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Nanoemulgel: a novel approach for topical delivery of hydrophobic drug

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ABSTRACT: Now days many of the new drugs that are being introduced to the market are hydrophobic in nature, making it difficult to delivering them; as a result, new strategies for incorporating hydrophobic drugs into Nanoemulgel should be developed. Modern medications have a hydrophobic character that causes low oral bioavailability, irregular absorption, and pharmacokinetic variability. In comparison to existing oral and topical drug delivery methods; this novel topical administration mechanism has been shown to be beneficial. Nanoemulgel, an innovative topical administration method, has shown unexpected advantages for lipophilic drugs in comparison to other formulations. Due to their dual characteristics i.e. a nanoscale emulsion and a gel base present in a single formulation—nanoemulgels are suitable candidates for drug delivery. These nanoemulgels are either oil-in-water or water-in-oil nanoemulsions that have been made to gel using a gelling agent. This formulation's gel phase is non-greasy, which encourages user compliance and stabilizes the product by lowering surface and interfacial tension. Additionally, it can bypass first-pass metabolism, target the site of action more precisely, and free the user from gastric/systemic incompatibilities. This review focuses on nanoemulgel as a more effective topical drug delivery technology and its advancements in research conducted by scientists worldwide. As a result, it can be concluded from this study's findings that nanoemulgel may be a more superior and efficient method of drug administration for the topical system.

KEYWORDS: Nanoemulgel; Nanoemulsion; Hydrophobic drugs; Topical delivery; Technologies

I. INTRODUCTION

Oral Route is the most preferred and major route of drug delivery. Many of the new drugs coming to the market are hydrophobic by nature. The hydrophobicity of the drug itself, however, makes difficulty in oral administration of about 50% of the drug molecules. Nearly 40% of new drug candidates exhibit low solubility in water i.e. they are hydrophobic in nature, which leads to the poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality.The formulation strategy is a constantly evolving process to get around those problems and concentrate on improving solubility. To increase the solubility of poorly soluble pharmaceuticals, a variety of techniques can be applied, including physical modification, chemical modification, and formulation development. To increase the solubility of weakly water soluble drugs, a variety of formulation techniques have been used, including particle size reduction to distribute through nanocarrier system, crystal engineering, amorphous formulation, various lipid formulation approaches, and so on. To get around these issues with lipophilic properties of compounds, newer lipid formulation techniques are gaining popularity. These techniques include incorporating a lipophilic component into an inert lipid vehicle, designing micro- or nanoemulsions, self-emulsifying formulations, liposomes, solid lipid nanoparticles, or lipid nanocarriers. In comparison to existing oral and topical drug delivery methods; this novel topical administration mechanism has been shown to be beneficial. Modern transdermal preparations, however, such as transparent gel, nanogel, and (micro/nano) emulgel, have demonstrated enhanced patient compliance in

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addition to enhancing the efficacy, stability, and safety of the formulation[1,2,3].

Out of all these formulation strategies, emulsion-based preparation can be regarded as a commercially viable way to get around the problem of inadequate bioavailability. Nanoemulsion can be a good alternative to conventional drug delivery methods because it can increase the bioavailability and permeability of lipophilic drugs by enhancing topical drug absorption. Nanoemulsion is further incorporated into gel matrix to prepare nanoemulgel which has even superior permeability and stability(3).

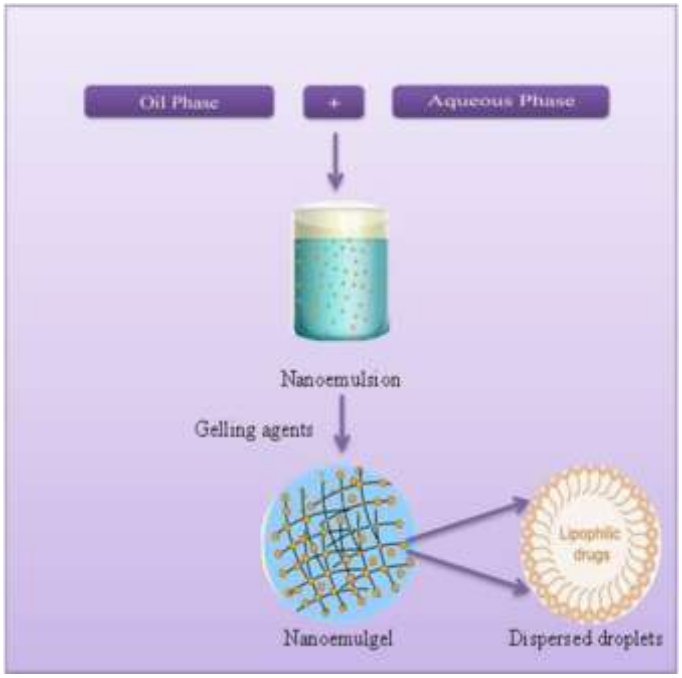

Fig. No.-Nanoemulgel (4)

➢ **Why Topical Drug Delivery Is Better**

Even while the oral route has higher patient compliance, it is nonetheless subject to a number of drawbacks, including gastrointestinal irritation, inevitable side effects, systemic toxicity, and hepatic first-pass metabolism. The use of a topical drug delivery method that is non-injurious, non-painful, and non-invasive can be an effective substitute to avoid all these problems. In comparison to the oral route, the topical route has a number of benefits and great potential for effective drug delivery. It has a number of benefits including enhanced drug bioavailability, first-pass metabolism bypass, no gastrointestinal discomfort, and tailored site-specific drug delivery with the least amount of systemic toxicity(3).

Apart from numerous benefits of traditional topical formulations, namely lotions, creams, and ointments have number of drawbacks such as their tendency to be sticky, stability problems, poor spreadability, etc., which reduce patient compliance. Due to these issues with the majority of semisolid preparations, the use of gelled formulation has expanded both in pharmaceutical preparations and in cosmetics. A gel is colloid that is typically 99% by weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelatinous substance present. Even though that gels have many benefits, hydrophobic drug delivery is a significant drawback. Therefore, an emulsion-based technique is being employed to get around this restriction so that even a hydrophobic medicinal moiety can benefit from gels' special qualities(5). This review focuses on nanoemulgel as a more effectivetopical drug delivery technology and its advancements in research conducted by scientists worldwide.

➢ **Nanoemulgel as topical drug delivery system(6,7)**

Nanoemulgel are nanoemulsions, either of the water-in-oil or oil-in-water type, that are gelled by combining with a gelling agent. Nanoemulgel is a stable and improved delivery system for hydrophobic or weakly water soluble medicines. In

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a nutshell, nanoemulgels are a combination of nanoemulsion and gel. Due to their dual characteristics i.e. a nanoscale emulsion and a gel base present in a single formulation—nanoemulgels are suitable candidates for drug delivery.

Because of their increased drug release properties and lack of greasiness and irritation, topical nanoemulgels can increase patient compliance. Nanoemulgels are becoming more and more popular in recent years due to their homogenous behavior and consistency of the hydrogel matrix.

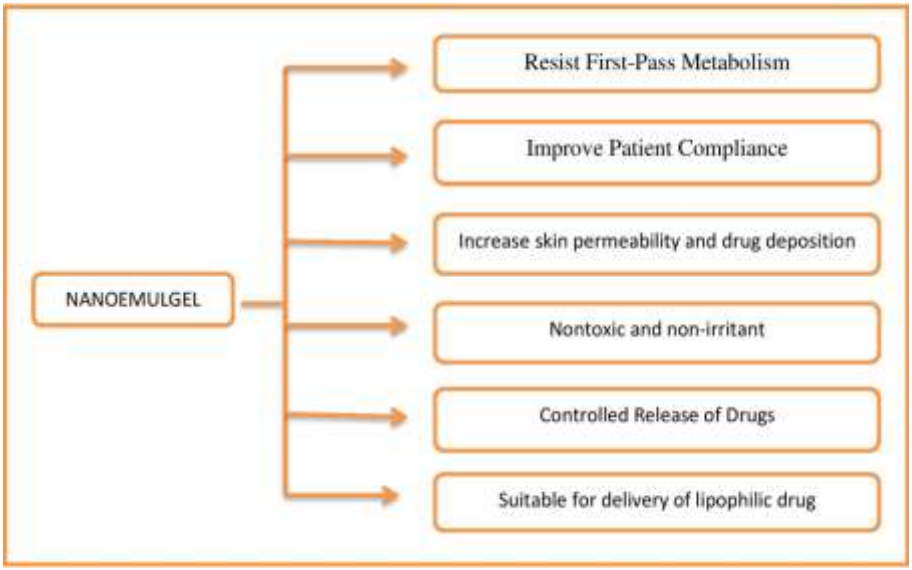

Fig. No.- Advantages of Nanoemulgel (8)

➢ **Mechanism of drug release from Nanoemulgel[9]**

When used as a topical delivery system, nanoemulgel operate as drug reservoirs, influencing how quickly medications are released from the inner stage to the outside phase and finally into the skin. These release mechanisms are influenced by the crosslink density and chain composition of the network polymer. In addition, a drug's propensities to diffuse out from the vehicle and pass through the barrier affects how well it can penetrate the skin and release the therapeutic ingredient. The oil droplets will be released from the gel network by applying nanoemulgel to undamaged skin. Once inside the skin's stratum corneum, the oil droplets wilcarry the medication molecules directly there without first passing through the hydrophilic phase

➢ **Technologies adopted in Nanoemulgel Preparation:**

Topical Application of a Nanoemulgel from a Self-NanoemulsifyingConcentrate: The self-nano emulsifying preconcentrate was dissolved in water containing the gelling component to create the gel. A 20% w/w solution of Pluronic® F127 was prepared in cold water. A 1 percent w/w chrysin concentration was obtained by mixing a transparent Pluronic® F127 solution at 10 °C with a nano emulsifying preconcentrate (10 percent v/w) containing 100 mg/mL of chrysin. To release the trapped air, the mixture was sonicated for five minutes in an ultrasonic water bath. In contrast, a gel with a 1% w/w chrysin dispersion was produced by completely dispersing the same quantity of chrysin in Pluronic® F127 gel.

Viscosity, droplet size, polydispersity index, and electron microscopy were all employed to describe the chrysinnanoemulgel intended for topical usage. The droplet size was ascertained by diluting the gel sample with water (1:100) and applying the same methodology as the drug delivery system that uses nano-emulsification.

For SEM photography, the nanoemulgel was captured in cryomode.Over the course of three months,the droplet size of the nanoemulgel was analyzed in order to look at the effects on size and size distribution. Chrysin analysis using RP-HPLC: The RP-HPLC technique for evaluating chrysin content was tested for accuracy, precision, specificity, and solution stability. The absence of any interference peaks during the analyte's

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retention time proved the technique's specificity[9,10,11,12]

Nanosized nasal emulgel of resveratonol: This study done with goal to create a nasal nano-emulgel for resvertrolusing carbopol 934 and polaxamer 407 as gelling agent.Here cold approach was applied to make nasal mucoadhesivenasal nano-emulgel.Toged rid of air bubbles, carbopol 934 was slowly added to developed optimal nanoemulsion and blended with constant slow stirring rate and then mixture was kept for chilling for overnight to allow complete swelling.The clean dispersion was obtained by adding polaxamer 407 with gently mixing.At the end triethanolamine was added for neutralization purpose to dispersion,the gel was done with the help of FTIR.The IR spectra of physical combination of mucoadhesive nasal nano-emulgel was taken.[13-17]

Thymoquinone loaded topical nanoemulgel for wound healing:It has been noted that the oil phase and Smix phase (surfactant and co-surfactant combination) for the synthesis of thymoquinone loaded nanoemulsions are established based on the outcomes of the emulsification efficiency inquiry (TQM-NE) and solubility study. The procedure of high-energy ultrasonication was used to develop TQM-NE. Five percent w/w (50 mg/g) of TQM was mixed with the oil phase and Smixed through the vortex mixture to create the coarse emulsion. The aqueous phase was then added while continuously vortexing for a minute. The coarse emulsion phase that hadbeen ultrasonically agitated was further agitated at a 40 percent ultrasonication amplitude for three, five, and ten minutes in a water bath. Researchers developed and evaluated eighteen formulations with different compositions in an effort to determine the optimal TQM-NE formulation. The TQM-NE formulations underwent triple testing for their thermodynamic stability, droplet size distribution, polydispersity index (PDI), zeta potential, viscosity, and drug concentration. In order to determine the TQM content in the enhanced TQM-NE formulations for the drug content analysis, 100 L of TQM-NE was diluted 1000 times with methanol, and the TQM content was then assessed using a UV-visible spectrophotometer at max at 254 nm.[17-20]

Methylcellulose-Based Nanoemulgel Loaded with Nigella Sativa Oil for Oral Health Management: As a gelling agent, high-viscosity methylcellulose E461 was utilized in this work. It dissolves in cold liquids to generate a transparent, viscous solution or gel that is naturally non-toxic and non-allergenic. The dental formulation was created in three steps, with minor adjustments, utilizing procedures from the literature.The Box-Behnken statistical design's surface methodology (RSM) was used to optimize dental nanoemulgel utilizing a quadratic model with 17 runs. The effects of formulation variables and elements, such as water (A), oil (B), and gelling agent (C), were seen on the two responses of the formulation, pH (R1) and viscosity (R2), using columns, cubes (standard error of design), and 3D graphs. ANOVA was used for the statistical analysis of the responses.[21-23]

Owing to its advantageous and useful characteristics for topical NSO distribution, the resultant NSO nanoemulgel showed great potential in the management of periodontal diseases. NSO will improve effectiveness and make a nanoemulgel formulation easier to apply, which will increase patient compliance. The enhanced mucoadhesiveness and cost-effectiveness of nanoemulgels are two more advantages that set them apart from conventional topical formulations. It is anticipated that the nanosized NSO droplets will help maintain tighter mucosal contact, increasing the surface area available for NSO penetration and the concentration of medication in the target area

It is also possible to look at how various emulsifiers and gelling agents affect the formulation's pH, viscosity, stability, drug release, and globule size. Moreover, NSO can be combined with different synthetic or natural antimicrobial agents to create nanoemulgel formulations that can be used in both preclinical and clinical testing. Further investigation, both preclinical and clinical, is required to ascertain the effectiveness of this formulation in treating periodontal disorders.

Novel Formulation of Fusidic Acid Incorporated into a Myrrh-Oil-based Nanoemulgel for the Enhancement of Skin Bacterial Infection Treatment: The myrrh essential oil-based nanoemulsions were created and optimized using the BBD process. The hydrogel base and improved nanoemulsion were used to generate FA-NEG. The developed FA-NEG possessed physical characteristics that made it appropriate for topical use. After skin application, it showed increased permeability without causing any irritation. FA-NEG and the blank nanoemulgel had much higher antibacterial activity in comparison to commercial fusidic acid. According to the study, fusidic acid

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and myrrh essential oil work in concert to provide a potent antibacterial effect. Topical application of fusidic acid and myrrh essential oil nanoemulgel systems could make them viable nanocarriers for antibacterial activities.Our long-term goal is to compare the healing rates provided by commercial fusidic acid solutions with those obtained by examining the formulation's effect on animal wounds infected with different bacteria.

Techno-bio functionality of Mangostin extract-loaded virgin Coconut oil nanoemulgel: Nanoemulsions comprising Mangostin extracts recovered by VCO, combined VCO-PG, and PG in the dispersion phase containing mixed surfactants (Tween20/Span20) were successfully produced by ultrasonication, and their HLB value was 15.1. The resultant nanoemulsions had an average droplet size of less than 100 nm and were globular in shape and uniformly distributed on the nanoscale. The most negative charge was exerted by the particles' zeta potentials, which suggested a stable dispersion. After multiple freeze-thaw cycles, all nanoemulsions produced with a surfactant with an HLB value of 15.1 stayed stable.Then anoemulsions' smaller droplet sizes demonstrated stronger antioxidant and antibacterial activities in comparison to their bulk extracts.

Components of Nanoemulgel:

1)Oil :

The oil phase that is lipid phase should be choosen on the basis of their ability to dissolve drug candidate and which type of emulsion is to prepare.Mineral oil is used as vehicle for drug in the preparation of nanoemulgel.e.g castor oil and various fixed oils(cotton seed oil,maizeoils,arachis oil) olive oil, coconut oil, eucalyptus oil, rose oil,clove oil etc[32,33]

2)Aqueous phase:

Distilled water is usually used as an aqueous phase in the preparation of nano-emulgel[30]

3) Surfactant :

A sufficiently stable film that can deform around the droplets with the ideal curvature is produced by the surfactant's amphiphilic structure, which permits the dispersion of two immiscible phases and lowers interfacial tension[34]

Surfactants are chemicals that can change the stratum corneum (SC) diffusion coefficient and enhance penetration into the skin by reversibly adhering to keratin filaments, destroying corneocytes, and so on. Depending on the concentration of the surfactant combination, different medications have varying effects on skin penetration. When the concentration of surfactant rose, the penetration of hydrophilic medicines was significantly enhanced.Non-ionic surfactants are generally favored over ionic surfactants due to their increased safety and widespread tolerancefor systemic absorption . For the lipid-based formulation, the two most widely employed surfactants are the polysorbates Tween 80® and Tween 20®.[35-38]

4)**Co-surfactant:**

An emulsion cannot be stabilized by a co-surfactant on its own. Rather, it works in concert with surfactant activity to enable the formation of both microemulsions (MEs) and nanoemulsions (NEs). Particularly a co-surfactant will reduce interfacial tension even more . Moreover, it promotes the ideal curvature of the interfacial film by enabling more oil to pass through the surfactant tails.

Phase properties are influenced by variations in surfactant and co-surfactant packing at the oil/water interface, and a crucial component in determining phase properties is the surfactant/co-surfactant ratio. Because they can change based on the surfactant, co-surfactant, and oil phase utilized, stable ratios cannot be established. A formulation study is typically employed in this situation to ascertain the optimal qualitative-quantitative mix. The most used screening technique is the pseudo-ternary phase diagram.With the use of the water titration method, the precise concentration range needed to generate the nanoemulsion was ascertained. By altering the Smix weight ratio, several diagrams may be created. The pseudoternary phase diagram is displayed in below figure.

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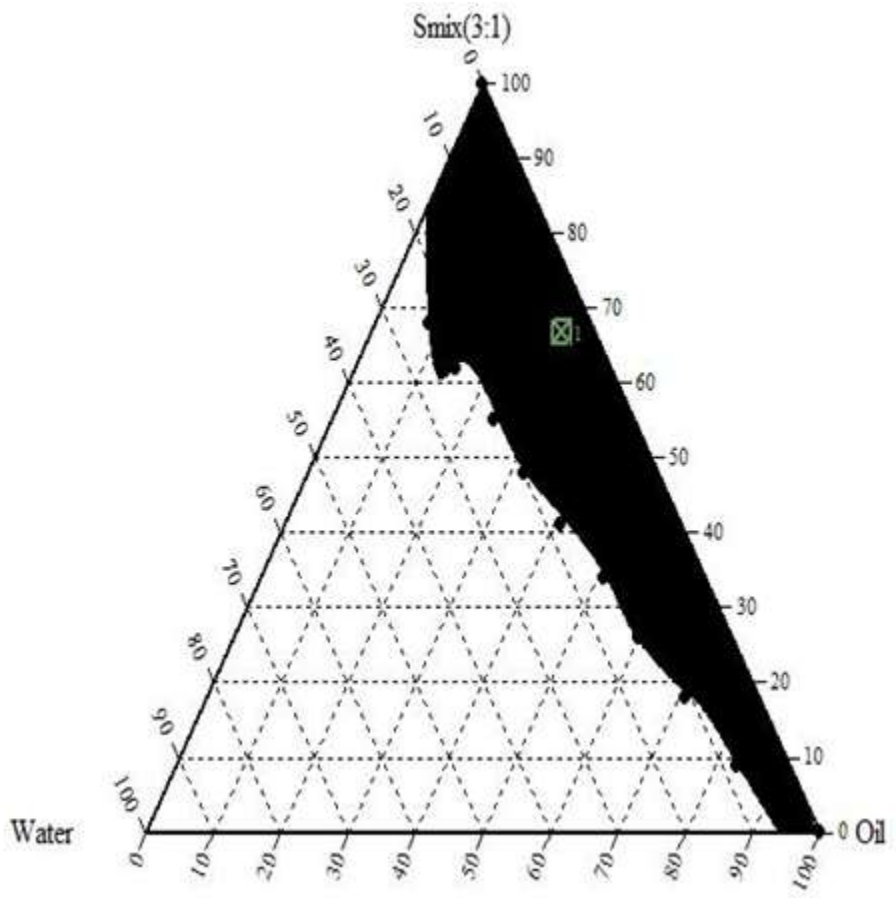

The clear, transparent portion of the nanoemulsion is represented by the shaded area, and the turbidity is represented by the unshaded area, in this schematic representation of the production of a pseudoternary phase diagram using the aqueous titration method.[38,39]

5)Gelling agent:

The gelling agent is a crucial component of nanoemulgel as it imparts texture to the formulation. The formulations become gelled structures when a gelling agent is introduced. Gelling agents come in two varieties: synthetic and natural

Research has been done on how a gelling ingredient affects the pace at which drugs release from emulgel. It has been found that there is an inverse relationship between the amount of medicine released and the gelling agent concentration. The produced emulgel showed variable viscosity that varied based on the concentration and kind of gelling agent, little to no thixotropy, and non-Newtonian shear thinning behavior. Formulations with a low level of carbopol or a combination of two gelling agents show more stability than other formulations, according to stability tests conducted under a variety of settings (such as centrifugation, temperature cycle test, or one-year storage).[39,40]

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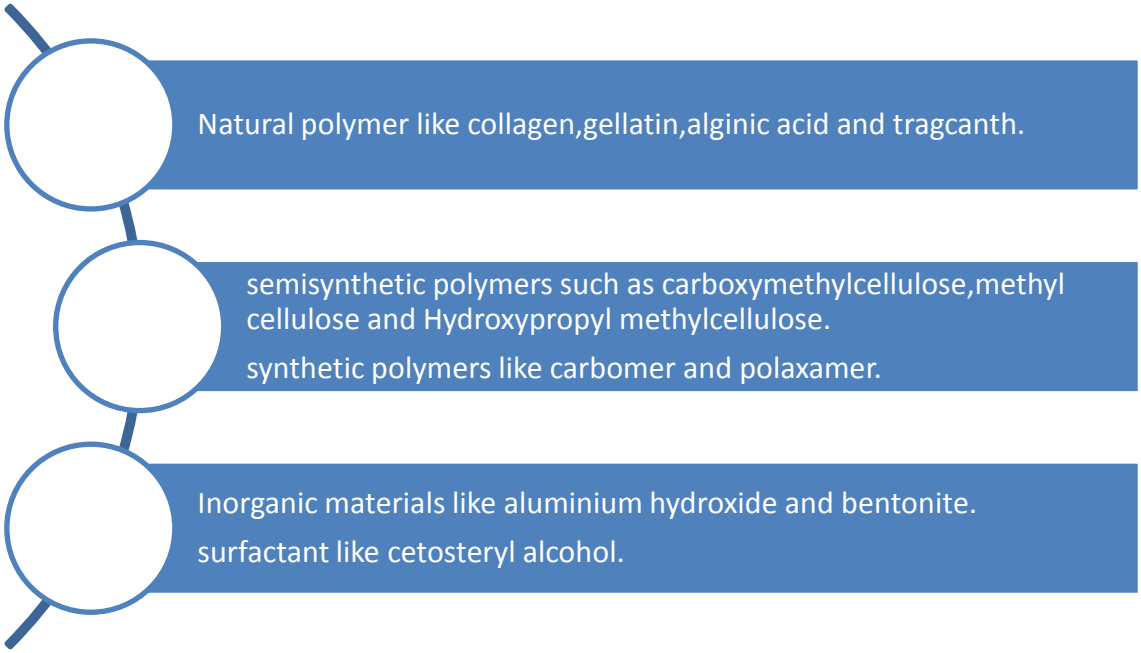
Gel forming agent can be classified as:[41]



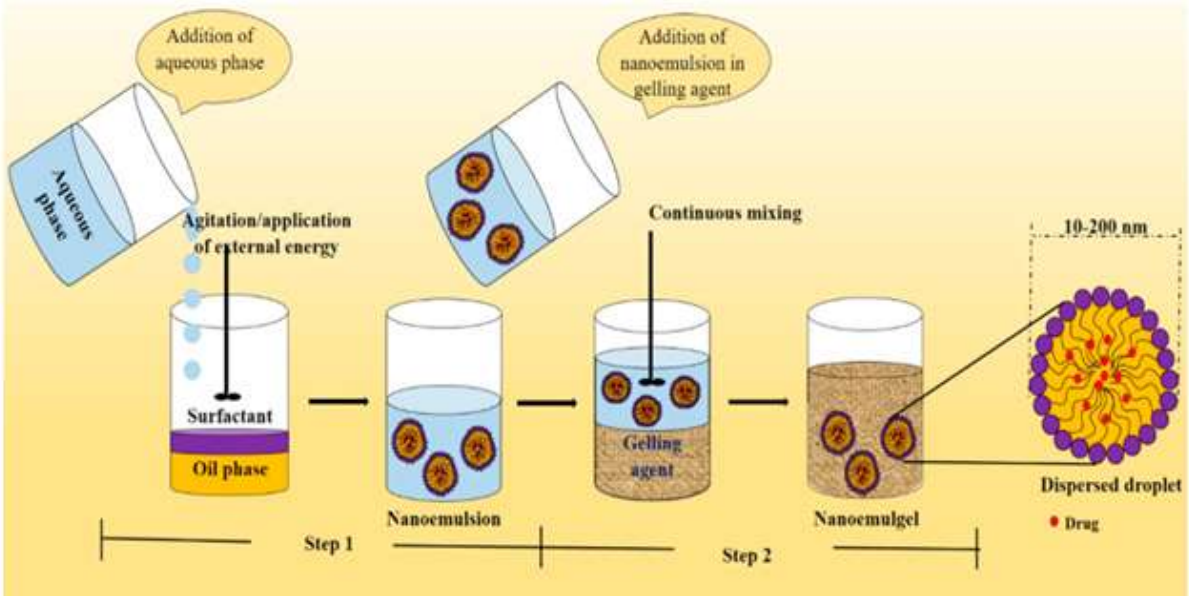
6)Other components:

Preservatives and antioxidants are examples of other additives that could be added to a nanoemulsion. Preservative agents are usually included in water-based systems to stop the growth of microbes. Since essential oils (Eos) are naturally occurring antimicrobials,preservatives are typically not required in systems based on Eos. The components of the formulation are kept from deteriorating by oxidation by antioxidants .

Method of preparation of nano-emulgel :

Preparation of nano-emulgel occur via multiple process in which formed nanoemulsionis incorporated in gel base as shown in fig.4.

Fig No.4:Schenatic Representation Of Nanoemulgel



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Step 1 :Preparation of nanoemulsion[18]

When compositions are blended and the interfacial tension between the oil and water interfaces is lowered, or when high energy is added to the heterogeneous mixture, nanoemulsions can form spontaneously. In order to create a thermodynamically stable nanoemulsion, both high-energy and low-energy emulsification techniques may be applied.

High energy method:[43]

The typical range of nanoemulsion droplet sizes is 5 to 500 nm, hence a significant amount of mechanical energy is needed to reach this size. Numerous methods, such as high-pressure homogenizers, ultrasonic generators, microfluidizers, and high-speed homogenizers, can be used to achieve high-energy input for fabrication.Using low amounts of emulsifier is the primary advantage of a high-energy mediated nanoemulsion formulation**.**

The initial stage in employing high-energy techniques is the mechanical stirring of an emulsion with droplet sizes in the micron range. The second stage involves using high-energy equipment to split large droplets into tiny droplets in order to transform the emulsion into a nanoemulsion.

Ultrasonication:[44]

The rough emulsion is converted into desirable nano-sized emulsion droplets using a sonicatorprobe.High-intensity sound waves having a frequency of even more than 20 kHz are generated by thesonicatorprobe.Which has the ability to shatter the rough emulsion into nano-sized droplets (5-500nm).Different types of probes Withvarying dimensions are available for reduction in size up to recommended values. The sonication inputIntensity, time, and the probe type affect the droplet scale

High-pressure homogenization technique:[45]

Extreme turbulence, and hydraulic shear, are commonly used in the development of nanoemulsions. In order to create nanoemulsions, surfactants and co-surfactants are forced through a piston homogenizer's tiny aperture at high pressure (500–5000 psi). The solution to the coalescence issue that can arise is to add extra surfactants to the mixture. High-pressure homogenization is a low-cost, highly efficient technique that may be applied on small and large scales to create nanoemulsions with particles as small as 1 nm. The dispersed and continuous phase viscosities, as well as homogenization cycles, affect the droplet size.The primary disadvantages are high energy consumption and processing temperature increases that could cause component damage. This strategy works well for a 20% oil nanoemulsion since a high oil content in the formulation reduces the productivity of the process.

Microfluidization:[56]

This approach uses a microfluidizer device, which utilizes a high-pressure positive displacement pump (500-20,000 psi) to force the product through an interaction chamber with stainless steel microchannels on the contact Area, resulting in the creation of very small sub-micron particles. The mixture is circulated through the microfluidizerTill it reaches the desired particle size. The final product is filtered to separate the smaller droplets from the biggerOnes and produce a homogeneous nanoemulsion

High-speed homogenization (rotor-stator homogenizer):[46]

In industry, high-speed homogenizers are frequently used for comminution, dispersion, and emulsification processes. They are affordable to purchase and easy to install in existing tanks and vessels. In many manufacturing businesses, the preferred emulsification method is often rotor-stator operations. Numerous investigations demonstrate that rotor-stator techniques can be used to create nanoscale droplets. But doing so requires careful consideration of the formulation parameters and approach

Low-energy method[47]

Low-energy emulsification processes require less energy than high-energy ones when producing nanoemulsions. They use the natural chemical energy of the system to create nanoemulsions with only a little stirring. Among the low-energy techniques are spontaneous emulsification and phase inversion

Spontaneous emulsification:[48]

Spontaneous emulsification is among the most practical techniques for preparing nanoemulsions. It consists of two liquid components: an organic component and an aqueous component. Water soluble solvents, co-surfactants, and surfactants are transferred from the organic phase into the aqueous phase. The procedure begins with the introduction of an organic phase—

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such as oil and surfactant—into an aqueous phase, which is composed of co-surfactant and water. The fast migration of water-miscible components into the aqueous phase, which raises the oil–water interfacial area, is what causes massive turbulence at the phase interface. Consequently, little oil droplets appear on their own.

Phase Inversion composition (PIC):[48]

Phase inversion composition is a more sophisticated kind of spontaneous emulsification (PIC). This method does not require the use of energy-intensive equipment and can create nanoemulsions at room temperature, in contrast to the high-energy method. Water is added drop by drop while oil and surfactant are mixed using a magnetic stirrer of laboratory quality. Then, without consuming much energy, a w/o nanoemulsion is created first as the water volume is increased, followed by an o/w nanoemulsion at the inversion point. In Figure 5, the PIC method for creating a nanoemulsion was displayed.

Phase inversion temperature technique (PIT):[47]

In the PIT approach, spontaneous surfactant curvature is reversed by a temperature change. The dehydration of polyoxyethelene (POE) groups in nonionic surfactants, such polyethoxylated surfactants, increases their lipophilicity and modifies the surfactant's curvature. Phase inversion consequently takes place, and a nanoemulsion is created.

- **Step 2: Preparation of nanoemulgel:**

By dissolving the polymer in purified water and continuously stirring it with a mechanical stirrer (4), the gel base is created. After the gelling agent and nanoemulsion are prepared, they are continually mixed until a nanoemulgel forms. Various polymeric gelling agents help to transform water in oil (w/o) or oil in water (o/w) nanoemulsion into thick and semisolid nanoemulgels.

Characterization of nanoemulgel:

a)visual inspection:

Visual inspection of the created nanoemulgel could be used to assess its homogeneity, color, and appearance.[49]

b)pH measurements:

The pH of nanoemulgel varies according to its intended use, such as on the skin or another type of mucous membrane. Human skin is reported to have a pH of 4.5 to 6[50]

c) Determination of viscosity:

For the gel to be applied to the skin effectively, its viscosity is essential. Gel needs to be aware of the rheological behavior. Viscosity is the fluid's resistance to flow; a higher viscosity corresponds to a higher resistance to flow. In general, fluid systems are divided into Newtonian and non-Newtonian categories. Higher viscosity fluids in Newtonian flow require more force per unit area, or shear stress, in order to produce a given shear rate. The viscosity in Newtonian flow remains constant despite variations in the shear rate. Non-Newtonian flow, in contrast to Newtonian fluid, is not constrained by the Newton low and experiences variations in viscosity due to variations in shear rate.[51]

d)Spreadability measurement:

The topical preparation's spreadability will dictate the resulting formulation's medicinal efficacy. Spreadability is the term used to describe how easily a gel covers the affected area and the skin at the application site. Spreadability of nanoemulgels is determined by their 'Slip' and 'Drag' qualities[52]

e)Droplet size measurements and polydispersity index:

A common method for determining droplet size is dynamic light scattering (DLS). The generated nanoemulsion's homogeneous droplet size is determined by measuring the polydispersity index (PDI).[53]

f)Zeta potential:

Since nanoemulgel is composed of both nanoemulsion and a gelling agent, the presence of various surface-active chemicals might cause the formulation to become electrically charged.[53]

g)Drug content:

Drug content is a crucial factor that establishes how much drug is overall present in prepared formulas; a higher drug content is linked to minimal drug loss during the production process.[50]

h) Accelerated stability study:

According to the guidelines set forth by the International Council for Harmonization (ICH), an accelerated stability study must be carried out. The formulations should be stored at 37±2°C, 45±2°C, and 60±2° for three months in the oven. Every two weeks, the sample should be analyzed

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for drug content using a suitable analytical technique. The stability is determined by measuring the gel's pH change or the degradation of the medication.(55)

Various application of nanoemulgel formulation:

Barkatali khan et al,2024() aimed to develop febuxostat (FXT) loaded nanoemulgel for transdermal delivery. nanoemulgel was prepared by high sheared homogenization technique and chaqracterized for thermodynamic stability,pHanalysis,drugcontent,zetapotential,viscosity,spreadability,FTIR,in vitro drug release and ex vivo peameation. In vivo anti-inflamatory activity was evaluated in albino rats by inducing edema in hind paws using carrangeenan. The study concluded that febustat loaded nanoemulgel can be safe and effective alternatiuve to oral therapy of febuxostat.(57)

Bahjatalhasso et al 2023 () attempted to develop nanoemulgel of mupirocin antibiotic which have poor skin permeability but it can be improved by nanoemulgel formulation based on eucalyptus oil or eucalyptol.The mupirocinnanoemul gel was prepared by incorporating a prepared MUP nanoemulsion into carbopol gel at a concentration of 0.75% in 1:1 ratio.the formulation were characterised and evaluated for their physicochemical and mechanical strength properties,rhelogical behavior, and in vitro skin permeation, deposition and antibacterial studies. two nanaoemulgel formulation prepared and both formulation showed stability at temperature of 4 and 25 for a period of 3 month. both showed all physical characterstics in appropriate way but both nanaoemulgel exhibited lower skin permeability compared to the marketed control.No more difference found in antibacterial activities of both formulation.The study revealed that potential use of the nanaoemulgel for targeting skin lesion where high skin deposition and low permeability are required in case of antibacterial agents.(58)

Solimanmohammadisamani etal 2022(),attempted to evaluate in vitro and in vivo skin permeation in oxybutynin nanoemulgel formulation successfully.Using design expert software oxybutynin nanaoemulgel formulation were prepared and optimized based on particle size,zeta potential anad physical stability.three polymers were used to prepare and optimize oxybutynin nanoemulgelbased on spredability and viscosity. In vitro drug release and ex vivo drug skin permeation were investigated for optimized formulation. The study revealed that simple gel did not permeate throughskin layers,thus, oxbnanoemulgel with effective skin permeation potential would be a novel promising drug delivery for hyperhidrosis management which may reduce systemic side effects(59)

w. soliman et al 2021 attempted to formulate curcuminnonoemulgel to improve its efficacay, because curcumin has low solubility and bioavailability. Using ultrasonication techniques and a high-speed homogenizer, the resulting nanoemulsion was created. The findings show that nanoemulgel exhibits the best enhancement ratio, steady state transdermal flux values, and superior skin penetration when compared to gels and emulgels based on curcumin. In vivo anti-inflammatory experiments, the curcumin-loaded nanoemulgel exhibited the lowest proportion of edema.(60)

E. Yeo et al, 2021 attempted to develope and evaluate a tocotrienol-rich naringeninnanoemulgel for the treatment of diabetic patients who suffer from chronic wounds. In vitro release of naringenin in this investigation showed a prolonged release profile from the prepared nanoemulgel (NG1) over a 24-hour period. However, the release from the nanoemulsion was much higher, perhaps because the scattered oil droplets lacked a polymer coating.(61)

D. Upadhyay et al, 2020 was prepared a finasteridenanoemulgel for treatment of male patterned baldness and they tried to improve drug permeability through the skin and enhance patient compliance by prolonging the contact time with the skin. Compared to drug release from solution, drug release from nanoemulgelwas substantially greater. Macroscopic examination of the nanoemulgel case showed improved hair growth. The rat skin's hair width and length were found to be significantly greater in the nanoemulgel-treated group as compared to the testosterone-treated group.(50)

Retinylpalmitatenanoemulgel was investigated for improved topical delivery by M. Algahtaniet al., 2020 (51). The results indicate that, in contrast to the aqueous dispersion, the nanoemulsion systems released 89–94% of retinylpalmitate in a 24-hour period. The delivery system that contained retinylpalmitate significantly increased permeability after topical administration.(27)

Anti-inflammatory and painkiller drug delivery with nanoemulgel is intended to have better pharmacodynamic activity as compared to

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other delivery methods. Md. Shadab et al., 2020 created a diclofenac sodium-loaded nanoemulgel and used the carrageenan-induced paw edema test to measure the anti-inflammatory impact of the product. The developed nanoemulgel significantly outperformed commercially available diclofenac gels in terms of its ability to reduce pain and inflammatory symptoms(67)

Morsy et al, 2019, have developed atorvastatin loaded nanoemulgel for wound healing. With emulgel formulations, atorvastatin loaded gel also were prepared. Atervastatin's in-vitro drug release profile, measured after six hours, was 44% from emulgel, 55% from nanoemulgel, and 65% from gel in all produced formulations. When atorvastatin was created as a nanoemulgel, it was able to penetrate skin much more easily. During the in-vivo wound healing experiments, the nanoemulgel containing atorvastatin exhibited the highest percentage of wound contraction. Histopathological examination after 21 days of atorvastatin-loaded nanoemulgel therapy showed a notable improvement in the skin's histological structure.(62)

There is great promise for the delivery of antipsoriatic medications via nanoemulgel. One very useful topical corticosteroid for the treatment of psoriasis is clobetasol propionate. Dadwal and associates endeavored to develop a topical nanoemulgel of clobetasol propionate by utilizing squarticles as a lipidicnanosystem, with the goal of enhancing the medication's therapeutic efficacy and sebaceous gland penetration. In terms of cumulative percentage retention, the created nanoemulgel retained a higher amount of clobetasol propionate than the commercial product

A terbinafineHclnanoemulgel was recently produced by M. M. Elmataeeshy et al., 2018 (54) and it was shown that this nanoemulgel is more costly than traditional emulsions. Terbinafine skin penetration from all developed nanoemulgel compositions was significantly higher than that of the commercial product.When treating Candida infections, the nanoemulgel formula's in-vivo antifungal activity outperformed that of the store-bought emulgel.(65)

A dental condition that needs to be addressed is tooth staining. The main ingredient in tooth bleaching or whitening products is hydrogen peroxide, and one of the precursors of hydrogen peroxide is carbamide peroxide (CP), which is a potentoxidant. S. Okonogi et al., 2021 developed a novel controlled release carbamide peroxide nanoemulgel (CP-NG) to reduce the release rate of carbamide peroxide (CP) using a controlled release formulation of o/w nanoemulsion and a solid dispersion method, using modified rice as gelling agent(66)

II. CONCLUSION

Topical drug delivery is best alternative when it comes to avoiding gastrointestinal difficulties.The three-dimensional structure of the Nanoemulgel system is derived from the incorporation of a gelling agent into a nanoemulsion-based system. With the addition of a gelling agent, which gives the system its three-dimensional structure, Nanoemulgel is a system based on nanoemulsion,the present nanosized particle allows deep entry in skin.The problem of typical cream like phase sepration as well as syneresis which is associated with gel formulation can be avoided by emulgelformulation.The hydrophobic drug can be effectively delivered via emulgelformulation.It can concluded that nanoemulgel is potentialformulation for effective drug delivery of hydrophobic drug as well as for conventional drug delivery system.

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