INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Advancement In Nanoemulsion And Nanogels Technology For Topical Drug Delivery

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ARTICLE INFO

Received: 17 May 2024
Accepted: 21 May 2024
Published: 31 May 2024
Keywords:
Nano emulsions, Nanogels, Drug Delivery, Topical Application.
DOI:
10.5281/zenodo.11403018

ABSTRACT

This review provides a depth information state of art of approach to advance drug delivery through Nano emulsion systems and nanogels for topical application. Nano emulsions and Nanogels mainly constitute of cutting-edge technology in drug delivery offering creative and innovative solutions to address limitations of conventional methods. This review provides full information of nanotechnology covering formulation, preparation technique, properties and advantages. Nano emulsion express superior stability and resistance to aggregation, making them ideal for various pharma companies, including biotechnology, medication therapy, cosmetics and diagnostics. In parallel nanogels, cross linked polymers networks, have emerged and promising carriers for both hydrophilic and hydrophobic chemical agents. This review mainly explains the diverse features of nanogels, including dimensions, shape, porosity and amphiphilicity, degradability which is able to tailored to meet specific drug development and information of all Nano emulsion and nanogels used in topical drug delivery.

INTRODUCTION

To address the significant concerns associated with conventional methods of drug delivery to overcome its disadvantages, a state-of-the-art approach to drug delivery has been devised[1]. The inception of the first nano emulsion dates back to 1940. Owing to a considerable positive tension at the interface between the oil and water phase, this type of emulsion lacks thermodynamic stability and enhance bioavailability. The purpose of this review is to provide a comprehension of the nano emulsion system and nanogels used in topical drug delivery[2]. Nano emulsions are emulsions prepared in nanometre dimensions so that to optimize the delivery of medicinal ingredient and to deliver drug into targeted site[3].

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reduced droplet size of nano emulsions, with relation to visible light wavelength, results in minimal visible light scattering. These emulsion isotropic system that is thermodynamically stable, wherein an agent something that emulsifies, such as a surface active agent and a auxiliary surfactant, is employed to homogenize two immiscible fluids into a singular phase to avoid phase separation. In contrast to other emulsions, nano emulsions exhibit superior kinetic stability against gravitational separation and aggregation and enhanced bioavailability of drug. Typically, the droplet diameter of small scale emulsions span from 20 to 200 nm. The fundamental distinction between an emulsion and a nano emulsion is its unique size and shape of the fragments scattered throughout the continuous period. The primary focus of this article is to deliver a thorough understanding of the formulation of nano emulsions, their preparation techniques, properties, advantages, and various applications. Nano emulsions have been produced as systems for the controlled release and delivery of biologically active substances to its targeted site and increased drug loading. They hold significant potential for application in the biotechnology, medication therapy, cosmetics, and diagnostics industries and in the treatment of serious disorder such as cancer. Macroemulsions, also referred to as emulsions, are typically defined as the dispersion of two immiscible phases within another. Traditional emulsions and nano emulsions primarily differ in two aspects: the particle dimensions and form within the ongoing phase as compare to nano emulsion. Nano emulsions exhibit significantly smaller particle diameter (ranging from 5 to 200 nm) as compared to traditional emulsions (0.1-100 μm).

ADVANTAGES OF NANOEMULSION

1. Since active lipophilic substances can be effectively solubilized by nano emulsion drug delivery devices, they offer a variety of uses such as used in serious disorders.
2. It could be utilized in place of vesicles and liposomes.
3. It increases the drug's bioavailability and drug loading.
4. It has no harmful or irritating properties.
5. Its physical stability has improved.
6. Nano emulsions have tiny droplets with a larger surface area, increasing absorption and enhance bioavailability
7. Food does not interfere in such kind of drug delivery system[4].

PROPERTIES AND APPILICATIONS OF NANOEMULSION

1. The nano emulsion is a small size ,have excellent stability, translucent appearance straightforward appearance, these properties make nano emulsion an alluring candidate these are their special characteristics[5]
2. Nano emulsions are a desirable contender for use in the culinary, cosmetic, pharmaceutical, food and drug delivery industries due to these characteristics. They can also be used as the foundation for creating advanced materials with special features.
3. Drug delivery systems increases solubility and medication loading in drug delivery improves bioavailability, regulates release, and enhances defense aganist the chemical and enzymatic degradation this is possible due to nano emulsions. The biopolymer alginate and the biocompatible polymeric surfactant F68 were present in the fluid medium in which the analysts disassembled the active components in pharmaceuticals into tiny fragments anisole into nanosized droplets of anisole. They then joined the nonstop phase, leaving a drop trapped in a hydrogel. A composite hydrogel is the next soft substance.

4. Compared to conventional emulsions, nano emulsions exhibit superior stability opposing flocculation, sedimentation, and cremeing, cracking Their huge droplet surface area and small droplet dimensions facilitate targeted medication delivery and have a good impact on drug of a fluid surface with beneficial moieties, such as creator macromolecules, Nano emulsions can be used as building blocks for the construction of more unexpected materials.

METHODS OF PREPARTION OF NANOEMULSION

HIGH ENERGY METHOD

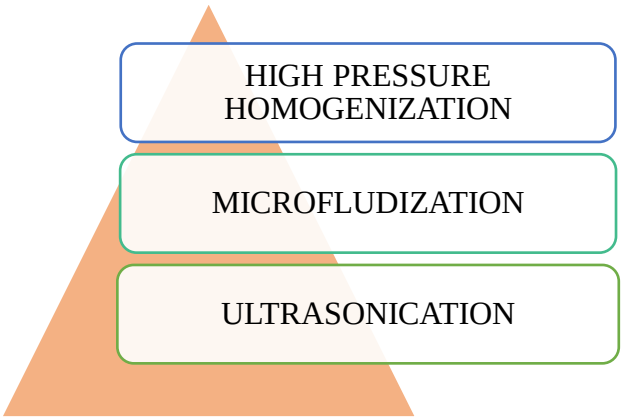

Fig 1: Methods of preparation of Nano emulsion

LOW ENERGY METHOD

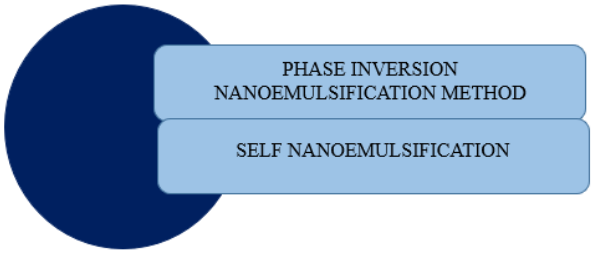

Fig 2: Low energy methods for preparation of Nano emulsion

PHASE INVERSION EMULSIFICATION METHOD:

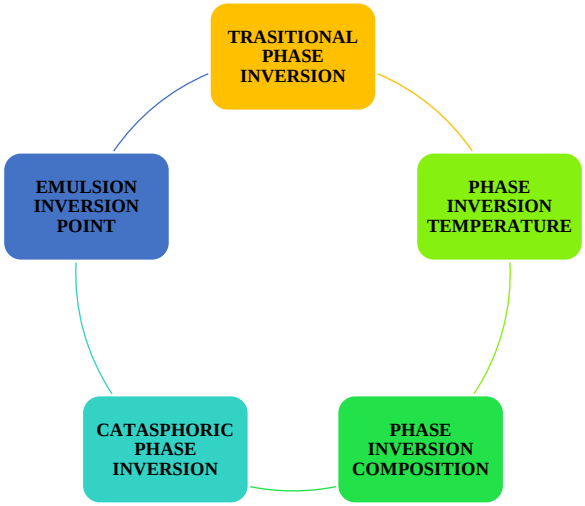

Fig 3: Phase inversion emulsification methods for preparation of Nano emulsion

HIGH ENERGY METHOD

Nano emulsion formulation is a common use of high energy technologies. In these methods of emulsification that involve high-energy, numerous apparatuses are employed to generate an exceedingly elevated level of mechanical energy for the purpose of creating diminutive droplets of Nano emulsions. Strong disruptive forces generated by high mechanical energy are utilized to break apart big droplets into Nano-sized droplets and create elevated kinetic-energy Nano emulsions. The selection of instruments utilized in the methodology of preparation, together with the operational conditions encompassing time, temperature, time starting material and composition and chacteristics exert detrimental influences on the dimensions of the Nano emulsion fragments. Mechanical tools like high-speed homogenizers, micro fluidizers, and ultras nicators are used to produce the disruptive forces . The most common methods for creating nano emulsions are high-shear stirring, high-pressure homogenization technique, high-pressure homogenizer, or piston homogenizer, and ultrasound. In the sections that follow, a few high-energy emulsification processes are covered. We may choose the formulation composition and have more control over the particle size by employing high energy technologies. High energy approaches can also regulate the emulsion's stability, rheology, and colour.

High-pressure homogenization:

Piston homogenizers, also referred to as high-pressure homogenizers, are utilized in procedures of high-pressure homogenization to prepare the Nano emulsion. For the development of the smallest particle sizes, high-pressure homogenizers offer a consistent flow and a high level of energy. By means of this technique, It can be generated with droplet diameter of approximately 1 nm. The mixed oil and aqueous phase under a high pressure of around 500-5000 psi via a small intake aperture while experiencing force. Consequently, the utilization of high-pressure homogenizers stands as the most widely used approach for the creation of Nano emulsions. In order to fabricate Nano emulsions with remarkably minute particle sizes (up to 1 nm), high-pressure homogenizers are employed to generate a highly disruptive force. The application of force to the liquid combination engenders extreme turbulence and hydraulic shear, leading to the formation of exceedingly thin emulsion particles. Throughout this process, several factors are combined to yield Nano emulsions with exceptionally small droplet sizes, encompassing cavitation[6]n, hydraulic shear, and high turbulence.

MICROFLUIDIZATION

Micro fluidization is a mixing technology that operates on a micro scale using a device known as a micro fluidizer. This process involves mixing the oil and aqueous phase using a micro fluidizer device. This process involves the passage of fluids through small channels, referred to as micro channels, under high pressure conditions ranging from 500 to 20,000 psi. An emulsion forms within the apparatus when the greasy and water phases are let to continue in an homogenizer inline. These micro channels, which facilitate mixing at a micro level, play a vital part in the micro fluidization process . The macro emulsion, consisting of aqueous and oil phases, is combined and subsequently directed through the micro fluidizer. This macro emulsion then travels through the micro channels at high pressure until it reaches the interaction chamber. Droplet size in the micro fluidization process reduces the homogenization pressure pressure rises when the dispersed to continuous phase viscocity ratio decreases or increases, and so on. Within the interaction chamber, two streams of macro emulsions collide at a high velocity, resulting in various forces such as shearing, cavitation, and impact. These forces

contribute to the formation of stable Nano emulsions. In comparison to homogenizers, micro fluidizers are capable of producing narrower and smaller particle size distributions for Nano emulsions..Additionally, micro fluidizers enable the production of stable Nano emulsions with lower concentrations of surfactant. Using the micro fluidization method, Y.J. Jo et al. prepared a β-carotene Nano emulsion with the following components: food protein such as whey protein isolate (WPI), soybean protein isolate , polyoxymethylene sorbitan monolaurate (Tween-20), , and medium chain triglycerides (MCT) oil. Micro fluidization techniques have been employed in the production of Nano emulsions for food ingredients. These techniques yield food-grade Nano emulsions with uniform droplet size distributions and enhanced stability.

LOW ENERGY METHOD

Low-energy techniques necessitate minimal energy for the creation of Nano emulsion systems. Low-energy emulsification methods technique use less energy due to their utilization of the internal chemical energy within the systems, and the production of Nano emulsions merely necessitates gentle stirring. Generally, low-energy approaches are not considered suitable for the production of food-grade. Nano emulsions due to their requirement for a high concentration of surfactant, which can have an adverse impact on the taste and safety of food formulations.

PHASE INVERSION EMULSIFICATION:

Nano emulsions are dynamic systems that do not possess the ability to form spontaneously. Consequently, the formation of these systems requires the application of either mechanical or chemical energy. The process of emulsification known as phase inversion emulsification involves occurring during emulsification process due to the spontaneous curvature during emulsification process. Nano emulsions are typically produced through the utilization of high-energy techniques, whereby mechanical energy is imparted by means of high-speed homogenizers, high-shear stirring, and ultrasound generators. Changes in the surfactant's spontaneous curvature occur as a result of alterations in parameters such as temperature and composition, which play a crucial role in the emulsification process. The PIT method is based on changes in molecular geometry and the solubility of non-ionic surfactants when the temperature of the Nano emulsion system is altered. The second mechanism, PIC, involves the utilization of Emulsion Inversion Point (EIP) The occurrence of transitional phase inversion primarily arises from changes in the spontaneous curvature or affinity of the surfactant, caused by variations in temperature and composition. On the other hand, catastrophic phase inversion occurs when the dispersed phase is continuously added until the dispersed phase droplets aggregate with each other, resulting in the formation of continuous/lamellar structural phases.

PHASE INVERSION COMPOSITION.

Phase Inversion Composition is a method that involves with volume fraction of water. Nevertheless, phase inversion in PIC is accomplished by altering the composition of the system as opposed to its temperature. When water was added to the oil phase to create W/O, the phase inversion mechanism took place. O/W water droplets form when the water volume increases. In PIC, a component, like water, is added to a mixture, and then oil-surfactant or oil is added to the mixture of water and surfactant. Interface curvature is the term for the inversion pathway.The water phase's surfactant's hydrophilic-lipophilic characteristics will balance, and the surfactant's spontaneous curvature will 230 Kumar and others.

PHASE INVERSION TEMPERATURE

Hydrophilic lipophilic balance (HLB) is one of the characteristics that drives the emulsion from O/W to W/O, and it is used to determine the Phase

Inversion Temperature. The PIT approach uses temperature changes to inverse surfactant spontaneous curvature. The emulsion is comprised of three distinct phases, namely oil, middle phase, and water, subsequently subjected to a swift cooling process until it reaches ambient temperature. Polyethoxylated surfactants, which are classified as non-ionic surfactants, experience dehydration of their POE groups. This dehydration process renders the surfactant more lipophilic and consequently brings about alterations in the surfactant's curvature. Recently, a study demonstrated that the Pressure Interference Test (PIT) can also be utilized as a technique to improve the extraction of oil through the evaluation of the conductivity parameter.

NANOGELS:

Nanogels are mainly cross-linked swellable polymer networks which form three dimensional hydrogels. It have a high water-holding capacity actually without dissolving into aqueous media.[6] Nanogels are nanotechnology which are increasing day by day and have become vast promising system of drug. It is physically self - assembling and have capacity to enclose hydrophilic and hydrophobic medicinal agents such as protein and small molecules DNA/RNA sequences, and even ultra-small nanoparticles.[7] Nanogels have excellent stability, drug loading capacity, biologic consistency, good penetration ability and environmental stimuli responsiveness. [8] Nanogels consists of various naturally occurring polymers can be used to create nanogels. There are many characteristics such as size, charge, porosity, amphiphilicity, softness, and degradability by doing changes in chemical composition.[9] Various ligands can modify nanogels to achieve active targeting and enhance drug accumulation in disease locations, increasing treatment results and precision.

ADVANTAGES OF NANOGELS-

As compared to other drug delivery methods, nanogels have a number of benefits, such as the following:

- Reduce adverse effect by direct targeting to target site and regulate controlled release of bioactive compounds[10]
- Nanogels having very long-lasting serum half-life since they don't clear kidney as well.
- Nanogels have special characteristics to encapsulate multiple bioactive chemicals in single formulation.
- After administration nanogels remains inert in the internal aqueous medium and systemic circulations and minimize risk of immune response.
- Due to their high affinity for aqueous solution easily nanogels can absorb water in aqueous media result may be swell or unwell as a result. Because of such kind of property, they are very perfect dosages form for delivering and absorbing proteins, peptides, macromolecules and big medication
- Nanogels are formulated in such way release in a sustained and controlled manner, reduce side effects and enhance therapeutic results.
- Various biomolecules there are compounds with different molecular weight can easily encapsulated by nanogels these molecules continuously in the biological membrane

TYPES OF NANOGELS-

Nanogels can be mainly classified into two main categories based on their cross-linking structure: that is physically cross-linked nanogels, which are cross-linked through non-covalent bonds such as hydrogen bonds, electrostatic interactions, and hydrophobic interactions, and chemically (covalent) cross-linked nanogels, which form crosslinking points through covalent bonds. They are mainly spheres in shape. Larger loading molecules are greatly compactible with nanogels and have hydrophilic character.[11]

MICELLES:

Micelles mainly consist of spherical amphiphilic structures surrounding with a hydrophobic centre and with hydrophilic shell. Hydrogen bonding produces core-shell morphological structures, where a hydrophilic polymer block encircles a hydrophobic core block segment, stabilizing the entire micelle. [12]

PEG-PEI (poly (ethylene glycol)-polyethyleneimine)-BASED DRUG DELIVERY:

PEG-PEI (polyethylene glycol – Polyethyleneimine) was the first nanogels to be discovered in 1999. Another illustration of a nanogels is this. Polyethyleneimine, or PEI, has mainly exhibit to be cytotoxic. Nanogels of PEG-PEI are mainly highly biocompatible. Main reason for this is PEG (polyethylene glycol). PEG shown non-toxic and non-immunogenic behaviour make the material less toxic and more soluble in water, increasing its biocompatibility compared to PEI alone. Size of nanogels is one of important properties that must be understood because it affects both the system's effectiveness as a drug release mechanism and its possible uses. PEG-PEI nanogels particles' modest size (20–220 nm) specially it improves penetration.

GREATER ABILITY OF NANOGELS TO LOAD DRUGS.

Higher loading capacity is most beneficial of nanogels because it required less carrier material mainly allowing best control over drug release improving safety and efficacy. Nanoparticle's loading capacity can be defined as the amount of drug loaded per unit weight of the nanoparticle and it also indicates percentage of mass that is composed of drug encapsulated material. Loading capacity can be mainly calculated by diving total amount of medicine which they contain. Nanogels have a higher capacity especially for drug loading due to functional group found in polymeric unit. Through functional group the ability of medication to transport and release are influenced by these functional groups. Functional groups are able to target by combining an antibody and drug.

SINGLE STIMULI RESPONSIVE NANOGELS

PH RESPONSIVE NANOGELS

The capacity of material to respond to outside stimuli make material smarter. In order to used external stimuli for smart DDS system smart material are only able to sense them. PH sensitive polymer nanogels have capacity of reacting to PH variations both in vitro and in vivo. Reversing nanogels for both rapid drug release at intended site and moderate drug release while circulating in the blood are created using polymers based on PH. Because of swelling in an acidic PH environment ionization status of nanogel changes. Specially for loading and release of biological substances nanogel PH dependent swelling responses may be useful. [12]

TEMPERATURE SENSITIVE NANOGELS.

Temperature Sensitive Nanogels display reduced exposure to normal cells enhanced therapeutic efficacy and low toxicity. There are many uses of the temperature sensitive nanogels include transdermal application, cancer therapy, microbial infections, and tissue restoration.

Influences in temperature have a impact on internal networks of nanogels as well as its size and interactions with foreign particles, which can result in the controlled release of biomolecules that have been loaded.

MAGNETIC FIELD RESPONSIVE NANOGELS.

At intended location, nanogels are capable to distribute drugs for extended period of time. The construction of a vectoring delivery at the necessary targeted place is a reproving concern for nanogels. Previously, super-para MNPs were employed for cell patterning, blood purification, targeted medication administration, clinical imaging, and biomarker detection in vivo. To

create innovate nanogels biomaterial is used for MNP'S inherent qualities and biocompatibility.

To increase gel networks or PH responsiveness the MNPs make the elastic hydrogel matrices magnetic field-sensitive. We can discover smart biomaterials and by magnetic field they can be controlled externally that respond to minute changes in tissue microenvironments by combining the benefits of intelligent hydrogels with MNPs.[13]

CORE SHELL NANOGELS.

By engaging poly (ethylene glycol)-methyl ether methacrylate (PEGDMA) as a stabilizer (shell) and NIPAM and 2-methacryloyloxy benzoic acid as a crosslinker (core) n a one-pot soap less emulsion polymerization, temperature- and pH-sensitive core-shell nanogels were created. By utilizing acid-labile cross-linker 9-divinyl-2,4,8,10-tetraoxaspiro [5.5]-undecane (DVA), the size of nanogels had roughly 100nm. By an ionic interaction between carboxylate group of and protonated amide group of drug high drug loading take place. FESEM, TEM, EDS, DLS, zeta potential, and FTIR are used to identify the characteristics of core shell nanogels.

REDOX RESPONSIVE NANOGELS.

Because of high concentrations of reducing agents like thioredoxin, reduced glutathione (GSH), and peroxiredoxin inside cells relative to their concentration in the extracellular environment, nanogels that are responsive to redox stimulation frequently contain cross-linking formed by disulfide bonds. They mainly formed random copolymers by post-polymerization modification of poly(pentafluoro phenyl methacrylate)-co-polyol go(ethylene glycol methacrylic amide) (PPFPMA-co-POEGMAM). Given self-assembly into micelles from these responsive nanogels were formed by addition of cyst amine as a cross-linking agent. They surround a model hydrophobic drug inside the micelles during their formulation, and they demonstrated release nature with or without GSH.[14]

LIGHT RESPONSIVE NANOGELS

Utilization of near infrared light, mainly which have wavelength between 650 to 900nm as stimulus to trigger drug release, with advantage mild reaction, high biocompatibility, ability for in situ polymerization for specific applications and low toxicity. Nanogels mostly have ability to react to light by changing their structure and conformation are light responsive nanogel. It is demonstrated that a novel type of polymer nanogel is light-responsive in the near-infrared (NIR) A photothermal nickel-bis(dithiolene) multiplex is used to crosslink the micellar aggregates of an ABA-type triblock copolymer. The copolymer's core is a thermosensitive polymer with an upper critical solution temperature (UCST), which effectively transforms optical energy into heat when exposed to near-infrared light.[15]

DEGRADABLE NANOGELS

It is manageable to display that nanogels' biodegradability can respond to environmental stimuli and provide a variety of uses, such as selective DDS. Sensitivity to stimuli may facilitate the controlled, smooth release of loaded medicines from nanogels and validate the removal of empty DDS following drug administration. Biodegradable polymer nanogels are nanogels which show responsiveness of stimuli which results in changes in gel volume water content, colloidal stability, mechanical strength, and other physical and chemical properties, thus improving the site-specific topical drug delivery.

APPLICATIONS OF NANOGELS

i. **Nanogels as a therapeutic drug carrier.**

1. Because of their outstanding swelling, nanogels have capacity enclosed up to 30% of the weight of pharmaceuticals and biological molecules molecules via covalent bonding, interactions between the hydrophobic and polymer chains, van der waals, and electrostatics forces.

2. These loading abilities are higher than those of polymeric micelles and liposomes, which is rare . Drug loading causes the nanogels to crumble, encasing the biological agent inside stable nanoparticles. Their collection can be terminated by addition of distributing hydrophilic polymers within a nanogel matrix for eg (polyethylene glycol) polymer which is hydrophilic chains emerge at the surface of the drug-nanogel combination during its collapse, enveloping the nanogel in a protective c

Protein therapy delivery using nanogels.

Because of its capacity to enclosed large number of biomacromolecules and protect them from degradation, nanogels have highly studied for delivery of peptides and proteins Akiyoshi and colleagues conducted groundbreaking research in which they discovered that the cholesterol modified pullulan self constructed various protein types spontaneously assemble into a compound with nanogel, primarily through hydrophobic interations.

Antipyretic drug transdermal drug delivery.

By utilizing emulsion solvent diffusion technique, acelofenac nanosized dispersion was formed and then added to Carbopol,940. The synthesis mainly showed excellent stability, perfect porosity properties and long-lasting drug release. It has been determined that encasing magnetic nanoparticles such as iron compound increase the stability and sensitivity of each mixture as compare to delivery of these agents as unencapsulated compound.

ii. Nanogels as carriers for herbal drugs.

It has been demonstrated that nanogels are very effective carriers that may carry both carry and can advance the qualities of herbal drugs. These materials provide lot of potential for use as a drug carrier in the development of herbal drugs due to their adaptability and versatility quality. The cooperation of all of a herb's active ingredients is crucial to its efficacy.

Unluckily there are many issues related to solubility of herbal drugs result in high systemic clearance and low absorption. Herbal medicines compounds in nanogels form helps to overcome such restrictions. Chitosan based aleo emodin loaded nanogels against psoriasis was seen; However, they are less effective as compare to acitretin-loaded chitin-based nanogels.[16]

iii. Nanogel based theranostics for CNS diseases and delivery across blood–brain barrier.

The utilization of the nanogels as a medication drug delivery mechanism for CNS disorders have limitless promise. High permeability and stimuli responsiveness, core-shell architectures, biodegradability, biocompatibility, high stability in physiological solutions, and high drug encapsulation efficiency are some of the discriminating characteristics of nanogels that set them.[17] The modified polymeric nanogels systems have a power and potential to act as brilliant drug carriers, by multiping efficacy of drug delivery. This is accomplished by increasing specificity towards target sites, they by minimizing adverse effects. Furtherer more these systems have capacity to advance pharmacokinetics of drug resulting in expanded circulation time. As a consequence, they increase greater bioavibility and therapeutic efficacy.

iv. Therapeutics.

Stimulus responsive nanogels are nanocarriers that liberates payloads in response to stimulus hence augmenting the therapeutic characteristics of the nanogels. Due to its mucoadhesive qualities, chiton was commonly used to formulate nanogels used in therapeutic eye drops.Succinyl-chitosan, a chitosan derivative, was formed and has capacity to self-crosslink, Stabilizing the nanostructure. The Greater affinity this nanogel for mucous epithelium than for native chitosan in the data highlighted the possibility of using it as a mucoadhesive enhancer.[17]

v. Hyaluronic Acid-Based Nanogels as Targeted Protein Delivery Vehicles.

Therapeutic protein formation has worn lot of attention recently alternative to traditional pharmaceuticals particularly for the treatment of cancer and other illnesses. However, because of their less bioavailability less in-vivo half-life physical and chemical instability, therapeutic proteins are systemically. Many strategies have been used to meet the large unmet medical needs in protein delivery; one of the most encouraging is a application of HA based nanogels such as their large interior area to contain macromolecules and their hydrophilic shell that inhibits protein degradation, make them special methods for loading and deliverying protein.

Ophthalmic nanogel.

In ophthalmic nanogel polyvinyl pryrrolidone nanogel is produced by polymerization activated by y radiation. To keep pilocarpine at the site of action in the allowable concentration for an expanded period of time it is used to encapsulate the drug.Using nanogel to stop bleeding even in serious glasses, bleeding can stop a molecule of protein in the solution mainly used to formulate nanogels. The protein has a mechanism that allow them to self-build into biodegradable gel at the nanoscale.[18]

CHARACTERSITICS OF NANOGELS

- **Nanogel Particle size**

The nanogel particle size mainly vary from 5 to 400nm. Effective size range is critical in stopping rapid renal segregation due, to these it is also adequate to prevent reticuloendothelial system uptake. As they are nanoparticles, they can pass through blood brain barrier and may also have capacity to penetrate further. Shape and size of nanogels can be shown by using spectra analysis with electron microscopy. Best surface area availability for enzyme loading and improved interactions between the immobilized enzyme and substrate are ensured by nanogel particles.

- **Electromobility**

The nanogel could be produced without the need of most advanced system or machinery, they can be formulated in comfortable manner using less energy. These are the primary advantages of nanogels. Simple homogenization andand encasing sonication are adequate systematic ensnaring and encasing a medication or therapeutic substance.[19]

- **Biocompatibility and degradability**

Natural and biodegradable polymers formulate nanogel. Because they are highly biocompatible and biodegradable, they do not cause collection in the organ. The nanogel can be formulated using chitosan, methyl cellulose, ethyl cellulose, with a range of polymers based on polysaccharids including dextrin, pullulan, and dextran. For the most part, polysaccharides are polymers made of carbohydrates, which are composed of repeated monosaccharide units joined by glycosidic linkages. In nature, these polymers are biodegradable, hydrophilic, stable, and non-toxic.[20]

- **Colloidal stability**

If we do differentiation between nanogels or Polymeric micellar nanogels and the surfactant micelles. Best stability is mainly shown by polymeric micelles nanogels as compare to surfactant micelles nanogels. Furthermore, they have a stable rate of dissociation, low critical micellar concentration and improved drug loading drug or bioactive molecule conservation.

METHODS OF PREPARTION OF NANOGELS.

Innumerable techniques for formulating have been developed over time. Nanogel formulation can be formulated by either polymerization or crosslinking depending on the raw material and crosslinking.

Crosslinking and polymerization

Cross Linking and Polymerization are two techniques which are used simultaneously to formulate nanogels. Since the maximum of the crosslinking agent and monomers used to create nanogels are soluble in water, hence aqueous solutions are usually employed for polymerization process. There are mainly three types of concurrent polymerization and crosslinking procedure for preparing nanogels can be differentiate precipitation polymerization, inversion emulsion polymerization, and microtemplate polymerization function according to different mechanisms.[21]

Emulsion – Solvent Diffusion Method

The modified emulsion solvent technique is mainly used for formulating nanogels. It mainly consists of four steps are as follows.The initial step, Step I A precise amount of drug disintregrate stirring, in ethanol and propylene glycol .Step II Using Carbopol mixed in water and continuous stirring, heat the mixture for 20 minutes while stirring magnetically, the aqueous phase is formed. Moreover, the drug phase is sonicated for ten minutes using an ultrasonic bath Sonicator. [22]

Preparation of Diclofenac Sodium Nanogel.

Accurate quantity of drug, polymer, and stabilizer are prepared in aqueous phase with Carbopol-940 introduced in aqueous liquid and heated while mixing continuously. By utilizing ultrasonic bath sonicator drug containing phase is sonicated. At the time of homogenization, the drug phase is gradually introduced drop by drop into the aqueous phase to formulate emulsion. The homogenizer transformed emulsion into nanodroplets and formulating an o/w emulsion. For an hour, homogenization was maintained. Triethanolamine is added and stirred continuously to form the nanogel. The highest speed of 8000 was used to prepare batches A1, A2, and A3 with varying compositions. In contrast, homogenizers were used to prepare prototype batches B1, B2, B3, and C1, C2, and C3 at various rpms of 5000, 6000, and 7000.[23]

Micromolding method.

The procedures resemble those used in photolithography. They can cause reduction in the requirement for pricey lithographic machinery and clean room spaces. During the processing, the cells were submerged in a hydrogel precursor solution that contained a photo initiator in water, PEGDA, or methacrylate (MeHA). The final combination was used to hydrophilic PDMS patterns that had been plasma-cleaned, and it was subsequently photo crosslinked by exposure to UV radiation.[24]

Internalization of Photochemistry and Photoisomerization.

A Process known as photoisomerization" occurs when a bond with restricted rotation changes conformation as a result of exposure to light. Molecular structure when exposure to the light they typically isomerize from trans orientation to cis orientation. Especially molecular structure with double bonds are prime examples. A Process mainly known as photoisomerization" occurs when a bond with restricted rotation changes conformation as a result of exposure to light. Excitation of photosensitizer-loaded Nanogel results in the production of two types of oxygen: singly and reactively. This can cause oxidation in the walls of the cellular compartment, which has a substantial influence on the publication of therapeutic drugs into the cytoplasm. Release tests were conducted on aspirin-loaded Az dextran Nanogel. The results demonstrated that the development of the azo group's econfiguration is caused by the photo regulation-induced cis-trans isomerization of azobenzene. As a result, the aspirin release profile is improved over the prior Configuration.[25]

Evaporation of the Solvent Method

The medication polymer blend is introduced into the the specified region of the watery phase over

the course of the two-hour therapy. A magnetic stirrer is utilized to give constant stirring at 1000 rpm during this process. Subsequently, the resultant nano sponges undergo further filtration before being cured in a hot air furnace set at 40°C for a whole day. Nanosporites which are dried then are cautionaly placed into vials for a long-term storage. It is suggested that the polymer be submerged in aqueous for two hours prior to the start of gel prepartion in order to produce a homogeneous dispersion. The polymer should then be agitated at a rotating speed of 6000 revolutions per minute. A pH-adjusting substance is used to change the pH. The optimized nano sponge suspension, permeability enhancers, and aqueous dispersion are mixed together.[26]

NANOEMULSIONS USED IN TOPICAL DRUG DELIVERY ARE AS FOLLOWS:

1. Anti-inflammatory drugs.

Ibuprofen nanoemulsion for transdermal drug delivery.

Formulation of a nanoemulsion containing Ibuprofen was formulated using sonication process and formulation of nano-emulgel containing ibuprofen was formulated by using sonicator processor. Ibuprofen was mainly found to soluble in phosphate buffered saline at concentration of 0.651 mg/mL which is less than threshold considered to standard for transdermal administration. When ibuprofen was evaluated at PH of 7.4, its log D value a measurement of coefficient between octanol and water was 1.343 ± 0.019 this show that ibuprofen may be best option for transdermal medication since it has both lyophilic and hydrophilic property. In ibuprofen formulations ibuprofen was added successfully to all drug delivery systems they work effectively to penetrate through skin deliver medications in enough quantity to cause no toxicity.[27]

Pioglitazone nanoemulsion for topical drug delivery.

Pioglitazone has been expanded in recent research to have therapeutic promise beyond mainly used as antidiabetic medicine this is because of its anti-inflammatory activity which make PGZ a viable option for topical treatment of dermatological conditions Its restricted skin permeability and poor aqueous solubility, however, make distribution difficult. Particularly in dermatology, nanoemulsions (NEs) have shown promise as a method to improve drug solubility, absorption, and diffusion. In these study a pioglitazone nanoemulsion was formulated with excipient having high potential for solubilizing medication.[28]

2. Antifungal drugs.

Amphotericin nanoemulsion for topical drug delivery.

In this study, Preparation of gel with nanoemulsion for topical medication administration amphotericin B with the aim to enhance and maintain skin penetration assessing in vitro antifungal effectiveness, and evaluating in vivo toxicity. Nanoemulsion was prepared by utilizing Tween 80, Transcutol P ,Sefsol 218 oil, a series of nanoemulsion was formulated by using slow spontaneous titration. Histopathological was carried out on rats to look into possibility for toxicology.[29]

Nanoemulsion ferrying miconazole nitrate.

A nanoemulsion preparation of antifungal illinesses utilizing excipients was ready to manage fungus related pharmaceutical research to introduce different approaches to enhance topical pentration. This study is in in vitro , in vivo and ex vivo result point to a feasible strategy for managing resistance.In this findings irritation study carry the haemolysis findings and confirmed no irritation after utilizing . [30]

Nanoemulsion for treatment of Psoriasis for topical application.

To maximize the solubility, skin deposition, and penetration of curcumin and to achieve therapeutic

efficacy for treatment of Psoriasis the nanoemulsion system was formulated. CUR-NEG was formulated using the cross-linked polyacrylic acid-based gel to improve patient comfort and effectiveness of curcumin nanoemulsion. [31]

3. **Nanoemulsion used in treatment of Psoriasis**

- Psoriasis is mainly skin condition which does not spread through physical touch and is not fital However, because of a person's imperfect look, this seemingly innocuous illness can cause social stigmatization and a loss of confidence. Conventional approaches to treating psoriasis involve topical medication applied to the skin's surface to stop cell proliferation or systemic medication taken internally to suppress immunological reactions in the body. Because they have fewer negative effects than systemic techniques, topical approaches are preferred. There are various novel drug delivery system including nanoemulsions, liposomes, nanoparticles among these nanoemulsions have been formulated to increase bioavibility and to make better therapeutic efficacy and safety. The advantage of nanoemulsion over other delivery technologies is its reduced production cost and simpler technique. [32]
- **Nanoemulsion containing leflunomide for treating melanoma.**

Anti-rheumatic medication like leflunomide that modifies illness and used in the treatment of melanoma. Due to its limited permeability and gastrointestinal adverse effects, oral administration is inconvenient. In order to get over these challenges, a self-nanoemulsifying approach was used to create an LFD nanoemulsion-based gel for transcutaneous administration. Transcutol® HP, Capryol® 90, and Cremophor® EL were employed in the carrier system as non-ionic hydrophilic surfactant, oil, and co-solvent. Because of Pluronic® F-127's thermoreversible characteristics, which both promote and delay medication penetration through the skin, it was chosen as the gelling agent. Tests for in vitro cytotoxicity revealed a marked reduction in cell viability and an accelerated rate of cell death. [33]

- **Nanoemulsion for treatment of Rheumatoid arthritis.**

One of the best NSAIDs that works well for treating arthritis is piroxicam. The current review demonstrates the production of a novel prepartion intended for topical use with the goal of reducing PXM adverse and increasing efficacy and bioavibility. PXM was successfully added to oils from soyabeans ,cremophor and arachis in a nanoemulsion formulation. The revised prepartion demonstrated a highest increase in bioavailability, increased analgesic effectiveness, acceptable particle diameter and in vitro release characteristics, and improved stability .[34]

NANOGELS USED IN TOPICAL DRUG DELIVERY ARE AS FOLLOWS.

- **Anti-inflammatory**

Tenoxicam is a NSAID drugs which is utilized in the treatment of inflammatory arthritis it consists of gastrointestinal side-effects and weak transdermal penetration. A study mainly focuses on to formulate nanogel with smaller particle diameter to enhance bioavailability and efficacy and access its benefits in inflammatory arthritis. The adapted diffusion emulsification- technique was utilized, and essential oils were added to increase skin penetration. The nanogel, with a particle size of 125.05nm, drug content of 97.05%, and a pH of 6.2, was found suitable for topical gel formulations. [35]

- **Anti-fungal**

As an antifungal, ciclopirox olamine has been used. Because Ciclopiroxa olamine when taken orally can irritate and ulcerate the gastrointestinal tract, it is used topically instead of orally. This study uses an antifungal nanogel that has been designed enhance in-vitro dispersion and in-vivo

release studies while also decreasing particle dimensions In order to create Ciclopirox olamine nanogel, homogenization process are used exhibiting an inflection point during nanogel formation. The nanogel give best local absorption and low systemic absorption, making it a promising approach for treating actio mycosis. [36]

- **Anti-cancer drug**

Anti-cancer medication compositions have the ability to revolutionize targeted cancer therapies. However, standardization and scaling up research are needed to expand knowledge and confirm safety. Clinical trials using CHP-based anticancer vaccines showed safety and effectiveness in generating antigen-specific T-cell responses and humoral immunity. However, clinical efficacy has been insufficient, and more research is needed to understand the precise immunological pathways of immune response generation. Start-up pharma companies are expected to utilize nanogels as a target delivery system for anticancer drugs.[37]

- **Nanogel in the treatment of Hyperplasia of Psoriasis**

The traditional antipsoratic method of phototherapy may be limited due to psoratic lessions might cause local hypoxia. Alkyl radical-based therapy can be used to treat psoriatic hyperplasia by generating oxygen-independent alkyl radicals. The study presents an administred nanogel topically that creates a network that respond to PH modification in the skin allowing. Rapid release of alkyl radicals at the intended location .The nanogels showed antipsoriatic activity in keratinocyte and animal studies. The nanogels can be delivered into the epidermis without causing cutaneous irritation. [38]

- **Topical Niacinamide Delivery to skin through Hybrid Nanogels Boosts.**

A hybrid nanogel was designed to enhances cutaneous administration of niacinamide, an antioxidant used to slow aging. The nanogels exhibited robust, porous macrostructures and improved skin penetration particularly. These promising nanogels could be included into after sun lotions or sunscreens to improve skin protection.[39]An inhibitor of cyclooxygenase is used for rheumatoid arthritis treatment. However, its partial solubility and high lipophilic nature make it challenging to develop topical formulations. A nanostructured lipid carrier (NLC)-based ACE hydrogel was developed for efficient transdermal delivery. The optimized formulation was incorporated into Carbopol® 940 gel and compared to the existing Mkt-gel formulation. The ACE-NLC-gel showed good rheological and texture characteristics, better skin distribution, and deeper penetration, making it a promising nanoscale lipid carrier for topical application.[40]

- **Terbinafine HCL nanogel**

In this study, a novel treatment for superficial fungal infections by using PH responsive Terbinafine Hcl loaded nanogels, which where then demonstrated for swelling, the result of dehydration, Particle dimension and drug release. When compared to Lamisil cream, the optimized nanogels demonstrated better skin retention and antifungal activity. Their efficacy was validated by in vivo investigations on animal models, suggesting that nanogels containing weakly soluble TBH would be a viable strategy.

LIST OF NANOEMULSIONS USED IN TOPICAL DRUG DELIVERY

Drug	Nano emulsion Formulations	Category	Applications	Key Findings
Amphotericin	Gel with nano emulsion	Anti-fungal Used in treatment of fungal infection.	Topical anti-fungal	Increased skin penetration in vitro anti-fungal and in vivo safety evaluation.
Pioglitazone	Nano emulsion	Anti-inflammatory Used in treatment of rheumatoid arthritis.	Topical drug delivery	Improved solubility, absorption and diffusion.
Miconazole nitrate	Nano emulsion	Anti- fungal Used in fungal infection	Topical anti-fungal Treatment	Effective management
Curcumin	Nano emulsion system with cross linked polyacrylic acid based gel	Psoriasis Treatment Immune system become overactive	Treatment of psoriasis	Skin deposition, improved solubility increased therapeutic efficacy for psoriasis
Leflunomide	Self-nanoemulsifying drug delivery system	Melanoma treatment Anti-cancer drug	Treatment of melanoma.	Increased transcutaneous administration
Piroxicam	Nano emulsion	Rheumatoid arthritis Autoimmune inflammatory disease.	Treatment of rheumatoid arthritis	Enhanced bioavailability Increased analgesic effectiveness and improved solubility.
Retinol	Nano emulsion	Topical anti-aging treatment	Anti-aging treatment topically	Increased skin penetration and prevent skin from aging

NANOGELS USED IN TOPICAL DRUG DELIVERY

Drug	Nanogel formulation	Applications	Key Findings
Tenoxicam	Nanogel with smaller particle dimensions	Anti-inflammatory agents Used in treatment of inflammation	Increased bioavailability and efficacy.

Anti-cancer medication	Nanogels as a targeted drug delivery in which drug is targeted to specific site used in treatment of cancer.	Anti-cancer drug Used in treatment of cancer.	Beneficial for revolutionizing targeted cancer therapy
Niacinamide	Hybrid nanogel for increased cutaneous administration.	Anti-aging skincare To reduce the appearance of wrinkles in the skin.	Enhanced skin penetration potential skin inclusions in after skin lotions.
Acelofenac	Nanostructured lipid carrier based	Rheumatoid arthritis Chronic inflammatory disorder	Effective transdermal drug delivery best skin penetration and skin distribution.
Nanogel for psoriasis	Administrated nanogel responsive to PH modification in the skin	Treatment of Psoriasis Immune system becomes overactive	Rapid release of alkyl radical at intended locations.
Aceclofenac	Nano structed lipid carrier	Rheumatoid arthritis.	Effective transdermal delivery best skin distribution.
Terbinafine HCL	PH responsive terabnafine HCL loaded nanogels	Antifungal Used in treatment of fungal infections	Best skin retention and antifungal activity.

CONCULSION

The review mainly highlights significant progress and transformational information potential of nanogels and nanoemulsion technologies in drug delivery specially in topical drug delivery. The review mainly covers topics such as feature benefits, methods for formulating nanoemulsions and nanogels for topical drug delivery. As compared to traditional emulsion these systems are made possible by emulsifying agents, have best kinetic stability resistance to gravitational separation aggregation.

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HOW TO CITE: Radhika Gupta, Nidhi Watane, Tanmayee Zade, Jayashree Taksande, Milind J. Umekar, Advancement In Nanoemulsion And Nanogels Technology For Topical Drug Delivery, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 5, 1816-1834. https://doi.org/10.5281/zenodo.11403018