Ind. J. Pharm. Edu. Res., 2023; 57(3s):s481-s498.
https://www.ijper.org

Review Article

Nanoemulgel: A Smarter Topical Lipidic Emulsion-based Nanocarrier

Suraj Mandal*, Prabhakar Vishvakarma

Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganga Nagar, Meerut, Uttar Pradesh, INDIA.

ABSTRACT

In the last few decades, researchers have put a lot of time and effort into making new pharmaceuticals. As a result, there are now a huge number of pharmacological chemicals that can be used to treat a wide range of diseases that are a problem for the healthcare system. More than 50% of these medications are classed as BCS (Biopharmaceutical Classification System) class II/IV, indicating that they have limited therapeutic value and are not further studied. In this way, it has been shown that lipoidal manufacturing is a good way to distribute these kinds of medicines. This suggests that a method based on nanotechnology has a lot of potential. Nanoemulgel, a gel composed of diverse nano-lipoidal compositions, has been shown to be an effective method for applying topical drugs. Nanoemulgel is an emulsion-based topical gel product. The correct gelling ingredient is added to emulsion globules made using high energy or low energy processes to form nanoemulgel. Nanoemulgels can be made from all kinds of polymeric polymers, surfactants, and fats that range in size from 5 nm to 500 nm. Nanoemulgel has several topical treatments for both short-term and long-term problems. The widespread use of nanoemulgel formulations of recently patented drugs in a variety of healthcare settings has once again shown that topical administration is better than other methods. Toxicological studies of the chemicals used in these formulations must, however, take into account how safe they are, since the way they are given has changed a lot.

Keywords: Nanoemulgel, Bioavailability, BCS class II and IV, Nanotechnology.

Correspondence:
Suraj Mandal
Research Scholar, Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganga Nagar, Meerut-250001, Uttar Pradesh, INDIA.
Email: sk8006721807@gmail.com
ORCID I'd: 0000-0001-5080-7855

Received: 23-01-2023;
Revised: 03-03-2023;
Accepted: 08-06-2023.

INTRODUCTION

The human skin has been used extensively as the major organ for the purpose of delivering various drugs and attaining the desired therapeutic effect throughout the history of traditional medicine. This has been done to provide the therapeutic impact that was intended. Similarly, the Transdermal Drug Delivery System (TDDS), which has been used in modern medical practice for many decades, has made a substantial contribution to health care by providing an attractive alternative to the oral route of drug administration. Transdermal Drug Delivery System (TDDS) is another option for administering medication to patients. Transdermal Drug Delivery Systems (TDDS) have progressed through three generations since its inception. These include the first, second, and third generations. Despite a variety of hurdles, distribution of newly approved medications is proceeding apace. As time passed and new obstacles presented themselves in the field of drug delivery, different generations of drugs were developed and categorized based on the size and physico-chemical properties of the active pharmaceutical ingredient, the techniques employed, and the presence or absence of chemical enhancers.[1]

Low-bioavailability medications authorized lately are not being developed further. Even though there have been changes in pharmaceutical distribution strategies and several approaches devised with the objective of boosting therapeutic efficacy, the problem remains the same. One or more variables, including reduced permeability and/or low solubility, may account for the poor bioavailability. To improve therapeutic efficacy, addressing the drug moiety's many pharmacokinetic properties is crucial. This includes solubility, permeability, and bioavailability. Nano-lipoidal delivery systems, a cutting-edge delivery method, increase bioavailability and stability.[2,3] Nanoemulsion is one of the best ways to give lipophilic or poorly bioavailable medicines topically. Nanoemulsion's direct skin application is beneficial. Nano-lipoidal delivery methods include SLNs, liposomes, microemulsions, and Nanostructured Lipid Carriers (NLCs). Nano-lipoidal delivery devices have several shapes. Pharmaceutically modified nanoemulsions with adequate gelling agents may be better transdermal dispersants for BCS class II and IV medicines. This nanoemulsion is skin-safe in its purest form. Nanoemulgels include gelling agents. The gel's high-water content is appropriate for emulgel formation. Comparatively,

DOI: 10.5530/ijper.57.3s.56

general emulsion,[4,5] the problem of droplet separation is greatly reduced if the size of the emulsion droplets is kept below 500 nm. Depending on the formulation, nanoemulsions may exhibit either transparency or opacity, making them an optically isotropic system. The globules in a nanoemulsion might be anywhere from 5 and 500 nanometers in diameter. Increased stability, enhanced solubility enhancement capacity, extemporaneous production, and a high drug loading capacity of both hydrophobic and hydrophilic medicines[6,7] are among the many qualities of nanoemulsions that are attracting the attention of the scientific community. Materials with such a composition may be processed into nanoemulsions, which consist of globules with sizes on the nanometer scale.

Many recently approved drugs, including transdermal formulations, that might have benefited from noninvasive administration have been pulled out of clinical use due to inadequate solubility and permeability. This is because transdermal administration is the safest and least intrusive method available.

In order to improve clinical use and therapeutic impact, nano-lipoidal formulations of medicines such nanoemulsion, microemulsion, and liposomes are being developed for transdermal application. These formulas include nanoemulsions. The supramolecular structures of the formulations not only improve bioavailability, but also solubilize the medication within the formulation and partition it into the skin, where it may have its intended therapeutic impact.[8,9] Why? Because the medicine is more easily absorbed by the body thanks to the improved solubilization inside the formulation. The most promising method of nano-lipoidal dispersion via the skin is a gel-based nanoemulsion called nanoemulgel. Yes, this is conceivable. This is because nanoemulgel has a number of desirable qualities that set it apart from other materials. These include easy spread ability, thixotropic behavior, grease lessness, quick removal, biocompatibility, and a host of similar benefits.

While oral administration is the more common method of drug delivery, transdermal distribution offers many benefits. The risk of pharmaceutical breakdown due to metabolic processes is much decreased here, and many incompatibilities created by the gastrointestinal tract environment may be corrected. This is due to the acidic conditions present in the digestive system. Topical medicine has the benefit of acting locally and systemically, and it is also very convenient to use.[10,11] Furthermore, the topical method is quite economical. For this reason, it's a popular option among people who want their medication to have as many positive benefits as possible. Both live and nonliving cells make up the skin's stratified structure. Connective tissue binds the various layers together. The dead cells that make up the stratum corneum at the epidermis's very top act as a protective barrier against microbial and outside aggressors. This protective layer sits directly on the epidermis's outermost layer. The epidermis is responsible for the skin's colour and serves as a protective barrier against water entering the dermis. The dermis is the second skin layer underneath the epidermis and contains the skin's perspiration and hair follicles. It's the skin's second layer down, just under the epidermis. Under the dermis lies a layer of deeper subcutaneous tissue called the hypodermis, or just the hypodermis. Consisting of a wide range of lipid- and connective-tissue types, as well as a lipid matrix, it is encased in a lipid matrix. The fatty acid, cholesterol, and other chemical components of the skin's lipid matrix are organized in a multilayer structure. As a result, it is built up in layers. Strange as it may seem, this compound acts as a protective shield between the skin and the outside body.[12] Barriers to drug entry into the systemic circulation and to drug concentration at the site of action have been explored. That's the only way the drug will be absorbed into the body's bloodstream. It's possible that a formulation with colloidal carriers in the shape of globules, such a nanoemulsion gel, might be the best option for fulfilling this need.

Nanoemulgel Fabrication Materials

The quantity of medication, water, and skin penetration pathway must be considered while preparing a nanoemulgel for topical drug delivery. While producing a product for systemic drug delivery, the amount of medicine loaded, water utilized, and nanoemulgel temperature must be considered.

Aqueous Phase

To make the most of the aqueous phase, nanoemulgels are often formulated using either ultra-purified water or distilled water. Emulgels are formed when an emulsion contains a gelling ingredient and undergoes a phase change.[13]

Oils and Lipids

The most crucial factor in formulating nanoemulsions is the oils and lipids employed, since they are the ones that define the need of other components like surfactants and cosurfactants. The inclusion of other components is also determined by the oils and lipids used.

In formulating nanoemulsions, triglycerides of various lengths and fatty acid compositions are often used.[14,15] Medium-Chain Triglycerides (MCTs) are favored over Long-Chain Triglycerides (LCTs) for emulsification due to MCTs' greater solubilizing ability.[16,17] This is because many recently authorized pharmaceutical active ingredients are limited in how permeable they can be or how soluble they can be in water. Since many drugs are more easily soluble in short-chain triglycerides like triacetin, tributyrin, tricaprin, etc., LCTs are often avoided in favor of these alternatives.[18,19] Triacetin, tributyrin, and tricaprin are all types of short-chain triglycerides. Make sure the oil phase is devoid of impurities like peroxides, free radicals, and unsaponifiable substances like sterols and polymers when choosing oil and/or other lipid components. The reason for this is because the oil

phase is what would really be utilized in the finished product, thus any impurities in it would be disastrous. This must be completed before choosing an oil or other lipid component. It is possible that the formation of several of these undesirable components during storage is to blame for the degradation of the oil phase and the subsequent instability of the formulation. Many of these unfavorable components may be produced throughout the storage period. The total number of hydrocarbon chains contained in a lipid is one of several factors considered when selecting lipids to be used in the creation of nanoemulsions. This might be related to the kind and quality of the emulsification technique used. Evidence suggests that lipids with a shorter carbon chain length are better than those with a longer one.[20] In fact, this is how emulsification works in general. This was learned via a comparison of the two lipid types. It is in this scenario that we may study and evaluate the various oils and lipids that can be used in the fabrication of nanoemulgels. We factor on the accessibility of these materials with any other relevant characteristics.

Vegetable Oils

These oils may be identified in the body as fatty acid glycerides, and their origin in plant life can be established. Numerous plant-based oils have received approval for use in the topical administration of medicines through a range of drug delivery techniques, including soybean oil, olive oil, peanut oil, coconut oil, almond oil, and castor oil.[21-23] Other oils, including castor oil, are also included among those that have been approved for use in this manner. Sesame oil and soybean oil are only a few of the many of these oils that are used in the creation of nanoemulgel.[23,24] These oils are not present in nature and are thought to be of considerably inferior quality for usage in a broad range of nano-lipoidal compositions due to the limited solubility of medicines. It has been noted that using these vegetable oils in topical nanoemulsion formulations reduces the barrier to permeation, which in turn encourages the penetration of medication into the skin.[25,26] When it comes to the creation of topical nanoemulsion, soybean oil is by far the most popular option out of all the vegetable oils that have previously been addressed.[21] Soybean oil may be used on its own or in combination with short- and medium-chain triglycerides. In topical nanoemulsion formulations, soybean oil has been shown to have a higher permeability than other oils like Tributyrin and Myglyol.[21] This has been shown to be true. This has been seen using a number of formulation techniques. The term "lecithin" refers to certain, unique kinds of phospholipids that are present in soybean oil. These lecithins serve as surface-active substances and have a stronger affinity for epidermal tissues.[27-30]

Newly developed gel-based nano-lipoidal phenytoin delivery technology by Siang Yin Lee *et. al.*, and his associates combines nano- and microemulsion. With the aid of both soybean oil and coconut kernel oil, this strategy proved successful. In contrast to cream-gel (56.42%) and macro-emulgel (51.51%), they were able to convincingly demonstrate that the nanoemulgel (93.12%) demonstrates much superior release.[23] They worked hard, and it paid off since this goal was accomplished. Wu H and his colleagues used olive oil as one of the components to make a topical nanoemulsion for the hydrophilic medication inulin. Olive oil was one of the key components of the nanoemulsion.

Fatty Acids and Alcohols

Plant oils include a broad range of fatty acids in significant amounts. Similar to carboxylic acids, fatty acids have a long aliphatic chain and may be either saturated or unsaturated in their natural state. Carboxylic acids make up the bulk of fatty acids.

Fatty alcohols are primary alcohols with a straight carbon chain and a high molecular weight. Long-chain alcohols are another name for fatty alcohols. Fatty alcohols are made from the natural fats and oils present in food and may range in carbon count from four to six to as many as twenty-two to twenty-six. A wide variety of oils that may be either categorised as fatty acids or alcohols have received the stamp of approval from the Food and Drug Administration (FDA) of the United States. Numerous distinct acids and alcohols, including oleic acid, undecylenic acid, cetyl alcohol, stearyl alcohol, and oleyl alcohol, are present in these oils.[21] Similar to other oils, they may be divided into two categories: Medium-Chain Fatty Acids (MCFA) and Long-Chain Fatty Acids (LCFA). The number of carbon atoms in each of these acids determines how long their chains are. LCFAs (C13-C24) are invariably found in their solid form, while MCFAs (C6-C12) may often be found in either a liquid or a semisolid condition. Because MCFAs have a lower melting point than LCFAs, this is the case. These fatty acids and alcohols not only have the potential to increase permeability but also serve as a penetration enhancer in a nanoemulsion-based gel delivery system.[8] Fatty acids disrupt the lipid structure of the subcutaneous layer, which actually makes it easier for items to pass through the skin.[32] Oleic acid was used to create a nanoemulgel that contains the non-steroidal anti-inflammatory drug piroxicam as the oil phase. The procedure of nanoemulsification was used to create this nanoemulgel. A medicine that is classified as BCS class II is piroxicam. The optimised nanoemulgel has the following ingredients: 35% Tween 80 and ethanol as a blend of surfactants and co-surfactants; 10% oleic acid as an oil; and 0.5% weight-per-weight carbopol. It also contains 0.5% medication. The created nanoemulgel exhibits indicators of increased permeability even if a chemical permeation enhancer was not used.[24]

Fatty Acid Ester and Glycerol

These kinds of lipids are the oil phase that are used most of the time while making nanoemulsions and microemulsions.

These oils are also the leading choice for topical medications due to their noticeably improved solubility in newly authorised active medicinal components. This is because they pierce the

skin so readily (APIs). Some of the characteristics of surfactants are present in these oils. This group of lipids may be further divided into monoglycerides, diglycerides, and triglycerides, with the majority of the triglycerides in this group being of the medium-chain form. Chemicals like caprylic acid and its many derivatives, butyric acid derivatives, glycerol triacetate, and other substances fall under this group of oils, but they are not the only ones. Additionally, oils that include other comparable compounds fall under this category. Topical nano-lipoidal formulations with caprylic acid derivatives have been shown to have increased permeability through the subcutaneous layer of skin, which in turn increased the formulation's total permeability.[31-33] This finding was enabled by the fact that the presence of these derivatives increases the overall permeability of the formulation.[34] Fatty acid esters are the kind of materials that are most often found in topical nanoemulsions and microemulsions. These substances include, among others, ethyl oleate, isopropyl myristate, and isopropyl palmitate. Additionally, it has been shown that using these oils increases the drug's capacity to partition across the skin's layers, acting as a permeability accelerator. After it was discovered that the usage of these oils enhances permeability, this finding was made. The antifungal drug allyl amine was developed in a nanoemulgel formulation using eucalyptus oil, Cremophore RH40 as the surfactant, and Labrafac (propylene glycol caprylate) as the co-surfactant. As a surfactant, cremophore RH40 was used. As a surfactant, cremophore RH40 was used. This formulation was very recently created. A Nanoemulgel formulation (NG) tested in an *ex vivo* skin permeation study showed skin permeability of around 20% for the medication, which was much greater than the permeability of the commercial cream (MC), which only showed permeability of 18%.

It was shown that the NG formulation preserved around 31% of the medicine after being administered to the skin, however the MC formulation only retained 20% of the medication. After 12 days of therapy, it was discovered that the NG formulation could cure the infected rat skin, whereas the MC formulation required around 16 days to completely clear the infection.[35] Because the NG formulation included NG, it was able to do this. In a study that is quite similar to the one that was just described, leflunomide, a disease-modifying anti-rheumatic drug, was combined with capryol 90 as the oil phase to create a nanoemulgel (LFD). Pluronic F127 is employed as a gelling agent, while Cremophore EL, Transcutol HP, and other surfactants are utilised in the process of acting as surfactants. These are used in addition to Capryol 90 in this. The final formulation has more overall permeability than the first one did. A significant improvement in flux, apparent permeability coefficient, steady-state diffusion coefficient, and drug deposition in skin was shown in *ex vivo* permeation through the abdomen skin of rats.[36] This resulted from LFD's nanoemulsification. A nanoemulsion-based emulgel containing the lipophilic medication flurbiprofen was created by Parasuram Rajam Radhika and her colleagues in a similar area of research. For the oil phase of this formulation, triacetin and linseed oil were combined, and Tween 80 was utilised as the surfactant. Increased permeability and a stronger anti-inflammatory effect were seen with this specific formulation.[37] In relatively recent experimental work, the fatty acid esters were used to create a nanoemulgel from the antiparkinson's medication selegiline hydrochloride with the help of isopropyl myristate, which served as the oil phase, and Span 85, Tween 80, and PEG 400, which served as the surfactants. Isopropyl myristate, which acted as the oil phase, assisted in achieving this. Isopropyl myristate was included into the oil phase to enable this.

Viscup160® was selected to be used as a gelling agent in the final formulation. The synthesised formulation showed a 3.69-times greater improvement in potency when compared to the enhancement ratio offered by the standard gel.

In addition to having a longer-lasting impact, NEGS4 (optimal formulation) demonstrated an improvement in bioavailability that was 5.53 times more than that of a conventional gel and 6.56 times greater than that of a tablet, respectively.[38]

Surfactants and Co-surfactants

Surfactants are crucial ingredients in the production of nanoemulgel because they not only assist the drug used to be more soluble, but they also contribute to the stability of the final formulation. In order to accomplish the above-mentioned goal, the surfactants may have a variety of chemical natures, such as cationic, anionic, or non-ionic natures. These surfactants are often called emulsifiers due to their function in the emulsification process. The types of surfactants that are most often employed in the production of nanoemulgel are non-ionic, such as polyoxyethylene sorbitan fatty acid esters and sorbitan fatty acid esters polyoxyethylene. In this region of the globe, the terms "tween 20, span 80," and "tween 80" are often used to refer to the function mentioned above.

Other nonionic emulsifiers are also preferred, such Poloxamer 124 and 188, Labrasol and Labrafac, and different castor oil derivatives including Cremophore EL and Cremophore RH. The emulsifiers are among them.

The selection of emulsifiers for the creation of nanoemulsions is a significant challenge and is accompanied by a number of toxicity concerns.

The increased concentration of surfactants may irritate the skin, which might make the user uncomfortable. Since non-ionic surfactants have substantially lower levels of toxicity than ionic surfactants, it is customary to choose them over ionic surfactants.[39] The primary goal of using co-surfactants is to lower the concentration of surfactants in a formulation. Along with the co-contribution surfactants make to the formulation's overall increase in thermodynamic stability, this is done. It is suggested that you employ a variety of various co-surfactants in

the nanoemulgel's composition. Ethyl alcohol, glycerin, PEGs, and transcutol HP are a few of them.

Permeation Enhancers

It is one of the most effective ways to increase the rate of transport through the skin and the adjacent layers.[40] A permeation enhancer is a key component of a topical drug delivery system, and the nanoemulsion or nanoemulgel is the best vehicle for it. The reason for this is because the nanoemulsion or nanoemulgel used topically is a water-based solution.

The primary function of these permeation enhancers is to improve the skin's permeability by interacting with skin components in a way that is transient and reversible. To improve the rate at which substances may permeate a barrier. In addition, it provides additional propulsion in the process of medicine penetration into the skin.[41] Several compounds, including linoleic acid, oleic acid, isopropyl myristate, and lecithin, are included in the nanoemulgel to improve penetration.

Gelling Agents

A gelling agent, one of the essential components of nanoemulgel, is responsible for the formulation's texture and, by extension, its appearance. Actually, these substances serve as agents that cross-link other molecules. A variety of gelling agents, such as Carbopol, poloxamer, tragacanth, HPMC, and others, may be utilized in the production of nanoemulgels.

Preservatives

This refers to the chemical agents used to prevent spoilage due to microbial assault and lengthen the shelf life of a composition. Common preservatives in nanoemulsion formulation include phenoxyethanol, benzalkonium chloride, benzoic acid, methyl paraben, and propyl paraben.[42]

Antioxidants

These are the chemical components that have been added to the formulation to prevent the oxidation of the different components. They have been included specifically for this reason. The antioxidants that are favored in topical nano-lipoidal formulation over other antioxidants include butylated hydroxyl toluene, ascorbyl palmitate, and butylated hydroxyl anisole.[43]

Manufacturing of Nanoemulgel

In practice, nanoemulgel production is a multi-step process involving the coupling of a nanoemulsion that has been generated with an appropriate gel base. As a result, we will discuss the formulation and production of nanoemulsion in the first section of this article, followed by the preparation and inclusion of gel foundation in the second section.

Preparation of Nanoemulsion

Nanoemulsions are non-equilibrium systems of structured liquid, therefore their formulation requires either a large quantity of surfactants or an extrinsic source of energy, or both. Depending on the kind of components and their concentration, high energy or low energy techniques may be used to synthesize nanoemulsions (Figure 1).[44]

High Energy Methods

To achieve a droplet size of nanoemulsions, which typically ranges from 5 to 500 nm, it is necessary to expend a large amount of mechanical energy. This is because the droplet size of nanoemulsions usually fluctuates in this range. It is possible to accomplish the goal of providing a substantial amount of energy for the manufacturing process through the application of a wide variety of methods.[45,46] Some of these methods include high-pressure homogenizers, ultrasonic generators, microfluidizers, and the high-shear stirring method. The advantage of a high energy mediated nanoemulsion formulation that is believed to be the most essential is the ability to employ low amounts of emulsifiers.[47] This is a substantial gain, especially when taking into account the problem of toxicity. When the method is done on a larger scale, such as in an industrial setting, the utilization of such a high amount of mechanical energy could make it less relevant.[44]

Low Energy Methods

For example, "low energy techniques" might mean anything from "spontaneous emulsification" to "phase inversion methods" to "emulsion inversion points" and beyond. The preference for these techniques is similar to that of energy-intensive processes.

The production of nanoemulsions does not need the use of high-energy methods, on the other hand. Smaller globules with a uniformly low Polydispersity Index (PDI) are produced when more surfactants are used.[48] This is because more surfactants are being used. These low-energy strategies benefit from phase transitions that occur during emulsification due to a shift in the surfactant's spontaneous curvature.[44] These shifts in phase take happen due to a shift in the surfactant's spontaneous curvature. When the surfactant's spontaneous curvature changes, the phase transition occurs.

The following is a summary of the nature of nanoemulsion that may be understood with the assistance of the details of the production method:

High Energy Methods

High-pressure Homogenization

For the purposes of this procedure, the globule size is reduced to the nanoscale range by using either a high-pressure homogenizer, also known as a microfluidizer, or a piston homogenizer. In the

microfluidizer technology's emulsification stage, in addition to impact, attrition, turbulence, and hydraulic shear, a very high pressure of around 500–20,000 psi is applied. This is one of the many factors that contribute to the formation of the emulsion. In connection with the procedure, this step is carried out. After the macro emulsion is changed into the coarse emulsion, the product goes through the exact same procedure a second time in order to create droplets with the necessary size and Polydispersity Index (PDI).[49] In order to transform the macroemulsion into the coarse emulsion, it is necessary for various distinct kinds of forces, such as hydraulic forces, shear forces, and cavitations forces, to work together. The number of cycles that the homogenization process goes through is an important component that must be present in order to obtain the required level of emulsification. During this procedure, just a trace amount of the surfactant is applied, and the possibility of contamination is quite low. When the homogenization process is of the piston kind, homogenizers use the colloid mill idea in order to complete the process.

As part of this method, the coarse emulsion is applied to a space with a diameter of less than 10 micrometres, which results in the formation of nanosized droplets.

Following a number of cycles of rotation accompanied by vigorous shear, the coarse emulsion is eventually transformed into droplets of the desired size.[15] In this area of the piston, the coarse emulsion is worked on by a rotor that rotates constantly and a stator that remains fixed.

Ultrasound Generation

It is possible for the coarse emulsion to be changed into the nanosized emulsion droplets that are sought for by the method with the help of a sonicator probe. The sonicator probe is capable of producing high-frequency sonication sound waves with a frequency of more than 20 kilohertz. The great intensity of the sound waves causes the coarse emulsion to be fragmented into very small droplets that are on the nanoscale (5-500nm). There are many different kinds of probes available in a variety of diameters, and all of them may be used for the same aim, which is to bring the size down to acceptable limits. Not only does the kind of probe that is used have a role in determining the size of the droplet, but also the quantity of input power and the length of time that the droplet is subjected to sonication.[50]

Low Energy Methods

The production of nanoemulsions by means of low-energy processes is a spontaneous event in which emulsification takes place as a result of a change in the curvature or interfaces of the components, primarily the surfactants that are used in the formulation. This change in curvature or interfaces causes the emulsification to take place. This shift takes happen as a consequence of a modification to either the curvature or the interfaces of the components. This alteration in the interface or curvature may be interpreted as a result of the temperature as well as the physico-chemical qualities of the material that was used in the formulation. These attributes were taken into account when the formulation was created. Because of this shift in circumstances, this comprehension is now feasible. The technique known as phase inversion temperature is used in situations in which the curvature of a surfactant changes even when the component parts remain same, but the temperature does vary. The term "phase inversion temperature" is often used to refer to this Particular Phenomenon (PIT). On the other hand, if a change in the interface is obtained by maintaining the same level of temperature while altering the type and concentration of components, the process is known as Phase Inversion Composition (PIC) or Emulsion Inversion Point (EIP).[51,52] These terms refer to the same phenomenon. These are two different words that allude to the same idea. Both "PIC" and "EIP" refer to "phase inversion composition," with "PIC" standing for "phase inversion composition" and "EIP" standing for "emulsion inversion point." The Spontaneous Emulsification (SE) technique is one of the low-energy methods that is generally acknowledged as being able to function on both a local and big scale. This is the case. It is possible for it to emulsify material on its own, even in the absence of any outside energy sources. The term "spontaneous emulsification" has been coined to describe this process (SE). Due to the fact that it involves the combining of two separate liquid phases, this technique is able to produce droplets of the specific size that is required.

Methods that have a low total energy usage may be classified into a number of different categories, some of which are as follows:

Phase Inversion Methods

Methods that include phase inversion are used in order to bring about the production of a nanoemulsion that is kinetically stable. This is done in order to achieve the goal of creating a nanoemulsion. These procedures are based on a number of different factors, some of which include temperature, the chemical environment of the component (including pH and ionic strength), and the various physico-chemical properties of the components that are used in the procedure. Temperature is an important factor because it affects the rate at which chemical reactions take place. This strategy has the ability to be categorised as either PIT or PIC depending on the many different aspects that are taken into account. During the process of emulsion creation, it is conceivable for an oil in water (o/w) emulsion to transform into a water in oil (w/o) emulsion, or vice versa. This can happen in any direction. This transformation is wholly dependent on the performance of the function of reversing the phases, and it requires the participation of the components that were discussed earlier in the course of the debate. During the Phase Inversion Temperature (PIT) method, the temperature of the formulation is changed in order to bring about a change in the geometry of the interface of the surfactant, which is primarily non-ionic in its nature. This change in the geometry of the interface of the surfactant is what is

known as the phase inversion. In order to achieve the results that are wanted, this step needs to be taken. On the other hand, the formulation has not undergone any changes in terms of how its components are put together. The transformation from an oil-in-water emulsion to an oil-in-oil emulsion is brought about by a slow rise in temperature. The transition is brought about as a result of the coarse emulsion being heated, which causes the surfactant to become solubilized in the oil phase. Because of this, the o/w emulsion will eventually turn into a w/o emulsion. At this point in the manufacturing process, the curvature of the surfactant is going to continue to have a negative value.[53] When the non-ionic surfactant is heated to an intermediate temperature, which is also referred to as the HLB temperature, it exhibits an affinity for both the aqueous and the oily phase that is comparable to the original state. At this temperature, the ternary system has an extraordinarily low interfacial tension, and the curvature typically reaches zero value spontaneously.[53] Additionally, the temperature causes the curvature to reach zero value spontaneously. In addition to this, the temperature is what ultimately leads to the curvature naturally reaching zero value. A ternary system would typically consist of either a D-phase bicontinuous microemulsion or a mixture of a D-phase bicontinuous microemulsion with lamellar liquid crystalline phases at this point in the process. Both of these possible arrangements can be carried out. Rapidly cooling single-phase or multiphase bicontinuous microemulsions that are maintained at either PIT or a temperature above PIT (transitional-phase inversion) is one method for producing nano-sized emulsion droplets with the desired polydispersity index.[53] This method can be used to create nano-sized emulsion droplets. Either single-phase or multiphase microemulsions can be used to accomplish this task successfully. Another object that can be observed here is this one. It is possible that the formulation of a medicine that is sensitive to heat could be jeopardised because the procedure includes operating at high temperatures for a major amount of its length.[15]

Its Phase Inversion Composition (PIC) technique maintains a steady temperature during the inversion process despite composition fluctuations. This distinguishes PIC from other methods. Pseudo ternary phase diagrams are best for phase inversion composition nanoemulsions. It represents phases most accurately. The biggest drawback of this process is that it uses more surfactant than previous methods, which requires more energy.[54]

Spontaneous Emulsification Method

One of the methods that is particularly well suited to manufacturing on an industrial scale is the generation of nanoemulsions using this technique. This process calls for the utilization of two distinct liquid phases, one of which is an aqueous liquid phase, and the other of which is an organic liquid phase. Specifically, the aqueous liquid phase and the organic liquid phase. This operation might be carried out in a laboratory, which provides an atmosphere that is both controlled and well-lit. The medication is pre-solubilized in the organic or oil phase, and this phase comprises components such as Capriole 90 or other comparable compounds like acetone, ethyl methyl ketone, and so on.[15] The drug is also pre-solubilized in the oil phase. During this phase, the pre- solubilized procedure is carried out in order to get ready for the next phase. The hydrophilic surfactant that makes up the aqueous phase can be subdivided into a wide variety of distinct subgroups. This surfactant is what makes up the aqueous phase. Two of these subgroups are the Tweens and the Spans, for instance. In this technique, the spontaneous formation of a nanoemulsion is achieved by first evaporating the organic phase, which is then followed by the addition of the organic phase to the aqueous phase in a progressive and calibrated manner. This sequence of steps results in the formation of a nanoemulsion. The nanoemulsion is created as a result of the stages that are performed in this order. After this stage of the process, the organic phase is completely removed from the procedure. After completing a certain number of iterations of this stage, the nanoemulsion will have been effectively produced. Using a magnetic stirrer to accomplish the required light stirring might make the process simpler and easier for you to complete. This will make the process easier on you as well. This results in the development of extremely minute convection currents, which are beneficial to the process of spreading oil droplets throughout the bulk solvent. These currents come into being as a direct consequence of the generation of microscopic convection currents.

Preparation of Gelling Agent

When making a nanoemulgel, the use of a gelling agent serves the objective of transforming the nanoemulgels physical form from liquid to semi-solid. This offers a number of benefits to the patient in terms of the patient's ability to cooperate with the process. The pH should be adjusted[55] after the polymer has been dissolved in the purified water and the mixture has been continuously agitated using a glass rod or any other suitable mechanical device until the desired consistency has been achieved. By following these steps, one is able to produce a number of distinct subtypes of the gel base, all of which will, in the end, be responsible for the gelling process. The production of the gelling agent is carried out in a wide variety of different experimental works by adding the polymer to the distilled water in a manner that is carried out in an environment that is characterised by a low temperature. In the cold technique, the components are added to purified water at a temperature of 20°C, and the gelling polymer is added after the water has been cooled to a temperature of 4°C.[56,57] This process is carried out in the order described above. The name given to this strategy is the "cold approach."

Incorporation of Gelling Agent

Once both the nanoemulsion and the gelling agent have been produced, they are combined to form the nanoemulgel.

Water-in-oil (w/o) or oil-in-water (o/w) nanoemulsions are transformed into thick, semisolid nanoemulgels using a variety of polymeric gelling agents at this stage. In response to mechanical stress, such as rubbing, this gel-like solid may reform into a solution-like liquid.

If you provide shear stress to a material and then reverse the process, you won't notice any difference in the volume of the substance.[58] The same is true if you apply shear stress to a sol and then turn it back into a gel. Thixotropy is the word used to describe this quality of the medicine. Numerous polymers have been used as gelling agents to produce nanoemulgels with the necessary properties for a wide range of applications.[59-63] These polymers include Carbomer 940, Carbopol 943, Chitosan, Carbopol 934, Carbopol 940, Poloxamer 407, Methyl cellulose, and many more.

In vitro Characterization Techniques of Nanoemulgel

Nanoemulgels are a kind of topical drug that may be applied directly to the skin in their unadulterated state. This material is produced by combining emulsified nanodroplets with a gelling agent, which results in the formation of the nanodroplets. In order to characterize the many physico-chemical properties that could simulate stability and the functionality that is desired in the dosage form, this semisolid dosage form calls for a wide variety of analytical techniques to be applied. These techniques can be found in a wide variety of settings. The zeta potential, droplet size, Polydispersity Index (PDI), pH, viscosity and related rheological analysis, swelling index, spreadability, and other characterizations of a nanoemulgel are some of the many important factors that contribute to the overall stability of a nanoemulgel as well as its other physico-chemical properties. Other properties of a nanoemulgel that are important include its ability to absorb light. In addition to these characterizations, essential aspects of the study into the dosage form include investigations into the permeability of the dosage form and *in vitro* release experiments. The following is a concise and easy explanation of the approaches, strategies, and procedures that may be utilised to explore major elements of a nanoemulgel. This will help you obtain a better understanding of the material.

Zeta Potential

Because a nanoemulgel is essentially a composition of nanosized emulsion droplets combined with a gelling agent, the formulation has the potential to exhibit an electrical charge as a result of the presence of a wide variety of surface-active chemicals. This is the case because a nanoemulgel is essentially a composition of nanosized emulsion droplets combined with a gelling agent. This is because nanoemulgel is basically a mixture of nanosized droplets of emulsion, which explains why this is the case.[64] When it comes to the long-term stability of the dosage form as a whole, the nature and specifics of the electrical charge that is located on the surface of emulsified droplets are of the utmost importance. Because of this, the medicine is protected from the surrounding environment by the electrical charge, which functions as a barrier. Taking a measurement of the electrical charges that are present at the shear plane is how the zeta potential is calculated; this measurement is taken at the shear plane. The shear plane is the distance between the surface of the globule and the area in the electrical field where the different counter ions attach themselves to the globules.[2] This distance is measured from the surface of the globule to the region in the electrical field. The surface of the globule is used as a reference point to estimate the distance to the electrical field. The specific sort of emulsifiers that are included inside it is what determines the surface charge of the mixture. If you use an anionic surfactant, the surface will end up with a negative charge; but, if you use a cationic surfactant, the surface will end up with a positive charge.[65] There are a variety of equipment that may be used for the purpose of zeta potential measurement, such the ZC-2000 (Zeecom-2000, Microtec Co. Ltd., Chiba, Japan), the Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments, USA), and others.[42,66]

Droplet Size Measurement and Polydispersity Index (PDI)

The droplet size and the polydispersity index are the two aspects of the nanoemulgel preparation that need to be determined with the utmost precision.

Because of the potential direct link, it may have with the stability, drug release, and *in vivo* performance of the dosage form, the size of the droplets or particles in any nano-lipoidal formulation is a crucial parameter for the inquiry.[67]

The size of the droplets in nanoemulgel may vary anywhere from 5 to 500 nanometers, depending on the specific application. On the other hand, the technique referred to as Dynamic Light Scattering (DLS), is the one that is employed most of the time for the purpose of determining the size of droplets. When using the dynamic light scattering approach, the transitional diffusion co-efficient is determined by calculating the interaction between the laser beam and the dispersion.[68] This is done by monitoring how the laser beam interacts with the dispersion. This is accomplished via the use of a technique that is known as dynamic light scattering. In order to achieve this goal, the technique of dynamic light scattering is put into practice. The Master sizer 2000 laser diffractometer is a piece of equipment that was developed and produced by Malvern Instrument in the United Kingdom. It has the potential to be used in the accomplishment of the aforementioned goal. There are also a variety of different devices that might be used, such as ones that make use of methods that include dynamic light scattering. The Stokes-Einstein equation is another method that may be used to the problem of calculating the average droplet size. However, in order for this approach to be effective, the dispersion must first be very diluted, and there must be no contact between the droplets. Only then can this method be considered valid.

It is feasible to determine the polydispersity index, which is also known as the particle size distribution, by analysing the intensity of the scattered light as a function of the angle between the incoming beam and the scattered beam. This process is described in more detail below. The principles outlined in the theory of light scattering have been used as a guide for this method.[69] An accurate depiction of the size dispersion of the droplet diameter may be obtained via the use of the polydispersity index.

According to the Stock's law, the mean droplet size can be obtained from an equation:

$$v = g/18 * D^2 * \rho d / \eta$$

Where:

v= rising velocity of the droplet (m/s)

g = gravitational constant (9.81m/s2)

D = droplet diameter (m)

ρd = density difference between heavy phase and light phase(kg/m3)

η = dynamic viscosity

Rheological Characterizations

It has been shown that the elements of a nanoemulgel that are responsible for the formation of the nanoemulgel include oil, surfactants, and a gelling agent respectively. It is possible for a seemingly minor change in the physico-chemical features of a formulation component to have a significant impact on the rheological qualities of a dosage form, such as the viscosity and flowability of the dosage form. This is because the rheological properties of a dosage form are directly related to how well the dosage form behaves when it is administered. Alterations in viscosity have the potential to have significant implications on stability properties, as well as on the release of medications and other biological processes. This is because viscosity is a property of fluids. In view of the issues discussed earlier, which suggest that it is vital to take into consideration, it is of the utmost necessity to understand the rheological characteristics of nanoemulgel. This information should be acquired as soon as possible. Viscometer is the name given to a variety of different measuring instruments that may be used to detect the degree to which a substance is thick or thin. Viscometers can be used to assess the degree to which a material is thick or thin.[70,71]

Mucoadhesive Property

Nanoemulgel formulations are typically delivered through the mucosal layer, such as the mucosa of the nasal cavity. It is very necessary to do study on the mucoadhesive force prior to utilising a delivery strategy such as this one. It is feasible to describe the mucoadhesive strength as the amount of force that is required to separate the dosage form from the nasal mucosal tissue. One way to think about this is as the amount of pressure that is required to open a jar. In this particular setting, the examination could benefit from a rethought methodology.[56,72,73] Within the context of this specific method, the nasal tissue taken from sheep may be used.

If you need to collect the necessary tissue, you need go to a slaughterhouse in your area. Utilizing the fresh tissue as soon as it has been divided into individual pieces is recommended for optimal results. For the purpose of carrying out the experiment, a force-displacement transducer that has been calibrated in the past is required. In this specific case, a cyanoacrylate glue is used in order to attach the exposed mucosal segment of the sheep nasal mucosa to the upper probe. This procedure was carried out so that the section could be examined. After that, the probe has to be connected to the transducer so that it may receive the electrical data that represents the force.[73] You may determine the bioadhesive force, which is also referred to as the detachment stress, by making use of the equation that is shown in the following sentence:

$$\text{Detachment stress (dyne/cm}^2) = mg/A$$

Here, g is the acceleration caused by gravity, approximately 980 cm/s^2, and m is the weight supplied to the balance to cause the gel to separate from the tissue. A is the surface area of the tissue.

Spreadability Testing

When choosing a topical administration method, one of the most crucial factors to consider is the needed amount of spreadability. By using a specialised instrument that includes a pulley connected to one end of a wooden block or glass as well as other components, it is able to assess the spreadability of the nanoemulgel dosage form. This equipment is used to examine spreadability using the "Slip" and "Drag" approach, which is described in references.[74,75]

APPLICATION OF NANOEMULGEL

Nanoemulgel stands out among other recently discovered drug delivery systems because it has become one of the most successful and promising innovative delivery methods for topical preparations that have a wide variety of pharmacological effects. As a result, nanoemulgel has become one of the most promising innovative delivery methods. Using various different pharmacological categorization systems, the effects of nanoemulgel drug delivery may be split down into the following categories.

Anti-inflammatory Application

A localised manifestation of the physiological reactions that occur throughout the body, inflammation is characterised by the affected part of the body generating redness and swelling in addition to pain.[76] Inflammation is a localised manifestation of the physiological reactions that occur throughout the body.

Inflammation could be caused by a large variety of underlying variables, any one of which could be accountable for it. A wide variety of medicinal approaches can be taken in the management of inflammatory conditions and their associated symptoms. These drugs can be obtained either through synthetic means or through organic means. It is hypothesised that the distribution of these drugs in the form of a nanoemulgel would result in a pharmacodynamic impact that would be superior to that which would be created by other methods of delivery. A typical nanoemulgel formulation of lornoxicam, which is a medication that is classified as a Nonsteroidal Anti-Inflammatory Medicine (NSAID), was produced not too long ago.[77] Lornoxicam is one of the drugs that fall into this category. It was possible to develop the lornoxicam formulation that is optimised for its efficacy with the assistance of a method that relies on spontaneous self-emulsification as its principal mechanism. This was accomplished with the help of the approach. The nanoemulgel that was manufactured contained, in descending order of the functions that they performed, a gelling agent that was manufactured from Carbopol 934, a surfactant that was manufactured from Tween 80, an oil that was manufactured from Labrafac, and a cosurfactant that was manufactured from Transcutol P with Pluronic F68. According to the results of the research that compared the recently produced nanoemulgel with conventional gel, the conventional gel has an enhancement ratio and permeability coefficient that are significantly lower than those of the nanoemulgel. The findings of the *in vivo* investigation indicate that the anti-inflammatory effects of nanoemulgel are significantly greater than those of regular commercial gel.[77] The discovery was made possible by contrasting the two distinctive types of gel. The oil of *Swietenia macrophylla* (SM), which possesses a variety of phytopharmacological properties,[78] including antioxidant, antimicrobial activity, anti-inflammatory activity, anti-HIV activity, anti-ulcer activity, anti-fungal activity, anti-malarial and anti-diarrheal activity, was utilised in another line of experimental research to develop a nanoemulgel dosage form. Investigations are now being carried out, the primary focus of which is to determine whether or not oil extracted from *Swietenia macrophylla* possesses the ability to inhibit inflammatory responses. In this particular scenario, the manufacturing process for the nanoemulgel involves first creating a nanoemulsion of SM oil and then incorporating that nanoemulsion into a hydrogel. The final product is a nanoemulgel. This procedure is carried out a great number of times until the desired outcome is accomplished. A nanoemulgel is what you receive after you're done. In this particular instance, the nanoemulsion of SM oil was created by employing both the self-emulsifying method and the phase inversion approach. These two processes were used in conjunction with one another. Sucrose monoester fatty acid was employed as the surfactant, and glycerol was used as the co-surfactant. The surfactant that was used was sucrose monoester fatty acid. At this time, both of these components were thrown into the pot and mixed together. A number of different grades of Carbopol, specifically 934 and 940, were utilised in order to achieve the required gelling effect. It was discovered that the nanoemulgel formulation that had been optimised had stable characteristics, such as an emulsified droplet size of 114 nm and a zeta potential of -43.1 mv. An anti-inflammatory test was performed by using carrageen, an induced rat paw oedema method, and it was discovered that the inhibition of inflammation by using SM oil nanoemulgel was higher in comparison to the simple oil solution.[79] This was discovered after an anti-inflammatory test was performed using carrageen, an induced rat paw oedema method. Following the completion of the anti-inflammatory test utilising the carrageen method, this was found to be the case. Because carrageen was employed in an experiment examining anti-inflammatory properties, this discovery was made possible by said experiment.

A nanoemulgel was created that contained the anti-inflammatory medicines aceclofenac and capsaicin with the purpose of conducting a proof-of-concept study that was somewhat comparable to the aforementioned one. During the course of the study, this nanoemulgel was utilised. Within the context of the present investigation, the researcher presents an original approach in order to compare the advantages of utilising nanoemulgel dosage form. This was done so that the findings of the study that came before this one could be highlighted more clearly. During this stage of the process, the nanoemulgel was produced, and a variety of its pharmacokinetic and pharmacodynamic properties were analysed. The findings of these experiments were compared to those of other research, such as studies involving nanoemulsions, nanomicelles, and formulations of Aceproxyvon that are available for purchase, as well as studies involving the free drug Aceclofenac and Capsaicin. The initial step of the experiment consisted of producing two distinct nanolipoidal formulations, namely the nanoemulsion and the nanomicelle, using the procedures that were specific to each of these types of nanolipoidal compounds. The nanoemulsion was made by first producing a combination of oils by combining olive oil and miglyol in a ratio of 1:1 to produce a combination of oils, and then producing a mixture of surfactants by combining Polysorbate 80 and Transcutol in a ratio of 1:1 to produce a mixture of surfactants. Finally, the nanoemulsion was produced by combining olive oil and miglyol in a ratio of 1:1 to produce a nanoemulsion. In order to create the nanoemulsion, both of these stages had to be performed multiple times. On the other hand, the nanomicelle was produced by employing the method of solvent evaporation throughout the manufacturing process. The contents of the mixture were vitamin E TGPS and acetone, respectively. The nanoemulgel was created in the end by repeatedly combining the nanoemulsion, the nanomicelle, and a gelling agent called carbopolon. This includes incorporating both of the dosage forms, namely the nanoemulsion as well as the nanomicelle, into the product. It was feasible to perform

the calculations necessary to determine the optimal value for the medication's concentration (sfinal). Research on *in vitro* release, research on skin permeability, and other *in vivo* tests were performed with the optimised nanoemulgel. It was shown that the combination of nanoemulgel and nanomicelle, which is also referred to as nanoemulgel, is superior to the independent methods of drug delivery as a direct result of this. This is due to the fact that the combined system makes use of the greatest number of different pathways that are accessible for the absorption of the active medicinal substances.[80] This is the factor that contributes to the combined system's high level of efficiency.

Anti-psoriatic Application

Psoriasis is an inflammatory disease that is characterised by chronic inflammation and is mediated by T lymphocytes. Psoriasis is characterised by chronic inflammation. Psoriasis may affect any region of the body, but the skin is where it manifests itself the most often. It is possible to recognise it by the abnormal patches that develop on the skin as a consequence of angiogenesis and epidermal hyperproliferation.[81] These patches are caused by the combination of the two processes. In addition to causing generalised itching throughout the body, it also causes inflammation in the tendons and joints. The bulk of the occurrences have a red hue to them, which seems to be the colour of the dots. Although there are several antipsoriatic drugs that may be used topically, it is difficult for these treatments to have a meaningful therapeutic effect due to their poor absorption. It is hoped that the nanoemulgel delivery strategy for antipsoriatic medications would result in good therapeutic advantages of these therapies. There is a great deal of optimism in this regard. It wasn't until recently that a medicine known as Betamethasone Dipropionate (BD), which is used to treat psoriasis, was included into the formulation of a nanoemulgel drug delivery system. During this phase of the process of developing the product, the production of the nanoemulsion made use of both eucalyptus oil and babchi oil as active components. Both oils are extracted from the babchi tree and eucalyptus tree. In this particular experiment, the surfactant and the co-surfactant were both determined to be tween 20, with ethanol serving as the latter. In addition, the co-surfactant was composed of Tween 20. In order to effectively finish the process of making nanoemulsion, the phase titration technique was applied. After that, carbopol 934 was used so that the transition from nanoemulsion to nanoemulgel could be expedited. This was accomplished with the goal of maximising efficiency.

According to the findings of pharmacokinetic testing, the newly created nanoemulgel makes it possible to reduce the number of times a dose is necessary while simultaneously boosting the medication's penetration. This is a significant advancement in drug delivery technology. In addition, the nanoemulgel formulation makes it feasible to have a controlled release of the medication over a longer period of time for the amount of time that was needed. This was a significant advantage. The carrageenan-induced paw edema technique was used to examine the anti-inflammatory impact of the optimised formulation, and the results showed that the optimised formulation had a better effect than the marketed gel formulation.[82] This was determined by comparing the anti-inflammatory impact of the optimised formulation to the marketed gel formulation. This was established by comparing the anti-inflammatory effect of the optimised formulation with the effect of the gel formulation that is already on the market.

In the framework of a separate proof of concept investigation, Swati Pund and her colleagues produced a nanoemulgel formulation of leflunomide with the goal of creating a possible antipsoriatic medication (LFD). Because LFD is one of the medications for psoriatic arthritis that was licensed relatively recently,[83,84] it is now considered to be one of the most successful and important treatments for the condition. LFD nanoemulgel shows a lot of promise for the treatment of rheumatoid arthritis and melanoma, despite the fact that many drugs that are currently available exhibit unproductive clinical benefits for these conditions due to a variety of unwanted side effects and a low permeability through the transcutaneous membrane. In spite of this, LFD nanoemulgel shows a lot of promise for the treatment of these conditions. This is because the nanoemulgel has been created in a way that makes it possible for it to penetrate the skin in a more straightforward manner. For the objectives of this investigation, a nanoemulgel version of LFD was created by first creating a nanoemulsion of the drug by a process that allows it to self-emulsify. In order to produce the nanoemulgel form, this step has to be taken. The oils, surfactant, and co-surfactant that were used in this procedure were as follows: Capryole 90, Cremophore EL, and Transcutol HP. These components were utilized in the order that they were listed. The procedure continued with the following step, which was the transformation of nanoemulsion into nanoemulgel. This stage was successfully completed with the assistance of pluronic F127. At the conclusion of the study, a formulation of LFD that had been optimized to be a stable nanoemulgel demonstrated a significant improvement in the drug's capacity to pass through the abdominal skin of rats. The researchers discovered indications of a significantly improved therapeutic response when they tested the efficacy of the medicine on human HaCaT, melanoma A375, and SK-MEL-2 cell lines. Their findings were published in the journal Cancer Research. The nanoemulgel has the potential to minimize the amount of medication that has to be supplied and, as a result, the dose-related toxicity.[36] This is because the nanoemulgel has increased permeability, in addition to its other pharmacokinetic properties.

Antifungal Application

Fungi infections, which may be brought on by a broad variety of skin conditions, are a common factor that plays a role in this

condition. Onychomycosis, one of the many fungal diseases, is a serious condition that accounts for half of the illnesses that affect the nails.[85] This condition is one of the many fungal diseases. This condition is brought on by a fungus that lives on the top layer of the nail, and it may spread to other nails.

Anti-fungal medicine ketoconazole belongs to the imidazole family of drugs and is classified as a BCS class II substance. Ketoconazole inhibits the growth of fungi. Patients who have a chronic mucocutaneous fungal infection of the nail and skin and who have a low likelihood of being healed by other treatments may want to consider taking ketoconazole in pill form and administering it orally. This is because ketoconazole is more effective than other treatments at curing mucocutaneous fungal infections. When compared to the usage of oral administration, the dispersion of ketoconazole via the use of nanoemulgel is often considered to be the most effective method of delivery. Asiya Mahtab *et al.*, and her coworkers put forth a lot of effort to develop a ketoconazole nanoemulgel with the purpose of accomplishing this goal and putting this concept into action. The very first nanoemulsion of ketoconazole was made using the high-pressure homogenization approach while the nanoemulgels were being manufactured. This method was employed to make the nanoemulsion. After this stage was finished, the next step was to create a pseudoternary phase diagram. This was the following step after this step was finished. In order to transform the nanoemulsion that had been generated in the prior stage into a nanoemulgel, a gelling agent known as Carbopol Ultrez 21 was used. According to the findings of the *ex-vivo* translingual permeation examinations, the optimised nanoemulsion, nanoemulgel, and drug solution formulations of KCZ had respective penetration rates of 62.49 2.98%, 77.54 2.88%, and 38.54 2.54% in goat foot after 24 hr. These rates were determined by the drug's ability to pass through the membranes of the goat foot. When compared to the drug solution, the antifungal action of the nanoemulgel demonstrated a much larger zone of inhibition against *Trichophyton rubrum* and *Candida albicans*.

The results of skin and histopathology experiments carried out on rat skin suggested that the produced nanoemulgel was safe for topical application and further demonstrated that it increased the skin's penetration.[86] Additionally, the results demonstrated that it increased the skin's permeability. In addition, the data revealed that it increased the amount of the material that was absorbed by the skin.

Maha E. Elmataeeshy *et al.*, and her colleagues developed a nanoemulgel that included terbinafine hydrochloride for the purpose of a more recent piece of research. This study was released in the academic literature not too long ago (TB). Antifungal medication that is produced synthetically as a derivative of allyl amine and has a very trace amount of solubility in water. This kind of therapy is referred as TB. It is highly effective in treating a broad variety of fungal diseases, any one of which may result in an infection in the fingernails or toenails. The terbinafine HCl nanoemulgel is made up of nanosized droplets of an emulsion. These droplets were produced by using a low-energy method and supplementing it with a pseudo-ternary phase diagram technique. In order to successfully produce the nanoemulgel, this step was taken.

During the process of making nanoemulsion, peceol was chosen to represent the oil phase in the resulting product. On the other hand, Tween 80 and propanol were chosen to perform the functions of the surfactant and the co-surfactant, respectively. Both of these substances are considered to be non-toxic. The gelling agent that is utilised during the second stage, which is the transformation of the nanoemulsion into the nanoemulgel, is carbopol 940. This gelling agent is employed during the subsequent step. After the nanoemulsion has been generated and its viability has been verified, the next step is carried out. Both the commercial product Lamisil emulgel and the improved nanoemulgel were subjected to a comparative *in vitro* investigation of penetration, as well as an *in vivo* evaluation to determine how effective they were against fungi. *In vitro*, the investigation was carried out in a test tube, and *in vivo*, the evaluation was carried out on living organisms. As a consequence of the testing, it was discovered that the nanoemulgel formulation has a significantly increased permeability and also reveals a more effective anti-fungal activity in comparison to the product that is currently available on the market.[87] This was shown to be the case.

Cardiovascular Application

It is now possible to topically give pharmaceuticals that fall into a wide variety of various pharmacological categories thanks to the ability of nanoemulgel to transport the drug into the systemic circulation. This opens up a lot of possibilities for the future of drug delivery. When using this state-of-the-art technology, it will be essential to make some cardiovascular medications that have a stronger pharmacokinetic impact in comparison to the normal dose form that is now accessible.

An investigation was conducted into the pharmacokinetic profile of the telmisartan nanoemulgel formulation, and the results were compared to the profile of the telmisartan standard gel formulation. Medication such as telmisartan is an example of a drug that may block angiotensin type II receptors. A procedure referred to as the phase diagram approach was used in order to effectively create telmisartan nanoemulgel. Labrafil M 2125 CS is used in the formulation of nanoemulgel as the oil component. Carbitol, which functions as a co-surfactant, Acrysol, which functions as a surfactant, and Acrysol, which functions as a surfactant are the other components of the formulation. For the purpose of facilitating the transformation of nanoemulsion into nanoemulgel, the gelling agent carbopol was used. Carbopol was used in order to attain this goal successfully. Experiments using an optimised version of telmisartan's nanoemulgel were carried

out *in vitro* and *in vivo*, and the results demonstrated that the nanoemulgel demonstrates better permeability in contrast to the normal gel formulation.[88] A pharmaceutical business was responsible for conducting these tests and trials. Telmisartan was used at various points all through the course of these studies.

Alopecia

Alopecia is a disorder in which there is a decrease in the quantity of body hair, or possibly a complete loss of hair.[89] Alopecia may also occur in women. Androgenic alopecia and alopecia areata are the two subtypes of alopecia that may be classified as "further alopecia".[90,91]

Minoxidil is a drug that has undergone a significant amount of study and has been given approval for use in the treatment of alopecia.[91] Although minoxidil is the drug of choice, its therapeutic effectiveness in many typical delivery techniques at the pharmacokinetic platform is poor.[92] This is despite the fact that minoxidil is the medication of choice. The administration of minoxidil by nanoemulgel may be an approach that is suitable[75] in order to acquire the therapeutic advantages that are needed.

The following is a summary of the method for the formulation of nanoemulgels for several different groups of medications: Table 1.

PATENTS RELATED TO EMULGEL PREPARATION

There has not been a lot of published research or any on patents on nanoemulgel formulation as of yet. On the other hand, nanoemulgel is a novel potential delivery system that may be employed for a wide variety of therapeutically active compounds, which is why formulation scientists and researchers working in the pharmaceutical industry are becoming increasingly interested in it. Over the last several years, a number of patent publications have been validated using Active Pharmaceutical Ingredients (APIs) sourced from both natural and synthetic sources (Active Pharmaceutical Ingredients). Neem oil is a component of a herbal mixture that is now being developed into a nanoemulgel form. This exact formulation may destroy sperm, according to certain reports. The three ingredients sodium lauryl sulphate, water, and neem oil combine to create a formulation's nanoemulsion component. The high-pressure homogenizer is a crucial component in the creation of the nanoemulsion.

The size of the emulsion droplets was discovered to range from 250 to 600 nanometers. At the very end of the manufacturing process, a gelling agent known as carbopol polycarbophil was added to the nanoemulgel.[103] It is well acknowledged that diclofenac is an NSAID (nonsteroidal anti- inflammatory drug). A European patent application by Novartis AG is focused on the diclofenac diethylamine emulsion-based gel.[104-107] This request was made from Europe. An assortment of the submitted patent applications are the subject of the data in Table 2.

Current And Future Prospective of Nanoemulgel

Nanoemulgel has emerged as one of the most promising options for the administration of medications through topical routes, as shown by the results of several the studies that are included in this review. This is something that can be understood because of the process of creating numerous new drug delivery methods, in which nanoemulgel has emerged as one of the finest possibilities. This is something that may be understood because of the process of creating numerous new drug delivery methods. Nanoemulgel was developed with the intention of improving the pharmacokinetics and pharmacodynamics of a wide variety of drugs that have a poor bioavailability and making these treatments more user-friendly for patients. Additionally, the development of nanoemulgel was

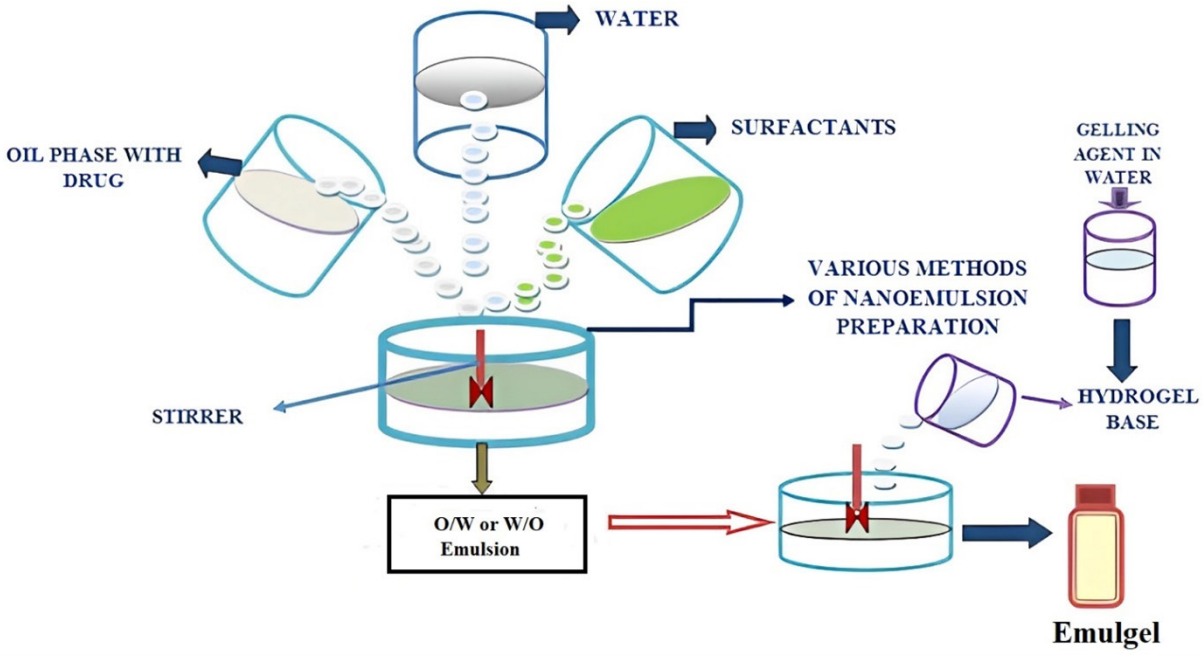

Figure 1: Schematic diagram of nanoemulgel preparation.

Table 1: A list of medications that have been formulated as nanoemulgel.

Sl. No.	Drug Incorporated	Composition of Nanoemulgel formulation	Application/Purpose of the formulation	Comparative PK/PD Effect	References
1.	Itraconazole	Oil: Eugenol, Surfactant: Labrasol, Co-Surfactant: TranscutolP, Lecithin Gelling Agent: Carbolpol.	For Antifungal purpose.	An increase in the rate of permeation. The 7.28 mg will be released in one day. diffusion control.	93
2.	Quercetin	Oil: Cinnamon oil, Surfactant: Tween 80, Co-Surfactant: Carbitol, Gelling Agent: Poloxamer.	Antibacterial as well as anti-inflammatory properties.	92.4% release in 6 hr, whereas quercetin-loaded gel exhibits less than 3% release in the same amount of time.	94
3.	Curcumin	Oil: Emu oil, Surfactant: Cremophor RH40, Co-Surfactant: Labrafil M2125CS, Gelling Agent: Carbopol.	For Anti-inflammatory Activity.	The anti-inflammatory effect of the nanoemulgel demonstrated substantial improvement when compared to the medicine in its pure form.	95
4.	Cyclosporine	Oil: Oleic acid, Surfactant: Tween 80, Co-Surfactant: Transcutol P, Gelling Agent: Guar gum.	Worked as Immunosuppressive agent.	An increase in permeability as compared to both the nanoemulsion and the formulation that is currently on the market.	96
5.	Glibenclamide	Oil: Labrafac Triacetin (1:1), Surfactant: Tween 80, Co-Surfactant: Diethylene glycol monoethyl Ether, Gelling Agent: Carbopol 934.	For Anti-hyperglycemic Property.	a relative improvement in bioavailability that is 3.92 times greater when compared to an oral medication suspension.	97
6.	Carvedilol	Oil: Oleic acid: IPM (3:1), Surfactant: Tween 20, Co-Surfactant: Carbitol, Gelling Agent: Carbopol-934.	Anti-hypertensive activity.	The plasma concentration was increased 6.41-fold compared to the commercially available formulation, which led to improved bioavailability.	98

Sl. No.	Drug Incorporated	Composition of Nanoemulgel formulation	Application/Purpose of the formulation	Comparative PK/PD Effect	References
7.	Meloxicam	Oil: Almond oil and peppermint oil (1:2), Surfactant: Tween 80, Co-Surfactant: Ethanol, Gelling Agent: carbopol 940.	Anti-inflammatory activity.	A higher rate of release when tested *in vitro* increased levels of bioavailability.	99
8.	Mangosteen Extract	Oil: vergin coconut oil, Surfactant: Tween 80, Co-Surfactant: Span 80, Gelling Agent: xanthan gum.	Anti-fungal, anti-bacterial, antioxidant, anti-viral and anti-tumoral.	Enhanced Skin Penetration of Nanoemulgel (95% of Its Total Mangostin Content), in Comparison to the Results Obtained from the Nanoemulsion Formulation.	100
9.	Ferulic Acid	Oil: Isosteryl isostearate, Surfactant: Labrasol, Co-Surfactant: Plurol isostearique, Gelling Agent: Carbopol 940.	Antioxidant activity.	The nanoemulgel has a significantly higher penetration rate (96.95%) than the gel (61%).	101
10.	Fluconazole	Oil: Capmul MCM, Surfactant: Tween 80, Co-Surfactant: Transcutol P, Gelling Agent: Carbopol 934.	Anti-fungal.	3.71 times more penetration than that of commercial eye drops, together with improved anti-fungal activity.	102

Table 2: A list of patented emulgel products: Where an emulsion with a gelling agent is used.

Sl. No.	Patent Name	Product	Inventors	Date	References
1.	WO2006082596A2	Neem oil contraceptive	Kamalinder Kaur Singh, Pratima Arun Tatke, Shruti Dhuru.	10th Aug, 2006	103
2.	EP 2 055 298 A1	Diclofenac gel Voltaren Emulgel	NOVARTIS AG.	06th May, 2009	104
3.	US20120093882A1	Voveran	Sunilendu Bhushan Roy, Shafiq Sheikh, Jay Kothari, Jitendra Patel.	19th April, 2012	105
4.	WO2008051186A2	Nanoemulsion containing Composition having anti- inflammatory activity	James R Baker NANOBIO CORPORATION.	02nd May, 2008	106

done with the intention of enhancing the pharmacokinetics and pharmacodynamics of a wide variety of drugs.

At the moment, a nanoemulgel formulation may be used to produce an indefinite number of lipophilic medicines that correspond to a wide variety of therapeutic categories. These formulations exhibit improved therapeutic characteristics. The therapeutic characteristics of these drugs are showing significant improvement. The nanoemulgel is put to use within the framework of the healthcare system for the treatment of a wide variety of acute and chronic disorders, such as those related with fungus, inflammation, cardiovascular difficulties, psoriasis, alopecia, and other conditions. Considering all of these benefits that are linked with the administration of medicine, the opportunities that exist for nanoemulgel in the future seem to have a good potential for financial gain. In addition, it is reasonable to anticipate that nanoemulgel as a delivery system will be a hope for a variety of drug categories that have been removed from the development pipeline for a variety of reasons such as low bioavailability, clinical inefficacy, and other factors similar to these. This is because nanoemulgel has the potential to be a hope for these drug categories. In particular, it is fair to predict that this will be the case since nanoemulgel has the potential to be an effective delivery method. This is the reason why it is reasonable to anticipate that this will be the case.

CONCLUSION

The advantages of topical nanoemulsion gel over conventional formulations of lipophilic drugs include improved penetration, pharmacokinetic profile, and therapeutic efficacy. In comparison to other topical administration techniques, nanoemulgel formulation is more patient-acceptable since it is less sticky and distributes more uniformly. The nanoemulgel system has the potential to become a highly efficient, secure, and globally recognized drug delivery technique for topical administration of lipophilic medicines. Notwithstanding certain limitations, nanoemulgel formulation shows promise as the new standard in the topical administration of lipophilic medications.

ACKNOWLEDGEMENT

The authors are thankful to his/her parents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

BCS: Biopharmaceutical Classification System; **TDDS:** Transdermal Drug Delivery System; **SLNs:** Solid Lipid Nanoparticles; **NLCs:** Nanostructured Lipid Careers; **O/W:** Oil in Water; **W/O:** Water in Oil; **LCTs:** Long Chain Triglycerides; **MCTs:** Medium Chain Triglycerides; **USFDA:** United States Food and Drug Administration; **MCFAs:** Medium Chain Fatty Acids; **LCFAs:** Long Chain Fatty Acids; **NG:** Nanoemulgel; **MC:** Marketed Cream; **LFD:** Leflunomide; **PEG:** Polyethylene Glycol; **PGs:** Propylene Glycol; **PDI:** Poly Dispersity Index; **PIT:** Phase Inversion Temperature; **PIC:** Phase Inversion Composition; **EIP:** mulsion Inversion Points; **SE:** Spontaneous Emulsification; **DLS:** Dynamic Light Scattering; **NSAID:** Nonsteroidal Anti-inflammatory Drug; **SM:** *Swietenia macrophylla*; **BD:** Betamethasone Dipropionate; **TB:** Terbinafine HCl; **APIs:** Active Pharmaceutical Ingredients.

REFERENCES

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-8. doi: 10.1038/nbt.1504, PMID 18997767.
2. Tamjidi F. Nanostructured Lipid Carriers (NLC): A potential delivery system for bioactive food molecules. Innov Food Sci Emerg Technol; 2103;(19):29-43. doi: 10.1016/j.ifset.2013.03.002.
3. Rahman M, Kumar V, Beg S, Sharma G, Katare OP, Anwar F. Emergence of liposome as targeted magic bullet for inflammatory disorders: current state of the art. Artif Cells Nanomed Biotechnol. 2016;44(7):1597-608. doi: 10.3109/21691401.2015.1129617, PMID 26758815.
4. Kim BS, Won M, Lee KM, Kim CS. *In vitro* permeation studies of nanoemulsions containing ketoprofen as a model drug. Drug Deliv. 2008;15(7):465-9. doi: 10.1080/10717540802328599, PMID 18712624.
5. Kale SN. Emulsion, micro-emulsion and nanoemulsion. Syst Rev Pharm. 2017;8(1):39-47. doi: 10.5530/srp.2017.1.8.
6. Abd E, Benson HAE, Roberts MS, Grice JE. Minoxidil skin delivery from nanoemulsion formulations containing eucalyptol or oleic acid: enhanced diffusivity and follicular targeting. Pharmaceutics. 2018;10(1):19. doi: 10.3390/pharmaceutics10010019, PMID 29370122.
7. Schroeter A, Engelbrecht T, Neubert RH, Goebel AS. New nanosized technologies for dermal and transdermal drug delivery. A review. J Biomed Nanotechnol. 2010;6(5):511-28. doi: 10.1166/jbn.2010.1149, PMID 21329045.
8. Kogan A, Garti N. Microemulsions as transdermal drug delivery vehicles. Adv Colloid Interface Sci. 2006;123-126:369-85. doi: 10.1016/j.cis.2006.05.014, PMID 16843424.
9. Rahman M, Akhter S, Ahmad J, Ahmad MZ, Beg S, Ahmad FJ. Nanomedicine-based drug targeting for psoriasis: potentials and emerging trends in nanoscale pharmacotherapy. Expert Opin Drug Deliv. 2015;12(4):635-52. doi: 10.1517/17425247.2015.982088, PMID 25439967.
10. Barry BW. Breaching the skin's barrier to drugs. Nat Biotechnol. 2004;22(2):165-7. doi: 10.1038/nbt0204-165, PMID 14755286.
11. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL. Challenges and opportunities in dermal/ transdermal delivery. Ther Deliv. 2010;1(1):109-31. doi: 10.4155/tde.10.16, PMID 21132122.
12. López O, Cócera M, Wertz PW, López-Iglesias C, de la Maza A. New arrangement of proteins and lipids in the stratum corneum cornified envelope. Biochim Biophys Acta. 2007;1768(3):521-9. doi: 10.1016/j.bbamem.2006.11.023, PMID 17292323.
13. Upadhyay PN, Bairagi M, Gujar S, Darwhekar G. Emulgel. A review. Asian J Pharm Life Sci. 2011;1(3):333-43.
14. Bandyopadhyay S, Katare OP, Singh B. Optimized self-nanoemulsifying systems of ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides. Colloids Surf B Biointerfaces. 2012;100:50-61. doi: 10.1016/j.colsurfb.2012.05.019, PMID 22766282.
15. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, *et al*. Nanoemulsion: concepts, development and applications in drug delivery. J Control Release. 2017;252:28-49. doi: 10.1016/j.jconrel.2017.03.008, PMID 28279798.
16. Calder PC. Hot topics in parenteral nutrition. Rationale for using new lipid emulsions in parenteral nutrition and a review of the trials performed in adults. Proc Nutr Soc. 2009;68(3):252-60. doi: 10.1017/S0029665109001268, PMID 19426581.
17. Manuel-y-Keenoy B, Nonneman L, De Bosscher H, Vertommen J, Schrans S, Klütsch K, *et al*. Effects of intravenous supplementation with alpha-tocopherol in patients receiving Total Parenteral Nutrition containing medium- and longchain triglycerides. Eur J Clin Nutr. 2002;56(2):121-8. doi: 10.1038/sj.ejcn.1601294, PMID 11857045.
18. Hippalgaonkar K, Majumdar S, Kansara V. Injectable lipid emulsions- advancements, opportunities and challenges. AAPS PharmSciTech. 2010;11(4):1526-40. doi: 10.1208/s12249-010-9526-5, PMID 20976577.
19. Choudhury H, Gorain B, Karmakar S, Biswas E, Dey G, Barik R, *et al*. Improvement of cellular uptake, *in vitro* antitumor activity and sustained release profile with increased bioavailability from a nanoemulsion platform. Int J Pharm. 2014;460(1-2):131-43. doi: 10.1016/j.ijpharm.2013.10.055, PMID 24239580.
20. Derle D, Sagar B, Pimpale S. Microemulsion as a vehicle for transdermal permeation of nimesulide. Indian J Pharm Sci. 2006;68(5):622-5. doi: 10.4103/0250-474X.29630.

21. Pawar KR, Babu RJ. Lipid materials for topical and transdermal delivery of nanoemulsions. Crit Rev Ther Drug Carrier Syst. 2014;31(5):429-58. doi: 10.1615/CritRevTherDrugCarrierSyst.2014010663.
22. Nastiti CMRR, Ponto T, Abd E, Grice JE, Benson HAE, Roberts MS. Topical Nano and microemulsions for skin delivery. Pharmaceutics. 2017;9(4):9040037. doi: 10.3390/pharmaceutics9040037, PMID 28934172.
23. Lee SY. Lipid-based delivery system for topical phenytoin. J Appl Pharm Sci; 2016;6 (11):14-20.
24. Dhawan B, Aggarwal G, Harikumar S. Enhanced transdermal permeability of piroxicam through novel nanoemulgel formulation. Int J Pharm Investig. 2014;4(2):65-76. doi: 10.4103/2230-973X.133053, PMID 25006551.
25. Bajerski L, Michels LR, Colomé LM, Bender EA, Freddo RJ, Bruxel F, *et al*. The use of Brazilian vegetable oils in nanoemulsions: an update on preparation and biological applications. Braz J Pharm Sci. 2016;52(3):347-63. doi: 10.1590/s1984-82502016000300001.
26. Deapsari penetration of ubiquinone (Q10) nanoemulsion using olive oil through rat skin. Int J Pharm Clin Res. 2017;9(2):169-72.
27. Scholfield CR. Composition of soybean lecithin. Reprinted from the jozmzal of the American Oil Chemists'. Society. 1981;58(10):889-92.
28. van Hoogevest P, Wendel A. The use of natural and synthetic phospholipids as pharmaceutical excipients. Eur J Lipid Sci Technol. 2014;116(9):1088-107. doi: 10.1002/ejlt.201400219, PMID 25400504.
29. Kato A, Ishibashi Y, Miyake Y. Effect of egg yolk lecithin on transdermal delivery of bunazosin hydrochloride. J Pharm Pharmacol. 1987;39(5):399-400. doi: 10.1111/j.2042. PMID 2886592.
30. Hoeller S, Sperger A, Valenta C. Lecithin based nanoemulsions: A comparative study of the influence of non-ionic surfactants and the cationic phytosphingosine on physicochemical behaviour and skin permeation. Int J Pharm. 2009;370(1-2):181-6. doi: 10.1016/j.ijpharm.2008.11.014, PMID 19073240.
31. Wu H, Ramachandran C, Weiner ND, Roessler BJ. Topical transport of hydrophilic compounds using water-in-oil nanoemulsions. Int J Pharm. 2001;220(1-2):63-75. doi: 10.1016/S0378-5173(01)00671-8, PMID 11376968.
32. Barry BW. Lipid-protein-partitioning theory of skin penetration enhancement. J Control Release. 1991;15(3):237-48. doi: 10.1016/0168-3659(91)90115-T.
33. Lopes LB, VanDeWall H, Li HT, Venugopal V, Li HK, Naydin S, *et al*. Topical delivery of lycopene using microemulsions: enhanced skin penetration and tissue antioxidant activity. J Pharm Sci. 2010;99(3):1346-57. doi: 10.1002/jps.21929, PMID 19798758.
34. Khani S, Keyhanfar F, Amani A. Design and evaluation of oral nanoemulsion drug delivery system of mebudipine. Drug Deliv. 2016;23(6):2035-43. doi: 10.3109/10717544.2015.1088597, PMID 26406153.
35. Syamala US. Development and optimization of allyl amine antifungal nanoemulgel using 23 factorial designs: for the treatment of Tinea pedis. Eur Sci J. 2013.
36. Pund S, Pawar S, Gangurde S, Divate D. Transcutaneous delivery of leflunomide nanoemulgel: mechanistic investigation into physicomechanical characteristics, *in vitro* anti-psoriatic and antimelanoma activity. Int J Pharm. 2015;487(1-2):148-56. doi: 10.1016/j.ijpharm.2015.04.015, PMID 25869452.
37. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. Int J Pharm. 2017;526(1-2):353-65. doi: 10.1016/j.ijpharm.2017.04.068, PMID 28461261.
38. Sonal S. Appraisal of transdermal water-in-oil nanoemulgel of selegiline HCL for the effective management of Parkinson's disease: pharmacodynamic, pharmacokinetic, and biochemical investigations. AAPS PharmSciTech. 2018;19(2):573-89.
39. Hauss DJ. Oral lipid-based formulations. Adv Drug Deliv Rev. 2007;59(7):667-76. doi: 10.1016/j.addr.2007.05.006, PMID 17618704.
40. Mortazavi S, Aboofazeli R. An investigation into the effect of various penetration enhancers on percutaneous absorption of piroxicam. Iran J Pharm Res. 2003;2:135-40.
41. Bashir I. Pathan. C Mallikarjuna Setty. Chemical penetration enhancers for transdermal drug delivery systems. Trop J Pharm Res. 2009;8(2):173-9.
42. Srivastava M, Kohli K, Ali M. Formulation development of novel *in situ* Nanoemulgel (NEG) of ketoprofen for the treatment of periodontitis. Drug Deliv. 2016;23(1):154-66. doi: 10.3109/10717544.2014.907842, PMID 24786482.
43. Ernoviya E. Optimization and evaluation of topical ketoconazole nanoemulsion. Asian J Pharm Clin Res 2018;11(5):143-6. doi: 10.22159/ajpcr.
44. Solè I, Maestro A, Gonzalez C, Solans C, Gutiérrez JM. Optimization of nano-emulsion preparation by low-energy methods in an ionic surfactant system. Langmuir. 2006;22(20):8326-32. doi: 10.1021/la0613676, PMID 16981744.
45. Mason TG. Extreme emulsification: formation and structure of nanoemulsions. J Phys Condens Matter. 2006;9(1):193-9. doi: 10.5488/CMP.9.1.193.
46. Graves S, Meleson K, Wilking J, Lin MY, Mason TG. Structure of concentrated nanoemulsions. J Chem Phys. 2005;122(13):134703. doi: 10.1063/1.1874952, PMID 15847485.
47. Jie P, Wu-jun D, Ling L. Effect of high-pressure homogenization preparation on mean globule size and large diameter tail of oil-in-water injectable emulsions journal of food and drug analysis. 2015;23(4):828-35.
48. Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J. Formulation of nanoemulsion: a comparison between phase inversion composition method and high-pressure homogenization method. Drug Deliv. 2015;22(4):455-66. doi: 10.3109/10717544.2013.866992, PMID 24329559.
49. Lovelyn C, Attama AA. Current state of nanoemulsions in drug delivery. J Biomater Nanobiotechnol. 2011;2(5):626-39. doi: 10.4236/jbnb.2011.225075.
50. Leong TS, Wooster TJ, Kentish SE, Ashokkumar M. Minimising oil droplet size using ultrasonic emulsification. Ultrason Sonochem. 2009;16(6):721-7. doi: 10.1016/j.ultsonch.2009.02.008, PMID 19321375.
51. Forgiarini A, Esquena J, González C, Solans C. Formation of nanoemulsions by low energy emulsification methods at constant temperature. Langmuir. 2001;17(7):2076-83. doi: 10.1021/la001362n.
52. Porras M. Properties of Water-in-Oil (W/O) nano-emulsions prepared by a low-energy emulsification method. Colloids Surf a Physicochem Eng Asp. 2008;324(1-3):181-8. doi: 10.1016/j.colsurfa.2008.04.012.
53. Chime SA. Nanoemulsions – advances in formulation. Characterization and applications in drug delivery. Appl Nanotechnol Drug Deliv. 2014;3:77-126.
54. Komaiko JS, McClements DJ. Formation of food-grade nanoemulsions using low-energy preparation methods: a review of available methods. Compr Rev Food Sci Food Saf. 2016;15(2):331-52. doi: 10.1111/1541-4337.12189, PMID 33371595.
55. MANDAL S, JAISWAL DV, SHIVA K. A review on marketed *Carica papaya* Leaf Extract (CPLE) supplements for the treatment of dengue fever with thrombocytopenia and its drawback. Int J Pharm Res. 2020;12(3).
56. Pund S, Rasve G, Borade G. *Ex vivo* permeation characteristics of venlafaxine through sheep nasal mucosa. Eur J Pharm Sci. 2013;48(1-2):195-201. doi: 10.1016/j.ejps.2012.10.029, PMID 23159662.
57. Res IR. 1972;6:571-82.
58. Barnes HA. Thixotropy-a review. J Non-Newt Fluid Mech. 1997;70(1-2):1-33. doi: 10.1016/S0377-0257(97)00004-9.
59. Arora R. Nanoemulsion based hydrogel for enhanced transdermal delivery of ketoprofen. Adv Pharm. 2014;2014:1-2. doi: 10.1155/2014/468456.
60. Khushboo. Formulation and evaluation of topical Nano emulgel of adapalene World. J Pharm Sci. 2015;3(4):1013-24.
61. Kaur A, Saxena Y, Bansal R. Intravaginal delivery of Polyphenon 60 and curcumin nanoemulsion gel. AAPS PharmSciTech. 2017;18(6):2188-202. doi: 10.1208/s12249-016- 0652-6. PMID 28070848.
62. Hosny KM, Banjar ZM. The formulation of a nasal nanoemulsion zaleplon *in situ* gel for the treatment of insomnia. Expert Opin Drug Deliv. 2013;10(8):1033-41. doi: 10.1517/17425247.2013.812069, PMID 23795561.
63. Elosaily GH. Formulation and *in vitro* evaluation of nystatin nanoemulsion-based gel for topical delivery. J Am Sci. 2012;2012(8):541-8.
64. Lakshmi P, Kumar GA. Nanosuspension technology: a review. Int J Pharm Pharm Sci. 2010;2(4):35-40.
65. Hasenhuettl GL. Synthesis and commercial preparation of food emulsifiers. Food emulsifiers and their applications. 2nd ed. New York: Springer Science+Business Media; 2008;11-37. doi: 10.1007/978-0-387-75284-6_2.
66. Araújo FA, Kelmann RG, Araújo BV, Finatto RB, Teixeira HF, Koester LS. Development and characterization of parenteral nanoemulsions containing thalidomide. Eur J Pharm Sci. 2011;42(3):238-45. doi: 10.1016/j.ejps.2010.11.014, PMID 21130164.
67. Silva HD, Cerqueira MÂ, Vicente AA. Nanoemulsions for food applications: development and characterization. Food Bioprocess Technol. 2012;5(3):854-67. doi: 10.1007/s11947-011-0683-7.
68. Horne DS. Light scattering studies of colloid stability and gelation. New physicochemical techniques for the characterization of complex food systems. London: Blackie Academic and Professional; 1995;240-67. doi: 10.1007/978-1-4615-2145- 7_11.
69. Saifullah M, Ahsan A, Shishir MRI. Production, stability and application of micro- and nanoemulsion in food production and food processing industry. Emulsions: nanotechnology in the agrifood industry. London: Academic press, Elsevier Inc 2016;3:405-42. doi: 10.1016/B978-0-12-804306-6.00012-X.
70. Chiesa M. Thermal conductivity and viscosity of water-in-oil nanoemulsions. Colloids Surf a Physicochem Eng Asp. 2008;326(1-2):67-72. doi: 10.1016/j.colsurfa.2008.05.028.
71. Lakshmana PS. Nanoemulgel for transdermal delivery of cyclobenzaprine hydrochloride: design, characterization and *in vitro* studies. Appro Drug Dev. 2017;1(5):555-75.
72. Jones DS, Woolfson AD, Brown AF, Coulter WA, McClelland C, Irwin CR. Design, characterisation and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. J Control Release. 2000;67(2-3):357-68. doi: 10.1016/S0168, PMID 10825567.
73. Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RS. Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan. AAPS PharmSciTech. 2006;7(3):67. doi: 10.1208/pt070367, PMID 17025248.
74. Kumar L, Verma R. *In vitro* evaluation of topical gel prepared using natural polymer. Int J Drug Delivery. 2010;2(1):58-63. doi: 10.5138/ijdd.2010.0975.0215.02012.
75. Kaur G, Narang JK. Topial Nanoemulgel KG. A novel pathway for investigating alopecia. J Nanomed Nanotechnol. 2017;8:472.
76. Srdan V. Stankov. Definition of inflammation, causes of inflammation and possible anti-inflammatory strategies. Open Inflamm J. 2012(5):1-9. doi: 10.2174/1875041901205010001.
77. Dasgupta S, Ghosh SK, Ray S, Kaurav SS, Mazumder B. *In vitro* and *in vivo* studies on lornoxicam loaded nanoemulsion gels for topical application. Curr Drug Deliv. 2014;11(1):132-8. doi: 10.2174/15672018113106660063, PMID 24266509.

78. Eid, A review on the phytopharmacological effect of *Swietenia macrophylla*. 2013;3:5.
79. Eid AM. Preparation, characterization and anti-inflammatory activity of *Swietenia macrophylla* Nanoemulgel. J Nanomed Nanotechnol. 2014;5(2):190. doi: 10.4172/2157-7439.1000190.
80. Nanomiemgel JS. A novel drug delivery system for topical application – *in vitro* and *in vivo* evaluation PLoS ONE. 2014;9(12):e115952. doi: 10.1371/journal.pone.0115952.
81. Rahman BS, Anwar F, Al-Abbasi FA, Kumar V. Nanotechnology- based Nano bullets in anti-psoriatic drug delivery: state of the art nanoscience in dermatology. Elsevier; 2016;157-66.
82. Sarfaraz Alam Md. Design and characterization of nanostructure topical gel of betamethasone dipropionate for psoriasis. J Appl Pharm Sci. 2012;2(10):148-58.
83. Herrmann ML, Schleyerbach R, Kirschbaum BJ. Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. Immunopharmacology. 2000;47(2-3):273-89. doi: 10.1016/S0162-3109(00)00191-0, PMID 10878294.
84. Kaltwasser JP. Leflunomide in psoriatic arthritis. Autoimmun Rev. 2007;6(8):511-4. doi: 10.1016/j.autrev.2006.12.001, PMID 17854740.
85. Elewski BE, Hay RJ. Update on the management of onychomycosis: highlights of the Third Annual International Summit on cutaneous antifungal Therapy. Clin Infect Dis. 1996;23(2):305-13. doi: 10.1093/clinids/23.2.305, PMID 8842269.
86. 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. doi: 10.1208/s12249-016-0488-0, PMID 26857516.
87. Elmataeeshy ME, Sokar MS, Bahey-El-Din M, Shaker DS. Enhanced transdermal permeability of terbinafine through novel nanoemulgel formulation; Development, *in vitro* and *in vivo* characterization. Future J Pharm Sci. 2018;4(1):18-28. doi: 10.1016/j.fjps.2017.07.003.
88. Aparna C. Enhanced transdermal permeability of telmisartan by a novel nanoemulsion gel. Int J Pharm Pharm Sci. 2015;7(4):335-42.
89. Parhi R, Terapalli BR, Teja BB. Formulation and *in vivo* evaluation of Minoxidil Topical gel. Turk J Pharm Sci. 2014;11(2):153-62.
90. Usmania BA, Kataria MK. Minoxidil emulgel for androgenic alopecia: A literature review including patents. Int J Pharm Drug Anal. 2017;5(3):49-58.
91. Olsen EA, Dunlap FE, Funicella T, Koperski JA, Swinehart JM, Tschen EH, *et al*. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. J Am Acad Dermatol. 2002;47(3):377-85. doi: 10.1067/mjd.2002.124088, PMID 12196747.
92. Rani D. Formulation development and *in vitro* evaluation of minoxidil bearing Glycerosomes. AJBR. 2016;4:27-37.
93. Sunitha S. Design, development and evaluation of nanoemulsion and nanogel of itraconazole for transdermal delivery. J Sci Res Pharm. 2014;3(1):6-11.
94. Aithal GC, Nayak UY, Mehta C, Narayan R, Gopalkrishna P, Pandiyan S, *et al*. Localized *in situ* nanoemulgel drug delivery system of quercetin for periodontitis: development and computational simulations. Molecules. 2018;23(6):1363. doi: 10.3390/molecules23061363, PMID 29882751.
95. Jeengar MK, Rompicharla SV, Shrivastava S, Chella N, Shastri NR, Naidu VG, *et al*. Emu oil-based Nanoemulgel for topical delivery of curcumin. Int J Pharm. 2016;506(1-2):222-36. doi: 10.1016/j.ijpharm.2016.04.052, PMID 27109049.
96. Mahesh B. Enhanced permeability of cyclosporine from a trans-dermally applied nanoemulgel. Pharm Sin. 2015;6(2):69-79.
97. Wais M. Formulation development *ex-vivo* and *in vivo* evaluation of nanoemulsion for transdermal delivery of glibenclamide. Int J Pharm Pharm Sci. 2013;5(4):747-54.
98. Singh BP, Kumar B, Jain SK, Shafaat K. Development and characterization of a nanoemulsion gel formulation for transdermal delivery of carvedilol. Int J Drug Dev Res. 2012;4(1):151-61.
99. Drais HK. Formulation characterization and evaluation of meloxicam nanoemulgel to be used topically. Iraqi J Pharm Sci. 2017;26(1):9-16.
100. Mulia K, Ramadhan RMA, Krisanti EA. Formulation and characterization of nanoemulgel mangosteen extract in virgin coconut oil for topical formulation. MATEC Web Conf. 2018;156:01013. doi: 10.1051/matecconf/201815601013.
101. Harwansh RK, Mukherjee PK, Bahadur S, Biswas R. Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress. Life Sci. 2015;141:202-11. doi: 10.1016/j.lfs.2015.10.001, PMID 26437269.
102. Pathak MK, Chhabra G, Pathak K. Design and development of a novel pH triggered nanoemulsified *in situ* ophthalmic gel of fluconazole: *ex-vivo* trans-corneal permeation, corneal toxicity and irritation testing. Drug Dev Ind Pharm. 2013;39(5):780-90. doi: 10.3109/03639045.2012.707203, PMID 22873799.
103. Kour SK. Herbal contraceptive formulations. WO2006082596A2, 2006.
104. NOVARTIS. Diclofenac in emulsion-gel form. EP. 2009;2(55):298 A1.
105. Bhushan RS, Shafiq S, Jay K, Jitendra P. Stable pharmaceutical composition of diclofenac US20120093882A1; 2012.
106. James R. Nanoemulsion containing Composition having anti-inflammatory activity. WO2008051186A2, 2008.
107. Azeem A, Rizwan M, Ahmad FJ, Iqbal Z, Khar RK, Aqil M, et al. Nanoemulsion components screening and selection: a technical note. AAPS Pharm Sci Tech. 2009;10(1):69-76. doi: 10.1208/s12249-008-9178-x, PMID 19148761.

Cite this article: Mandal S, Vishvakarma P. Nanoemulgel: A Smarter Topical Lipidic Emulsion-based Nanocarrier. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s481-s498.