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A Review on Nanogels

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Abstract

The term nanogels is described as nanosized particles assembled using physically or chemically cross-linked polymer networks that swell in a suitable solvent. Nanogels are three-dimensional hydrophilic networks. These studies incorporate features for topical drug delivery, owing to their relatively high drug-encapsulation ability, consistency, tunable size, effortless preparation, insignificant toxicity, and stability in the presence of serum including stimuli responsiveness. These are water-soluble and allow immediate drug loading in aqueous media. These are synthesized using a vast number of methods which include photolithographic technique, membrane emulsification, and polymerization techniques. When nanogels are used as dermatological preparations they have extended exposure times on the skin and as a result, extend the duration of therapeutic potency due to the entrapment of nanoparticles in the gel matrix.

Keywords: Nanogels; Nanoparticles; Cross linkage; Polymerization; Antiseptic

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Introduction

Nanogel can be termed as the dispersion of hydrogel by physical and chemical cross-linking polymer at the nanoscale size [1]. The dimension of nanogels ranges from 20-200 nm [2]. Nanogels are 3D hydrophilic networks that absorb large quantities of water or physiological fluids without changing the internal network of the structure [3]. Nanogels have bulging and degradation properties along with properties like adjustable size, large surface area, and excess water content. By using nanogels drugs can be delivered in a prolonged and predetermined manner. Due to the three-dimensional structures of nanogels, drugs, polymers, and dispersed liquid phases were entrapped easily [4]. The pores of nanogels can entrap micro molecules or macromolecules. They behave as carrier molecules for drugs and are designed in a way that they can easily absorb biologically active compounds by the formation of biomolecular interactions like salt bonds, and hydrophobic or hydrogen bonding [5]. Nanogel exhibits properties between solids and liquids [6]. When nanogels are used as topical preparation the assumption is that the entrapment of nanoparticles in the gel matrix will increase exposure time on the skin and as a result raises the duration of therapeutic potency [7]. It consists of a small number of solid components entangled with polymers dispersed in a considerable amount of liquid in which solids form a 3D network forming the nanoscale size leading to the increased surface area providing bioconjugation of active targeting sites [1]. Nanogels are suited to administer as hydrophobic and hydrophilic drugs, charged solutes, and additional diagnostic agents. This property was influenced by the variety of functional groups involved in the network of polymer chains, crosslinking density, and the kind of crosslinking agent incorporated in the polymeric matrix. Nanogels were formulated as polymeric micellar nanogel designs that express gradual rates of dissociation, fair equilibrium over the surface active agent micelles, less critical micelle concentrations, and, prolonged retention of loaded drugs. They are administered through various routes, like oral, pulmonary, nasal, parenteral, intraocular, etc. The drug is released by pH-responsive, thermosensitive, volume transition, photochemical internalization, and Photoisomerization mechanism [8].

Advantages of nanogels [9]

Nanogels are regarded as more beneficial than other drug delivery systems for several reasons, Including:

1. Biocompatibility and degradability: Nanogel is produced from natural or synthetic polymers. Due to their high biocompatibility and biodegradability avoids their accumulation in organs. Chitosan, methylcellulose, ethyl cellulose, and diverse polysaccharide-form polymers such as dextran, pullulan, and dextrin are utilized to prepare the nanogel. These polymers are stable, non-toxic, hydrophilic, and biodegradable.

2. Swelling characteristics in aqueous media: Nanogels have a good affinity to aqueous solutions, resulting in their capacity to swell or dwell, imbibing water when positioned in an aqueous medium. This is the most useful aspect of nanogels as it makes them the best prospects for the uptake and delivery of proteins, peptides, bio-macromolecules, and bulky drugs. Swelling occurs only when osmotic pressure is exerted by medium ions and an imbalance in the polymer's network swelling pressure.

3. High drug loading capacity: Nanogels have greater drug loading capacity in contrast to traditional dosage forms. This is primarily due to the swelling property which allows the formulation to absorb an enormous amount of water which will provide cargo space sufficient to contain salts and biomaterials. There are also a few other factors that also contribute to the high loading capacity, such as the composition, molecular weight, the possible interactions between the drug and employed polymer, and the different functional groups in each polymeric unit.

4. Permeability and particle size Due to their nanosize, surface charge and hydrophobicity Nano gels have good skin permeability: Nanogels consist of less particle size, surface charge, and hydrophobicity can significantly improve permeability. Due to their small particle size i.e. diameter of 20-200nm, they are capable of permeation by diffusion through tissues or endothelium and in some cases through a particular transport system.

5. Colloidal stability: While handling nanoparticles, there is a tendency for aggregation that compromises colloidal stability. Increasing zeta potential (minimum of ±30 mV) which results in greater repulsive forces between particles that electrostatically stabilize them. Other techniques involve the incorporation of a surface modifier like PEG (polyethylene glycol) that produces steric effects and hydration forces to give a stable nanosuspension.

6. Non-immunologic response: This sort of drug delivery system does not give rise to any immunological responses. Nanogels are inert in the bloodstream and the internal aqueous environment and do not induce any immunological responses in the body.

7. Ease of synthesis: The synthesis of nanogels is a stress-free process where mechanical energy is not employed and harsh conditions are not involved. This process does not include the introduction of organic solvents. Hence the drug can be loaded effortlessly without being exposed to any sort of robust conditions throughout the preparation process.

8. High encapsulation stability: To provide maximum therapeutic effects and minimum toxicity or side effects drug molecules loaded into the nanogel need to be retained and not be transported out or leak prematurely while circulating.

9. Controlled and sustained drug release: To enhance the therapeutic efficacy of the drug and avoid its adverse reactions nanogels are formulated in such a manner that they are capable of releasing drugs in a pre-determined and prolonged pattern at the target site.

10. Response to stimuli: Nanogels can be used as a targeted drug delivery system and drugs can be targeted to a particular site without compromising on its while dispersing to reach the target site and the drug released voluntarily to the appropriate stimulus.

11. Targeting: The nanogels can be used as a targeted drug delivery system by attaching to the surface ligands, target determinants, or via "passive" targeting techniques including extravasation in the pathological sites and retaining in the microvasculature. The chemical modification of nanogels to incorporate ligands leads to targeted and triggered drug delivery and drug release.

12. Low toxicity: The nanogels should be highly biocompatible and free from toxicity, and should be biodegradable with non-toxic degradation products that are readily removed from the body.

Limitations of Nanogel

1. It is expensive to remove the surfactant and the solvent at the end of the preparation process.

2. Adverse effects might occur if any scraps of polymers or surfactants remain in the body [9].

3. Limited drug-loading capacity and suboptimal regulation of drug release

4. The drug-polymer interaction may lead to a collapse in the structure, hence irreversibly trapping the drug molecules and improving the hydrophilicity of the nanogel matrix [4].

Nanogels may be regarded as superior drug delivery systems than the others due to [8]

1. The size and surface characters can be controlled to avoid rapid clearance by reticuloendothelial cells, allowing passive and active drug targeting.

2. Controlled and sustained drug release at the target site, enhancing the therapeutic efficacy and reducing side effects. Drug loading is moderately high and may be achieved without chemical reactions; this is a crucial factor for preserving the drug activity.

3. Capability to reach the smallest capillary vessels because of their minute space, and to penetrate tissues either via paracellular or transcellular pathways.

4. These are highly biocompatible and biodegradable.

Applications of Nanogels [10]

Nanogels are established with great efficacy in the therapy of

- Cancer treatment
- Autoimmune disease
- Neurodegenerative disorders
- Diabetes
- Inflammatory disorders
- In stopping bleeding
- Used for delivering the drugs intracellularly
- Local Anesthetic
- Vaccine delivery
- Bone regeneration

Marketed Formulations of Nanogel [11]

S.No. Product Name Applications

1. Zyflex nanogel relaxes the muscle and erases the body pain

2. Oxalgin nanogel it gives deeper action and quick penetration

3. Sane care nanogel Reduces accumulated fat on abdomen, arms, legs, etc.

4. Augen nanogel it is an eye care gel with deep penetration properties

5. H A nanogel Reduces tooth decay and reduces bad breath

6. Revivagenix nanogel it is an anti-wrinkle cream that gives hydration to the skin

Classification of Nanogels [8]

Nanogels can be classified based on the cross-linking, response to stimuli (e.g., pH, temperature, light, ionic strength, etc.) and methods of preparation.

Classification of Nanogels based on their behavior towards specific stimuli

a. Non-responsive nanogels: When non-responsive nanogels come in touch with water, they absorb it, resulting in swelling of the nanogel.

b. Stimuli-responsive nanogels: Environmental conditions, like temperature, magnetic field, ionic strength, pH, influence the extent of swelling of the nanogels. Changes in any of these environmental factors, which act as stimuli, will lead to an alteration in the behavior of the nanogels as a response, hence the term stimuli-responsive nanogels. Multi-responsive nanogels respond to more than one stimulus.

Classification of Nanogels Based on the type of linkages of polymeric gel structure

a. Physically cross-linked nanogels: These are also called pseudo gels, which depend greatly on the features of the polymer used in their products including polymer composition, temperature, the concentration of the polymer, type of cross-linking agent, and ionic strength of the medium. Weak linkages like Vander Waals forces, hydrogen bonding or hydrophobic, electrostatic interactions are the forces that form this type of nanogels. Physically cross-linked nanogels can be produced within a short time through several simple methods. These techniques involve a variety of procedures such as the association of amphiphilic blocks, self-assembly, aggregation of polymeric chains as well as complexation of oppositely charged polymeric chains.

b. Liposome Modified Nanogels - Liposome-modified nanogels are physically cross-linked, stimuli-responsive nanogels, which are studied as transdermal drug delivery devices, owing to their unique properties. These include the incorporation of poly [N-isopropyl-acrylamide] co-polymeric groups into the liposomes, resulting in a high degree of responsiveness to both pH and temperature.

c. Micellar Nanogels - Micellar nanogels are produced by supramolecular self-assembly of hydrophilic and hydrophobic blocks or by graft copolymers in an aqueous solution. Micellar nanogels consist of a hydrophilic shell (corona), made of polymer blocks, surrounding a hydrophobic core, and stabilizing the whole micelle. The purpose of this conformation is to provide sufficient space to contain drugs or biological macromolecules just by physically entrapping these particles inside the borders of the shell, thereby acting as a drug delivery system. The hydrophilic shell interacts with aqueous media as micelle penetrates the tissues, by forming hydrogen bonds to shield the hydrophobic core that is holding the drug at its target cells. This procedure shields drug molecules from being hydrolyzed or degraded by enzymes.

d. Hybrid Nanogels - The particles of a nanogel dispersed in an organic or inorganic medium is known as a Hybrid nanogel. Self-assembly and aggregation of amphiphilic polymers. Hybrid nanogels have significance, particularly, as drug delivery approaches for insulin and anticancer drugs.

e. Chemically cross-linked nanogels: Chemically cross-linked nanogels are formed by networks of strong covalent bonds and other permanent chemical linkages. The strength of linkage is dependent on the sort of functional groups present in molecules of the nanogel network. In order to synthesize this type of nanogels, polymeric chains are cross-linked at specific points, called the cross-linking points, which are determined by the multifunctional crosslinking agent available. Using distinct polymers and different cross-linking methods leads to the production of nanogels with a variation of properties for several applications. Moreover, the physicochemical properties can be altered depending on the type of cross-linking agent utilized to deliver polymer and the position of cross-linking points.

Synthesis of Nanogels Fundamental Criteria in NG Synthesis [12]

Exceeding the swelling behavior, which can be categorized as a 'superior' property of the NGs, the main features to be regarded in the synthesis of the nanomaterials are biocompatibility, biodegradability, colloidal stability, surface area, loading capacity ensuring a prolonged and targeted drug delivery, and active/passive drug release due to the small particle size and the surface properties. Additionally, other features that can be tuned by carefully controlling the NG synthetic routes include

- Release of both water-soluble and oil-soluble bioactive compounds;
- Versatility in route of administration (i.e., mucosal or parenteral pathway);
- By the mononuclear phagocytic system the reduced nanogel elimination and low immunogenicity are seen;
- Optimized nanogel permeability;
- Increment in the solvability of low-molecular-weight drugs.
- Decrease in the drug load compared to standard drug administration.

Nanogels are generally comprised of natural and synthetic polymers or a combination. However, the formulation may contain inorganic components or the grafting of specific bio-moieties on the polymeric backbone. In the first case, nanogels work as imaging probes, including a wide range of diagnostic and distinct agents for various biomedical applications. These systems increase the half-lives of circulating molecules and favor the serving molecules like ligands, antibodies, or peptides. In the second case, the conjugation of targeting ligands, antibodies, or peptides encourages the mechanism of NG active/passive targeting at the site of interest and the controlled release of the therapeutic payload. Physicochemical properties such as viscosity, density, and rheology represent the basis of nanogel design.

Traditional NG Synthesis

The strategies for nanogel synthesis are split into chemical and physical ones. Generally, the chemical synthesis delivers nanonetworks with strong covalent bonds that enhance the colloidal stability under *in vitro* and *in vivo* conditions, necessary for limiting the leakage of the payload induced by unwanted dissociation of the gel network. These bonds can be differentiated into cleavable linkers based on the response to specific external stimuli (pH and temperature variations); stable bonds provide the gel with the capability to retain its shape under Physico-chemical stress. Chemical crosslinking is the most advanced and most flexible strategy for NG production. The Physical assembling of NGs is a steady aggregation mechanism directed by reversible Non-covalent connections. Despite the moderately weak nanostructure due to the physically crosslinking nature, this procedure is more adaptable because chemical reactions are not involved, and it is carried out under mild conditions in aqueous media.

Photolithographic Techniques [13]

Photolithography was studied to fabricate three-dimensional hydrogel particles or nanogel for drug delivery. This technique requires the development procedures for surface treatment of stamps or replica molds to enable the release of molded gels. Photolithography includes five steps they are

- In the first step, the UV cross-linkable polymer, which contains low surface energy, as a substrate is emitted on the pre-baked photoresist-coated water.
- The polymer is molded into designs on the silicon wafer by stuffing the quartz template into the polymer and exposing it to intense UV light.
- Later, the particles with a thin residual interconnecting film layer are uncovered by removing the quartz template.
- Eventually, the residual thin layer was removed using a plasma containing oxygen that oxidizes it.
- The fabricated particles were directly collected by dissolving or dissolution of the substrate in water or buffer. In this procedure, stamps or replica molds were treated to provide the surface-specific properties that allow molded gels to liberate the incorporated agents.

Emulsion polymerization technique

Emulsion-based polymerization works through the formation of monodisperse kinetically stable droplets in a continuous phase. The motive underlying this process was to maintain polymerization in a confined space (the droplets), whose size would influence the dimension of the final product. The diffusion of organic droplets possessing reactive monomers/polymers in an aqueous solution (oil-in-water, O/W emulsion) was marked as direct emulsion polymerization; whereas the aqueous droplets distributed in an organic medium (water-in-oil, W/O emulsion) was known as inverse emulsification polymerization. NG formulation implies the use of monomers, initiators, catalysts, and crosslinking agents. Generally, the process occurs in three steps: nucleation, precursor nanoparticle growth, and polymerization

Membrane emulsification

In this technique, the dispersed phase was passed through the membrane (glass or ceramic), which possesses uniform pore size. Under specific conditions, the emulsion droplets or microgels with specific morphology were formed on the surface of the membrane, and later, with a continuous phase that is flowing across the membrane, these fabricated emulsion droplets or microgels were recovered. These fabricated emulsion droplets can be in different emulsion formations such as water-in-oil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water (W/O/W). The size of the formed droplet was controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane.

Precipitation polymerization [14]

A fundamental characteristic of precipitation polymerization is that the reaction system is homogeneous. In further terms, all monomers, crosslinkers, and initiators are homogeneously dissolved in the same reaction medium before the reaction. The size of the polymer chain rises as the polymerization reaction advances. When the polymer chain extends to a certain length, the generated phase is separated to form polymer colloidal particles and finally nanogels.

Dispersion polymerization

In this method, most ingredients as well as monomers, chemical compound stabilizers, and initiators area unit soluble in an organic solvent as a continual section. At the onset, the chemical process occurs in an extremely jelled reaction mixture; but, the shaped polymers become insoluble within the continuous medium, ultimately resulting in the formation of stable dispersion of chemical compound particles with an asset of mixture stabilizers.

Photo-Induced Crosslinking Polymerization

The application of irradiation in the formulation of nanogels is becoming popular due to its bacteriostatic effect, additive-free nature, multifunctional nature, tunable particle diameter, and ability to promote cross-linking. In the technique of irradiation, water molecules break down into hydroxyl radicals and hydrogen atoms with the potential to convert polymers into microradicals, leading to intermolecular crosslinking, which promotes nanogel formulation. Consequently, the crosslinking viscosity can be adjusted by controlling the wavelength or energy of the laser.

W/O heterogeneous emulsion method

W/O emulsion strategies involve typically Two steps: emulsification of binary compound droplets of water-soluble biopolymers in continuous oil section with associate degree aid of oil-soluble surfactants and cross-linking of biopolymers with soluble crosslinkers.

Reverse micellar method

This procedure involves a W/O dispersion, analogous to the inverse (mini) emulsion method; yet, a huge quantity of oil-soluble surface-active agents are used to form a thermodynamically stable micellar solution comprise of aqueous droplets dispersed in the continuous oil phase. The resultant micellar droplets have a submicron size ranging from tens to hundreds of nanometers in diameter.

Inverse (mini) emulsion polymerization

- A W/O emulsion was formed from a mixture consisting of aqueous biopolymer droplets and a persistent oil phase using either a homogenizer or a high-speed mechanical stirrer.
- As a result aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents.
- The crosslinked microgel particles are prepared as a dispersion in organic solvents purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization.
- The size of the microgel particles can be controlled by the number of surfactants and cross-linking agents added as well as stirring speed during the generation of an inverse emulsion.

Inverse Microemulsion Polymerization

This method was explored for the preparation of distinct nanogels. It delivers thermodynamically stable microemulsions upon the addition of an emulsifier above the critical threshold. This procedure includes aqueous droplets, stably dispersed with the aid of an enormous amount of oil-soluble surfactants in a persistent organic medium; polymerization occurs within the aqueous droplets, producing stable hydrophilic and water-soluble colloidal nanoparticles containing a diameter of less than 50–100nm.

Heterogeneous controlled/ living radical Polymerization [8]

Polymerization C-reactive protein has been studied as a tool for the synthesis of well-controlled polymer– protein/peptide bioconjugates. Varied ways for C-reactive protein are developed; but, the foremost successful techniques embrace atom transfer radical chemical process (ATRP), stable atom chemical process (SFRP), and reversible addition-fragmentation chain transfer (RAFT) chemical process.

a. Atom transfer radical polymerization

ATRP is the prime C-reactive protein technique, sanctionative the preparation of a good spectrum of polymers with planned relative molecular mass and comparatively slender relative molecular mass distribution (Mw/Mn < 1.5). ATRP also permits the composition of copolymers with fully different chain architectures, like block, comb-shaped, brush shape, and multimedia star copolymers.

b. Reversible Addition fragmentation transfer (RAFT) process

Through RAFT, a polymer undergoes a series of reactions with dithioester compounds; these reactions include reversible addition, reversible degradation of adducts, and chain transfer reactions and control the molecular mass of the polymer during free radical polymerization. RAFT technology can change the micelle structure of amphiphilic polymers by altering the length, configuration, and properties of the polymers.

Conversion of macroscopic gels to nanogels:

Various synthetic methodologies were recognized to prepare macroscopic gel networks and are easy to design because it is not essential to maintain the synthetic parameters as are needed in nanogel or microgel synthesis to control the size. The macroscopic gel networks were generally formulated by bulk polymerization, which produces a solid network structure with macroporous blocks. These blocks were then crushed, grounded, and sieved to obtain gels of desired particle size. However, this was a time and energy-consuming process and results in a considerable loss of material. Nevertheless, micro-and nanogels obtained from this method have particles of different shapes and sizes.

Reverse microemulsion polymerization technique

Microemulsion was formed by adding an aqueous phase dropwise into the oil phase. The emulsion was transferred to a 60°C water bath and stirred at 400 rpm using a magnetic stirrer, kept overnight at room temperature. Supernatants were decanted and pellets are collected. The microemulsion is thermodynamically stable.

Drug Loading [15]

Nanogels are extensively used as carriers of therapeutic agents. A nano delivery system should possess a high drug-loading capacity, by reducing the required number of carriers. Drugs could be incorporated into nanogels by

- Covalent Conjugation
- Physical entrapment
- Self-assembly

Covalent conjugation

Covalent conjugation of biological agents was achieved during nanogel synthesis. For example, enzymes modified with acrylic bodies were copolymerized with acrylamide by inverse microemulsion or dilute aqueous solutions to obtain nanosized hydrogels. Covalent conjugation of the drug with cross-linked nanogels provides additional stability to the encapsulated drug. Polysaccharides that possess hydroxyl groups readily interact with the carboxyl group in the drug by forming esters linkages. In such instances, premature drug release can occur due to the

cleavage of functional group bonds by enzymes like esterases. In addition, by introducing easily cleavable linkers, degradable nanogels were synthesized for a mixture of applications.

Physical Entrapment

The incorporation of proteins in cholesterol-modified pullulan nanogels and siRNA in HA nanogels by physical entrapment. Additionally, hydrophobic molecules can be incorporated into the nonpolar domain formed by hydrophobic chains present in nanogels. In many cases, loading was achieved due to hydrophobic interaction in the drug molecules with the nanogel resulting in relatively low degrees of loading (not more than ca. 10%).

Self-Assembly [8]

The self-assembly process, was defined as the autonomous association of components into structurally well-defined aggregates. It has many beneficial features such as – it is cost-effective, versatile, and facile. This process occurs due to the system's thermodynamic minima, resulting in stable and robust structures. Molecular self-assembly is illustrated by diffusion followed by specific association of molecules through noncovalent interactions, including electrostatic and/or hydrophobic associations. Individually, such interactions are weak but influence the structural and conformational behavior of the assembly due to the large number of interactions involved. While contrarily charged polysaccharides bind voluntarily due to electrostatic attractions, interactions amid neutral polysaccharides are likely weaker, and nonexistent, a modification with chemical entities able to trigger assembly being necessary. This sort of amphiphilic polymer can be constructed using various routes: hydrophobic chains transplanted to a hydrophilic backbone, hydrophilic chains grafted to a hydrophobic backbone (grafted backbone) or altering hydrophilic and hydrophobic segments (block polymer).

Drug Release Mechanism of Nanogels [16]

The liberation of drugs from nanogels at the targeted site of the action occurs in the following ways

a. Simple diffusion of the drug from the nanogel

b. Degradation of nanogel

c. pH stimulus

d. Ionic exchange with the environment

e. External energy source

a. Simple Diffusion

The diffusive release of the drug from the gel is a consequence of the concentration difference with the environment. The drug diffuses from an area of higher concentration (inside the gel) to a lower concentration (surrounding).

b. Nanogel degradation

Degradable nature of nanogels promises lower toxicity and prevents unwanted accumulation upon repeated administration. Easily cleavable bonds can be introduced into the polymer backbone. The degradation is in response to specific reducing compounds, pH, or even enzymatic activity. The encapsulation by hydrophobic interaction has reduced the rate of drug degradation.

c. pH-responsive mechanism

This mechanism was based on the fact that polymers involved in the preparation of a nanogel possess pH-sensitive functional groups that deionize in the polymeric network. The deprotonation impacts an upsurge in osmotic pressure, swelling, and porosity of the polymer which initiates the liberation of the electrostatically bonded molecules. The pH-stimulated release from the gel is a result of the ionization of pendant groups. As mentioned in the name, drug release responds to pH differences in the surrounding environment. The release of the drug will take place at the suitable pH which signifies that the release is primarily achieved in a targeted area of the body that possesses that ph.

d. Displacement by ions present in the environment

Nanogel polymer consists of pendant anionic or cationic groups. In an aqueous environment, these groups undergo ionization at the appropriate pH and ionic strength. This produces a fixed charge on the polymer causing electrostatic repulsion and thereby enlarging the pores of the gel. Hence, there was an enhanced influx of water into the gel, leading to nanogel swelling and drug release. Another way for the drug release is through displacement with counterions. When a cationic nanogel containing a negatively charged drug is in interaction with the negatively charged particles in the environment/cell surface, the drug was exchanged for the negatively charged particle.

e. Thermosensitive and volume transition mechanism

Few nanogels are reactive at specific temperatures known as volume phase transition temperature which means they display a transformation in volume according to the temperature. If the neighboring channel is below VPTT, the polymer becomes hydrated and quenched simultaneously inducing swelling and releasing the drug-loaded. Above the VPTT contrary appears and the nanogel contract suddenly and the content flows out. Previously, thermoresponsive nanogels were employed to rupture cellular networks when they grow and rise in volume. So, some changes were applied to thermosensitive drug-containing nanogels, like altering the ratio of the polymer to achieve a low critical solution temperature. The hydrogen bonds with water were cleaved and separation of the aqueous phase and the nanogel aggregates occurs; thereby, releasing the entrapped drug into the environment.

f. Photoisomerization and Photochemical internalization

Photoisomerization refers to a procedure in which a bond of limited rotation undergoes some conformational transformations due to exposure to light. When photosensitizers are loaded with nanogel, they give rise to two species of oxygen (singlet and reactive) which result in the oxidation of cellular component walls that influence the release of therapeutic agents into the cytoplasm.

The energy-triggered drug release involves a chromophore molecule bound to the polymer and photothermal effect. When the chromophore-containing nanogel was illuminated with light at its resonance wavelength, the light energy was transformed into heat energy by non-radiative relaxation. The volume phase transition is observed due to the rise in temperature leading to the release of the drug into the surroundings.

Preparation of Nanogels

The selection of the preparation method depends on the physicochemical characteristics of the polymer and drug to be loaded. The preparation of nanogels includes the following methods

Emulsion-Solvent Diffusion Method [1]

The nanogel preparation from the Emulsion-Solvent Diffusion method involves the following steps

- The precisely weighed amount of the drug was dissolved in a water-miscible solvent with continuous stirring (organic phase).
- The aqueous phase was formulated by dissolving polymer and gelling agent in water with continuous stirring and heating, later the drug phase was sonicated for 10min using an ultra bath Sonicator.
- The drug phase was added drop by drop to the aqueous during high-speed homogenization for 30min at 6000rpm to form an emulsion. The emulsion was
- Converted into a nanodroplet by a homogenizer resulting in O/W emulsion formation.
- The formed O/W emulsion was homogenized for 1 hour at 8000rpm and triethanolamine is added with continuous stirring to form nanogel.

Nano Precipitation Method [17]

- The organic phase comprising drug and polymer were dissolved in organic solvents was mixed with the aqueous phase containing water and surfactant which results in precipitation of the polymer. Polymeric nanoparticles were formed after solvent evaporation.
- The gel was prepared by the dispersion method. Dispersing gelling agent in water for 2hrs for swelling. Once the particles were swelled it was placed for stirring and the prescribed amount of nanoparticle dispersion was in the gelling agent.
- The pH was maintained by adding triethanolamine.

Emulsion-solvent evaporation method [18]

- The disperse phase possessing the drug and polymer in water-immiscible solvent was added gradually to a definite portion of the aqueous phase at a speed of 1000 rpm with the magnetic stirrer for 2hrs.
- The formed nanosponges were collected by filtration and dried at 40°C in a hot air oven for 24hrs and were packed into vials.
- The polymer should be initially soaked in water for the gel formation for 2hrs and dispersed by agitation at 6000 rpm by utilizing a magnetic stirrer to get smooth dispersion.
- pH adjuster was added to neutralize the pH. The formerly prepared optimized nanosponge suspension and permeation enhancers were added to aqueous dispersion.

Reverse micellar method [8]

The polymer and drug added to the surfactant dissolved in an organic solvent. The crosslinking agent was added and stirred overnight.

- The evaporation of solvent takes place which results in dry mass after purification of nanoparticles present in the buffer was obtained.
- The gelling agent dissolved in water was prepared. The nanoparticles obtained were mixed with an aqueous phase comprising a gelling agent, resulting in the formation of nanogel.
- pH adjuster was added to neutralize the pH.

Modified emulsification - diffusion method [19]

- The drug of a certain amount was weighed and mixed in a solvent-containing polymer. This organic phase comprises the drug-polymer mixture added to the aqueous phase with constant stirring at a speed of 5000-10000 rpm. The organic phase was added into an aqueous stabilizer solution at a pace of 0.5 ml/ min drop by drop using a syringe positioned with a needle.
- The resulting dispersion was stirred for 6 mins at 10,000-25,000 rpm and was subjected to sonication for 5-10min.
- Then double filtered water was added gradually to the dispersion with continuous stirring for 1 hour to induce diffusion of organic solvent into a continuous phase.

Evaluation of Nanogels [20]

Appearance

The nanogel bases were inspected visually for clarity, color, and appearance of any particles.

Homogeneity

The homogeneity was determined with the visual inspection of the nanogel formulation. They were tested for their appearance and the existence of any aggregates.

Measurement of particle size, polydisperse index, particle distribution

The mean size of the nanogels were measured by using Malvern MasterSizer 2000 MS and Zeta sizer, and values were recorded.

Determination of pH

The pH of the nanogel formulation was measured utilizing the digital pH meter Electrolab®.. A small quantity of formulation was moved to a beaker comprising a specific volume of purified

water. The electrode was dipped into the formulation and the pH of nanogel was noted.

Drug content

The drug content present in the formulation was calculated using scanning through UV Spectrophotometer and High-performance liquid chromatography.

Spreadability

This parameter of nanogel was determined by utilizing two slides (5 cm2). The 0.5g of the formulation was put in the middle of two slides and held aside for 1 min. The diameter of the spread circle of nanogel was measured and compared.

Infra-red spectroscopy

The IR spectrum of nanogels was obtained by using an FT-IR spectrophotometer, in the IR range of 4000-400 cm^{-1}.

Scanning electron microscopy (SEM)

The surface morphology of nanogel formulation was determined by scanning electron microscopy using a 20kV electron beam at magnifications X30, X500, X1000, and X3000. Samples were prepared by placing the droplet of nanoparticulate dispersion of samples onto an aluminum metal plate and dried under vacuum to form a dry film, which was then observed under the scanning electron microscope.

Viscosity

The Brookfield Rheometer with spindle no 64 at 10 rpm was used to determine the viscosity of the nanogel formulation. The assembly was connected to a thermostatically controlled circulating water bath maintained at 25°C. The viscosity was determined and added up to the beaker encased with a thermostatic jacket. The spindle was allowed to move into nanogel and the values were noted.

In-vitro drug release study

The Franz diffusion cell apparatus was utilized to study the in-vitro drug release of the formulation. The formulation was spread on a dialysis membrane which was positioned in the middle of the donor-receptor chamber of the Franz diffusion cell. The temperature was maintained at 30°C. This assembly was subjected to magnetic stirring and stirred continuously using a magnetic field. The % drug liberated from nanogel formulation was calculated.

Stability study

Accelerated stability of nanogel was carried out according to ICH guidelines. The stability study was performed at 25 ±2°C and 60 ±5% RH in an environmental stability chamber over three months to assess the stability of topical nanogel. The formulation was transferred to amber-colored glass vials plugged and kept in the stability chamber. The consistency, drug content and in-vitro drug release were measured after three months.

Conclusion

Nanogels have drawn extensive research interest for applications in targeted drug delivery, diagnosis, biosensing, and separation of biological substances. Nanogels have been helpful in providing the better action or potency of the drug due to their small particle size, as the less the particle size the more the surface area and hence more the action. Nanogels exhibit the features of both the hydrogel and nanoparticles that make them a unique carrier system in that the hydrogel properties allow nanogels to accommodate an enormous quantity of water and hence increase their drug loading capacities, impart tissue-like properties, and make them flexible while the nanometric size of these particles allow them to enter deeper tissues, escape invasion by the reticuloendothelial system, provide site-specific delivery, etc. So far studies over nanogels have collected enough evidence to prove nanogels as potential targeting carriers that can deliver bioactive substances by topical delivery of skin for conditions like skin cancer, wounds, inflammation, local anesthesia, etc.

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