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## A METICULOUS ACCOUNT ON NANOEMULSION IN SKINCARE: APPLICATION TO RECENT DEVELOPMENT

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**ABSTRACT:** Nanoemulsions have garnered a lot of interest in recent decades as a result of their unique characteristics. These carriers are optically transparent, non-equilibrium, thermodynamically stable dispersion of nano-sized particles. Nanoemulsions possess great potential for pharmaceuticals, cosmetics, and other application areas ranging from the Oil to the food industry. Incorporating nanotechnology into cosmetic formulations is the newest and most cutting-edge technology accessible. With the ability for excellent dispersion of active substances, merging textures, and controlled delivery into the desired layers of skin, nanoemulsions are becoming increasingly popular in skincare products. Advantages of nanoemulsion over cosmetic technologies (such as liposomes, emulsions and microemulsions) include ease of manufacture, adjustable particle sizes, excellent kinetic stability, and low surfactant levels, as well as market benefits like the ability to be manufactured in a variety of forms, such as spray, foam, liquid and cream have accelerated their use. The fundamental objective of this review is to systematically discuss the components, properties, and capabilities of nanoemulsions as final application products for skincare and other cosmeceutical applications as well as to describe how formulators have been preparing nanoemulsions using multiple techniques (e.g., microfluidization, high-pressure homogenization, and ultrasonic emulsification). The review further highlights current challenges and opportunities, with an emphasis on recent progress and various applications, to encourage systematic evaluation and selection of nanoemulsion in skincare to reduce the number of investigations and improve study design to achieve target formulations.

**INTRODUCTION:** Cosmetics are characterized as skin-enhancing, skin-cleaning, and skin-nurturing products. Cosmeceutical is a new sector in the personal care or cosmetics industry with a wide range of applications. Cosmeceuticals contain biologically active chemicals with health and therapeutic benefits on the surface applied and improved appearance<sup>1</sup>. Cosmeceutical research is rapidly expanding in personal care fields, ranging

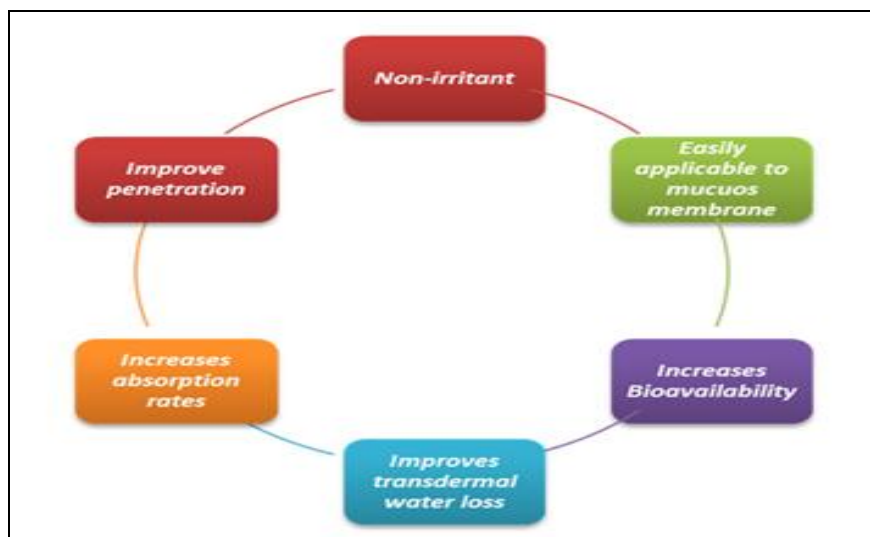
from beauty products to skincare and various body care products<sup>2, 3</sup>. There has been a greater emphasis on high-quality commercial items and meeting customers' growing demand in the cosmetic and personal care fields in recent years. Researchers have several challenges in terms of product performance, sustainability, and safety.

Because of its potential benefits and specific application above conventional technologies, nanotechnology in the formulation of these sorts of high-quality goods has gained popularity among formulators in recent years<sup>4</sup>. Nanopharmaceuticals, or nanotechnology in medicine and pharmaceuticals, have grown exponentially, with nanoemulsion, nanospheres, nanosuspension, nanotubes, nanoshells, nanocapsules, lipid

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nanoparticles and dendrimers among the most commonly used<sup>5</sup>. Antibiotics, DNA encoded drugs, vaccine administration cosmetic, and topical preparations are typical applications<sup>6</sup>. Nanotechnology is employed in cosmeceutical applications because of its benefits, such as boosting the stability of cosmetic ingredients, improving penetration capabilities, and providing a pleasant skin feel<sup>1,7,8</sup>. According to the literature, nanoemulsions are a dispersion of oil and water and specific surfactant that contains a thermodynamically stable and homogeneous system with nanoscale particle size by mechanical forces to form a dispersion medium<sup>7</sup>. Nanoemulsion is the very minute oil-in-water dispersions containing droplet size diameters less than 100 nanometers. They have various characteristics such as freshness, purity, transparent appearance, high solubility, low viscosity, simplicity, high kinetic stability. They are easily absorbed in the skin, resulting in fluids to gels like cosmetic products<sup>9,10</sup>.

Some of the properties are illustrated in **Fig. 1**. Nanoemulgel is a nanoemulsion-based hydrogel matrix that may be used to increase skin penetration in skin and body care products<sup>11</sup>. There are two types of emulsion applications in cosmetics: oil in water emulsion and water in oil emulsion<sup>10</sup>. Nanoemulsion has an essential role in skin care products provide better dispersion and controlled delivery of active ingredients through the derma layers of the skin<sup>12</sup>. The current review paper focuses primarily on the applications of nanotechnology in skin care products and the various preparation techniques used to prepare the nanoemulsion, such as high and lower energy emulsification methods and the benefits and drawbacks that occur during the process. It further highlights current market trends, future scope, and innovative approaches based on current knowledge, prior study, and numerous technology resources. The main motive of the review is to give a broad idea of nanoemulsion technology, which is employed in skincare products.



**FIG. 1: PROPERTIES OF NANOEMULSION**<sup>5,6,13</sup>

### Preparation of Nanoemulsion:

**Advantages of Nanoemulsion:** As nanoemulsions have a greater surface area than macroemulsions, they have a more efficient transport system<sup>5</sup>. Nanoemulsion is a metastable and highly delicate system by nature with the comparison of the microemulsion<sup>10</sup>. It has a wide range of formulations and products, including gels, lotions, all types of creams, transparent milk, clear gels, and many more with varying aesthetic characteristics, richness, skin feel, and rheological behaviors. Nanoemulsion helps to solubilize drugs

and improve the bioavailability of poorly soluble hydrophilic and lipophilic drugs<sup>14</sup>. It improves transdermal water loss and skin barrier function<sup>5</sup>. Some of the key advantages are highlighted in **Fig. 2**. It helps the drugs from being oxidized and hydrolyzed because of encapsulation. Nanoemulsion has an evident fluidity character that enhances formulation treatment efficacy and is safe for use due to the absence of any thickener agent or colloidal components. Nanoemulsions are thermodynamically stable systems, which permits the system to self-emulsify. In comparison to

microemulsions, nanoemulsions require a smaller amount of surfactant. In the manufacture of the microemulsion 20–25, percent surfactant is needed, whereas 5–10 percent surfactant suffices in nanoemulsion. Nanoemulsion also provides market benefits, such as the ability to be manufactured in various forms, including spray, foam, liquid, and cream <sup>5</sup>. It can be used to deliver fragrances in personal care products. It is advantageous when utilizing chemically unstable substances since

nanoemulsion shields them from oxidative and UV deterioration. It provides a pleasant skin feel as well as a pleasing aesthetic character <sup>15</sup>. Furthermore, because of the droplets' small size, they may deposit uniformly across substrates. Wetting, spreading, and penetration may be aided by the low surface tension of the entire system and the weak interfacial tension of the oil in water droplets <sup>8</sup>.



FIG. 2: ADVANTAGES OVER TRADITIONAL EMULSION <sup>5, 10, 14, 13</sup>

**Disadvantages of Nanoemulsion:** A large amount of surfactant and cosurfactant required for stability is one of the downsides <sup>6, 13</sup>. For high melting compounds, they have a restricted solubilizing ability. The formulation is an expensive procedure since particle size reduction requires much energy. The pH and temperature determine its stability, and stability may be an issue during the storage of nanoemulsion <sup>13, 15</sup>. Ostwald ripening, which happens due to the rapid curvature of tiny droplets displaying better solubility than large droplets with a small radius of curvature, is a significant issue with nanoemulsion <sup>15</sup>.

**Composition of Nanoemulsion:** The following are the critical ingredients in nanoemulsion <sup>5, 12, 16</sup>.

- Vegetable oil (carrier for active reagents or the reagent itself).
- Emulsifiers (Surfactant/Co-Surfactant).
- The aqueous phase (usually water or alcohol).
- Antioxidants and preservatives are also utilized as additions.

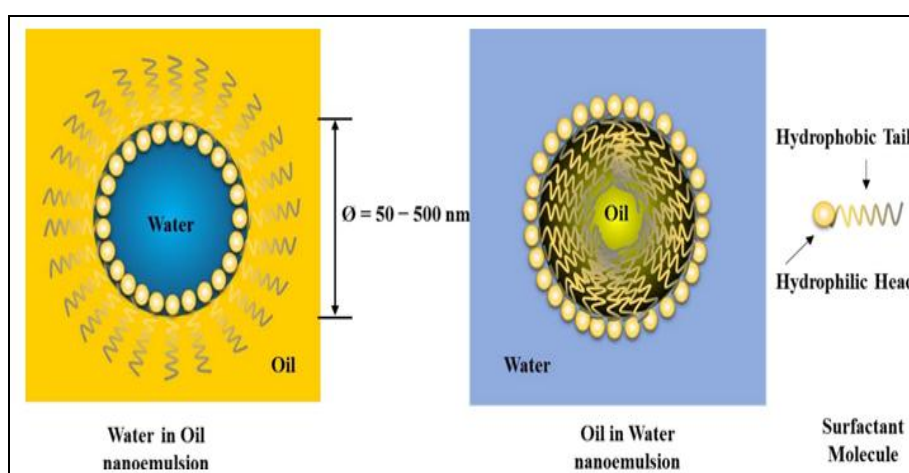
TABLE 1: COMPONENTS OF NANOEMULSION FORMULATIONS <sup>5, 12, 16, 17</sup>

Key Components	Examples
Water	Deionized water, Distill water
Oil	Captex 8000, Myritol 318, Captex 200, Witepsol, Captex 355, isopropyl myristate, etc.
Surfactant	Tween 80, Capryol 90, Tagat TO, Gelucire 44/14, 50/13, Imwitor 191, 380, 742, 780K, 928, 988, Lauroglycol 90, PEG MW > 4000, Labrafil M 1944 CS, M2125 CS, Softigen 701, 767, Cremophore RH 40, PlurolOleique CC 497, etc
Co-surfactant	Glycerin, Ethylene Glycol, Propanol, Propylene Glycol, Transcuto IP, Ethanol.
Additives	Polyhydric humectants like glycerol, propylene glycol, sorbitol, etc., ethoxylated or acetylated lanolin derivatives, specialized cosmetic ingredients and extracts, essential oils, and many more

Nanoemulsion is made with various types of oil. These oils are commonly used in skincare because of their emollient qualities and compliance with the non-polar constituent of the stratum corneum of the skin. Several oils are used to make nanoemulsions, including andiroba oil and copaiba oil. Raspberry oil, Sesame Indicum and nonionic surfactants produced a very stable nanoemulsion with an HLB value of 8.0 and a strong antioxidant capacity. The nanoemulsion containing rice bran oil could treat skin conditions such as atopic dermatitis and psoriasis<sup>12, 15, 17</sup>. According to several studies, surfactant blends are more productive and advantageous than isolated surfactants.

Surfactant blends disperse and dissolve both phases efficiently, using less surfactant and improving nanoemulsion stability. Since there is a connection between droplet size and the surfactant used, the appropriate surfactant must be chosen<sup>15, 17</sup>.

**Types of Nanoemulsion:** A good mixture of surfactants and co-surfactants stabilizes the interface in all three forms of nanoemulsions. Surfactants with an HLB value of 4–6 are suitable for the production of water-in-oil nanoemulsion<sup>7, 12</sup>. **Fig. 3** represents the simple structure of nanoemulsion consisting of surfactant micelle.



**FIG. 3: SCHEMATIC REPRESENTATION OF WATER-IN-OIL AND OIL-IN-WATER NANOEMULSIONS WITH SURFACTANT MICELLES**<sup>7</sup>

**Preparation of Nanoemulsion:** The fundamental idea of nanoemulsion preparation techniques is to keep droplet sizes below 600nm. The preparation of nanoemulsion requires high amounts of energy which can be provided by mechanical means. "High-Pressure Homogenization" or "Microfluidization" is the most commonly utilized processing technique<sup>18</sup>. There are a few factors to bear in mind during the nanoemulsion preparation procedure<sup>19</sup>. First, surfactants should be specifically selected to achieve ultra-low interfacial tension. Furthermore, the interface must have been flexible or fluid enough to allow nanoemulsion to develop<sup>12, 20</sup>. Finally, it is required that the surfactant be mixed with an oily phase to prepare nanoemulsion. Many elements influence the final quality, particularly oil viscosity, molecular surfactant HLB, plus solvent miscibility. The application of high-energy emulsification for oil-containing cosmetic nano emulsification has been reported<sup>21, 22</sup>.

Low and high energy methods are utilized to create nanoemulsions from a milky emulsion. Emulsions created with mechanical equipment, including a high-pressure homogenizer, high shear stirrer, or an ultrasonic generator, are referred to as high-energy emulsions. Another approach, known as low-energy emulsification, creates emulsions by using the chemical energy present in the substance<sup>21</sup>. **Table 3** in recent work, microfluidization and ultrasonication were used to develop nanoemulsion. Although ultrasonication was easier to use and clean, microfluidization produced a nanoemulsion with smaller droplets<sup>23</sup>.

**Low Energy Technique:** Low-energy approaches entail creating nanoemulsions by spontaneous emulsification without the need for any devices or energy. Low-energy techniques for forming nanoemulsions include phase inversion composition and phase inversion temperature, with the former becoming less energy-intensive.

The procedure involves combining two liquid phases: a lipophilic phase through which a hydrophilic surfactant is introduced and subsequently solubilized<sup>5, 19</sup>.

**Phase Inversion Composition (PIC):** The Phase Inversion Composition technique of producing nanoemulsions necessitates a progressive diluting of the oil phase well with the water phase or conversely<sup>24</sup>. In some portions of the emulsification pathway, this causes a phase inversion process<sup>25</sup>. Before adding another continuous phase, the scattered phase must be well blended with the continuous phase. And then, would it be preferable to reorganize the scattered phase into tiny droplets. Although much less energy-intensive, the low-energy technique has limitations due to the usage of large quantities of surfactant and the necessity for perfect control of the physicochemical properties. The technique is inappropriate for large-scale emulsion creation since the products are susceptible to coalescence and creaming<sup>7, 12</sup>.

**Phase Inversion Temperature (PIT):** The Phase Inversion Temperature is a temperature-dependent technique that provides some flexibility in preparing the nanoemulsion. It can be performed numerous times by adjusting the mixing temperature until nanodroplet quality is achieved. When employing nonionic surfactants, the emulsion's stability can be improved by altering the temperature. This technique uses for various essential oil preparation<sup>26</sup> for cosmetic applications such as black pepper<sup>27</sup>. At low temperatures, this causes a change from such oil in water emulsion to water in oil emulsion, and even at higher temperatures, this forces a change to oil in oil emulsion. The emulsification technology is based on the concept of very low interfacial tensions. Its self-emulsification method involves nanoscale droplets containing lamellar layers on their surfaces, which are much less stable with time<sup>12, 28, 29</sup>.

**High Energy Methods:** High energy nanoemulsions necessitate the employment of specialized devices to enhance the water in oil interfacial areas for the generation of sub-micronic droplets. The utilization of high-energy systems has been extensively studied in this context.

The produced force must be many orders of magnitude greater than the momentum. Larger droplets are burst into tiny sizes due to the ensuing fluid tensions in such severe conditions. The strong tensions between both the two immiscible liquid phases are ruptured, resulting in smaller droplets. The produced force must be several orders of magnitude more than numerous major interfacial energies and then huge interfacial surfaces to generate nanoscale regions<sup>19, 20</sup>.

**High-shear stirring using a Rotor System:** This high-speed mixing method is propelled by hydrodynamic shear. Several emulsification devices have been used to create emulsions on an industrial level. Shear stress level, manufacture sequence, and propeller homogenization are all elements that influence control droplet diameter during the procedure. The technique was discovered to be very successful in the production of different nanoemulsions. The dimensionless Reynolds number has been commonly used to represent shear pressures associated with high stirring. A comparable operational concept, agitation, was preserved in the production procedure. It has been discovered to create droplets that are propelled in a manner comparable to the mobility of tiny particles in the air. The action is comparable with oil in the aqueous emulsions procedure but with bigger droplets and a more focused force on the droplet surface<sup>7, 29</sup>.

**High-pressure Homogenization:** High-pressure homogenization is one of the most common methods for preparing nanoemulsions. The method uses strong cavitation to disturb and generate tiny oil droplets. It aids in reducing polydispersity of oil droplets and droplet size. However, high-pressure homogenization involves inherent problems with productivity and componentry. It may be used to make oil in water liquid nanoemulsion with less than 20% oil phase. As a result, it is inappropriate for creating high pressure over some combination of the oil phase, surfactant, and co-surfactant<sup>12, 15, 30</sup>.

**Ultra-sonication:** Because of its outstanding energy efficiency, low-end blending need, as well as cheap manufacturing cost, ultrasonic nanoemulsion is increasing in popularity among formulators<sup>31, 32</sup>. The disturbance of a falling

bubble increases emulsion blending within the collapsing bubble. These bubbles disintegrate quickly, causing shock waves. Which effect causes highly localized turbulence and large shear forces to transverse the liquid, resulting in high velocity.

Unfortunately, the technique is still restricted to laboratory studies<sup>33</sup>. Despite its vast potential, the technique's uses have been confined to tiny quantities at a time<sup>23, 34</sup>.

**Microfluidization:** Microfluidization is a high-energy technique that employs a device known as a microfluidizer. It guides the flow stream into the interaction chamber's small channels named microchannels using a displacement pump at increased pressure (500-20000psi).

It is more effective than ultrasonication, but it is less practical owing to manufacturing expenses, apparatus contamination, and aseptic treatment.

The mixed techniques begin with high-shear churning to produce microemulsions comprising certain ingredients. Nanoemulsion droplets are made as a result of successive diffusion of nano-emulsifiers over the interphase barrier.

The large quantities of emulsion are subsequently filtered through some nitrogen-filled filter to eliminate big droplets, delivering a homogeneous nanoemulsion. It offers a limited number of droplets smaller than 50nm in size. The method is similar to ultrasound, except the small droplet size is<sup>7, 15</sup>.

**TABLE 3: MANUFACTURING OF NANOEMULSION**<sup>7, 16, 18, 28, 35</sup>

Emulsification process	Mechanism or process of emulsification	Advantages	Disadvantages
<b>Low energy</b>			
Phase inversion temperature	Changing the interfacial film curvature by varying the temperature. Low flow and quenching temperature T facilitate nanodroplet production by lowering interfacial tension at the PIT	Permits scale-up production. Less costly. Low-flow process	It is required to have liquid crystal or mid-range microemulsion phases present Heating is required Nonionic surfactant needed, More likely to Ostwald ripening, Limited stable temperature range
Phase inversion composition	Dilution of the dispersion medium during the chance to replace the curvature of such diffusion layer Low flow is used to minimize interfacial tension, resulting in a change from water in oil to oil in water and the formation of Nanodroplets	Allows scale-up production less costly no heating required	It is required to have liquid crystal or middle-range microemulsion phases present. The incorporation of one phase into another must be done gradually. More limited range of compositions compared to high-energy methods. Ostwald ripening is highly possible Oil and water must be soluble in each other
<b>High energy</b>			
A rotor/stator arrangement is used for high-shear stirring.	As a result of the concentrated transmission of energy, enormous shear stresses are generated. Energy dissipation rates at the mixing head are very localized	Permits Scale-up production. Allowing consistent production with a stirring speed of up to 36,000 rpm of emulsion.	More power consumptions than traditional mechanically stirred vessels
High-pressure homogenization	Cavitation, Shear and collision	Less process time. Allows for the choosing of surfactant and emulsion inner structure across low-energy procedures	Not capable of thermo- or shear-sensitive compounds costlier equipment
Ultrasonication generator/sonication	Cavitation	Less expensive equipment Allows for the choosing of surfactant and emulsion inner structure across low-energy procedures	They are only used for producing small quantities of emulsions at a time
Microfluidization	The mechanism is High-pressure injection	-	Only recommended for small manufacturing and is much more expensive than other equipment

**Characterization:** The density, droplet size, turbidity, pH measurement, viscosity, refractive index, phase separation, etc., must be performed to characterize nanoemulsion<sup>36</sup>. **Table 4** covers a variety of characterization methods. In addition, the following significant stability variables are affected by a variety of factors that influence nanoemulsion formulation:

- ✓ Surface tension and intramolecular attraction are the two factors that cause particles of the dispersion medium to coalesce. It can, however, be decreased by adding the appropriate surfactant<sup>13</sup>.
- ✓ The dispersed phase's high solubility in the scattered medium may result in Ostwald's ripening, which is the transition of smaller droplets having lower Laplace pressure to

bigger droplets with higher Laplace pressure<sup>13</sup>.

- ✓ The emulsions are affected by zeta potential as well as droplet size. According to a study conducted, additives do not affect the nanoscale stability of droplet emulsions, but they alter the interfacial morphology of droplet emulsions<sup>37</sup>. The stability of emulsions stability was not only dependent on electrostatic stabilization. The steric part should be the principal factor of a potential electrostatic stabilization nanoemulsion in this situation. Pharmaceutical and cosmetic formulations of high-level hydrolyzable active could be created utilizing a nonionic surfactant nanoemulsion and a reverse phase emulsion technique<sup>38</sup>.

**TABLE 4: CHARACTERIZATION OF NANOEMULSION**<sup>7, 9, 13, 29, 38</sup>

Characterization	Technique
Droplet Size Distribution	It is generally determined using electron microscopy and light scattering techniques.
Solubilization of Dye	The water-soluble dye is primarily soluble in the aqueous phase of the water in oil droplets; however dispersible in the oil in the water globule. An oil-soluble dye is soluble inside the oil phase of the oil in the water globule but dispersible in the aqueous phase of the water in the oil globule
Durability test	Water may be used to dilute the oil in water nanoemulsions, but not water in oil nanoemulsions.
Conductance measurement	Because water is an exterior phase, oil in water can carry electricity. Conductivity measurements help determine the characteristics of continuous phase as well as phase inversion events
Dynamic Light scattering measurement	Nanoemulsion structural and dynamic properties may be determined via dielectric measurements
Polydispersity	Detected at 900 in dynamic light scattering spectrophotometer
Phase Analysis	A photon Correlation spectrophotometer is used to determine the Polydispersity index and mean diameter of the sample
Interfacial Tension	They are performed using a conductometer by measuring electrical conductivity
Viscosity	A spinning-drop system may be used to test that very low interfacial tension. Interfacial tensions can be determined by spinning a minimum density stage drop in a cylindrical capillary loaded with a maximum density phase while evaluating the drop's shape
pH	The viscosity of nanoemulsion can be measured by Brookfield viscometer at different shear rates.
Refractive Index	By using a pH meter
Electroscopy	Using Abbe Refractometer
Thermodynamic stability studies	It helps to study the Morphology and structure of nanoemulsion. Electron microscopy is required for nanoemulsion to get accurate and crucial knowledge regarding structural characteristics
Zeta Potential	Nanoemulsions are characterized using scanning electron microscopy) as well as transmission electron microscopy. However, the most frequently used is Cryo TEM to visualize nanoemulsion. The limitation of Cryo TEM is high financial effort and time-consuming sample preparation. Cryo EELS and methods like freeze-fracture directly may be employed in the future to characterize nanoemulsion
	For thermodynamic stability investigations, the heating-cooling cycle, freeze-thaw cycle, as well as centrifugation can be used
	Zeta potential is measured using a zeta sizer and determines surface charge on droplets, i.e., represents electrical characteristics of emulsion droplets

**Current Challenges:** Oil-in-water nanoemulsions improve the solubility of insoluble drugs in water by dispersing them in the oil phase. Depending on

the kind of oil employed, they also increase the directivity of drugs towards the lymph, preventing hepatic first-pass metabolism. Surfactants are used

at high concentrations in both nanoemulsions, which may cause toxicity and irritation. As a result, nanoemulsions are frequently made with human-safe surfactants and commonly consumed components that have been designated Normally Recognized as primarily safe by Food and Drug Administration<sup>39</sup>. The stability of the nanoemulsion is a significant challenge. Due to their tiny droplet size, the Ostwald ripening mechanism breaks nano-emulsions<sup>20</sup>. The use of various oils and oil mixtures can help them last longer<sup>40-42</sup>. Many challenges exist in nanoemulsion and topical drug delivery technology advancement, including successfully delivering pharmaceuticals drugs through to the skin and controlling the boundary for topical drug administration<sup>18</sup>.

The rheology features of nanoemulsion are significant for delivering drugs through the derma layer of skin because of their small particle size, low viscosity, and spreadability. As a result, therapeutic applications of nanoemulsion have been limited and the strategy of combining nanoemulsion with a gelling mechanism may help resolve this issue<sup>11</sup>. Low solubility, short biological half-life, low bioavailability, pronounced side effects, stability, and regulatory problems are significant obstacles in developing any medicinal product<sup>43</sup>. A lipid-based system, including microemulsion, nanoemulsion, solid dispersion like solid lipid nanoparticles and nanostructured lipid carrier or liposomes, recently became famous for improving solubility and bioavailability<sup>14</sup>.

**Recent Developments:** Several pieces of literature on the application and developments of nanoemulsion that contain last decade information<sup>44</sup>. A group of researchers developed a fullerene-integrated nanoemulsion to combat skin aging. Reactive oxygen species are formed inside the epidermis and dermis layers of the skin due to repeated exposure to ultraviolet radiation, leading to skin aging<sup>45</sup>. Antioxidants generated by the human body may also be insufficient to combat the excessive radicals produced. An external excess of antioxidants is necessary to counteract the detrimental effects on the cells. Fullerene is a potent free radical scavenger that surpasses natural antioxidants by forming radical adducts after successive additions, outperforming natural

antioxidants. A biocompatible oil-based transporter for fullerene that increases skin absorption is desired to minimize skin aging effects. The novel fullerenes were administered transdermally to test if they affected human skin structure regulation and collagen improvement. The study utilized biophysical measures to look at skin hydration and transepidermal dehydration<sup>46</sup>.

It is challenging to create an effective colloidal technology that addresses the limitations of the existing sunscreen compositions. Organic and inorganic (mineral) absorbers are the two types of nanoemulsions. Pluronic F68 was used to stabilize them, and they were produced utilizing an ultrasonication technique<sup>47</sup>. Cosmetics can include natural phytoactive substances. Plant-derived bioactive chemicals have been utilized in cosmeceuticals for millennia to address photoaging, irritation, loss of hair, lip care, psoriasis, UV damage inside the skin (face, lips), hair, and nail care. UV rays can induce skin sunburn, endothelial cell necrosis, as well as a reduction in immune function. With skincare, several natural phytobioactive substances can help avoid these negative consequences. These phytobioactives, on the other hand, have issues such as less skin penetration, lower whitening effects, and lower pro-longevity. Nanotechnology has the potential to solve these difficulties<sup>3</sup>.

The PIC technique and a high-shear apparatus can be used to make nanoemulsions utilizing plant-based polyphenols. The color and odor of the finished items may vary as a consequence of the stability issue. Conventional surfactants, such as Tween 80 and Span 80 combinations, could readily achieve small droplet sizes. In some literature, tocopherols/tocotrienols and gamma-oryzanol are mentioned abundant in the unsaponifiable fractions of rice (*Oryza sativa*) bran oil, which are well-known for solid antioxidant capabilities. Nanoemulsions seemed to be superior in delivering insoluble amphiphilic antioxidants with high photostability in this situation<sup>47</sup>. There are various applications of nanoemulsion along with liposome technology<sup>34</sup>. Researchers used a natural sucrose ester mixture as the only surfactant in their nanoemulsion, which resulted in structural and long-term stability<sup>48</sup>. Nanoemulsion better transport lipophilic compounds than liposomes in



cosmetics. Because of their bioactive characteristics, nanoemulsions are becoming increasingly popular. The Nanogel approach uses a simple procedure and apparatus to create submicron emulsions from a critical oil-in-water ratio. It is ideal for reducing transepidermal water loss, increasing skin production, and increasing active component penetration. These characteristics suggest that it might be instrumental in sun care products and moisturizing or anti-aging creams, where nanotechnology is currently employed in various products<sup>5,12</sup>.

Flores et al. discovered that hydrogels, including tea tree oil nanoemulsion plus nanocapsules, had an anti-edematogenic impact and aid wound healing in research. Formulations were able to reduce the edema and skin damage induced by UVB exposure. The presence of nanocapsules and nanoemulsions in hydrogel did not affect the spreadability of the formulation. These formulations can be used for the topical treatment of inflammatory disorders<sup>49</sup>. Topical nanoemulsion can be used in antimicrobial and anti-inflammatory treatment<sup>50</sup> for use in burn wounds<sup>51</sup>. For instance, citral essential oil is widely used as an antimicrobial agent, but citral oil is hydrophobic and unstable in normal conditions at room temperature. Hence, nanoemulsion of citral oil is made to keep its bacterial activity under normal conditions, hydrophilic, and microencapsulate it by protecting the compound. Citral-in-water nanoemulsion was prepared using ultrasonic emulsification. Antimicrobial activity against bacteria was observed by citral<sup>52</sup> and thymol<sup>53</sup> nanoemulsion.

These considerations may be employed in the agrochemicals, cosmetics, and pharmaceuticals sectors to rationally develop nanoemulsion-based delivery systems for essential oils depending on the intended antimicrobial activity. PEG (Polyethylene glycol)-free nanoemulsions are used in cosmetics as they are low viscosity, do not contain any emulsifier, and have good storage stability. For impregnating emulsion used in moist tissue, its market worth is increasing. They have the main application in makeup remover and baby care. The PEG-free emulsion is preferred in the market as natural ingredients in cosmetics are highly appreciated by consumers. The Tego wipe system has used the PIC technique for manufacturing, and

these wipes have many applications in baby care, face care, and body care products, and makeup removal<sup>5</sup>. M. Kong et al. found that a without alcohol oil/hyaluronic acid-containing based nanoemulsion may be used as a transdermal transporter for an active lipophilic component. As per the observed result, this nanoemulsion could diffuse through the stratum corneum and penetrate further into the dermis without any chemical enhancers. Transmembrane gradients, carrier properties, and penetration enhancers are all crucial factors in penetration. As a result, the nanoemulsion can be successfully employed in skincare applications to deliver active lipophilic substances percutaneously<sup>54</sup>.

Topical antibacterial activity may now be obtained with nanoemulsion, which was previously only possible with systemic antibiotics. Glucan polysaccharides derived from *Ganoderma lucidum* were integrated into a palm olein-based nanoemulsion produced utilizing an ultrasonication method. It could be potentially used for various skincare applications<sup>32</sup>. Curcumin nanoemulsions with an average particle size of 85 nm have been produced utilizing a self-nano-emulsifying technique and exhibited improved transdermal availability, excellent penetration, and no degradation<sup>3,55</sup>. Genistein-loaded nanoemulsions were integrated into hydrogels with a range of sizes of 250 nm, allowing for efficient transport of the bioactive chemical to the epidermis for a beauty-based treatment.

Vitamin E nanoemulsion<sup>56</sup> was developed to create nanoemulsion methods for skin protection qualities, including anti-wrinkle, improved skin moisturization and illness prevention<sup>13</sup>. By adding particular ligands to nanoemulsion is another procedure, skin cells may be directly targeted. In a nanoemulsion developed by N. Atrux-Tallau et al., droplet size was controlled in a narrow range from encapsulation. Advantages were stability for longer-term, optical transparency, and extended range of texture<sup>55</sup>. Wen-Chien Lu et al. prepared D-Limonene nanoemulsion using mixed surfactants using ultrasonic emulsification of various droplet sizes. It was discovered that when the HLB value increased, the droplet size shrank. The permeation is influenced mainly by droplet size, and the droplet depends on HLB values in d-limonene nano

emulsification<sup>57</sup>. The use of specific ligand inclusion into nanoemulsions to identify particular skin cells like keratinocytes and fibroblasts has been investigated. According to the findings, specific ligands can target certain skin cell types by enhancing their adherence to cells. More research has been done to see if a ligand-targeted nanoemulsion can distribute a brightening active (licorice) to melanocytes. The addition of caproyl-HA to licorice-loaded nanoemulsion greatly enhanced its capacity to decrease melanin content on melanocytes *in-vitro*<sup>47</sup>. Proper new nanoemulsion structures, including double nanoemulsions, may be created by the molecular design of amphiphiles, such as d-block polypeptides, that allow appealing chemical surface activity and loading and tailored transport hydrophobic and hydrophilic bioactive compounds. Sophisticated methods like post flow evaporating ripening have already been developed for various constituents involving viscous liquids<sup>28</sup>.

Nano-cosmeceuticals include creams and lotions made with Buriti oil (*Mauritia Flexuosa*), palm oil esters with water, plus virgin coconut oil in water<sup>44</sup>. Nanoemulsion is used as a vehicle for drug delivery<sup>58</sup>, Nano-system formulation<sup>59</sup>, Multiple or multiphase Nanoemulsion<sup>60</sup>, psoriasis treatments<sup>61</sup>, Thermo-responsive gel<sup>62</sup> and thermo-sensitive nanoemulgel<sup>63</sup>. Nanoemulsions containing whitening or lightening agents are most likely to be appreciated by cosmetic customers. They have properties like skin penetration enhancement, high incorporation power, and high stability<sup>21</sup>.

**Applications:** Nanoemulsions' benefits and features have opened up a plethora of possibilities, which may be divided into the following categories:

**Cosmetics:** Nanoemulsions in cosmetic products are important because they include a lipophilic core; they appear to be better at carrying lipophilic compounds than liposomes, making them essential platforms for the dispersion of active substances in specific skin layers and controlled distribution<sup>64</sup>. Nanoemulsions are suitable in cosmetics since they are non-irritant and non-toxic and may be readily applied to the skin. Nanoemulsion further enhances intake by dispersing the drug in the emulsion's

internal phase, allowing for more contact time between both the emulsion droplets and the nasal mucous membranes<sup>65-67</sup>.

### **Oil Industry and EOR (Enhanced Oil Recovery)**

**Mechanism:** Nanoemulsion holding oilfield chemicals are commonly used for deposit clearing, wellness treatments via scale resistance and acidizing, and flow security. Nanoemulsion has the most significant impact on the EOR process because it assists in the extraction of residual oil through reservoir rock. The pore necks in reservoir core rock and stone packs are shorter than the nanoemulsion droplet size, designed to increase penetration and susceptibility without filtration. As a result of the density disparities between the two stages, gravity does not separate them. The use of substances and innovation, devices, and procedures in nanoemulsion has a crucial length scale of around 1-100nm. Relying on the indicated physicochemical characteristics of nanoemulsion, the stranded residual oil discovered in the reservoir rocks during primary and secondary collection is successfully retrieved by capillary forces<sup>29</sup>.

**Parenteral Delivery:** Parenteral delivery of drugs with low solubility via the intravenous method is an issue due to the minimal quantity of drugs administered at the intended location<sup>65, 68</sup>. When delivered parenterally, nanoemulsion solutions provide considerable advantages over microemulsion methods due to their small particles<sup>69, 70</sup>. Nanoemulsion also clears more slowly than coarse particle emulsion, prolonged residence period in the body<sup>65</sup>.

**Oral, Nasal and Topical Drug Delivery:** Oral and nasal<sup>71</sup> nanoemulsion formulations provide several benefits over traditional formulations, including improved absorption, higher positive clinical potency, and reduced drug toxicity<sup>65, 68, 72</sup>. As a result, nanoemulsion delivery of steroids, diuretics, hormones and antibiotics has already been proven to be effective<sup>65</sup>.

**Ocular and Pulmonary Delivery:** Oil-in-water nanoemulsion has also been studied for ocular delivery and their ability to dissolve poorly soluble medicines, improve absorption, and achieve a sustained release characteristic<sup>65, 68, 73</sup>. In the field of ocular delivery, there is a wealth of literature and

research. An oil-in-water emulsion improves the transport of lipophilic drugs to the eye<sup>39,40</sup>.

**Nanoemulsion in Biotechnology:** Enzymatic catalysis in nanoemulsions has also been used in the synthesis of peptides, esters, and sugar acetals, as well as other hydrolysis processes and steroid transition<sup>37</sup>. In micro emulsion-based procedures, lipases are the most often used enzymes<sup>14</sup>.

**Nanoemulsion as Non-toxic Disinfectant Cleaners:** Commercial uses for a revolutionary non-toxic disinfection cleaner include healthcare, hospitality, tourist, food production, and military applications<sup>37</sup>. This product does not require any warning labels. It is non-irritating to the eyes and maybe safely absorbed through the skin, inhaled, or swallowed<sup>15</sup>.

**Skincare Application:** The skin is the biggest organ in the human body and is made up of several layers. It protects the body from environmental harm. Molecules can get through the skin barrier through a variety of different routes. Intercellular, follicular, transcellular, and lipid pathways are the three most common substances to permeate the skin<sup>74</sup>. The hypodermis is mainly made up of hypertrophic adipocytes and serves as the body's heat barrier. The dermis has been the skin's primary support and feeding component, containing fibroblasts, lymphatic arteries, collagen, blood, hair follicles, nerve, sweat glands. The hypodermis is mainly made up of hypertrophic adipocytes and serves as the body's heat barrier.

The dermis has been the skin's primary support and feeding component, containing fibroblasts, lymphatic arteries, collagen, blood, hair follicles, nerve, sweat glands, blood, sebaceous glands and elastin. Fatty acids, Ceramides<sup>75</sup> and cholesterol generate a "cement-like" layer in the skin. Reactive oxygen species caused by oxidative damages, including UV, photochemical and free radicals' reactions, have a role in various skin diseases, including certain photoaging, irritation and photocarcinogenesis. The universal skin-aging mechanism is divided into two main types: intrinsic and the other is extrinsic aging, which would be another unpleasant trend for consumers. Intrinsic aging is a natural method that is influenced by genetics.

It is an irreversible degenerative phenomenon in which the dermis extracellular matrix structure gradually deteriorates, resulting in the loss of firmness and elasticity. Extrinsic aging appears as deep age spots and rough and hyperpigmented skin as a result of sun or UV radiation exposure. Due to their absorption into the dermis, UVAs are primarily responsible for extrinsic aging processes. UVBs induce sunburns and encourage the growth of skin cancers. As a result of the increased prevalence of skin diseases, high-quality products with high performance, safety, and cost benefits for customers are being developed. To restore these disrupted skin barriers, researchers have used nanoemulsion innovation to minimize or overcome these restrictions<sup>47</sup>.

Nanoemulsion improves the permeation of drugs through the skin, which integrates the interest of researchers. The smaller the size of particles, the more amount of drug can be incorporated in the formulation<sup>11</sup>. Nanoemulsions are extensively used in lotions, deodorants/Perfumes<sup>76</sup>, essential oil-based mosquito repellent<sup>77</sup> and other formulation<sup>78</sup>, nail enamels, and sunscreens as they make skin healthier<sup>1,79</sup>. Cosmeceutical for skincare products stimulates collagen development, which enhances skin texture and performance. Skincare cosmeceuticals in nanoemulsion have gained importance due to controlled delivery and effective penetration<sup>7</sup>. Nanoemulsion can be considered advanced dispersion of actives that penetrate easily by particular skin layers<sup>5</sup>.

The nanoemulsion technique was first used in the Olay™ brand by Procter & Gamble in 2005. Natural antioxidants are used to reverse the sign of skin aging. They have radical scavenging activity and can reduce the reactive oxidative species, thus counteracting oxidative damage by UV radiation and thereby helping to improve skin aging. The in vitro efficacy and toxicity data are still in need; however, in vitro data indicate that anti-aging microemulsions and nanoemulsions are potential formulations<sup>66,80</sup>.

**Sunscreen:** Antioxidants are encapsulated in nanoparticles and are widely used as nanoemulsions. Nanoemulsion scavenges the free radicals generated due to overexposure to UV radiations.

There are various forms of UV filters, such as organic and inorganic. Synthesized sunscreens have many shortcomings, including forming a chalky film, odor, greasy residue, toxicity, and reduced attractiveness. L'Oreal Paris is the most well-known nano-based sunscreens maker incorporating inorganic and nano pigments based on metal oxides, such as titanium dioxide and zinc oxide. A recent study suggests the use of sunflower oil<sup>81</sup> or pomegranate seed oil emulsion increased skin protection against photodamage<sup>3</sup>.

**Anti-aging Products:** Dry skin, loss of texture, decreased oil production, loose skin, stretch marks, and skin weakening are all symptoms of aging, and wrinkles are the result. It is thought that the human skin can be rejuvenated, and collagen can reverse wrinkle formation. Anti-aging products generally contain either antioxidants or cell regulators<sup>82</sup>. Nanotechnology is used as an anti-wrinkle because of the increased delivery process of bioactive ingredients. Revitalift by L'Oreal Paris was among the most widely marketed anti-wrinkle treatments that use small-sized lipid vesicles innovation. Nanosomes containing Pro-retinol A are included in this package. Nanosomes are sound delivery systems that may reach the human bloodstream in a variety of ways. The anti-aging activity of a nanoemulsion system created utilizing *Eysenhardtia platycarpa* leaves flavanones and 70 nm nanoparticles were shown to be enhanced<sup>3,83</sup>.

**Moisturizer:** Nanoemulsion is a moisturizer that contains active phytoingredients and improves the appearance of the skin. They produce a film on the skin's outermost layer, known as the stratum corneum, which acts as a barrier to keep the skin hydrated. Nanoemulsion from rice bran oil has a practical moisturizing effect and protects skin diseases such as psoriasis and atopic dermatitis. Vegetable oils are considered as future alternatives in increasing moisturizing effects<sup>3</sup>.

**Future Outlook:** In the future, rational design approaches, rather than time-consuming experiments, can be used to produce more cost-effective and green cosmetics<sup>84, 85</sup>. New encapsulating agents will be evaluated more safely. Consumers nowadays are looking for dual advantages, such as specific health advantages and cosmetic or cosmeceutical advantages<sup>86</sup>.

Numerous studies, such as toxicological and microbiological testing, chronic toxicity and carcinogenicity tests, and undertaking safe human use studies for cosmetics, must always be carried out<sup>7</sup>. There might be some limitations based on environmental issues, product functioning, and health risks. Issues have been expressed about the potential hazards of nanoparticles penetrating the skin after already being applied to it<sup>87</sup>.

Adaptations in the skin barrier, such as dermatitis, cuts, and scrapes, may impact nanoparticle uptake<sup>1</sup>. Complaints were made about the potential hazards of nanoparticles penetrating the skin<sup>3</sup>. The hazard of cosmetic chemicals found in fish tissues, effluent discharged, and groundwater has been linked to biomagnification and bioaccumulation in the live tissues of animals higher up the food chain under specific investigations. Natural cosmetic active components instead of synthetic active elements can be used to alleviate this problem. The scientific committee on consumer products has issued a warning about the hazardous properties of insoluble nanoparticles used topically in cosmetics. Side effects are possible due to extensive use<sup>7</sup>.

Many scientists are interested in nanoemulgel because it can be used to produce various medicines to treat a variety of skin diseases. The oil droplets will either enter the skin's stratum corneum and transport the medication molecules straight to the skin's stratum corneum, bypassing the aqueous phase of nanoemulsions<sup>11</sup>.

Many exciting studies in the pharmaceutical area require more intricate and extensive investigation to determine the nanoemulsion technique's potential impact<sup>88</sup>. Some examples of approaches include: skin diseases treatments<sup>89</sup> like atopic dermatitis treatment<sup>90</sup> and skin wound healing<sup>91</sup>, polymer synthesis for cosmetic application<sup>92</sup> mainly edible polymer<sup>93</sup>, hair treatments<sup>94</sup>, percutaneous<sup>95</sup>, dermal<sup>96</sup> and transdermal<sup>97</sup> delivery.

**CONCLUSION:** Nanoemulsions have been widely used in cosmeceuticals as drug delivery techniques due to their ability to dissolve non-polar active compounds. Several major cosmetics companies have begun to invest in various preparation processes of nanoemulsion, and some

products are already on the market. However, further investigation of the nanoemulsion systems is needed, especially in terms of surfactant-free systems.

Another very typical purpose of nanoemulsion is to mask the disagreeable taste of greasy liquids, and nanoemulsion can also preserve drugs that are susceptible to oxidation and hydrolysis, as mentioned in the review. It is useful for transdermal drug delivery systems because of its excellent penetration across the skin barrier and minimal irritancy.

The rundown of nanoemulsion preparation and physical characterization techniques in this review will give the formulator a comprehensive grasp of the techniques available. Because of its submicron particle diameter and other advantages, the effective nanoemulsion delivery method included in cosmetics may be implemented for usage in other fields such as food and pharmaceuticals, beverages, and other sectors.

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