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

OPEN ACCESS

Review Paper

Nanoemulgel: A Novel Nanocarrier Approach for Effective Topical Drug Delivery

Ruturaj Jadhav[a]*, Rajanikant Ghotane[b], Pranali Patil[b], Sarika Suryawanshi[c], Dr. Anand Gadad[c]

[a]*Department of Pharmaceutical Quality Assurance, Ashokrao Mane College of Pharmacy, Peth Vadgaon-416112, Kolhapur, Maharashtra, India.*
[b]*Department of Pharmaceutical Chemistry, Ashokrao Mane College of Pharmacy, Peth Vadgaon- 416112, Kolhapur, Maharashtra, India.*
[c]*Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth Vadgaon- 416112, Kolhapur, Maharashtra, India.*

ARTICLE INFO

Published: 11 May 2025
Keywords:
Nanoemulgel, Topical drug delivery, Nanoemulsion, Drug solubility, Controlled release
DOI:
10.5281/zenodo.15381511

ABSTRACT

Nanoemulsions are a recent opportunity for drug delivery through skin, a hybrid system of emulsions and gels. Nanoemulsions are stable surface-active agent systems of dispersions of small droplets of oil in water extending confinement of the surface area for drug absorption. They can be added to the gel structure in which case it forms a plastic mass that can be conveniently applied on the skin for a long time. Nanoemulsions possess skin penetration enhancing ability through the enhancement of the drug delivery into the stratum corneum. Furthermore, contents of the gel enable control of the release so that treatment can be for a longer duration. This reduces the adverse effects on the patients and helps in concentrating the treatment at the site of interest. For this purpose, several gelling agents like carbomers, xanthan gum are used to obtain the required viscosity and stability so that the formulation is stable during use and storage. In summary, nanoemulgels have a wide range of applications in topical delivery systems and resolving the problems of low drug solubility and skin permeation. Ongoing research and development are crucial to fully explore their potential in clinical applications, paving the way for more effective treatments in dermatology and beyond.

INTRODUCTION

The techniques for administrating drugs into the human being have evolved over the last few decades to include the oral, sub-lingual, rectal,

***Corresponding Author:** Ruturaj Jadhav
Address: *Department of Pharmaceutical Quality Assurance, Ashokrao Mane College of Pharmacy, Peth Vadgaon- 416112, Kolhapur, Maharashtra, India*
Email ✉: jadhavruturaj0760@gmail.com
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.

parenteral, inhalation, transdermal and topical techniques. Topical drug delivery is where a drug formulation is placed with the aim of treating conditions, like inflammatory and skin diseases. [1] The administration of topical therapies may have enormous therapeutic advantages. One of the key advantages of topical delivery is the provision of increased drug bioavailability since it avoids the gastrointestinal (GI) tract and first-pass metabolism. As a way to overcome the difficulties related to the lipophilic properties of the drugs like stability and bioavailability enhancement, novel lipid-based formulations, including solid lipid nanoparticles (SLNs), Nanostructured lipid carriers (NLCs), liposomes, nanoemulsion (NE), and nanoemulgel (NEG) are all becoming an ideal system.[2] The enormous importance of these systems in several industrial branches may be due to their kinetic stability and a surfactant efficiency that can be reached even at low concentrations. The term nanoemulsions can also apply when the emulsions appear in a milky, translucent, and transparent form depending on droplet size. There are two major types of nanoemulsions, namely w/o and o/w. They are either prepared through low or high energy emulsification techniques. The sizes of the droplets created in nanoemulsions, which range typically from 20 to 200 nm, which protect the systems from physical instability, flocculation, and creaming. [3] The formulation of nanoemulsions using safe biocompatible agents has led to many proposals involving the release of drugs and other biologically active agents via various administration methods. In particular, oil in water nanoemulsions is considered to be good carriers and encapsulating systems for lipophilic actives. [4] Nevertheless, owing to their low viscosity, it becomes a challenging task to use nanoemulsions for topical administration. One of the ways to overcome the limitations of the above-mentioned systems is the incorporation of 'oil in water' (o/w) nanoemulsions containing lipophilic active compounds into hydrogels. [5] Crosslinked hydrophilic polymers three dimensional networks are commonly known as hydrogels. Hydrogels have the ability to contain large amount of water as well as biological fluids owing to the multiple hydrophilic functional groups present in the polymeric chain. Chitosan, gelatine, xanthan are examples of polymers either fully synthetic or obtained in nature which can be made into hydrophilic gels. Numerous lipophilic bioactive substances have been proposed for distribution using hydrogels based on nanoemulsions. [6,7] Traditional topical formulations like ointments and creams often face issues such as stickiness, poor spreadability, and instability, leading to patient noncompliance. Modernizing these formulations into clear gels and Emulgel improves effectiveness and patient adherence, making them increasingly popular in pharmaceuticals and cosmetics, though delivering hydrophobic drugs remains a challenge. [8] When Nanosized emulsions are mixed into gel-based form, it is called as nanoemulgels (NEGs). NEGs utilize gelling agent that enables nanoemulsions to be made into a gel form providing stability, thickness, with a non-oily appearance for instance, NEs are low viscous and low spreadable, have poor skin carry over and are not amenable to scaling up. Gels do not alone efficiently immobilize hydrophilic molecules. Each part of the combination has its own limitations. [9] The limitations of either system's application can be remedied using an innovative approach with NEGs. These work by enabling lipid soluble drugs with the oil phase of a nanoemulsion which then infused with gel to form a NEG. This decreases the fluidity of the nanoemulsion and makes it possible to load a lipophilic drug within a hydrogel. [10] Nanoemulsion droplets, by covering a large skin surface area, enhance the permeability of lipophilic drugs, improving their pharmacokinetic and pharmacodynamic properties. Unlike

traditional topical formulations, which suffer from issues like hygroscopicity, instability, or rancidity, NEG formulations avoid these drawbacks. As a result, patient compliance is significantly improved. [11] As a delivery system, NEGs are employed in management of numerous inflammatory skin diseases, including psoriasis, dermal fungal infections, acne, and pimples, as well as inflammation related to osteoarthritis and rheumatoid arthritis. [12]

Mechanistic Approach of Nanoemulgel Delivery via Topical Route:

The stratum corneum is the most effective barrier in controlling the penetration and entrance of drugs delivered topically. In cases where skin disorders or penetration enhancers disrupt the skin, the subcutaneous (SC) layer is breached, and tight junctions serve as an auxiliary barrier. [13] There are three routes - paracellular, transcellular and trans appendageal - through which the medication molecule can penetrate the body. Accessing the skin is primarily accomplished on the basis of the paracellular mechanism, whereby the drug penetrates into the corneocytes through the lipid system. Small lipophilic molecules (< 500 Dalton) are capable of passing through this channel Since NEGs have the potential to transport the drug along all three pathways through the skin, they enhance topical delivery. [14]

Scope of Nanoemulgel for Topical Delivery:

Compared to traditional lipophilic drug formulations, an Emulgel containing topical nanoemulsions is a preferred option because of its enhanced pharmacokinetics, greater absorption capabilities, and hence, improved therapeutic efficacy. They also have better spreading characteristics and lesser stickiness as compared to the conventional topical administration options. [15] Among other formulations, the oil-free base enables a higher liberation of medicament. The problem of phase separation and creaming encountered with traditional emulsions is eliminated and better spared ability is achieved with the addition of nanoemulsion in the gel matrix. For certain dermatological conditions, a gel containing encapsulated nanoemulsion is more beneficial. [16] Hydrophilic drug administration, in turn, in the future can become more effective and dependable with nanoemulsion-gel based formulations. This is because most of the anti-skin infection agents are hydrophobic in nature and thus, can be successfully applied as Nanoemulgels. [17]

Active methods for enhancing topical delivery to skin:

1. Ultrasound (Sonophoresis or Phonophoresis):

Ultrasound is also referred to as sonophoresis or phonophoresis and generally refers to the application of ultrasound that enhances drug permeation to skin. Ultrasonic waves are of two principal frequency ranges, that is, high (2 MHz to 16 MHz) and low (20 KHz to 100 KHz) frequencies. the guiding variables are primarily the frequency, the duration and the intensity of the ultrasonic waves applied. [18] By rupturing the stratum corneum's intercellular lipid bilayer, ultrasound exhibits encouraging promise for enhancing transdermal medication distribution. Increased skin permeability and localized transport have also been observed when hydrogels with a low-frequency ultrasonic coupling medium are used. Ultrasonography causes thermal effects in which it raises the temperature of the skin. Irrespective of the electrical properties, dissociation constants, ionization and molecular weight of the medication, sonophoresis techniques are useful in drug delivery. [19]

2. Laser radiation and photomechanical waves:

This technique of removing the skin's subcutaneous layer has been demonstrated to improve the administration of both hydrophilic and lipophilic medications. [1] By means of photodynamic waves directed to the surface of the skin, the medication is allowed to penetrate the stratum corneum (SC) through the transiently formed channel. Low radiation exposure of approximately 5-7 J/cm^2 causes minimal ablation from the incident wave and enables successful transmission at a depth of up to 50-400 μm. Within minutes, the wave of a single laser pulse was found to enhance the permeability of the skin to such an extent that macromolecules could penetrate into the skin. A single-photon-dynamic laser pulse of 23 ns duration is capable of administering dextran macromolecules of 40 kDa weight and 20 nm latex particles. [20]

3. Electroporation:

Electroporation enables the introduction of fluids into the cells by generating fluidic nanometer-sized pores in the lipid bilayers of the stratum corneum after subjecting the skin to relatively higher electric pulses for a shorter time. [21] Other studies have also shown that, the low molecular weight drugs such as fentanyl and timolol, as well as high molecular therapeutics including heparin and calcitonin, is enhanced by the delivery of high voltage pulses (50-500 V) for one second. [22]

4. Iontophoresis:

Introducing a small electric potential difference facilitates the ion's passage all over the membrane in iontophoresis techniques. [23] Through the use of an electrode of the same polarity as the charged drug, a very minimal appropriate medical current (0.5 mA/cm2 or even lower) is applied to inject ionic (charged) drugs into the patient's body. The drug is consequently forced into the skin through electrostatic repulsion. It is also known that the transdermal delivery of proteins and peptides can be enhanced by using lower currents for briefer periods. [24] The effectiveness of the iontophoresis method in cell penetration is influenced by several factors including the characteristics of the drug molecule including mobility, polarity and valency, the parameters of the electrical cycle applied, and the composition of the drug formulation. [25]

5. Skin puncture and perforation devices:

Much like microneedle gadgets created employing microfabrication approach, these devices cause damage to the skin barrier using needle like structures or blades which produce holes or incisions in the skin upon contact with it. Depending on the technique employed after the disturbance of the skin, methods of delivery can be either active or passive [26]

6. Radio-frequency:

By inserting a tiny, needle-like electrode straight into the skin and applying high frequency alternating electricity (~100 kHz), radiofrequency (RF) thermal destruction creates microscopic channels in the corneum layer that let drugs in. [27] Drug transport across the skin is facilitated by ionic vibrations in the connective tissue when skin cells are subjected to extremely strong frequencies (100–500 kHz). These vibrations are meant to ablate the cells in a specific area of the skin by localizing the warmth there.[28]

7. Magnetophoresis:

This enhancing technique includes applying an electromagnetic field surrounding the solute that penetrates the skin. Benzoic acid, for example, is a diamagnetic substance that improves its diffusion properties when surrounded by a magnetic field. The main disadvantage of this strategy is that it

may change the properties of the stratum corneum. [29]

METHOD OF PREPARATION FOR NANOEMULGEL:

Nanoemulgel containing internal nanosized droplets of oil or any other hydrophobic material dispersed in a hydrophilic matrix. The following are some general methods for preparing Nanoemulgel:

1. High-pressure homogenization technique:

The technique involves creating nanosized droplets of the oil phase which are conveniently suspended in a hydrophilic gel matrix by high-pressure homogenizer. The emulsification together with shearing is effective in reducing the droplet size resulting in stable nanoemulgel. [30] Great turbulence and hydraulic stress are produced on the products, resulting in extremely thin emulsion droplets, when a mixture of two fluids—an oily and an aqueous phase—is forced through a tiny inlet at extremely high pressures (500–5000 psi). As the total number of homogenization cycles increases, the emulsified size of particles will get finer.[31]

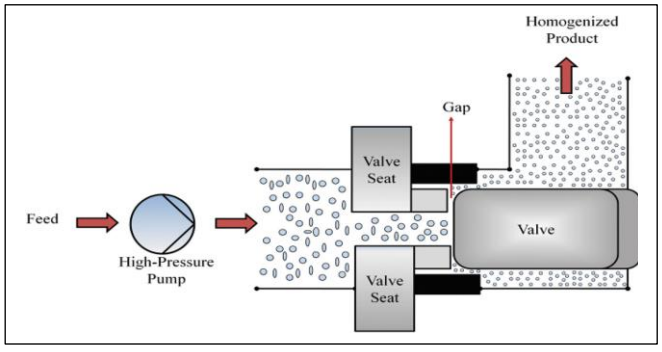

Figure No. 1: Working of High-Pressure Homogenization. [31]

2. Ultrasonication method:

Ultrasonics has been found to assist in generating nanoemulsions as a function of decreasing the size of the globules. In this method, an ultrasonic wave of 20 kHz is used to agitate the previously prepared emulsion mixture, leading to the formation of nanometer sized droplets. The emulsion produced is then forced through a high shear zone in order to generate droplets of narrow size distribution. [32] In this method, a water jacket is applied to control the temperature. In the ultrasonic emulsification, sonication which involves the use of sonication probes i.e. the sonotrodes has been used. These sonotrodes which are made up of piezoelectric quartz crystals. The supplied voltage to these sonotrodes leads to their expansion and compression. It is generally used in the situations where the droplets of size less than 0.2 μ are desired. [33]

3. Microfluidization technique:

Utilizing a device called a microfluidizer, the mixing process is called "microfluidization." This device uses a powerful positive displacement pump running between 500 and 20,000 psi to force an item into the contact chamber, which is composed of microscopic channels called "microchannels." The product travels via the tiny channels and onto an impingement zone, producing tiny particles in the sub-micron range. The two solutions—the aqueous phase and the oily phase—are combined and passed through an internal homogenizer to produce a coarse emulsion. The coarse emulsion undergoes further processing in a microfluidizer to produce a stable nanoemulsion. The coarse emulsion is frequently sent through the reaction chamber microfluidizer until the desired particle size is achieved. [34]

4. Solvent evaporation method:

This process involves creating a solution of drug and later emulsification it in a separate liquid that isn't the drug's solvent. Solvent evaporation leads to drug precipitation. High shear stresses,

which regulate crystal formation and particle aggregation, can be produced using a high-speed stirrer. [35]

5. The phase inversion Method:

Phase inversion composition (PIC) is an enlarged form of spontaneous emulsification. This methodology produces nanoemulsions at room temperature rather than requiring energy-intensive apparatus like the high energy approach or solvents like the spontaneous emulsification method. Oil and surfactant are stirred at room temperature using a magnetic stirrer on a laboratory scale that feeds water drop by drop. A w/o nanoemulsion occurs initially when the volume of water is raised, following with an o/w at the opposite, requiring a significant amount of energy, as seen in Fig. 5.2 [36] The formation of nanoemulsion is influenced by several variables, including surfactant structure, concentration, phase transition area, bulk viscosity, and interfacial tension. This method is sometimes called catastrophic inversion since it involves increasing the size percentage of the scattered phase.

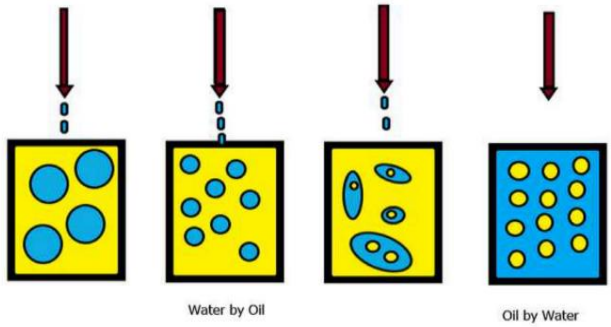

Figure No. 2: Phase inversion composition method. [37]

6. Spontaneous Emulsification:

Three main procedures take place: Preparing a homogeneous organic solvent containing both hydrophilic and lipophilic surfactants in a water-miscible solvent and insoluble oil. The organic phase was injected to the aqueous phase while the latter was stirred magnetically, producing an oil-in-water emulsion. The water-miscible solvent was then removed under lower pressure by means of evaporation. [38]

FORMULATIVE COMPONENTS OF NANOEMULGEL:

1. Aqueous Phase:

With regard to the gelling substance, this part is what transforms the emulsion through an Emulgel. Nanoemulgel is usually made using ultra-purified or distilled water. [39]

2. Oils and lipids:

Synthesis of any nanoemulsion requires careful consideration of the selection of each lipid component that will be used, primarily due to the fact that the amount of either oil or lipid component included in any formulation is in most cases dependent on the type of emulsion as well as the dissolvability of the given component. Generally, the oil which has the maximum potential to melt the drug candidate is used. This is because, for the preparation of the emulsion, the drug has to be melted in the oil phase and retained within. [40] There are three types of oils and lipids that are allowed in the synthesis of nanoemulsions. Triglycerides can be termed as short-chain, medium-chain, or long-chain (SCT, MCT, and LCT). Soybean oil, sesame oil and other had cooking oils that are oil liquids, are incorporated to form the oily phase. [38]

3. Surfactants:

The surfactant's amphiphilic characteristic, which reduces interfacial tension and provides a relatively steady film that is capable of deforming with respect to the droplets with the appropriate curvature, permits two immiscible phases to

disperse. Surfactants contaminants penetrate scalp more efficiently by obstructing corneocytes and modifying the diffusion coefficient of stratum corneum (SC) by reversibly binding to keratin filaments. [41] Drugs have a different skin penetration profile, which refers to the amount of drug delivered across the skin, for every specific dosage of surfactant combination. The penetration of a hydrophilic medication improved significantly as the concentration of surfactant increased. It is common practice to include non-ionic surfactants in formulations because they have a better safety profile and are less likely to be absorbed systemically compared to ionic surfactants. Tween 20® and Tween 80® are the major surfactant utilized in the lipid-based formulation. [42]

4. Co-surfactants:

A co-surfactant promotes microemulsions (MEs) and nanoemulsions (NEs) rather than only stabilizing an emulsion with surfactant activity. Specifically, a co-surfactant will additionally lower the interfacial tension. This allows for greater curvature of the interfacial layer since more oil can be inserted between the tails of the surfactants. [43] The structural arrangement of surfactants and co-surfactants for oil in water nanoemulsion, which is dependent on the concentration of the surfactant and co-surfactant, in turn affects phase characteristics. In this respect, the optimal qualitative-quantitative composition is generally determined by trial formulation research. Common screening method, like pseudo-ternary phase diagram. The precise concentration range for the creation of the nanoemulsion using the water titration method was ascertained using this methodology. The Smix weight ratio can be changed to create different diagrams. Figure 6 shows the pseudoternanry phase diagram. [44]

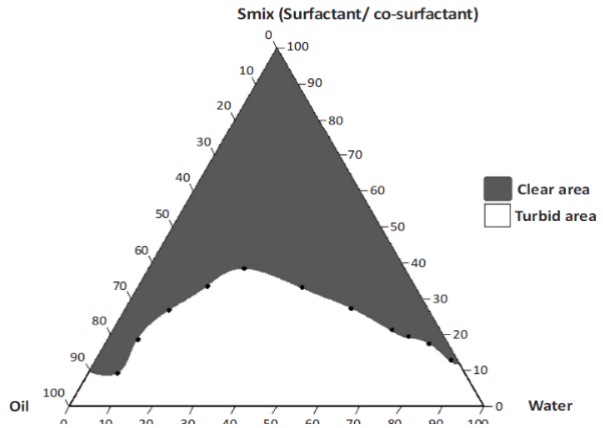

Figure No. 3: Pictorially how a pseudoternary phase diagram is constructed using aqueous titration method, the area shaded in black colour corresponds to the clear transparent region of the nanoemulsion while the rest of the regions stay unshaded which is the area of turbidity. [44]

5. Gelling Agent:

The gelling agent is considered one of the most crucial aspects of a nanoemulgel formulation since it provides the formulation with a specific texture. The formation of gel-like structure occurs in formulations with the inclusion of the gelling agent. Gelling agents can be classified into two principal groups: natural gelling agents and synthetic gelling agents. The Emulgel technology research shows how gelling agents affect drug release in a particular formulation. Greater quantity of medicine delivery decreases the concentration of gelling agent. As far as specific stability tests carried out in different cycles of temperature, centrifugation is concerned, compositions including two gelling agents or small amount of carbopol in the system were shown to be more stable than other compositions. [45]

Gel-forming agents fall into one of the following categories:

1. **Natural polymers:** Alginic acid, Tragacanth, Gelatine and Collagen.
2. **Semisynthetic polymers:** Hydroxypropyl Methylcellulose, Carboxymethyl Cellulose.

3. **Artificial polymers:** Poloxamer, Carbomer.
4. **Inorganic substances:** Bentonite, Aluminum Hydroxide.
5. **Surfactant:** Cetosteryl Alcohol. [46]

6. Carbomers:

Crosslinking of polymers of acrylic acid termed as carbomers are developed using allyl ethers of pentaerythritol or allyl sucrose. Numerous carbomer grades are existent, for example: 934 presents the minimum degree of cross-linking; 981, a moderate level of cross-linking, and 940 as the maximum cross-linking density. Depending on production requirements and the level of cross-linking. In general, carbopol have been shown to absorb a significant amount of water under conditions of pH 4 to 6. Carbopol particles in water can expand to a thousand times of their initial volume, and a diameter of hundred times, creating a gel. Therefore, Carbopol particles are able to form a gel in the presence of water upon the addition of organic amines which act as neutralizers. [47]

a. **pH Modifiers:**

The pH level showed that the nanoemulsion was stable. An ideal pH range for skin is between 5.4 and 5.9. Sodium hydroxide and triethanolamine are two most often used. [48]

b. Other components:

Preservatives and antioxidants are examples of additional additives that might be added to nanoemulsion. Generally, water-based systems need a preservative chemical to stop bacteria from growing. Since essential oils (EOs) are naturally occurring antimicrobials, preservatives are typically not needed in EO-based systems. [49]

Stages of Nanoemulgel Formulation Design:

1. Screening of components:

When determining the final formulation, the results of the preliminary formulation tests must be taken into consideration. At this stage, the ability of oily phase to dissolve the drug substance is also evaluated. The selection of the surfactant and cosurfactant ratios is informed by the parameters that were used to design the nanoemulsion, their dispersive properties with the oil, and the type of emulsion formed (oil-in-water or water-in-oil). One of the ways of breaking this uncertainty is to draw a pseudoternary phase diagram, which allows determining if a certain concentration of these ingredients is enough to form a nanoemulsion. This also shows the proportion of these three ingredients, which helps maintain the stability of the nanoemulsion at the point of development in the region of nanoemulsification. [50]

2. Preparation of Nanoemulsion:

The dissolution of medicaments, surfactants, and cosurfactants takes place depending on the solvent selected, which in this case would be either an aqueous or oil phase. The aqueous phase and oil phase are firstly heated separately and subsequently other phases are gently introduced to the mix with constant stirring until the desired temperature is attained. [17] Low-energy techniques like solvent diffusion and self-nano emulsification or high-energy techniques like high-pressure homogenization and ultrasonication can be used to create nanoemulsions. Because they are more efficient and don't require specialist equipment, low-energy approaches are recommended. [45]
Several formulation compositions and the particle size can be modified using high-energy methods can be used to adjust the emulsion's colour, rheology, and stability. High-energy techniques minimize phase sizes by utilizing mechanical forces, but they can also cause thermodynamic

instability by overheating components, particularly for medications that are heat-sensitive. Low-energy techniques are more energy-efficient because they utilize the system's chemical energy, protecting heat-labile components and halting the evaporation of volatile essential oils. The other point of view is that low-energy emulsification technology makes possible tremendous increases in energy efficiency by harnessing the chemical energy inherent in the system. [39] By using less energy, this method stops heat-labile components from degrading. As to prepare important nanoemulsions from essential oils and prevent their volatile components from evaporation in a proper manner, the most generally used technique would be the low energy or spontaneous technique. [51]

3. Preparation of gel base:

Gel preparation is done by incorporating gelling agents into water until total hydration occurs. Therefore, the polymer of choice is incorporated into distilled water and subjected to continuous stirring for a certain fixed period at a certain fixed temperature and speed so that complete swelling is achieved. Lastly, the gel base's pH is changed to ensure optimal absorption by the topical system.

4. Incorporation of Nanoemulsion into Gel Base:

Diagram showing how to prepare nano-emulgel by (A) mixing the watery (water + gelling agent) phase with the oil (oil + drug) phase (B) incorporating a nano-emulsion into the aqueous phase (water plus gelling agent). [52]

Characterization of nanoemulgel:

1. Drug content:

Amount of drug is a crucial factor that establishes how much drug is included overall in the produced formulas; a greater drug content is linked to less drug loss during the production process.

2. pH measurement:

The Nanoemulgels pH varies according to its targeted application, for instance, skin or other mucosal surfaces. Studies indicate that a typical pH of human skin falls between the range of 4.5 to 6. [53]

3. Spreadability:

The coverage of the NEG on the dermis, or the skin, and its uniformity, determines the effective dose achieved. This is done with the use of the parallel plate (slide and drag) method, which entails the placement of a sample in-between two flat glass slabs and compressing the same for specific duration.

Spreadability is calculated using the formula below:

M × L/T = Spreadability (S)

Where, L is the length of glass slabs, M is the weight connected to upper glass slab and T is the time taken to pull apart the glass slabs. [54]

4. Swelling index:

Apply one gram of the prepared topical nanoemulgel onto a suitable round porous aluminium foil and then place it on 10milliliters of 0.1 N NaOH solutions. After a duration, a sample is

taken out and the weight is measured until there is no change in it.

The SW percentage is defined as below; SW %= [(Wt-Wo) / Wo]*100.

In this equation, Wo is the weight of the nanoemulgel before the measurement, Wt is the measure of swelled nanoemulgel at time t (i.e.,

after several minutes) and (SW) is the swelling in percent. [55]

5. Droplet size and polydispersity of Nanoemulsions:

A nanoemulsion gel (NEG) droplet's hydrodynamic diameter is defined as the diameter of a hypothetical solid sphere that dissipates at the same rate as the drug molecule. The polydispersity index (PDI) which indicates the droplet size distribution corresponds to the measured difference between the droplets mean size and the size variance. [56] The droplet size along with PDI influences the drug discharge, stability of formulation and vivo/ vitro formulation's performance. Evaluating batch-to-batch uniformity is vital, with nanoemulsions ≥500 nm appearing hazy and those between 50-200 nm being clear. The master or zeta sizer measures size and PDI, while dynamic light scattering (DLS) specifically quantifies globule size. [57]

6. Zeta potential:

The formulation of nanoemulsions employs several surfactants, which give them an electrical charge. The stability increases with the increase in zeta potential which enhances repulsion and disallows the coming together of the globules. Charge modulators can also be used to manipulate the surface charge thereby altering the zeta potential. [55] To achieve stability an emulsion must contain both cationic and anionic surfactants that are measured using Zetasizer®, Malvern Nanosizer, nano-ZS ZEN 3600 and ZC-2000 to obtain the zeta potential values. [58]

7. Determination of Viscosity:

For skin application, the gel's viscosity is essential. Gel must comprehend how it behaves rheologically. A fluid's viscosity is its resistance to flow; the higher the viscosity, the higher the flow resistance. In general, fluids fall into one of two categories: Newtonian or non-Newtonian systems.[48] In Newtonian flow, a fluid with a higher viscosity requires more force per unit area (shear stress) to generate a given shear rate. Newtonian flow means that there are changes in the shear rate but the viscosity remains the same. Viscosity in fluids that exhibit non-Newtonian flow, however, is not constant and depends on the shear value at any point in time; hence, they do not obey the laws of Newton's fluids.[59]

8. Spreadability measurement:

The topical preparation's spreadability will determine the resulting formulation's medicinal effectiveness. Spreadability is the term used to describe how easily a gel covers the skin's application site and affected region. The spreadability of nanoemulgels is assessed using their "Slip" and "Drag" characteristics.[60]

9. In-vitro diffusion studies:

A Franz diffusion cell is used to investigate the diffusion of the generated nanoemulgel. A transparent membrane is used for the investigation. Diffusion is carried out using a phosphate buffer with a pH of 7.4 for eight hours at 37±1°C after 0.5g of the sample is deposited on the membrane. Every hour, a new buffer solution is added to the millilitre (ml) of each sample. The collected samples are analysed using the proper analytical method.[1]

CONCLUSION

This review emphasizes the potential of Nanoemulsion Gels (NEGs) as an advanced delivery of drug system, particularly for improving the permeability and bioavailability of medications applied topically. NEGs combine the benefits of a gel base and nanoscale emulsion in one formulation, offering stability, improved skin

penetration, and protection of active ingredients from degradation. By enhancing drug diffusion through the epidermis, NEGs can avoid systemic side effects, target specific sites, and bypass first-pass metabolism. They have shown efficacy in treating various conditions, such as psoriasis and acne. Despite the challenges in stability over time, production, and commercialization, NEGs (Nanoemulgels) are also thought to have potential for the creation of topical anti-inflammatory medications.

REFERENCES

1. Tapfumaneyi P, Mohammad I, Mohammad Y, Roberts MS. Recent Advances and Future Prospective of Topical and Transdermal Drug Delivery Systems. Frontiers in Drug Delivery. 2022 Sept 5; 2: 57732. Doi: https://doi.org/10.3389/fddev.2022.957732
2. Ahmad MZ, Ahmad J, Alasmary MY, Akhter S, Aslam M, Pathak K, Jamil P, Abdullah MM. Nanoemulgel as an approach to improve the biopharmaceutical performance of lipophilic drugs: Contemporary research and application. Journal of Drug Delivery Science and Technology. 2022; 72: 103420. Doi: https://doi.org/10.1016/j.jddst.2022.103420.
3. Gupta A, Eral HB, Hatton TA, Doyle PS. Nanoemulsions: formation, properties and applications. Soft Matter. 2016;12: 2826-2841. Doi: https://doi.org/10.1039/C5SM02484H.
4. Demisli S, Mitsou E, Pletsa V, Xenakis A, Papadimitriou V. Development and study of nanoemulsions and nanoemulsion-based hydrogels for the encapsulation of lipophilic compounds. Nanomaterials. 2020;10(12):1-15. Doi: https://doi.org/10.3390/nano10122463.
5. Komaiko, Jennifer & Mcclements, David. (2015). Food-grade nanoemulsion filled hydrogels formed by spontaneous emulsification and gelation: Optical properties, rheology, and stability. Food Hydrocolloids. 46. Doi: https://doi.org/10.1016/j.foodhyd.2014.12.031
6. Lai WF, Rogach AL. Hydrogel-Based Materials for Delivery of Herbal Medicines. ACS Appl Mater Interfaces. 2017 Apr 5;9(13):11309-11320. Doi: https://doi.org/10.1021/acsami.6b16120.
7. Marafon P, Fachel FNS, Dal Prá M, Bassani VL, Koester LS, Henriques AT, Braganhol E, Teixeira HF. Development, physico-chemical characterization and in-vitro studies of hydrogels containing rosmarinic acid-loaded nanoemulsion for topical application. J Pharm Pharmacol. 2019 Aug;71(8):1199-1208. Doi: https://doi.org/10.1111/jphp.13102.
8. Lal DK, Kumar B, Saeedan AS, Ansari MN. An Overview of Nanoemulgels for Bioavailability Enhancement in Inflammatory Conditions via Topical Delivery. Pharmaceutics. 2023 Apr 7;15(4):1187. Doi: https://doi.org/10.3390/pharmaceutics15041187.
9. Liu Y, Weng P, Liu Y, Wu Z, Wang Z. Citrus pectin research advances: derived as a biomaterial in the construction and applications of micro/nano-delivery systems. Food Hydrocoll. 2022; 133:107910. Doi: https://doi.org/10.1016/j.foodhyd.2022.107910.
10. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 2014 Mar 1;20(7): 1126-67.Doi: https://doi.org/10.1089/ars.2012.5149.
11. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. Int J Pharm. 2017; 526:353–365.Doi: https://doi.org/10.1016/j.ijpharm.2017.05.004

12. Gorzelanny C, Mess C, Schneider SW, Huck V, Brandner JM. Skin barriers in dermal drug delivery: which barriers have to be overcome and how can we measure them? Pharmaceutics. 2020; 12:684. Doi: https://doi.org/10.3390/pharmaceutics12070684.
13. Yu YQ, Yang X, Wu XF, Fan YB. Enhancing permeation of drug molecules across the skin via delivery in nanocarriers: novel strategies for effective transdermal applications. Front Bioeng Biotechnol. 2021;9:646554. Doi: https://doi.org/10.3389/fbioe.2021.646554.
14. Zoabi A, Touitou E, Margulis K. Recent advances in nanomaterials for dermal and transdermal applications. Colloids Interfaces. 2021; 5:18.Doi: https://doi.org/10.3390/colloids5010018.
15. Uddin S, Islam MR, Chowdhury MR, Wakabayashi R, Kamiya N, Moniruzzaman M, Goto M. Lipid-Based Ionic-Liquid-Mediated Nanodispersions as Biocompatible Carriers for the Enhanced Transdermal Delivery of a Peptide Drug. ACS Appl Bio Mater. 2021 Aug 16;4(8): 6256-6267. Doi: https://doi.org/10.1021/acsabm.1c00563.
16. Haider M, Abdin SM, Kamal L, Orive G. Nanostructured Lipid Carriers for Delivery of Chemotherapeutics: A Review. Pharmaceutics. 2020 Mar 23;12(3):288. Doi: https://doi.org/10.3390/pharmaceutics12030288.
17. Wöll S, Schiller S, Bachran C, Swee LK, Scherließ R. Pentaglycine lipid derivates - rp-HPLC analytics for bioorthogonal anchor molecules in targeted, multiple-composite liposomal drug delivery systems. Int J Pharm. 2018 Aug 25;547(1-2):602-610. Doi: https://doi.org/10.1016/j.ijpharm.2018.05.052
18. Phatale V, Vaithe P, Jha S, Patil D, Agrawal M, Alexander A. Overcoming skin barriers through advanced transdermal drug delivery approaches. J Control Release. 2022; 357: 361–80. Doi: https://doi.org/10.1016/j.jconrel.2022.06.023.
19. Pereira TA, Ramos DN, Lopez RFV. Hydrogel increases localized transport regions and skin permeability during low-frequency ultrasound treatment. Sci Rep. 2017;7: 2765. Doi: https://doi.org/10.1038/s41598-017-02815-5.
20. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomater Res. 2021 Jul 28;25(1):24. Doi: https://doi.org/10.1186/s40824-021-00226-6.
21. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the Stratum Corneum. Pharmaceutics. 2015 Oct 22;7(4):438-70. Doi: https://doi.org/10.3390/pharmaceutics7040438.
22. Preat V, Vanbever R. Skin Electroporation for Transdermal and Topical Drug Delivery. Transdermal Drug Deliv. 2002; 123:227-54. Doi: https://doi.org/10.1016/S0169-409X(02)00023-7.
23. Kogure K, Fukuta T. Transdermal drug delivery by iontophoresis. Drug Deliv Syst. 2021;36: 198-208. Doi: https://doi.org/10.2745/dds.36.198.
24. Dhote V, Bhatnagar P, Mishra PK, Mahajan SC, Mishra DK. Iontophoresis: A Potential Emergence of a Transdermal Drug Delivery System. Sci Pharm. 2012;80:1-28. Doi: https://doi.org/10.3797/scipharm.1108-09.
25. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomater Res. 2021 Jul 28;25(1):24. Doi: https://doi.org/10.1186/s40824-021-00226-6.
26. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery

systems: current and future prospects. Drug Deliv. 2006 May-Jun;13(3):175-87. Doi: https://doi.org/10.1080/10717540500455975.

27. Lee JW, Gadiraju P, Park JH, Allen MG, Prausnitz MR. Microsecond thermal ablation of skin for transdermal drug delivery. J Control Release. 2011 Aug 25;154(1):58-68.Doi: https://doi.org/10.1016/j.jconrel.2011.05.003.
28. Lin CH, Aljuffali IA, Fang JY. Lasers as an approach for promoting drug delivery via skin. Expert Opin Drug Deliv. 2014 Apr;11(4): 599-614. Doi: https://doi.org/10.1517/17425247.2014.885501.
29. Harneet Marwah, Tarun Garg, Amit K. Goyal & Goutam Rath (2016) Permeation enhancer strategies in transdermal drug delivery, Drug Delivery, 23:2, 564-578, DOI: https://doi.org/10.3109/10717544.2014.935532.
30. Shelke MB, Godage RK, Mankar SD. Nanoemulgel as Recent Drug Delivery System: Updated Review. Asian Journal of Research in Pharmaceutical Sciences. 2024; 14(3):327-0. doi: https://doi.org/10.52711/2231-5659.2024.00052.
31. Malik, T., Sharma, R., Ameer, K., Bashir, O., Amin, T., Manzoor, S., & Mohamed Ahmed, I. A. Potential of high-pressure homogenization (HPH) in the development of functional foods. International Journal of Food Properties, 2023;26(1): 2509–2531. Doi: https://doi.org/10.1080/10942912.2023.2249262.
32. Ashaolu TJ, Akinmoladun A, Akinmoladun F, et al. Nanoemulsions for health, food, and cosmetics: a review. Environ Chem Lett. 2021;19(3):1295-1312.Doi: https://doi.org/10.1007/s10311-021-01216-9.
33. Gurpreet K, Singh Sk. Review of Nanoemulsion Formulation and Characterization Techniques. Indian Journal of Pharmaceutical Sciences. 2018;80: 781-789. Doi: https://doi.org/10.4172/pharmaceutical-sciences.1000422.
34. Amin N, Das B. A review on formulation and characterization of nanoemulsion. Int J Curr Pharm Res. 2019;11(4):1-5. Doi: https://doi.org/10.22159/ijcpr.2019v11i4.34925.
35. Doiphode AR, Patwekar SL, Guhade N, Gole V, Rode A, Shaikh S. An Overview on Nanoemulsion. Asian Journal of Research in Pharmaceutical Sciences. 2022; 12(3):239-4. Doi: https://doi.org/10.52711/2231-5659.2022.00042.
36. Solè, C.M. Pey, A. Maestro, C. González, C. Solans, J.M. Gutiérrez, Nanoemulsions prepared by the phase inversion composition method: Preparation variables and scale up, J. Colloid Interface Sci. 2010; 344(2): 417–423. Doi: https://doi.org/10.1016/j.jcis.2009.11.046.
37. Safaya M, Rotliwala Y.C. Nanoemulsions: A review on low energy formulation methods, characterization, applications and optimization technique. Materials Today: Proceedings. 2020;27: 454-459. Doi: https://doi.org/10.1016/j.matpr.2019.11.267.
38. Kim YH, Ghanem AH, Mahmoud H, Higuchi WI. Short chain alkanols as transport enhancers for lipophilic and polar/ionic permeants in hairless mouse skin: mechanism(s) of action. Int J Pharm. 1992;80: 17-31. Doi: https://doi.org/10.1016/0378-5173(92)90258-4.
39. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, Chourasia MK. Nanoemulsion: Concepts, development and applications in drug delivery. J Control Release. 2017 Apr 28; 252: 28-49. Doi: https://doi.org/10.1016/j.jconrel.2017.03.008.

40. Mahmoud H, Al-Suwayeh S, Elkadi S. Design and optimization of self-nanoemulsifying drug delivery systems of simvastatin aiming dissolution enhancement. Afr J Pharm Pharmacol. 2013;7(22): 1482–500. Doi: https://doi.org/10.5897/AJPP2013.3631.
41. Gupta A, Eral HB, Hatton TA, Doyle PS. Nanoemulsions: formation, properties and applications. Soft Matter. 2016 Mar 21;12(11):2826-41. Doi: https://doi.org/10.1039/c5sm02958a.
42. Pavoni L, Perinelli DR, Bonacucina G, Cespi M, Palmieri GF. An Overview of Micro- and Nanoemulsions as Vehicles for Essential Oils: Formulation, Preparation and Stability. Nanomaterials (Basel). 2020 Jan 12;10(1):135. Doi: https://doi.org/10.3390/nano10010135.
43. Flanagan J, Singh H. Microemulsions: a potential delivery system for bioactives in food. Crit Rev Food Sci Nutr. 2006;46(3): 221-37.Doi: https://doi.org/10.1080/10408690590956710.
44. Azeez AR, Alkotaji M. Nanoemulgel as a recent drug delivery system. Mil Med Sci Lett. 2022; 91(2):128-139. Doi: https://doi.org/10.31482/mmsl.2021.035.
45. Shahin M, Hady SA, Hammad M, Mortada N. Novel jojoba oil-based emulsion gel formulations for clotrimazole delivery. AAPS PharmSciTech. 2011 Mar;12(1): 239-47. Doi: https://doi.org/10.1208/s12249-011-9583-4.
46. Soni A, Chaudhary A, Singla S, et al. Review on: Novel Approach in Pharmaceutical Gel. J Curr Pharma Res. 2018;9(1):2576–88. Doi: https://doi.org/10.22270/jcpr.v9i1.2548.
47. Islam MT, Rodríguez-Hornedo N, Ciotti S, Ackermann C. Rheological characterization of topical carbomer gels neutralized to different pH. Pharm Res. 2004 Jul;21(7):1192-9.Doi: https://doi.org/10.1023/b:pham.0000033006.11619.07.
48. Choudhury H, Gorain B, Pandey M, Chatterjee LA, Sengupta P, Das A, Molugulu N, Kesharwani P. Recent Update on Nanoemulgel as Topical Drug Delivery System. J Pharm Sci. 2017 Jul;106(7):1736-1751. Doi: https://doi.org/10.1016/j.xphs.2017.03.042.
49. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. Int J Pharm. 2017 Jun 30;526(1-2): 353-365. Doi: https://doi.org/10.1016/j.ijpharm.2017.04.068
50. Wang J, Shi A, Agyei D, Wang Q. Formulation of water-in-oil-in-water (W/O/W) emulsions containing trans-resveratrol. RSC Adv. 2017; 7: 35917–27.Doi: https://doi.org/10.1039/C7RA07265G.
51. Esmaeili F, Zahmatkeshan M, Yousefpoor Y, Alipanah H, Safari E, Osanloo M. Anti-inflammatory and anti-nociceptive effects of Cinnamon and Clove essential oils nanogels: an in vivo study. BMC Complement Med Ther. 2022 May 20; 22(1): 143.
52. 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 Jan 3;15(1):164. Doi: https://doi.org/10.3390/pharmaceutics15010164.
53. Upadhyay DK, Sharma A, Kaur N, et al. Nanoemulgel for efficient topical delivery of finasteride against androgenic alopecia. J Pharm Innov. 2020; 1–12.Doi: 10.1007/s12247-020-09483-9.
54. Djiobie Tchienou GE, Tsatsop Tsague RK, Mbam Pega TF, Bama V, Bamseck A, Dongmo Sokeng S, Ngassoum MB. Multi-response optimization in the formulation of a topical cream from natural ingredients. Cosmetics. 2018; 5(1): 7.Doi: https://doi.org/10.3390/cosmetics5010007.

55. Sneha K, Kumar A. Nanoemulsions: techniques for the preparation and the recent advances in their food applications. Innov Food Sci Emerg Technol. 2022; 76: 102914. Doi: https://doi.org/10.1016/j.ifset.2021.102914.
56. Rehman A, Iqbal M, Khan BA, Khan MK, Huwaimel B, Alshehri S, Alamri AH, Alzhrani RM, Bukhary DM, Safhi AY, Hosny KM. Fabrication, In Vitro, and In Vivo Assessment of Eucalyptol-Loaded Nanoemulgel as a Novel Paradigm for Wound Healing. Pharmaceutics. 2022 Sep 19;14(9): 1971. Doi: https://doi.org/10.3390/pharmaceutics14091971.
57. Chen X, Jaiswal A, Costliow Z, Herbst P, Creasey EA, Oshiro-Rapley N, Daly MJ, Carey KL, Graham DB, Xavier RJ. pH sensing controls tissue inflammation by modulating cellular metabolism and endo-lysosomal function of immune cells. Nat Immunol. 2022 Jul;23(7): 1063-1075. Doi: https://doi.org/10.1038/s41590-022-01231-0.
58. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 2014 Mar 1;20(7): 1126-67.Doi: https://doi.org/10.1089/ars.2012.5149.
59. Yang L, Du K. A comprehensive review on the natural, forced, and mixed convection of non-Newtonian fluids (nanofluids) inside different cavities. J Therm Anal Calorim.2019; 1–22. Doi: https://doi.org/10.1007/s10973-019-08987-y.
60. Priyadarshini P, Karwa P, Syed A, Asha A. Formulation and Evaluation of Nanoemulgels for the Topical Drug Delivery of Posaconazole. J. Drug Delivery Ther. [Internet]. 2023 Jan. 15;13(1):33-4. Doi: http://dx.doi.org/10.22270/jddt.v13i1.5896.

HOW TO CITE: Ruturaj Jadhav*, Rajanikant Ghotane, Pranali Patil, Sarika Suryawanshi, Dr. Anand Gadad, Nanoemulgel: A Novel Nanocarrier Approach for Effective Topical Drug Delivery, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 5, 1583-1597. https://doi.org/10.5281/zenodo.15381511