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REVIEW ON FORMULATION AND EVALUATION OF NANOGEL

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ABSTRACT

The term 'Nanogel' is defined as the nanosized particles formed by physically (or) chemically crosslinked polymer network that swells in a good solvent. Nanogels are crosslinked nanoscale particles made of flexible hydrophilic polymer ranging from 100-1000 nm. Nanogel are 3D network. Due to their relatively high drug encapsulation ability, consistency, effortless preparation, negligible toxicity, and stability in the presence of serum, including stimuli responsiveness, these studies integrate characteristics for topical drug delivery. Due to the entrapment of nanoparticles in the gel matrix, nano gel used as dermatological preparation has prolonged exposure times on the skin, thereby extending the duration of therapeutic efficacy. These are water-soluble and allow immediate drug loading in aqueous media. These are syntheses by various methods like precipitation polymerization, photolithographic technique, micro-molding method, membrane emulsification, reverse micellar methods, etc. Where properties of nanogel should be definite size, swelling, high loading capacity, and stability. Promethazine hydrochloride is a first-generation antihistamine used for the treatment of allergic conditions, nausea and vomiting, and motion sickness. Promethazine, originally known as 3,277 R.P., is an N-dimethylaminopropyl derivative of Phenothiazine that was developed in France in 1946. Promethazine antagonizes a variety of receptors, allowing it to be used for a few indications including allergic reactions, pain, sedation, nausea, and vomiting. The application of nano gel in various diseases like allergic conditions, autoimmune disease, local anesthesia, ocular drug delivery, and topical drug delivery. The drug delivery method using nano gel needs more in-depth research to better understand how cells and molecules interact with them and how to overcome limitations.

KEYWORD: Nanogel, nano-scale particle, cross-linkage, 3-D network, gel matrix, topical drug delivery, polymerization, promethazine hydrochloride, allergic condition, anti-histamine, high loading capacity.

INTRODUCTION

Nanogel can be termed as the dispersion of hydrogel by physical and chemical cross-linking polymer at the nanoscale size. It was first introduced by cross-linked bifunctional networks of a poly-ion and a non-ionic polymer for the delivery of polynucleotides. Although soluble in water, nanogels differ from linear macromolecules with comparable molecular weight in their properties. Nanogels are 3D hydrophilic networks that absorb large quantities of water or physiological fluids without changing the internal network of the structure. Nanogel are typical formulation usually size range of 100 nm, to maintain the three-dimensional structure by varying solvent quality and branching the volume fraction can be altered. Since gene delivery has now become possible within cellular organelles for gene silencing therapy, Nanogels have transformed the field of gene therapy. Due to the three-dimensional structures of nanogels, drugs, polymers, and dispersed liquid phases were entrapped easily. Nanogels have revolutionized the field of gene therapy because they have made it possible to deliver genes within cellular organelles for gene silencing therapy. 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. As a result of specific delivery system anticipation, the nano-sized microgel and hydrogel have arisen. A large variety of polymer systems and the easy alteration of their physico-chemical characteristics have given advantageous forms of nanogel formulations. Nanogel exhibits properties between solids and liquids. Despite its use as a drug delivery system, nanogel has been studied for longer periods in the production of other substances like quantum dots, dyes, and other diagnostic agents. Nanogels are mostly used in sensing, diagnostics, and bioengineering, but in spite of that, it is also used in drug delivery. 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 raise the duration of therapeutic potency. Nanotechnology is an innovative technology that offers a broad range for a smart drug manufacturing and delivery (nanomedicine) approach that involves the synthesis and characterization of materials or molecules, Design, and devices that have constructive function at a manometer scale. the studies conducted in university labs and pharmaceutical

companies from around the globe reported that novel nano-sized particulate drug delivery systems (DDS) have had a significant effect on disease prevention, diagnosis, and treatment. Nanogels are suited to be administered 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 nano gel 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 mechanisms

ADVANTAGE

1. **Biocompatibility and degradability:** Nanogel is produced from natural or synthetic polymers. Due to their high biocompatibility and biodegradability avoid their accumulation in organs.
2. **Permeability and particle size Due to their nano-size, 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.
3. **Colloidal stability:** While handling nanoparticles, there is a tendency for aggregation that compromises colloidal stability. Increasing zeta potential (minimum of ±30 mV) results in greater repulsive forces between particles that electrostatically stabilize them.
4. **Non-immunologic response:** This sort of drug delivery system does not give rise to any immunological responses.
5. **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.
6. **Swelling characteristics in aqueous media:** Nanogels have a good affinity to aqueous solutions, Swelling occurs only when osmotic pressure is exerted by medium ions and an

imbalance in the polymer's network swelling pressure. Resulting in their capacity to swell or dwell, imbibing water when positioned in an aqueous medium.

7. **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.
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 leaked 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. **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.

DISADVANTAGE

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.
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.

NANOGEL DRUG DELIVERY IS CONSIDERED BETTER THAN OTHERS DUE TO

1. Capability to reach the smallest capillary vessels because of their minute space, and to penetrate tissues either via paracellular or transcellular pathways.
2. The size and surface characters can be controlled to avoid rapid clearance by reticuloendothelial cells, allowing passive and active drug targeting.
3. 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.

PROPERTIES OF NANOGEL

1. Biocompatibility and degradability

Nanogel is synthesized by using natural or synthetic polymers. For preventing deposition in systemic circulation this polymer plays a vital role as these are biocompatible and biodegradable. In addition to this, the formulation of nanogel Chitosan, poly-acrylic acid, methylcellulose, sodium alginate, and several polysaccharide-based polymers like dextran, pullulan, and cyclodextrin can be used. Carbohydrate-based polymers like Polysaccharides are typically formed of repeating monosaccharide units linked by glycosidic bonds. These polymers are biodegradable, stable, hydrophilic, and non-toxic in nature.

2. Particle size

In the endothelial area of skin tissue nanogel can easily diffuse and in some cases through a specific pathway. Due to particle size, many routes of administration face the challenge of crossing the Blood Brain Barrier (BBB). So, to overcome this issue, nanogels were developed which have a size in the diameter range from 20-200 nm.

Nanogels are effective in avoiding the basis of physiological parameters like hepatic filtration, tissue extravasation, tissue diffusion the rapid renal exclusion due to the range of size in 10-100 nm. However small enough to avoid the uptake by the reticuloendothelial system. Small particle size results in good permeation capabilities, and kidney excretion Size of nanoparticles is a vital factor in the biodistribution of long-circulating as well.

3. Colloidal stability

Preventing the development of aggregation into the bloodstream due to the surface charge of polymers inhibits the development along with their associated problems. This could be due to higher repulsive forces between particles leading to nanogel stabilization which is altered by increasing the zeta potential. Polyethylene glycol is also a chemical method used to integrate surfactants which produce a steric effect and hydration forces to give a stable nanosuspension.

4. High water content/swellability

Nanogels have rapid swelling and de-swelling properties due to their high-affinity functional group of polymers.

5. Non-immunologic Response

This nanogel drug delivery system usually doesn't produce any immunological responses.

6. Softness

In the biomedical field and biodistribution, the softness of nanogel is a crucial parameter and it can be adjusted by variation on the structure of nanogel.

7. Solubility Nanogels are able to solubilize diagnosis agents and hydrophobic agents in their core or networks of gel. In addition, lyophilic molecules can be solubilized into lipophilic domains presented in some nanogels.

8. Higher Drug Loading Capacity

The higher drug-loading capacity of nanogels depends on the functional group present in the polymeric unit. These functional groups are very helpful in drug carrying and releasing, despite these functional groups having the ability to conjugate the drug and antibodies for targeting purposes. These hanging functional groups of polymeric chains provide the initiating the hydrogen bonding and wander wall forces of interaction within the gel network. Therefore, eases the drug-carrying capacity.

9. Electromobility

Nanogels is prepared without harsh condition and employs energy like sonication or homogenization, which is critical for encapsulating biomacromolecules.

10. Colloidal Stability

Over the surfactant micelles nanogels or polymeric micellar nanogel systems have a higher stability and exhibit slower rate of dissociation, lower critical micelle concentrations, and longer retention of loaded drugs.

APPLICATION

① Cancer treatment
② Autoimmune disease
③ Neurodegenerative disorders
④ Diabetes
⑤ Inflammatory disorders
⑥ In stopping bleeding

⑦ Used for delivering the drugs intracellularly

⑧ Local Anesthetic

⑨ Vaccine delivery

⑩ Bone regeneration.

MARKETED FORMULATION

1. Zyflex nano gel relaxes the muscle and erases the body's pain
2. Oxalgin nano gel gives deeper action and quick penetration
3. Sane care nanogel Reduces accumulated fat on the abdomen, arms, legs, etc.
4. Augen nano gel is an eye care gel with deep penetration properties
5. H A nano gel Reduces tooth decay and reduces bad breath
6. Revivagenix nano gel is an anti-wrinkle cream that gives hydration to the skin.

CLASSIFICATION OF NANOGEL

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

1. NANOGEL BASED ON LINKAGE 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 are 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 the polymer and the position of cross-linking points.

2. NANOGEL BASED ON THEIR

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, and 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.

CRITERIA FOR NANOGEL SYNTHESIS

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

SYNTHESIS OF NANOGEL

A.TRAFITIONAL NANOGEL SYNTHESIS

1. 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.
2. 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.
3. Chemical crosslinking is the most advanced and most flexible strategy for NG production.
4. 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.

B. PHOTOLITHOGRAPHIC THECNIQUES

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

1. 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.
2. 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.

3. Later, the particles with a thin residual interconnecting film layer are uncovered by removing the quartz template.
4. Eventually, the residual thin layer was removed using a plasma containing oxygen that oxidizes it.
5. 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.

C. EMULSION POLYMERISATION

1. Emulsion-based polymerization works through the formation of monodisperse kinetically stable droplets in a continuous phase.
2. 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.
3. 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.
4. NG formulation implies the use of monomers, initiators, catalysts, and crosslinking agents.
5. Generally, the process occurs in three steps: nucleation, precursor nanoparticle growth, and polymerization.

D. MEMBRANE EMULSIFICATION

1. In this technique, the dispersed phase was passed through the membrane (glass or ceramic), which possesses uniform pore size.
2. 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 flowed across the membrane, these fabricated emulsion droplets or microgels were recovered.
3. 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).
4. The size of the formed droplet was controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane.

E. PRECIPITATION POLYMERIZATION

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

F. DISPERSION POLYMERIZATION

1. In this method, most ingredients as well as monomers, chemical compound stabilizers, and initiators are unit soluble in an organic solvent as a continual section.
2. 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.

G. PHOTOINDUCED CROSSLINKING POLYMERIZATION

1. 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.
2. In the technique of irradiation, water molecules break down into hydroxyl radicals and hydrogen atoms with the potential to convert polymers into micro radicals, leading to intermolecular crosslinking, which promotes nanogel formulation.
3. Consequently, the crosslinking viscosity can be adjusted by controlling the wavelength or energy of the laser.

H. WATER IN OIL 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.

I. REVERSE MICELLAR METHOD

1. 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 comprised of aqueous droplets dispersed in the continuous oil phase.

2. The resultant micellar droplets have a submicron size ranging from tens to hundreds of nano-meters in diameter.

J. INVERSE (MINI) EMULSION POLYMERIZATION

1. 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.
2. As a result aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents.
3. 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.
4. 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.

K. INVERSE MICROEMULSION POLYMERIZATION

1. This method was explored for the preparation of distinct nanogels.
2. It delivers thermodynamically stable microemulsions upon the addition of an emulsifier above the critical threshold.
3. 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.

L.HETEROGENEOUS CONTROLLED (OR) LIVING RADICAL

M. CONVERSION OF MACROSCOPIC GEL TO NANOGEL

1. 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 nano gel or microgel synthesis to control the size.
2. The macroscopic gel networks were generally formulated by bulk polymerization, which produces a solid network structure with macroporous blocks.
3. These blocks were then crushed, grounded, and sieved to obtain gels of desired particle size.

4. However, this was a time and energy-consuming process and resulted in a considerable loss of material. Nevertheless, micro-and nanogels obtained from this method have particles of different shapes and sizes.

N. REVERSE MICROEMULSION POLYMERIZATION TECHNIQUE

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

POLYMERIZATION

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 the 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-shaped, and multimedia star copolymers.

b. Reversible Addition fragmentation transfer (RAFT) process

Through RAFT, a polymer undergoes a series of reactions with thioester 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.

DRUG LOADING

The drug can be incorporated into nano gel by 3 technique

1. Covalent Conjugation

2. Physical entrapment
3. Self-assembly

1. Covalent conjugation

a. 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].

b. Covalent conjugation of the drug with cross-linked nanogels provides additional stability to the encapsulated drug.

c. Polysaccharides that possess hydroxyl groups readily interact with the carboxyl group in the drug by forming ester linkages.

d. In such instances, premature drug release can occur due to the cleavage of functional group bonds by enzymes like esterases.

e. In addition, by introducing easily cleavable linkers, degradable nanogels were synthesized for a mixture of applications.

2. Physical Entrapment

a. The incorporation of proteins in cholesterol-modified pullulan nano gels and siRNA in HA nano gels by physical entrapment.

b. Additionally, hydrophobic molecules can be incorporated into the nonpolar domain formed by hydrophobic chains present in nanogels.

c. In many cases, loading was achieved due to hydrophobic interaction in the drug molecules with the nano gel resulting in relatively low degrees of loading (not more than ca. 10%).

3. Self-Assembly

a. The self-assembly process was defined as the autonomous association of components into structurally well-defined aggregates.

b. It has many beneficial features such as – it is cost-effective, versatile, and facile.

c. This process occurs due to the system's thermodynamic minima, resulting in stable and robust structures.

d. Molecular self-assembly is illustrated by diffusion followed by specific association of molecules through noncovalent interactions, including electrostatic and/or hydrophobic associations.

e. Individually, such interactions are weak but influence the structural and conformational behavior of the assembly due to the large number of interactions involved.

f. While contrarily charged polysaccharides bind voluntarily due to electrostatic attractions, interactions amid neutral polysaccharides are likely weaker and non existent, a modification with chemical entities able to trigger assembly being necessary.

g. 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

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

The 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 a 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 is 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 nano gel aggregates occurred; 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 NANOGEL

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.

1. Emulsion-Solvent Diffusion Method

The nano gel 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 10 minutes using an ultra bath Sonicator. The drug phase was added drop by drop to the aqueous during high-speed homogenization for 30 minutes 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 was added with continuous stirring to form nanogel.

2. Nano Precipitation Method

The organic phase comprising the drug and polymer was 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 2 hours 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.

3. Emulsion-solvent evaporation method

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 2 hours. The formed nanosponges were collected by filtration and dried at 40°C in a hot air oven for 24 hours and were packed into vials. The polymer should be initially soaked in water for the gel formation for 2 hours 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.

4. Reverse micellar method

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.

5. Modified emulsification - diffusion method

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

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.

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.

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.

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

Appearance

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

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.

Drug content

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

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}

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℃. 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℃. 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

They provide safety, efficacy and more patient compliance hence are more superior to any other vesicular system. Nanogel have become promising carriers not only for topical treatment of local but also for systemic disorders. They can be explored in the future for delivery of various drugs through transdermal delivery. Formulation of nanogel in the form of vesicles in gel may improve their viscosity and hence increase their residence time on the site of action.

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