e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

REVIEW ON: NANOEMULSION

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ABSTRACT

Emulsions are liquid-liquid dispersions in which tiny droplets of one liquid phase are distributed throughout the other liquid phase. Because of their appealing qualities—such as their small size, high surface area per unit volume, improved dispersion of active hydrophobic components, and enhanced absorption—nanoemulsions—emulsions with sizes ranging from tens to hundreds of nanometers—have a wide range of potential uses in pharmaceutics, foods, and cosmetics. Beginning with an introduction of emulsion kinds, preparation, and stability, the article gives a general review of nanoemulsions for drug delivery. Surfactants are essential for creating and maintaining nanoemulsions.

Small molecule, particle, phospholipid, peptide, and protein surfactants are among the several forms of surfactants that are enumerated. The uses of nanoemulsions in drug delivery as nanomedicine are then discussed. Lastly, the topic of clinical uses for nanoemulsions is covered.

To address the main shortcomings of traditional medication delivery systems, a sophisticated way of distribution has been created. This review provides a thorough understanding of a nanoemulsion system. Nanoemulsions are emulsions made at the nanoscale that are intended to enhance the delivery of active medicinal substances. These are the thermodynamically stable isotropic systems where an emulsifying agent, such as a surfactant or co-surfactant, is used to combine two immiscible liquids into a single phase. Nanoemulsion droplets are usually between 20 and 200 nm in size.

The size and shape of the particles scattered throughout the continuous phase are the primary distinction between an emulsion and a nanoemulsion. Giving a general overview of the formulation, preparation process, characterisation methods, assessment criteria, and different applications of nanoemulsion is the main goal of this paper.

Keywords: High-Pressure Homogenization, Emulgents, Drug Delivery, Nanoemulsion.

I. INTRODUCTION

Drug molecules are transported by nanoemulsions, which are colloidal particle systems of submicron sizes. They are between 10 and 1,000 nm in size. These carriers are solid spheres with an amorphous, lipophilic, negatively charged surface. Site specificity can be improved by using magnetic nanoparticles. As a medication delivery mechanism, they reduce toxic reactions and side effects while increasing the drug's therapeutic efficacy. Major uses include reticuloendothelial system (RES) infection treatment, liver enzyme replacement therapy, cancer treatment, and immunization. A biphasic system with one phase deeply distributed in the other phase as tiny droplets with a diameter of 0.1 to 100 μm is called an emulsion.

The presence of an emulsifying chemical (also known as an emulsifier) can stabilize this thermodynamically unstable system. While the outer phase is referred to as the dispersion medium, external phase, or continuous phase, the dispersed phase is also known as the interior phase or discontinuous phase. Another name for the emulsifying agent is interphase or intermediate. A miniemulsion, which is a fine oil/water or water/oil dispersion stabilized by an interfacial coating of surfactant molecules with droplet sizes ranging from 20 to 600 nm, is also referred to as a "nanoemulsion." Nanoemulsions' small size makes them translucent.

Oil in water nanoemulsions, in which oil is distributed throughout the continuous aqueous phase, water in oil nanoemulsions, in which water droplets are distributed throughout the continuous oil phase, and bi-continuous nanoemulsions are the three forms of nanoemulsions that can develop.

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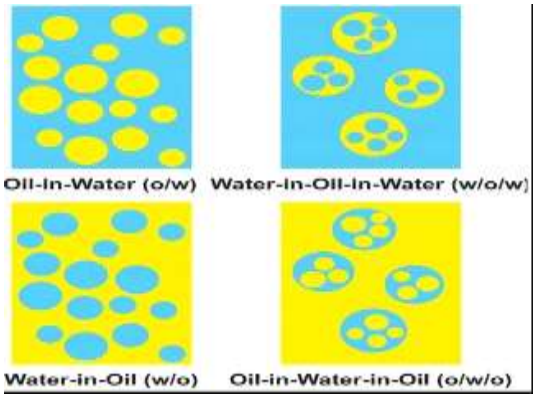
High Pressure Homogenisation

High pressure homogenization is a mechanical technique that entails the application of high pressure, reaching up to 400 MPa, to force a fluid through a narrow homogenizing nozzle. This process exposes the liquid to extreme shear stress, resulting in the creation of fine emulsion droplets. The size of the droplets produced is inversely related to the diameter of the nozzle aperture and directly related to the pressure applied; thus, smaller nozzle openings and higher pressures yield smaller droplets. The primary objective of this process is to diminish the size of particles and droplets from the micron scale to the nanometer scale.

The Avestin Emulsiflex series of high-pressure homogenizers is well-suited for applications such as cell rupture (cell lysis), the creation of ultrafine emulsions, the production of nanoparticles, and the formulation of homogeneous liposomes. In addition to their use in biomolecular sciences, Emulsiflex homogenizers find applications across the pharmaceutical, cosmetic, and food sectors. Specifically, in the dairy industry, these homogenizers improve texture and mouthfeel by producing nano-emulsions, enabling the reduction of fat content without sacrificing flavor, thereby promoting healthier food options.

Types of emulsion

Emulsions, in their most fundamental state, consist of a hydrophilic phase and a hydrophobic phase, with one phase dispersed within the other (see Fig. 1). These emulsions can be categorized as oil-in-water (O/W), where tiny oil droplets are suspended in water, or as water-in-oil (W/O) emulsions, where water droplets are dispersed in oil. The complexity of these systems can be increased by creating an emulsion within another emulsion, resulting in double emulsions such as water-in-oil-in-water (W/O/W) or oil-in-water-in-oil (O/W/O) emulsions. The conventional method for producing double emulsions involves a two-step process: first, the creation of the internal emulsion, followed by the formation of a second emulsion that encapsulates the initial one. The formation and stabilization of double emulsions present additional challenges, including the need to maintain the integrity of the initial emulsion during the creation of the outer emulsion. This process requires both lipophilic and hydrophilic surfactants to stabilize the interfaces between the oil and water phases, and double emulsions are more susceptible to degradation and coalescence due to diffusion between the phases (Leister & Karbstein, 2020). Recent research has focused on the generation of uniform double emulsions using microfluidic devices, which have promising applications in food science and as microreactors or templates for particle synthesis (Ran et al., 2017; Zhao & Middelberg, 2011; Zhao, 2013).



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1. Pickering Emulsion

Emulsions, whether oil-in-water (O/W) or water-in-oil (W/O), can be stabilized by extremely small particles located at the oil-water interface, which create a steric barrier that prevents coalescence. This concept was first introduced by Pickering in 1907. The particles that effectively stabilize Pickering emulsions possess dual wettability, meaning they can interact with both phases of the emulsion. This characteristic enables them to reside at the oil-water interface, generally providing enhanced stability compared to conventional surfactants. Furthermore, innovative applications for Pickering emulsions arise from the potential to utilize the particles on the droplet surface for additional functionalities, such as catalysis or antimicrobial properties

High internal phase emulsions (HIPEs) are characterized by an internal phase exceeding 74.05%, which contrasts with the majority of emulsions where the internal phase constitutes a minimal fraction (less than 10%) of the overall emulsion volume (Pulko & Krajnc, 2012). HIPEs have been utilized as templates for the creation of porous polymer monoliths through the polymerization of monomers dissolved in the continuous phase. More recently, they have also served as templates for the development of tissue-repairing porous hydrogels (Krajnc, Leber, Štefanec, Kontrec, & Podgornik, 2005; Nalawade et al., 2016). However, the polymer monoliths produced using HIPE templates tend to be quite fragile due to the high surfactant content and the thinness of the polymer walls. Consequently, ongoing research is investigating medium internal phase emulsions (MIPEs) as a potential alternative for creating more robust polymer monoliths (Wu, Menner, & Bismarck, 2013).

2. Nanoemulsion

Nanoemulsions are characterized by droplet sizes that range from 10 to 1000 nanometers. Typically, these emulsions comprise a combination of oil, water, and a surfactant. The choice of surfactant is essential for the formation and stabilization of nanoemulsions. Although nanoemulsions are thermodynamically unstable, they exhibit kinetic stability, meaning that phase separation will occur if allowed sufficient time. These nanoemulsions have been developed for a variety of applications, including pharmaceuticals, food products, and cosmetics. It is crucial that they are biocompatible and free from toxic effects for all these uses. Consequently, the selection of oils and surfactants is of paramount importance. Biocompatible options, such as vegetable oils or pharmaceutical-grade oils, are preferred. Additionally, proteins and lipids are commonly utilized as surfactants to enhance the stability of nanoemulsions

Advantages of nano-emulsion:

- It can be used as a substitute for vesicles and liposomes.
- To improve the bioavailability of the medication.
- It is non-irritating and non-toxic by nature.
- There is now more bodily stability.
- To increase the palatability of nutritious oils.
- To cover up the bad taste and smell of prescription drugs.
- To enhance medication absorption through the skin.

Disadvantage of Nano-emulsion:

- Not as consistent as other types of dosage has a short shelf life.
  - In order to stabilize the nanodroplets and cause them to cream and crack (break), a high concentration of surfactant and cosurfactant is used.
- Restricted capacity to dissolve highly soluble substances; nontoxicity is required for usage in medicinal applications.

Composition:

The following are the main parts of the microemulsion system:

1. Phase of oil
2. The primary surfactant, or surfactant
3. Secondary surfactant, or co-surfactant
4. Co-Solvent

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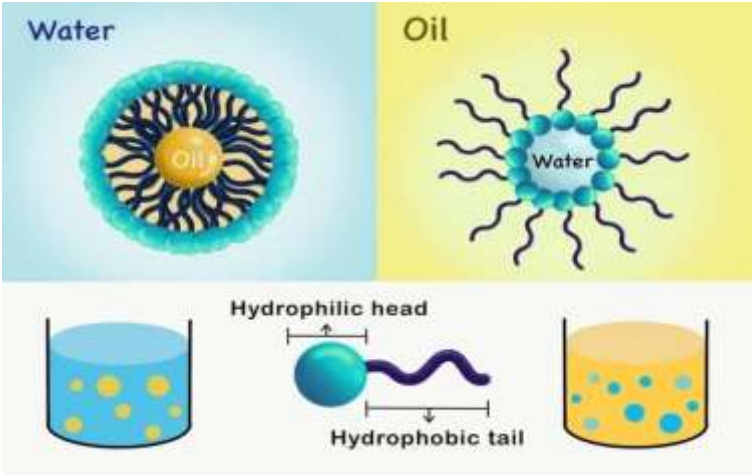
Phases of oil

Oil phase is the second most significant vehicle after water because it can improve absorption across the body's lipid barrier and solubilize lipophilic medication molecules. Oil's unique capacity to permeate cell membranes makes it very useful for lipophilic active drug delivery. The swelling of the surfactant's tail group region is influenced by the oil phase. Short chain alkanes have a greater degree of penetration than long chain alkanes.



The primary surfactant or surfactant

Research indicates that in order to reduce the O/W interfacial tension to a point where a microemulsion can develop spontaneously, high quantities of single-chain surfactants are required. However, by creating separate interfacial film curvatures at the lowest surfactant concentration, co-surfactants can be added to create a stable microemulsion composition. 11–16 Co surfactants have fluidizing groups, such as unsaturated bonds, which make the contact more fluid. This leads to the spontaneous formation of micro emulsions by altering the HLB value and dissolving the structure of liquid crystals or gels.

Secondary surfactant, or co-surfactant

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Co-Solvent

Organic solvents like ethanol, polyethylene glycol (PEG), and propylene glycol (PG) are examples of complementary solvents. They help dissolve lipid-soluble drugs and surfactants at comparatively high concentrations. Co-solvents and co-surfactants are hence interchangeable terminology. The nano-emulsion Nano-emulsions, which are dispersions of nanoscale particles, are produced by mechanical force, whereas micro-emulsions happen spontaneously.

II. METHODS OF PREPARATION

Method of high energy emulsification:

High-pressure homogenization with ultrasonication Low-power emulsification of Phase-inversion composition, phase-inversion temperature, and solvent displacement

Method of High-Pressure Uniformity:

A specially designed high-pressure homogenization device is used to produce nanoscale particles. When the water and oil push through a small input aperture at extremely high pressures (500–5000 psi), phase separation takes place.34 Consequently, extremely small particles are produced by intense turbulence and hydraulic shear. But this method requires a lot of heat and energy. Pressure and homogenization cycles are the

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direct causes of particle size.35 As pressure and homogenization cycles rise, particle size falls. This method is easy to scale up.

The process of microfluidization:

In This method creates high pressure (500–20,000 psi) using a micro fluidizer, a specifically designed device. First, mix the oil and water phase to create a coarse emulsion. In order to produce nanoscale small particles, this device consists of an interaction chamber with tiny microchannels that force coarse emulsion into an impingement area. After that, uniform particles are produced by filtering.

The use of ultra-sonication:

This method is based on the theory that the cavitation threshold, which establishes the border where fine nanoparticles develop, rises in tandem with an increase in external pressure and an ultrasonic field delivered to a coarse emulsion.

Method of phase inversion:

This process is based on the phase transition temperature, or the temperature at which a phase change occurs. Whereas W/O emulsions perform better in higher temperatures, O/W emulsions perform better in cooler temperatures. Rapid cycles of heating and cooling create fine particles. Non-ionic surfactants, such as poly-oxyethylene, become hydrophilic at low temperatures and lipophilic at high ones as a result of the dehydration of the polymer chain.

Unexpected Emulsification:

This is a simple method that uses a volatile organic solvent made up of oil, water, and hydrophilic and lipophilic surfactants. This mixture is made consistently by magnetic stirring. The water-miscible solvent is then evaporated under vacuum to create the nano-emulsion.

Method of Solvent Evaporation:

In this process, combine the drug and organic solvent first, using a suitable surfactant. The O/W emulsion is then created by combining the continuous phase. The drug-loaded microspheres can then be filtered or centrifuged after the organic solvent has been evaporated using a vacuum, heat, or ambient conditions.

The Hydrogel Method:

The solvent evaporation method and this process share certain similarities. High shear pressures are used to produce a drug-solvent nano-emulsion that is miscible with the drug anti-solvent.

Nanoemulsion Stability

Nanoemulsions represent thermodynamically unstable systems that tend to separate into two distinct phases over time. However, the presence of surfactants can significantly prolong this timeframe, effectively rendering the emulsions kinetically stable. A well-formulated emulsion can maintain its original characteristics for extended periods, ranging from months to years. This stability is crucial for the application of nanoemulsions in various fields, particularly in emulsion nanomedicine, where any alterations in formulation over time could adversely affect patient health. Therefore, it is essential to comprehend the mechanisms underlying emulsion destabilization and stabilization to ensure that nanoemulsions are adequately prepared and stored. The DLVO theory, introduced by Derjaguin and Landau, as well as Verwey and Overbeek, elucidates emulsion stability as a result of two independent forces: attractive van der Waals interactions and repulsive electrostatic double layer forces. Since these forces are considered independent, the total energy of interaction can be estimated by the simple addition of the attractive force (FA) and the repulsive force (FR), yielding the total interaction energy (FT) at specific distances, which provides a reliable estimation of stability up to approximately 5 nm.

$$FT = FA + FR$$

When droplets are widely spaced, the repulsive forces prevail in the interaction energy, promoting the stability of the colloid. However, as the droplets come closer together, the attractive forces start to take precedence, leading to destabilization. The DLVO theory explains that when the attractive forces are dominant, the emulsion experiences colloidal destabilization. This destabilization can occur through four primary mechanisms (Fig. 2): coalescence, flocculation, creaming/sedimentation, and Ostwald ripening.

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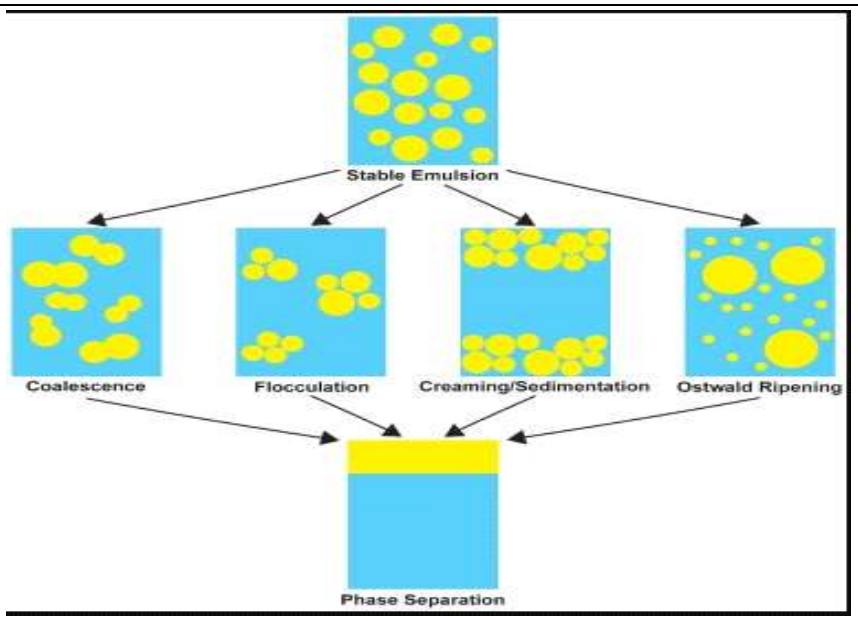

Figure Depiction of mechanisms and pathways involved in emulsion destabilization. Coalescence refers to the process where two or more droplets merge to minimize interfacial energy. Flocculation describes the aggregation of adjacent intact droplets into clusters. Creaming and sedimentation pertain to the movement of droplets either upwards or downwards within a solution due to density differences. Ostwald ripening involves the enlargement of larger droplets at the expense of smaller ones. These processes may occur concurrently; however, they are suppressed by adequate electrostatic and steric stabilization, which are crucial for applications in drug delivery.

Coalescence refers to the process by which two or more small droplets in close proximity combine to form a single, larger droplet. This phenomenon occurs as droplets move closer together and undergo deformation, resulting in the creation of a thin film of the continuous phase. The thinning of this film is influenced by the flow of the continuous phase and the surfactant present along the film's surface. Variations in the film's thickness can result in rupture when it reaches a critical thinness (Dickinson & Miller, 2001; Ivanov, Danov, & Kralchevsky, 1999). The thinning of the film is often explained by the Marangoni effect, which describes the mass transfer along an interface due to gradients in interfacial tension (Mackay & Mason, 1961). When the droplets merge, the overall surface area decreases, which in turn reduces the interfacial energy of the system and leads to a decrease in Gibbs free energy.

Flocculation refers to the process by which dispersed, intact droplets aggregate into clusters within a solution, with these clusters being separated by a thin film of the continuous phase. The presence of this film provides stability by hindering the coalescence of the emulsion through electrostatic repulsion. It is important to differentiate between stability against coalescence and stability against flocculation, as emulsions can easily flocculate and subsequently coalesce slowly, or the reverse may occur (Hubbard, 2002). The nature of flocculation can be either reversible or irreversible, contingent upon the strength of the attractive forces at play in the interaction. Once flocculation has taken place, the likelihood of coalescence increases due to the reduced distance between the droplets (Ivanov et al., 1999).

The phenomenon of creaming and sedimentation in emulsion droplets occurs when droplets with a different density than the dispersed phase migrate to either the top or bottom of the solution (Oprea & Grumezescu, 2017). This process, akin to flocculation, heightens the chances of droplet coalescence by increasing the likelihood of interactions among droplets. Effective management of this process is crucial for the food industry, which incurs significant costs annually, and can be mitigated through the incorporation of viscous polysaccharides (Robins, 2000). Additionally, creaming may result from the clustering of droplets into a larger floc network, which can happen spontaneously or be facilitated by polysaccharide bridging, leading to improved separation kinetics (Dickinson, Golding, & Povey, 1997; Robins, 2000).

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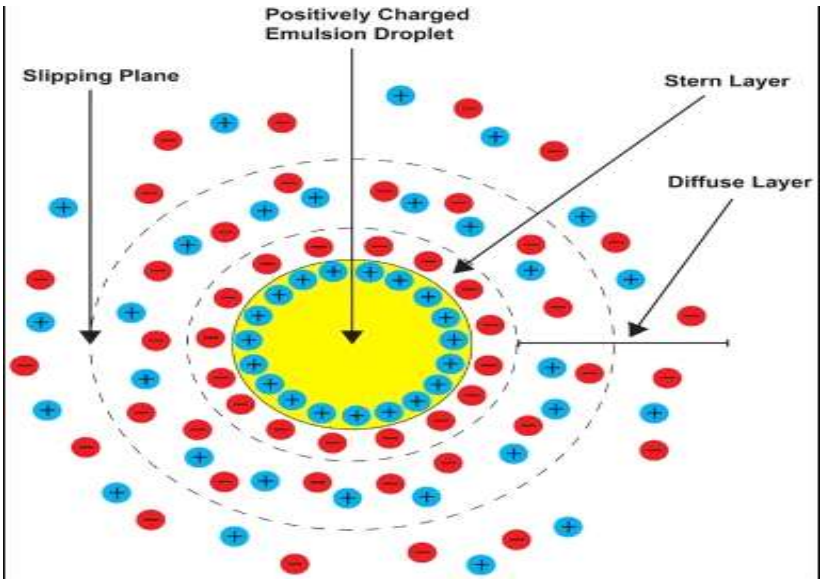
The DLVO theory posits that the stabilization of emulsions is facilitated through two distinct mechanisms that serve to repel or hinder the interaction between droplets, thereby diminishing the likelihood of destabilization. The first mechanism is electrostatic repulsion, wherein droplets with similar charges generate a repulsive force as they come near one another. The second mechanism is steric stabilization, which occurs when a dense surface layer obstructs droplet interactions, creating a significant energy barrier that prevents coalescence.

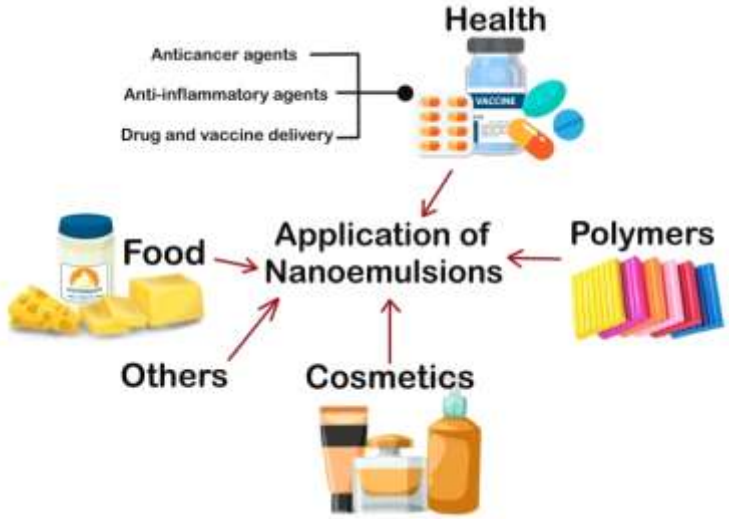


III. APPLICATION

Using nanoemulsions to deliver drugs Several drug delivery techniques, such as topical, ocular, intravenous, intamuscular, intranasal, and oral delivery, use nanoemulsions. They use their adjustable charge and rheology to produce aqueous solutions and their lipophilic nature to dissolve medications that are insoluble in water. Nanoemulsions are employed as ultrasound imaging agents and provide benefits for hydrophobic medications .

Verbal Transmission By loading drugs—especially protein drugs—into lipids, lipids can be employed as nanoemulsions to improve the absorption process overall and increase drug absorption in the GIT

Topical administration It is difficult to improve the penetration of medications for topical application because of their poor dispersibility and skin-irritating properties. Soybean lecithin, tween, and poloxamer are examples of nanoemulsions that combine a concentration gradient and improved penetration.



Cosmetics using nanoemulsion For optimal dispersion of active substances in skin layers and controlled cosmetic delivery, newer materials (NEs) are becoming more and more crucial. They facilitate skin penetration and are appropriate for carrying lipophilic substances, which raises the concentration of active ingredients. Additionally, NEs contain bioactive properties that improve the function of the skin barrier and decrease trans-

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epidermal water loss. Their lack of creaming, sedimentation, flocculation, and coalescence makes them suitable for use in cosmetics . To increase the efficacy of skincare products, TRI-K Industries and Kemira have created a new gel based on nanotechnology called Kemira NanoGel. By converting an oil-in-water concentration into submicron emulsions, the novel NE Carrier technology reduces trans epidermal water loss and increases skin formation. This technique gives skin a pleasant sensation and is very helpful in moisturizing, anti-aging, and sun care products.

IV. CONCLUSION

There are several advantages to using nano-emulsion for drug delivery. They have the potential to affect a number of industries, including biotechnology, cosmetics, and pharmaceuticals, because they may be utilized with almost any delivery mechanism. This novel method was developed to address the poor absorption and low miscibility of certain drugs with the lipid components of cell membranes. Traditional approaches to improving bioavailability are nearly unable to overcome the challenges posed by the growing number of insoluble medicines.In order to lay the foundation for many more successes in the field, this study reviewed the current methods and elements for successful nano-emulsion-based drug delivery. The literature offers ample evidence of the effectiveness of this approach in addressing current bioavailability issues. The applications of nano-emulsion are limited by its instability. The stability of the formulation can be increased by regulating several factors, such as the type and concentration of surfactant and co-surfactant, the kind of oil phase, the processes used, process variables, and the inclusion of additives throughout the interphases of the nano-emulsion formulation.

Nanoemulsions have garnered considerable attention over recent decades for a variety of applications, attributed to their distinctive structures and characteristics. They can be efficiently produced on a large scale through industrial techniques such as high-pressure homogenization and ultrasonication. Due to their diminutive size and the ability to incorporate components with varying degrees of hydrophobicity—such as hydrophobic drugs in the dispersed oil phase and hydrophilic proteins in the continuous aqueous phase—nanoemulsions hold significant promise in fields including food, cosmetics, and pharmaceuticals. For instance, they have been developed to facilitate the delivery of hydrophobic drugs and have served as adjuvants in vaccines, highlighting their clinical relevance. Following these clinical achievements, nanoemulsions are being further refined for advanced applications, such as immunotherapy and targeted therapy, by integrating multiple functionalities. This includes encapsulating drugs or imaging agents within the oil droplets and modifying the surface of the nanoemulsions with targeting ligands or antibodies to enhance targeted delivery and immunotherapeutic effects. Although many of these preclinical investigations are still in the nascent stages, a more systematic approach and a deeper understanding of the intricate interactions between nanoemulsions and biological systems—from cells to tissues and organs—will facilitate the advancement of their practical clinical applications.

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