

NANOEMULGEL SYSTEMS: A COMPREHENSIVE REVIEW OF FORMULATION,
MECHANISMS, AND APPLICATIONSRohith Menon^{1*}, Shripathy D.² and Shabaraya A. R.³

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574143.**ABSTRACT**

A new family of hybrid formulations known as nanoemulgels combines the advantages of gels and nanoemulsions to provide special benefits for drug delivery systems. These formulations, which offer superior stability, controlled release, and bioavailability for both hydrophobic and hydrophilic medicines, usually comprise nano-sized droplets distributed inside a gel matrix. Better penetration and targeted distribution, especially for topical treatments, are made possible by the thick consistency of gels and the small particle size and large surface area of nanoemulsions. In various kinds of therapeutic domains, such as dermatology, transdermal medication administration, and cosmetic formulations, nanoemulgels have demonstrated considerable potential. This review highlights the benefits of nanoemulgels over traditional systems by examining their formulation processes, characterisation methods, and possible uses. Future directions for improving their design and therapeutic efficacy are also covered, along with issues pertaining to their stability, scalability, and safety. In general, nanoemulgels offer a flexible foundation for cutting-edge drug delivery systems and represent an inventive method of improving the functionality of pharmaceutical and cosmetic products.

KEYWORDS: Nanoemulgel, Nanoemulsion, Controlled release, Topical application, Drug permeation.**INTRODUCTION**

In comparison to oral delivery, topical drug administration may have a number of benefits, including avoiding first-pass metabolism, improving patient acceptance (i.e., non-invasiveness), allowing for immediate treatment withdrawal, and ensuring a continuous medication supply to maintain consistent plasma profiles—especially for medications with a short biological half-life.

The major goal of topical formulations should be to enter the skin and do so sufficiently to exert a therapeutic impact on the targeted locations. They should also be easy to use and acceptable. Because of the stratum corneum barrier function, which restricts the penetration of the majority of exogenous substances, only a very small number of formulations are commercially available despite the significant potential of these products for dermal application.^[1]

Recently approved low-bioavailability drugs are not being further developed. The issue still exists even though pharmaceutical distribution systems have changed and various methods have been developed to increase therapeutic efficacy. The low bioavailability could be caused by one or more factors, such as decreased permeability and/or low solubility. Addressing the various pharmacokinetic characteristics of the drug

moiety is essential to enhancing therapeutic efficacy. Solubility, permeability, and bioavailability are all included in this. One innovative delivery technique that improves stability and bioavailability is nano-lipoidal delivery devices. One of the finest methods for topically administering lipophilic or poorly accessible medications is nanoemulsion. The direct application of nanoemulsion to the skin is advantageous. SLNs, liposomes, microemulsions, and nanostructured lipid carriers (NLCs) are examples of nano-lipoidal delivery systems.^[2]

Despite their many benefits, nano-emulsions are limited by their low viscosity, which results in low retention time and spreadability. These issues can be overcome by converting the nano-emulsion into a nano-emulgel by using an appropriate gelling agent. Nano-emulsions are heterogeneous colloidal mixtures of oil and water, with one component as a dispersed phase and the other as a continuous phase. An emulsifier, a surfactant, is adsorbed at the interface between the dispersed and continuous phases, lowering the surface tension and stabilizing the system.^[3,4,5]

The nano-emulgel, which is a combination of gel and emulsion, functions as a colloidal system. Like other nano-carriers, the emulsion component enhances penetration and shields the medication from hydrolysis

and enzymatic destruction. Maintaining the drug's therapeutic concentrations for an adequate amount of time is just as crucial as improving the drug's penetration through the skin. The gel component decreases surface and interfacial tension, increasing thermodynamic stability, and increases viscosity and spreadability, which enhance retention time. Compared to other nano-carriers, nano-emulgel has a number of benefits, including a high drug loading capacity, improved penetration, diffusion, and little skin irritation.^[6,7]

Nanoemulsions have particles that range in size from 10 to 200 nm, while traditional emulsions have particles that range from 1 to 20 μm . It has previously been investigated to alter the rheological behavior of nanoemulsions using biocompatible gels with weak interactions with surfactants. Carrageen, xanthan gum, carbomer 980, carbomer 940, and carbomer 934 variant gel matrices have all been used to boost the viscosity of nanoemulsion for transdermal administration. When nanoemulsion is incorporated into a gel matrix, nanoemulgel is created, which may be more appropriate for transdermal delivery than nanoemulsion alone. By decreasing surface and interfacial tension and increasing the aqueous phase's viscosity for improved topically applied administration, it enhances the stability of the nanoemulsion.^[8]

Advantage Of Nanoemulgel^[9]

- The drug's affinity for oil dictates stability, and the distribution of oil droplets in the gel foundation enhances the stability of the nanoemulsion.
- Compared to previous topical formulations that have been explored, the nanoemulgel has several advantages, such as the preference to avoid first-pass metabolism.
- Incorporation of Lipophilic drugs.
- Better skin permeability and drug disposition.
- The drug release is controlled by the nanoemulgel.
- Improved patient compliance.
- Patients of all ages can accept topical treatment, which is always preferred over oral and parenteral drug delivery.
- The nanoemulgels can be stopped or cleaned off at any moment in the event of any negative effects or localized skin irritation.
- Additionally, a strong concentration gradient caused by good skin adherence with high solubilizing strength increases medication penetration as it descends

DISADVANTAGES OF NANOEMULGEL^[10]

- Certain drugs don't absorb well through the skin.
- For those who have contact dermatitis, the medication and/or excipients may cause skin irritation.
- Drugs with larger particle sizes are more difficult to absorb through the skin.
- The potential for allergic responses.

Important Component of Nanoemulgel^[11]

- a. Oils:** Mineral oils are typically utilized as the drug delivery system in nanoemulsions. This includes castor oils, different fixed oils (such as cottonseed, maize, and arachis oils), olive, coconut, eucalyptus, rose, and clove oils, among others.
- b. Aqueous Phase:** Distilled water is frequently utilized as an aqueous phase in the creation of hydrogel and nanomulsion.
- c. Surfactant and Co-Surfactant:** These substances are employed to provide emulsification during formulation and to regulate the stability of the created nanoemulsion throughout time. The type of emulsion determines the general surfactant selection. (W/O or O/W) E.g. Span 80 (Sorbitanmonooleate), Acrysol K 140, Polyethylene-glycol-40-stearate, Acrysol, Labrasol, Stearic acid, Plurol Oleique, Tween 80 (Polyoxyethylene-sorbitan-monooleate), Labrafil, Sodium stearate, Where agents like Transcutol, Captex, Cammul, Migyol, etc. can be used as co-surfactant or co-solvents.
- d. Gelling Agent:** Gelling agents are polymers that are necessary to provide the structural network needed to make gels. For instance, natural cellulose derivatives such as agar, tragacanth, guar gum, xanthan gum, semi-synthetic and synthetic carbapol, polxamer, and HPMC
- e. Permeation Enhancers:** These substances interact with various skin constituents to create a transient, reversible increase in permeability. They may act through a variety of processes, such as
 - i. Disrupting the highly compact structure of SC.
 - ii. Improving partition of drug or solvent or co-enhancer into the SC.
 - iii. Interacting intercellular protein.

Causing conformational changes in protein or solvent swelling is the key for alternating polar path. Some enhancers improve the fluidity of protein in SC, where some act on both pathways by disrupting multilaminar pathway. They can increase the diffusion of drug through skin proteins. Type of enhancer has a significant impact product designing E.g. Eucalyptus oil, Linoleic acid, Lecithin, Oleic acid, Chenopodium oil, Isopropyl myristate, Urea.

CRITERIA FOR SELECTION OF SURFACTANTS^[12]

The HLB value of the surfactant is an important variable for selecting the proper surfactant. The surfactants are either w/o type (HLB of 3–8) or o/w type (HLB of 8–16). In w/o emulsions, low HLB value surfactants i.e., less than 8 are utilized. Alternately Spans and Tweens are used for o/w emulsion as their HLB value is more than 8. A mixture of Span and Tween provides better stability to an emulsion system compared to pure Span or Tween containing preparations. Thus, using a proper mixture of surface-active agents is essential to formulate an ideal nano-emulsion. Based on the charge, the surfactants are

of four main categories i.e., cationic, non-ionic, anionic, and zwitterionic nature.

Table no. 1: Types of surfactants.

Cationic	Non-ionic	Anionic	Zwitterionic
hexadecyl trimethyl ammonium bromide	Poloxamer 124 and 188	sodium dodecyl sulphate	Phospholipids
cetyl trimethyl ammonium bromide	Tween 20	sodium bis-2-ethylhexylsulfosuccinate	phosphatidylcholine
quaternary ammonium compounds	Caproyl 90		
dodecyl dimethyl ammonium bromide			

Toxicity should be considered while selecting the surfactant as it may lead to irritation of the gastrointestinal tract or skin based on the route of administration. Ionic surfactants are usually not preferred due to their toxicity and non-biocompatibility. The safety, biocompatibility and being unaffected by pH or ionic strength alteration make non-ionic surfactants an appropriate choice.

The surfactants derived from natural sources such as bacteria, fungi, and animals are being considered as a potential option, due to their safety, biodegradability, and biocompatibility. Bio-surfactants show a similar mechanism in decreasing surface tension along the interface due to amphiphilic properties. This is mainly due to the presence of non-polar short fatty acids and polar functionalities as the tail and head respectively. They are more bio-compatible and safer than synthetic surfactants.

Techniques used to create emulgel^[13]

Step 1: Formulation of O/W or W/O emulsions

The first stage in emulsion formulation is determining if water-soluble materials are soluble in the aqueous vehicle and oil-soluble components are soluble in the oil vehicle. The two phases were mixed together in a turbulent mixing medium to ensure that they would disperse into droplets. Although a mechanical stirrer is used throughout the emulsion production process, ultrasonifiers, homogenizers, colloid mills, or mechanical stirrers are typically used when emulsification is done for industrial purpose.

Step 2: Formulation of gel base

In a mixture vessel, the excipients or water-soluble materials are mechanically stirred until they dissolve completely in the aqueous vehicle, then the hydrophilic polymer is gradually added. The fluid is stirred until the polymer dissolves and the pH remains within the appropriate range. Excessive stirring can cause air to become trapped in beneficial gels, so the rate of mixing should be moderate.

Step 3: Addition of emulsion into gel base with steady blending

To produce emulgel, the gel and emulsion stages mix together at a 1:1 ratio.

Preparation of Gel Phase

The polymer is dispersed in purified water using a mechanical shaker and agitated at a moderate speed to form the gel phase for the formulation. Triethanolamine (TEA) is then added to adjust the pH to a range of 6–6.5.

Preparation of Oil Phase for Emulsion

Emulsifiers, such as Span 20, are dissolved in the oil phase to create a light liquid paraffin mixture.

Preparation of Aqueous Phase

An emulsifier, such as Tween 20, is dissolved in purified water to form the aqueous phase.

Preparation of Drug Solution

The drug is dissolved in ethanol to create a uniform solution.

Procedure for nanoemulgel preparation^[14]

A non-equilibrium formulation of structured liquids, nano-emulgel is made with energy, surfactant, or both. They are spontaneously formulated by mixing the components. This is accomplished by either increasing the energy present in the biphasic system or lowering the interfacial tension between the two immiscible phases' surfaces. Depending on the order in which the oil and aqueous phases are mixed, several nano-emulgel synthesis techniques have been documented. To create an emulsion, the oil phase is introduced to the aqueous gel phase while being stirred and then homogenized. Several processes, such as adding a complexing agent or altering the pH to the proper level, transform the sol form of the gelling agent in the emulsion into gel.

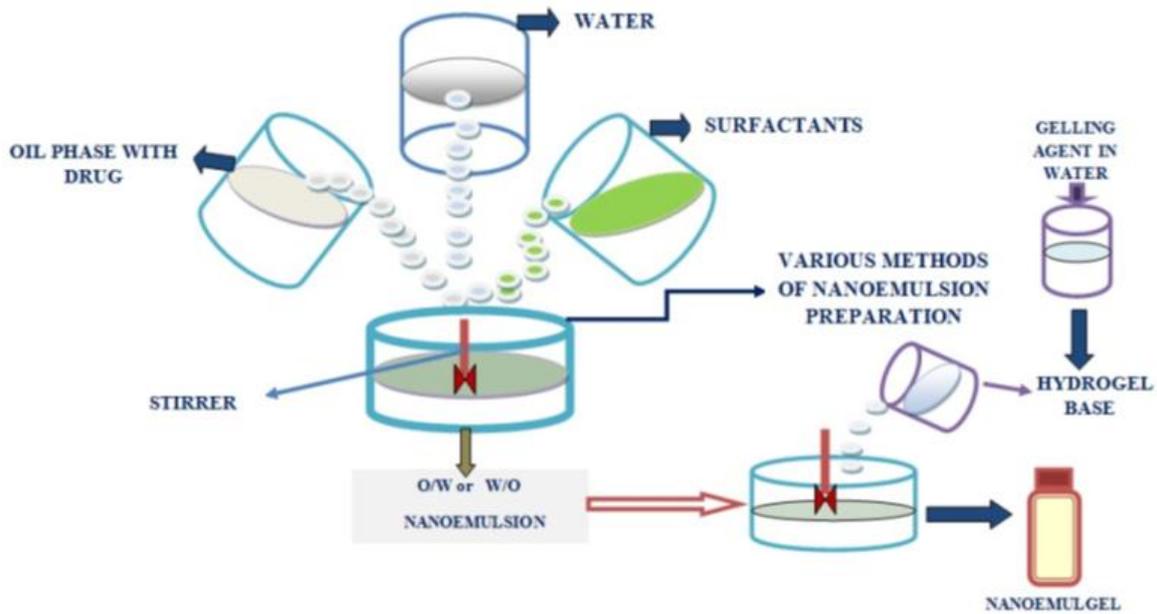


Fig no.1: Preparation of nanoemulgel.

METHOD OF PREPERATION

1. High energy methods^[15]

A considerable amount of mechanical energy is required to reach the usual size of a nanoemulsion droplet, which is between 5 and 500 nm. The use of low emulsifier concentrations is the primary benefit of employing a high-energy mediated nanoemulsion formulation. The mechanical stirring that produces an emulsion with

droplet sizes in the micron range is the initial stage in using high-energy techniques. The utilization of low emulsifier concentrations is the primary benefit of employing a high-energy mediated nanoemulsion formulation. In the second stage, the emulsion is converted into a nanoemulsion by splitting large droplets into tiny ones using high-energy equipment.^[15]

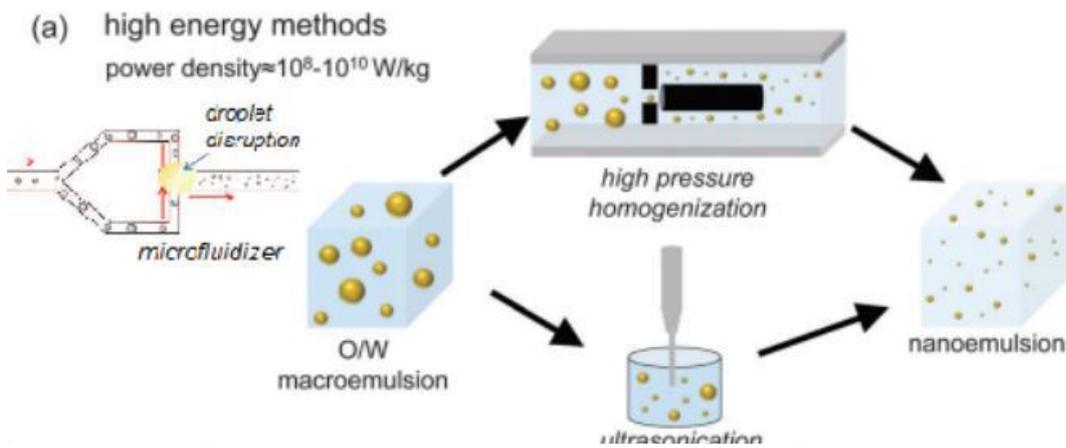


Fig no. 2: Overview of high energy for preparing O/W nanoemulsions.

High-pressure homogenization technique

The production of nanoemulsions frequently uses a range of forces, most notably cavitation, severe turbulence, and hydraulic shear. Surfactants and cosurfactants are pushed through a tiny hole in a piston homogenizer at high pressures (500–5000 psi) in order to create nanoemulsions. An affordable and incredibly effective method for producing nanoemulsions with particles as small as 1 nm is high-pressure homogenization, which may be used on both small and large sizes. The addition of more surfactants to the mixture resolves the potential coalescence problem. The droplet size is influenced by

homogenization cycles and the dispersed and continuous phase viscosities.^[15]

High-speed homogenization (Rotor-stator homogenizer)

High-speed homogenizers are widely used in industry for emulsification, dispersion, and comminution procedures. Installing them in pre-existing tanks and containers is simple. Rotor-stator operations are the primary emulsification method in many manufacturing industries. They produce nanoscale droplets using rotor-stator

techniques. It requires careful selection of the formulation parameters and technique.^[15]

Ultrasonication

The rough emulsion can be converted into the required nano-sized emulsion droplets by using a sonicator probe. High-intensity sound waves produced by the sonicator probe at frequencies higher than 20 kHz have the potential to break up the hard emulsion into nanometer-sized (5–500 nm) droplets. These probes come in a variety of sizes and can be reduced in size up to predetermined thresholds. Time, probe type, and sonication input intensity all affect the droplet scale.^[15]

Microfluidization

This method uses a microfluidizer device that uses 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 region,

creating very small sub-micron particles. Until the required particle size is reached, the resultant mixture is constantly run through the microfluidizer. The final product is filtered to separate the larger and smaller droplets and create a uniform nanoemulsion.

2. LOW ENERGY METHODS^[16]

Low-energy emulsification procedures were developed after studying the cumulative behaviour of the oil, surfactants, co-surfactants, drug, watery component, hydrophilic lipophilic balance of the utilised oil surfactant blend, and operation temperature.

Emulsification that happens on its own is one low-energy technique. These methods produce tiny droplets by using the system's stored energy. Low energy methods might not always be feasible, depending on the kind of oil and emulsifier that are available.

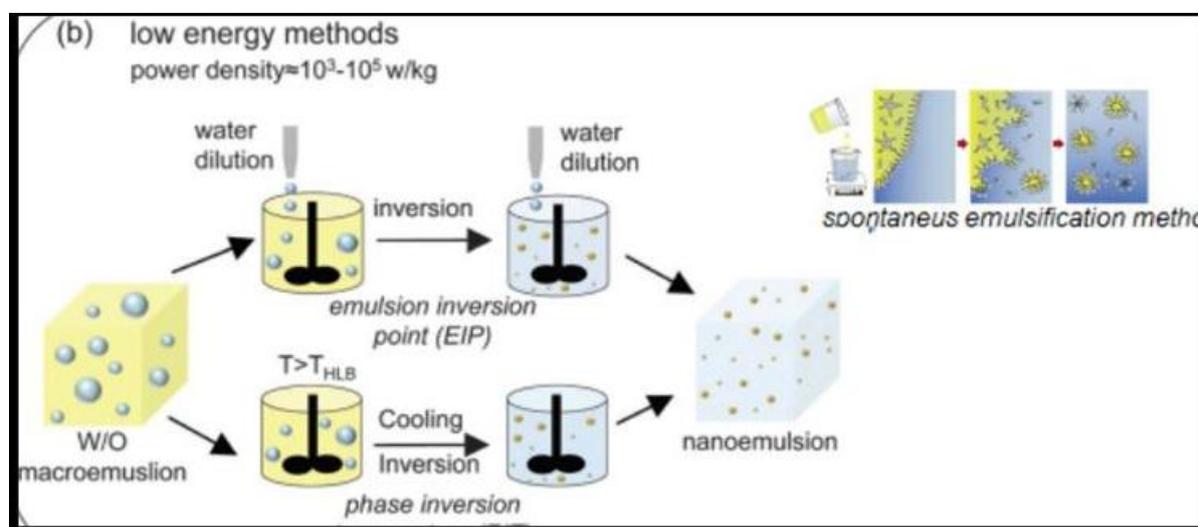


Fig no.3: Overview of low energy methods for preparing O/W nanoemulsions.

a. Spontaneous emulsification

The process used to create polymeric nanoparticles, known as nanoprecipitation, is similar to spontaneous emulsification. Oil is used in place of polymer. The process creates two phases: an oil-soluble surfactant called Span, an organic solvent that is partially water miscible, such as acetone or ethyl acetate, and an oil-based or organic phase, such as mygliol, that contains a drug. To create small nanoscale emulsions, the organic phase is added dropwise to the aqueous stirring phase (though the opposite, i.e., adding water to oil, is equally possible in the case of W/O emulsions).

b. Phase Inversion Temperature

This approach produces a fine dispersion because of the chemical energy originating from phase transitions created by the emulsification pathway. An emulsion can undergo phase inversion in one of two ways: either by altering the composition of the emulsion while keeping its temperature constant, or the other way around.

- Transitional Inversion: This is caused by shifting variables that impact the system's HLB. For instance, the electrolyte concentration and/or temperature.
- Catastrophic inversion: caused by utilising surfactant combinations to alter the surfactant's HLB number at a constant temperature.

c. Membrane Emulsification:

One low energy method for producing nanoemulsions is membrane emulsification. This method creates an emulsion with a narrow size distribution range and uses relatively little surfactant. With this method, a scattered phase passes across a membrane to generate a continuous phase. One disadvantage of this strategy is its poorly dispersed phase flux, which causes problems through the membrane during scale-up.

d. Emulsion Inversion Point

This method involves changing the system's composition while maintaining a steady temperature. To produce

kinetically stable nanoemulsions, structures are created by gradually diluting the material with water or oil.

CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM^[17]

Water titration method was adopted to develop a pseudo-ternary phase diagram to draw the nanoemulsion zone and individual components. In different glass tubes, oil

was mixed thoroughly with S/Co-S at different ratios (1:1,1:2,2:1 ratios). Aqueous phase was then added drop wise into each tube followed by 2min vortex mixing and allowed to equilibrate after light magnetic stirring for 20min. After equilibrium establishment, the mixtures were described in term of flowability and phase clarity. The clear emulsion with good flowability was declared as nanoemulsion.

Table no. 2: pseudo ternary phase studies.

Sl.no	Weight of oil	Surfactant & Co-Surfactant mixture Mixture(w/w)	Amount of water to be added
1.	1	9	
2.	2	8	
3.	3	7	
4.	4	6	
5.	5	5	
6.	6	4	
7.	7	3	
8.	8	2	
9.	9	1	

EVALUATION^[18]

1. Visual inspection

The developed gel and emulgel were visually inspected for colour, homogeneity and appearance. The pH value of the preparations was verified at room temperature using a pH meter.

2. Spreadability

The spreadability of the transdermal formulations was determined using the spreadability apparatus, which consists of a wooden board with a scale and two slides made of glass. It controls the area in which the preparation can freely spread after being applied to the skin. One gram of gel, emulgel or nanoemulgel preparations were added between the two glass slides (20 cm × 20 cm) and a standard load was placed over it for 1 min. The spreadability value was calculated by measuring the diameter of spreading area of the formulations.

3. Size and size distribution^[19]

The particle size and polydispersity (PDI) nanoemulgel were determined by measuring their dynamic light scattering. Each sample was diluted with distilled water at a ratio of 1:100 before the analysis. The measurement was conducted at a 90° scattering angle and 25 °.

4. Morphological evaluation

Scanning electron microscopy was used to examine the morphology of the prepared nanoemulgel. Briefly, 10 mg samples were diluted with 1 mL distilled water; following this, one drop of the diluted sample was allowed to dry at room temperature and was then coated with gold under vacuum on metal stubs and inspected at 5 kV.

5. In vitro release

Emulgel's in vitro drug release experiments were conducted on diffusion cells using egg membranes. Carefully, this was clamped to one end of the dialysis cell's hollow glass tube. The dialysis membrane's egg membrane was coated with 1g of emulgel. PBS (pH 7.4) solution was newly made and put into the receptor chamber. The total amount of gel that was put into the tube to dissolve the medication. A magnetic stirrer agitated the receptor chamber. The samples (1 ml aliquots) were taken at the necessary intervals and, following the proper dilutions, were examined for drug content using a UV visible spectrophotometer set at 261 nm. For each time interval, the total amount of drug release was calculated using cumulative adjustments.

6. Stability study

The samples were stored in firmly closed plastic containers and kept over a period of 6 months in refrigerator at 4 °C and in a stability chamber at 25 °C with relative humidity 60 %. The samples were evaluated for their physical characteristics and in vitro drug release at the specified period of time.

7. Viscosity measurements and rheological behaviour^[20]

A Brookfield L was connected to a thermostatic water bath adjusted to 25°C. Viscosity was measured on each base by using spindle 40. A defined amount (1 g) of each gel base was placed inside the plate and carefully closed. The measurement was started by operating the viscometer at 0.6 rpm, the speed was gradually increased and the measurement was recorded when the torque reached 10% was obtained by plotting the shear rate as a function of the shear stress.

8. Droplet size, polydispersity, and Zeta potential of Nanoemulsions

Dynamic light scattering (DLS) otherwise called photon correlation spectroscopy (PCS) is used to analyze the fluctuations in the intensity of scattering by droplets/particles due to Brownian motion. Nanoemulsions droplet size, zeta potential and polydispersity can be assessed by PCS using a particle size analyzer.

9. Accelerated stability studies^[21]

Best formulation is subjected to stability testing at $40\pm 2^\circ\text{C}$ and $75\pm 5\%$ RH conditions for 2 months. Parameters such as appearance, drug content, phase separation and in-vitro release were examined at two-month intervals.

APPLICATIONS

1. RHEUMATOID ARTHRITIS (RA)^[22]

Celecoxib has very poor oral bioavailability and aqueous solubility Nanoemulgel make some effort to improve its permeability and diffusibility. The main advantages of the nanoemulgel formulation are due to the presence of dual nature; means hydrophilic and hydrophobic bases which can deeply penetrate within the skin. Moreover, it also improves nanoemulsion stability by declining the surface and interfacial tension and also increases the viscosity of the aqueous phase for proper drug administration. Nanoemulgel has addition advantages such as it is more adhere toward skin surface and leads to higher concentration gradients toward skin hence assured better penetration.

2. TOPICAL ANTIBIOTIC^[23]

Mupirocin (MUP) is an effective topical antibiotic with poor skin permeability; however, its skin permeability can be improved by a nanoemulsion formulation based on eucalyptus oil or eucalyptol. Despite this improvement, the nanoemulsion has limitations, such as low viscosity, low spreadability, and poor retention on the skin. To overcome these limitations, the aim of this study was to develop a nanoemulgel formulation that would enhance its rheological behaviour and physicochemical properties. The MUP nanoemulgel was prepared by incorporating a preprepared MUP

nanoemulsion into Carbopol gel at a concentration of 0.75% in a 1:1 ratio.

3. WOUND HEALING^[24]

Thymoquinone is a natural bioactive with significant therapeutic activity against multiple ailments including wound healing. The poor aqueous solubility and low skin permeability limit its therapeutic efficacy. The present investigation aimed to improve the biopharmaceutical attributes of thymoquinone to enhance its topical efficacy in wound healing. A nanoemulsion-based hydrogel system was designed and characterized as a nanotechnology-mediated drug delivery approach to improve the therapeutic efficacy of thymoquinone, utilizing a high-energy emulsification technique. The black seed oil, as a natural home of thymoquinone, was utilized to improve the drug loading capacity of the developed nanoemulsion system and reduced the oil droplet size to <100 nm through ultrasonication.

4. ANTIFUNGAL^[25]

Luliconazole has been a wonder drug for treating superficial fungal infections. Current formulations are limited by very poor and slow skin absorption, requiring long-term, repetitive dosing to completely cure the condition. Nanoemulgel formulation (1% w/w) has been formulated and comprehensively tested, with the results compared to the commercially available formulation, the nanoemulgel formulation was found to be safe, non-irritant, and more effective with no drug reaching the systemic circulation. Therefore, employing an NE as a carrier for enhanced topical delivery of Luliconazole is a viable option.

5. ACNE VULGARIS^[26]

Acne vulgaris is a common chronic skin disease that affects around 9.4% (approx. 650 million people) of the global population. Growing research in the field of nanomedicine over the years has now been exploited in management of various human disorders. The nanomedicine concept has an immense opportunity for the effective management and control of acne disease by designing a novel, low-dose topical delivery system. Topical nanoemulsion-based gel preparations are said to have various benefits over the conventional formulations.

EXAMPLES OF VARIOUS MARKETED FORMULATION^[27]

Table no.3: various marketed formulations.

Name of product	Manufacturer	Formulation
VoltarenEmulgel	Novartis Consumer Health	Active ingredients:100g Diclofenac diethylamine corresponding to 1g diclofenac sodium, propylene glycol. Base: Fatty emulsion in an aqueous gel to which isopropanol and propylene glycol have been added.
ReumadepEmulgel	ErbozetaEnergia Verde	Arnica, Ashwagandha, Myrrh, Ginger, Rosemary, Cloves, Mint.
MeloxicEmulgel	Provet	Meloxicam
BenzolaitAzEmulgel	Rordermal	Benzoylperossido 10%
EmulgelLeverageMonodose	THD LAB Farmaceutici	
Coolnac Gel Emulgel 1%	Chumchon	Diclofenac Diethylammonium

RESEARCH RELATED TO NANOEMULGEL

1. Salem *et al.* developed nanoemulgel for direct brain targeting of Resveratrol, a widely used neuroprotective, cardioprotective, anti-inflammatory, antioxidant and anticancer drug. Optimized ratio of tween 20, transcutool and capryol 90 has been used as an emulsifier, and, carbopol 934 and poloxamer 407 were used as gelling agents. The obtained nanoemulgel system showed a globule size of 30.65 nm with 100% transmittance and drug solubility up to 159.9 ± 6.4 mg/mL. In vivo pharmacokinetic study, in vitro release, ex vivo permeation, nasal mucosa toxicity and the release kinetic studies were also performed with optimized nanoemulgel formulation, where developed nanoemulgel of Resveratrol showed enhanced permeability and bioavailability on delivery through intranasal route.^[28]
2. Quercetin is known for its antimicrobial, anti-inflammatory properties and is used in treatment of periodontitis. Scientists have prepared Quercetin loaded emulgel using low energy emulsification method using water as aqueous phase and cinnamon oil as oil phase, and tween 80 and carbitol as Smix. The maximum solubility of the drug was observed to be $125 \mu\text{g}/200 \mu\text{L}$. Nanoemulgel was further prepared using poloxamer 407 as a base (23% w/v). The molecular dynamics simulation study was carried out to study the process of gelation and the role of each component. The viscosity of the obtained nanoemulgel was $30,647 \pm 0.32$ CPs at 37°C . Further developed Quercetin loaded nanoemulgel showed promising potential in controlled drug release for periodontitis with enhanced solubility and bioavailability of drug.^[29]

FEW PATENTS ON EMULGEL FORMULATION^[30]**Table no. 4: patented formulations.**

S.no	Patent nos.	Title	Inventors	Year
1	US 6113921A	Topical and transdermal delivery system utilizing submicron oil spheres	Doron Friedman, Joseph Schwartz, Haim Avi	1993
2	US0058224658A	Topical composition containing hyaluronic acid and NSAIDs	Falk, Rudolf Edgar, Asculai, Samuel Simon	1995
3	WO2002017905A2	Treatment of burns	Anczewicz Jacek, Kienzler Jean-Luc, Sallin Dominique, Schumann Phyllis	2002
4	2,007,129,162	Pharmaceutical preparation for transdermal use	Cristina Cavallari, Barbara Luppi, Pietra Anna Mariya Di, Lorenzo Rodriguez	2007
5	EP2214642A1	Topical composition	Fabienne Caillet-Bois, Isabelle Rault, Michel Steiger	2008

MAJOR CHALLENGES OF NANOEMULGEL DRUG DELIVERY SYSTEM^[31]

In spite of the distinct advantages, there are some existing challenges to overcome for the nanoemulgel drug delivery system including preparation method to stability related issues. Preparation of nanoemulsion requires high energy. Even though few low-energy methods exist, but are not perfectly suitable for large scale manufacturing and normally need higher amounts of surfactants. But, use of high amount of surfactant causes skin irritation and contact dermatitis.

CONCLUSION

In conclusion, nanoemulgel systems represent a promising advancement in the field of pharmaceutical and cosmetic formulations. By combining the benefits of both nanoemulsions and gels, nanoemulgel systems offer enhanced drug delivery, improved bioavailability, and greater stability compared to conventional formulations. Their unique properties, such as small particle size, high surface area, and the ability to encapsulate both hydrophilic and lipophilic compounds, make them suitable for a wide range of applications, from topical treatments to controlled release systems.

However, despite their potential, there are still challenges to overcome, including the scalability of production methods, long-term stability, and ensuring patient safety in clinical settings. Continued research into the development of novel excipients, improved manufacturing techniques, and the optimization of formulation parameters is essential for fully realizing the potential of nanoemulgels.

In summary, while nanoemulgel technology is still evolving, it holds great promise for advancing therapeutic and cosmetic delivery systems. As research in this area progresses, nanoemulgels are expected to play a significant role in improving the efficacy and safety of drug delivery, paving the way for more effective treatments and patient-centric care.

REFERENCES

1. Morteza SK, Saeedi M, Akbari J, Eghbali M, Babaei A, Hashemi SM, *et al.* Development of a novel nanoemulgel formulation containing cumin essential oil as skin permeation enhancer. *Drug Deliv Transl Res.* 2022; 24(5): 1–11.

2. Mandal S, Vishvakarma P. Nanoemulgel: A smarter topical lipidic emulsion-based nanocarrier. *Indian J Pharm Educ Res.* 2023; 57(3): 481–98.
3. Donthi MR, Munnangi SR, Krishna KV, Saha RN, Singhvi G, Dubey SK. Nanoemulgel: a novel nano carrier as a tool for topical drug delivery. *Pharmaceutics.* 2023; 15(1): 164–78.
4. Shukla T, Upmanyu N, Agrawal M, Saraf S, Saraf S, Alexander A. Biomedical applications of microemulsion through dermal and transdermal route. *Biomed Pharmacother.* 2018; 108: 1477–94.
5. Nastiti C.M.R.R, Ponto T, Abd E, Grice JE, Benson HAE, Roberts MS. Topical nano and microemulsions for skin delivery. *Pharmaceutics.* 2017; 9(2): 37–43.
6. Aithal GC, Narayan R, Nayak UY. Nanoemulgel: a promising phase in drug delivery. *Curr Pharm Des.* 2020; 26(2): 279–91.
7. Anand K, Ray S, Rahman M, Shaharyar A, Bhowmik R, Bera R, *et al.* Nano emulgel: emerging as a smarter topical lipidic emulsion-based nanocarrier for skin healthcare applications. *Recent Pat Antiinfect Drug Discov.* 2019; 14(1): 16–35.
8. Bhura MR, Bhagat KA, Shah SK. Formulation and evaluation of topical nanoemulgel of adapalene. *World J Pharm Sci.* 2015; 18(7): 1013–24.
9. Thakur S, Rajinikanth PS, Deepak P, Jaiswal S, Anand S. Withdrawal notice: Novel treatment strategies for management of psoriasis: current update and future perspective. *Curr Drug Deliv.* 2021; 15(1): 164–68.
10. Damayanthi D, Chella D, Durga V. Nanoemulgel: a comprehensive review for topical drug delivery. *Int J Pharm Pharm Res Human.* 2022; 30(2): 271–86.
11. Malay NJ, Chandresh PP, Bhupendra GP. Nanoemulgel: innovative approach for topical gel-based formulation. *Nanoemulgel Innovative Approach Top Gel Based Formulation.* 2018; 14(1): 21–31.
12. Donthi MR, Munnangi SR, Krishna KV, Saha RN, Singhvi G, Dubey SK. Nanoemulgel: a novel nano carrier as a tool for topical drug delivery. *Pharmaceutics.* 2023; 15(1): 164–78.
13. Sabalingam S, Siriwardhene MA. A review on emerging applications of emulgel as topical drug delivery system. *WJARR.* 2022; 13(1): 452–63.
14. Sultana N, Akhtar J, Khan MI, Ahmad U, Arif M, Ahmad M, *et al.* Nanoemulgel: for promising topical and systemic delivery. In: *Drug Development Life Cycle.* 2022; 9(3): 39–46.
15. Vazir A, Joshi A, Kumar K, Rajput V. Nanoemulgel: for promising topical and systemic delivery. *Int J Pharm Drug Anal.* 2023; 11(4): 8–13.
16. Azeez AR, Alkotaji M. Nanoemulgel as a recent drug delivery system. *Mil Med Sci Lett.* 2022; 91(2): 1–12.
17. Gupta SK. Formulation and evaluation of nanoemulsion-based nanoemulgel of aceclofenac. *J Pharm Sci Res.* 2020; 12(4): 524–32.
18. Abdallah MH, Lila AS, Unissa R, Elsewedy HS, Elghamry HA, Soliman MS. Preparation, characterization and evaluation of anti-inflammatory and anti-nociceptive effects of brucine loaded nanoemulgel. *Colloids Surf B Biointerfaces.* 202; 20(5): 118–68.
19. Jilby S, Arun R. Formulation and evaluation of lamotrigine nanoparticles incorporated in situ gel for epilepsy. *Int J Pharm Pharm Res.* 2018; 13(4): 177–94.
20. Mahtab A, Anwar M, Mallick N, Naz Z, Jain GK, Ahmad FJ. Transungual delivery of ketoconazole nanoemulgel for the effective management of onychomycosis. *AAPS PharmSciTech.* 2016; 17(6): 1477–90.
21. Mandal S, Vishvakarma P. Future aspects and applications of nanoemulgel formulation for topical lipophilic drug delivery. *Eur J Mol Clin Med.* 2023; 10(1): 20–3.
22. Bhattacharya SA, Prajapati BG. Formulation and optimization of celecoxib nanoemulgel. *Asian J Pharm Clin Res.* 2017; 10(8): 353–65.
23. Alhasso B, Ghorri MU, Rout SP, Conway BR. Development of a nanoemulgel for the topical application of mupirocin. *Pharmaceutics.* 2023; 15(10): 23–87.
24. Algahtani MS, Ahmad MZ, Shaikh IA, Abdel BA, Nourein IH, Ahmad J. Thymoquinone loaded topical nanoemulgel for wound healing: formulation design and in vivo evaluation. *Molecules.* 2021; 26(13): 38–63.
25. Kaur M, Shivgotra R, Thakur S, Kour R, Singh M, Shahtaghi NR, *et al.* A novel nanoemulgel formulation of luliconazole with augmented antifungal efficacy: in vitro, in silico, ex vivo, and in vivo studies. *J Drug Deliv Sci Technol.* 2023; 89(9): 105–121.
26. Ahmad J, Gautam A, Komath S, Bano M, Garg A, Jain K. Topical nanoemulgel for skin disorders: formulation approach and characterization. *Recent Pat Antiinfect Drug Discov.* 2019; 14(1): 36–48.
27. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, *et al.* Nanoemulsion and nanoemulgel as a topical formulation. *IOSR J Pharm.* 2015; 5(10): 43–7.
28. Salem HF. Nanosized nasal emulgel of resveratrol: preparation, optimization, in vitro evaluation and in vivo pharmacokinetic study. *Drug Dev Ind Pharm.* 2019; 45(10): 1624–34.
29. Aithal GC. Localized in situ nanoemulgel drug delivery system of quercetin for periodontitis: development and computational simulations. *Molecules.* 2018; 23(6): 1363.
30. Ojha B, Jain VK, Gupta S, Talegaonkar S, Jain K. Nanoemulgel: a promising novel formulation for treatment of skin ailments. *Polym Bull.* 2022; 79(7): 4441–65.
31. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. *Int J Pharm.* 2017; 526(1): 353–65.