to fabricate nanoparticles hydrogels (nanogels) as new advanced DDS, which is made of polymeric cross-linked networks. The variety of available types of polymers, nature of cross-linking, and industrial preparation technique, allow us to obtain nanogel with desired properties and enable the encapsulation of hydrophobic drugs, DNA/RNA, protein, and small molecules. We use many emulsion techniques in the preparation by employing high shearing force, emulsifiers, or surfactants. Also prepare by auto-aggregation, using free radical, UV-light, or reduction in size by crushing, grinding, and sieving. The swelling and deswelling of nanogel controlled the loading and release of drug in response to the presence of water, and their responsiveness to environmental changes as temperature and pH, also enhanced targeting, controlled the cytotoxicity, and the side effects profile.

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