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# A review article: Drug delivery systems, preparation techniques, and biological applications using nanoemulsion as a novel platform

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**ABSTRACT**

Nanotechnology, particularly nanoemulsions (NEs), is an essential topic that has piqued the interest of researchers over the years. These significant molecules feature a spherical solid structure, a lipophilic amorphous negative charge surface, with small droplet size, and a large surface area, all of which contribute to the promising future of nanomedicine and the importance of NEs in a variety of sectors. The advantages and disadvantages of the components, preparation, characterization, assessment, and applications as a delivery medication system are summarized in this review paper. There are two different methods for NEs preparation: the high and low energy methods. In high energy methods, high-pressure homogenization, ultrasonication micro fluidization, and Spontaneous emulsification are described thoroughly. Low energy approaches emphasize phase inversion temperature, solvent evaporation technology, and hydrogel technologies. Low-energy procedures should be preferred over high-energy methods since they utilize less energy and do not necessitate the use of specific instruments. The transdermal application, aerosolized, ingestible NEs, and parenteral techniques are the four primary lines of biomedical uses of NEs as a delivery strategy. To summarize, these novel strategies are very promising, but additional research is needed to fully understand the relationship between NE formulation and physiological and pathological problems associated with diverse preparation, characterization, and administration routes.

## INTRODUCTION

The majority of newly invented medications have an issue with poor solubility, which leads to poor drug absorption[1]. Also, owing to their weak solubility in water, poor bioavailability, poor stability, poor metabolism, poor active efflux mechanism, and first-pass metabolic effects, the therapeutic effectiveness of naturally available potential natural plant products is restricted [1,2]. This serves as a roadmap for the development of various medication delivery systems. On the other hand, many medications are difficult to transport effectively and efficiently to various body areas using traditional drug delivery methods. As a result, a variety of ways have been used to improve drug solubility, sustainability, bioavailability, and permeability[3].

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In this regard, developed innovative drug delivery systems and carriers for medications should ideally achieve some conditions, such as proper drug distribution at a rate oriented by the body's needs, over the course of treatment, and passing the active component of the drug to the site of action[4]. The bioactivity of weakly water-soluble medications can be considerably increased by putting them into various emulsion-based delivery systems, according to pharmaceutical industry research[5].

The use of novel drug delivery technologies, such as nanocarrier delivery, to overcome phytochemicals' physicochemical and pharmacokinetic limitations improved the controlled release and even efficacy of bioactivities. This breakthrough demonstrates nanomedicine's bright future as a potential option for overcoming and managing a variety of chronic conditions[6]. Nanoemulsions are colloidal particle systems that operate as therapeutic drug carriers. NEs have a droplet size range of 20 to 500 nm [7-9].These

crucial molecules have a solid spherical form with a lipophilic amorphous negative charge surface [10]. Nanotechnology and nanoscience are commonly regarded as having enormous potential to help a wide range of research and applications where poor solubility and complexity are problems. When nanoemulsions are utilized as a medication delivery mechanism, they increase the drug's therapeutic effectiveness while reducing side effects and toxic responses. Treatment of infections of the reticuloendothelial system (RES), vaccination[11], enzyme replacement therapy in the liver [12], and cancer treatment [13] are all examples of major enforcement. Antibiotics[11], DNA-encoded drugs, cosmetic and topical preparations are administered in a variety of methods, including pulmonary, oral, intranasal, and ocular[14]. Nanoemulsion is a thermodynamically unstable system, typically contains oil, water and an emulsifier . An emulsifier is necessary for the formation of tiny droplets because it reduces the interfacial between the oil and water phases of the emulsion and stabilizes it [15].

Surfactants are commonly utilized as emulsifiers, however proteins and lipids have also been found to be useful in the creation of nanoemulsions [16]. The dispersed phase, also known as the discontinuous phase, is the internal phase, whereas the dispersion medium, external phase, or continuous phase is the name of the outer phase. The emulsifying agent is also known as intermediate or interphase. There are three kindes of nanoemulsion which can be formed, as follows: (a) oil in water nanoemulsion in which oil is dispersed in the continuous aqueous phase, (b) water in oil nanoemulsion in which water droplets are dispersed in continuous oil phase, and (c) bi-continuous nanoemulsions. Nanoemulsions are transparent because of their small size[10]. The focus of research over the last decade or so has been on preparing nanoemulsions using a variety of methods, which can be divided into two categories: high-energy and low-energy methods [17]. To make small droplets, high-energy methods such as high-pressure homogenization (HPH) and ultrasonication15 use a lot of energy (B108 1010 W kg_1). Low-energy methods, on the other hand, take advantage of specific system properties [8]. Our review begins with a discussion of the basic science of NEs formulation and its relation to medical applications, followed by a discussion of its benefits and drawbacks, method of preparation, and critically discussed therapeutic routes to improve drug bioavailability into body organs and systems.

**Advantages of Nanoemulsion**

1-Because nanoemulsion improves drug bioavailability, it could be used as a substitute for liposomes, which are small artificial vesicles with a spherical shape made from cholesterol and natural nontoxic phospholipids and used for drug delivery [18].
2- Nanoemulsions are kinetically stable [7].
3- Because of their larger surface area, they have a higher absorption ratio.
4-Increaze bioavailability of functional compounds [19].
5- It does not have any toxicity and irritability [20].
6- It can be used for the skin and mucous membranes externally, and if the formula contains surfactants, it can also be taken orally.
7- Nanoemulsions are suitable for human and veterinary therapeutic study because they do not harm healthful human and animal cells.
8- It provides preferable uptake of oil-soluble complement in tissue culture techniques [21,22].
9- It is easy to formulate in different forms like foams, creams, and sprays, liquids [23].
10- It helps to solubilize lipophilic drug.
11- it is useful in taste masking.
12- A little amount of energy is required for preparation [10].
13-Nanoemulsions can transfer both hydrophilic and lipophilic compounds [14].
14- Fast and effective penetration of the drug molecule.
15- Ameliorate the effectiveness of a drug by reducing the total dosage and thus reducing side effects.

**Disadvantages of Nanoemulsion**

1. To stabilize the nanodroplets large amounts of surfactant and cosurfactants must be used.
2. Restricted solubilizing capability for high melting substances.
3. PH and temperature have great effects on nanoemulsion stability [24].

4-Instability of nanoemulsion due to Oswald ripening effect.

5-Requires expensive special application techniques, such as high pressure homogenizers as well as ultrasonic and expensive equipment such as the Microfluidiser

6- The advantages of using nanoemulsions over macroemulsions have not been proven [25, 9].

**The main components of nanoemulsion**

As shown in the table, a nanoemulsion is made up of oil, emulsifier, and aqueous phases [1]. Any sort of oil, such as corn oil, castor oil, coconut oil, and so on, can be used. When water and oil are mixed together, a crude transient emulsion is formed, which separates into two phases due to the coalescence of scattered globules. It is critical to achieve a high total droplet surface area/volume [27], by overcoming interfacial tension between nanoemulsion liquid components and producing very small molecules [17]. Emulsifying agents, often known as surfactants, are soluble in both fat and water and enable fat to be uniformly distributed in water. Examples include tweens and spans, hydrophilic colloids such as acacia and alginic acid, and others. In addition to emulsifying properties, an emulsifier should be nontoxic and have a taste, odor, and chemical stability that is compatible with the finished product. The following are some of the most important characteristics of emulsifying agents:

(1) The ability to reduce the surface tension.

(2) In contrast to most microemulsion phases, it should be adsorbed quickly around dispersed phase globules and form a perfect and cohesive film to prevent coalescence. Usually, a short-range repellent interaction between surfactant-coated droplet interfaces inhibits droplet coalescence even over very long time periods, producing nanoemulsions long-lived metastable states [28].

(3) It should aid in the development of appropriate viscosity and zeta potential in the system in order to provide optimal stability.

(4) It should be usable even at low concentrations. Around the dispersed globules, emulsifying agents produce monomolecular, multimolecular, or particulate films [10].

**Table 1: Components of Nanoemulsions [29]**

| Components | Examples |
|---|---|
| oils | Corn oil, peanut oil ,coconut oil, evening prime rose oil, mineral oil, olive oil, linseed oil and castor oil. |
| Emulgents | Natural lecithins, castor oil derivatives and phospholipids. |
| Surfactants | Sterylamine ,polysorbates, polysorbate 80, polysorbate 20, castor oil, PEG300, caprylic glyceride , polyoxy 6o and sorbitan monooleate. |
| Co-surfactants | Ethanol, PEG300, glycerin, PEG400, polyene glycol and poloxamer. |
| Tonicity modifiers | Glycerol, xylitol and sorbitol. |
| Anti-oxidants | Ascorbic acid and tocopherol |
| Additives | Lower alocohol (ethanol), 1,3-butylenes glycol, propyelene glycol, , glucose, fructose, maltose and sucrose. |

**Nanoemulsion preparation methods**

Nanoemulsions are typically prepared using one of two methods: (a) high energy procedure and (b) low energy procedure [8]. High-pressure homogenization, ultrasonic emulsification, high-energy stirring, microfluidization, and membrane emulsification are all examples of high-energy emulsification methods [30]. The low-energy emulsification techniques include Emulsion inversion point, phase inversion temperature, spontaneous emulsification Solvent Evaporation Technique, and hydrogel method [31]. It is possible to combine an approach that combines high-energy and low-energy emulsification to prepare reverse nanoemulsion in a very viscous solution [8&10] figure (1).

**High-energy emulsification method**

**1-High Pressure Homogenization**

The high pressure homogenization process is the most widely utilized approach for nanoemulsion preparation. The piston homogenizer (Figure 1) is used in this process to generate nanoemulsions. The macroemulsion is forced to flow through a tiny aperture at a pressure of 500 -5000 psi during the procedure [32]. Several factors, such as severe turbulence, hydraulic shear, and cavitation, combine in the process to produce nanoemulsions with very small droplet sizes. This method can be repeated until the final product reaches

the desired droplet size [25]. Producing small droplets in the submicron range necessitates a significant amount of energy. During the high-pressure homogenization process, a considerable amount of energy combined with rising temperatures may cause component impairment [32]. Proteins, nucleic acids, and enzymes, for example, may deteriorate [29].

**2-Ultrasonication**

Because ultrasonic is particularly effective in lowering droplet size, it was one of the initial applications in producing emulsion more than fifty years ago. The sonicator probe is used to deliver energy in this manner. It includes a piezoelectric quartz crystal that expands and contracts in response to changing electric energy. When the sonicator's tip makes contact with the liquid mixture, mechanical vibration and cavitation ensue. Cavitation occurs when rapid pressure changes cause the creation and collapse of vapour cavities in a liquid. When these cavities collapse, intense shock waves propagate throughout the solution in close proximity to the tip's radiating face, breaking the distributed droplets. As a result, ultrasonography may be utilized to create emulsions with droplet sizes as small as 0.2 micrometers in seconds [29&10]. The emulsion was subedit to fix the composition before being agitated at an ultrasonic frequency of 20 kHz per layer, which caused the droplet to break into nano droplets. To avoid damaging the proteins, enzymes, or nucleic acids in the emulsion, the temperature must be regulated and maintained using cold water or an ice jacket. This process can only be used to make small batches of nanoemulsions [11&33].

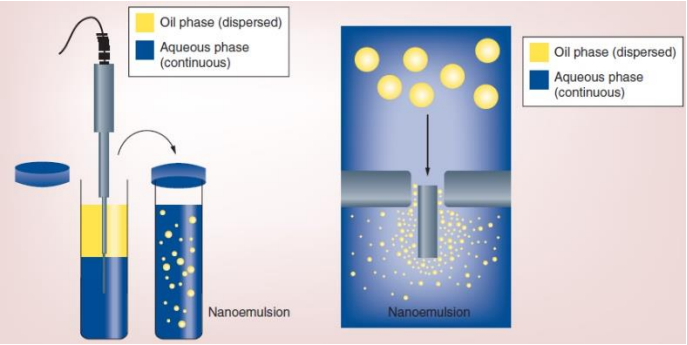


**Figure 1. The common techniques used for the formulation of nanoemulsions [34].**

**3-Micro fluidization**

Micro-fluidization is a beneficial mixing technique that employs the usage of a microfluidizer. Using a high-pressure positive displacement pump, a rapidly flowing stream of premixed emulsion is pushed through stainless steel microchannels (100) to induce strong dimensional flow (500-20,000psi). to obtain the desired particle size the coarse emulsion is repeatedly pushed through the interaction chamber micro-fluidizer. After that to produce a homogenous nanoemulsion the emulsion should be purified from big droplets by filtration under nitrogen [9, 10, &29].

**4-Spontaneous emulsification**

It involves these steps:

(a) Production of homogeneous organic solution composed of lipophilic surfactant with oil and in water-miscible solvent and hydrophilic surfactant, (b) Under continuous magnetic stirring, the aqueous phase has been injected by the organic phase, forming an o/w emulsion, (c) the aqueous phase is removed by vaporization under decreased pressure [34].

**2-Low energy method**

Low-energy emulsification methods are becoming increasingly important for micro/ nanoemulsion preparations due to the demand for high-level energy and expenses. Low-energy emulsification processes rely on the system's intrinsic chemical energy and require less energy, as seen in Figure (2).

**1-Phase inversion method**

Fine dispersion is made possible by the chemical energy released during phase transitions during emulsification. The appropriate phase transitions are created by varying the composition at constant temperature while keeping the alternate parameter constant, or by changing the temperature at constant composition while keeping the alternate parameter constant. The theory behind phase inversion temperature (PIT) is that the solubility of polyoxyethylene-type surfactants vary with temperature. Because the polymer chain dehydrates as the temperature rises, this surfactant becomes lipophilic. Surfactant monolayers have a large positive spontaneous curvature at low temperatures, generating an oil-swollen micellar solution phase [23&30].

**2- Solvent Evaporation Technique**

This procedure entails making a drug solution and then emulsifying it in a non-solvent liquid for the drug.

Deposition of the medication occurs as the solvent evaporates. A high-speed stirrer can be used to control crystal formation and particle aggregation [35].

**3. Hydrogel Method**

It works in the same way as the solvent evaporation method. The drug solvent is miscible with the drug anti-solvent, which is the only difference between the two procedures. Crystal growth and Ostwald ripening are inhibited by higher shear forces [30].

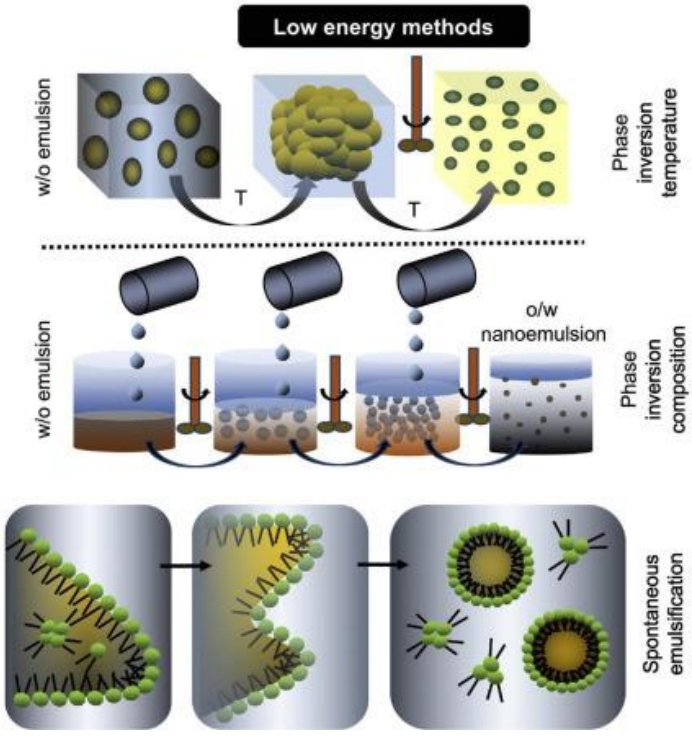


**Figure (2): Schematic representation of preparation of nanoemulsion by low-energy methods [36].**

**Factors to be considered during nanoemulsion preparation**

1- Surfactant selection is critical since it is the most significant component of the nanoemulsion, allowing for ultralow interfacial tension, which is a prerequisite for producing nanoemulsion. They are not supposed to create lyotropic liquid crystalline "micro-emulsions" phases. The phases that are most commonly utilized with the co surfactant include systems containing short chain alkanes, alcohols, water, and surfactants.

2- To make nanoemulsion, the concentration of surfactant must be high enough to set the microdroplets. Excess surfactants prevent induced coalescence by allowing fresh surface area of nanoscale to be fastly covered during the process of emulsification[37] .

3-The surfactant must be resilient or liquid enough to support the formulation of nanoemulsion.

4-Finally, for Oswald ripening to be avoided, the dispersed phase must be extremely insoluble in the dispersion media [10&37].

**Characterization and Evaluation of Nanoemulsion**

Nanoemulsion droplet size analysis, transmission electron microscopy(TEM), viscosity determination, refractive index, *in vitro* skin permeation studies, [12], skin irritation test, *in vivo* efficacy study ,surface characteristics and thermodynamic stability studies are among the parameters used to characterize nanoemulsions [23] .

**1-Stability of Nanoemulsions**

Because of the small droplet size and vast surface area of nanoemulsion systems, stability is one of the most critical factors, and this is influenced significantly by the surface charge of the droplets. Because of the Brownian motion, the small droplet size of nanoemulsions provides stability against sedimentation or creaming, and as a result, the diffusion rate is higher than the sedimentation rate generated by gravity force [38]. The nanoemulsion is tested for stability by storing it in the refrigerator and at room temperature for several months. During this period of storage, their viscosity, refractive index, and droplet size are measured to get a good understanding of their stability, and negligible variations in these characteristics indicate formulation stability. Nanoemulsion formulations are stored at elevated temperatures for this purpose, and samples are taken and examined at regular intervals [39]. At each time interval, the amount of medication degraded and remaining in the nanoemulsion formulation is determined [25]. The main process for nanoemulsion instability is ostwald ripening or molecular diffusion, which is caused by emulsion polydispersity and the differential in solubility between tiny and big droplets [38]. The lack of an internal phase, sedimentation, creaming, and maintaining protection against microbial contamination, as well as the preservation of appearance, color, odour, and consistency, are all characteristics of nanoemulsion

stability [40]. As a result, emulsion instability can be categorised as follows:

**2-Flocculation and creaming**

The process of clumping of tiny particles and globules together to produce large clumps that settle so quickly in the emulsion faster than individual globules is named flocculation. Creaming is the process of causing dispersed globules to rise up to form a concentrated layer. Creaming is the result of flocculation. In general, nanoemulsions have better shelf stability when it comes to gravitational creaming. When the intensity of the droplets and the medium are not similar, sedimentation occurs, as seen below: Creaming happens if the density of the medium is more than that of the disperse phase, however, there is no creaming if the intensity of the disperse phase is greater than that of the medium.

**3-Cracking**

Cracking is the separation of the dispersed phase of a nanoemulsion as a layer. While a creamed emulsion can be rebuilt by shaking or agitation, this process is irreversible and indicates persistent instability. The following factors can cause emulsion cracking: (1) addition of unsuitable emulsifier, (2) emulsifier decomposition or precipitation, (3) addition of a common solvent in which both oily and aqueous phases are miscible, (4) extremes of temperature cold or hot, (5) microorganisms contamination, (6) creaming [41].

**4-Diversified instability**

When stored at excessively high or low temperatures or in the presence of light, light and temperature have a significant impact on nanoemulsion and can cause it to deteriorate. As a result, emulsions are often packaged in airtight, colored containers and kept at room temperature [10].

**5-Phase inversion**

It is the conversion of an o/w emulsion to a w/o emulsion and vice versa. It is the result of a physical process. Variations in the phase volume ratio, the addition of electrolytes, and temperature variations can all cause phase inversion [10].

**Applications of Nanoemulsions**

Drug formulations have a number of drawbacks, but nanoemulsion has the ability to mitigate and overcome many of them. Nanoemulsions improve the wettability and/or solubility of poorly water-soluble medicines. As a result, alternative routes of administration increase their pharmacokinetics and pharmacodynamics. The droplets work as a reservoir of pharmaceuticals when they are associated with the optimal nanodroplet size or even when they are mixed with the vital elements, allowing nanoemulsion to be a multipurpose podium to treat numerous disorders. In recent years, a variety of essential characteristics of nanoemulsions have been described, including effective drug liberation at an acceptable pace, drug uptake control, longer activity, reduced side effects, and drug protective capabilities against enzymatic or oxidative operations. Surfactants, liquid lipids, and even drug conjugates contributed to nanoemulsion's great flexibility. These properties open up new possibilities for developing nanoemulsions with broad-spectrum applications [42]. Topical, ocular intravenous, intranasal, and oral drug administration are all possible with nanoemulsion. The lyphophilic characteristic of nanoemulsions is used in these applications to solvate water-insoluble drugs. The nanoemulsion's small droplet size reduces the impact of gravitational force on the droplets and controls and diminishes both the creaming and sedimentation processes of the emulsion, preventing coalescence and then surface fluctuation, stability, and tunable charge to produce aqueous solutions that can be easily delivered to patients [29].

**1-Transdermal Delivery of NEs**

arkinson's and Alzheimer's illnesses, cardiovascular ailments, depression, anxiety, cancer, and other diseases and disorders have all been treated with transdermal medicinal treatments. The epidermal barrier, which is required for good penetration of the bioactive, is, nevertheless, a significant disadvantage that limits the utilization of this route of administration. Drugs can predominantly permeate the skin by three routes: hair follicles, sweat ducts, or directly across the stratum corneum, all of which restrict their absorption and limit their bioavailability [43].The low viscosity of NE, as well as the presence of an aqueous part in the formulation, contributed to the drug's effective passage through the SC. When researchers compared their NE to a gel formulation, they noticed the effects of viscosity, hypothesizing that low viscosity, when combined with

other characteristics such droplet size, would result in a more effective NE, it also increases the surface area in touch with the skin, allowing for easier penetration [44]. The principal skin barriers must be controlled in order to acquire better results from drug pharmacokinetics and targeting. Controlling and improving the redistribution of locally applied drugs through the cutaneous blood and lymphatic system is also critical. The dispersed phase of O/W nanoemulsions permits improved solubility of lipophilic medicines in the oil phase, while the continuous phase provides a gentle, skin-friendly environment that can dissolve biopolymers such as alginate for modifying the formulation rheology, appearance, and texture [43]. By analyzing the amount of the lipophilic substance _-caryophyllene, scientists evaluated the difference in penetration profile between copaiba oil NE with Tween 20 as the surfactant and the oil alone. When copaiba oil was applied alone, penetration and retention investigations revealed that the lipophilic substance was only discovered in the Stratum corneum layer, failing to enter into the epidermis and dermis, while the copaiba oil NE was successfully identified in the stratum corneum, epidermis, and dermis, suggesting NE's natural capacity to penetrate and retain in skin layers more efficiently than the medication alone[45]. Despite the fact that follicular delivery is not a common route for hydrophobic compounds, when synthesized in o/w NEs, such medications collect near hair follicles [46]. To investigate skin penetration, a fluorescent dye (Nile red, 0.1 percent w/w) was added to a capsaicin o/w NE. Capsaicin is a lipid-soluble active element having a variety of therapeutic applications, including cancer treatment, inflammation, and cardiovascular system (CVS) illness treatment. It would be critical to be able to give capsaicin while avoiding the effects of its first pass effect. Deep permeation of the tailored NE through pig skin layers was observed. The tested NE demonstrated red fluorescence deep into the dermis, reaching up to 700 _m, with strong fluorescence intensity across all skin layers. Near the hair follicles, the brightest fluorescent area was discovered. Through the hair follicle, capsaicin o/w NEs can easily permeate and accumulate in the skin [47]. The binding of a positively charged NE to negatively charged skin has been described as a contentious mechanism, with some researchers attributing increased drug accumulation and retention in skin layers, and hence a reduction in permeability, to this mechanism. The permeation of lipophilic permeants has been reported to be improved by hydrating the skin and dilation of the SC intercellular aqueous and lipid channels. Furthermore, despite the well-known facts that oily medications pass through the lipid pathway and that the area of the pore pathway is disregarded, altering the permeation pathway of lipophilic permeants to follicular delivery utilizing o/w NEs was described. [46]. A large number of research have focused on the use of NEs for topical medication delivery [48]. It demonstrates the benefit of continuous state controlled drug delivery over a long length of time, as well as the possibility of self-administration, which may not be available with the parenteral route. The patient can turn off the drug delivery at any time by removing the transdermal patch. The medication has a nice skin feel thanks to the nanoemulsion's transparent nature and fluidity. It's also seen as a promising technology because of its long-term stability, low elaboration costs, thermodynamic stability, lack of organic solvents, and strong output practicality. They were also able to boost the drug's blood concentration and bioavailability while avoiding gastrointestinal side effects such as irritation and bowel ulcers [43 &25].

**2-Aerosolized NEs**

Because of its huge surface area for local drug interaction and absorption, low enzymatic activity, accessible vasculature, avoidance of first-path metabolism, and weak epithelial barrier, the lung is the most essential target for drug administration. For the treatment of respiratory illnesses, rapid and quick delivery to the site of action offers a bright future for establishing new routes in the treatment of a variety of respiratory diseases [49]. Many nanocarriers, such as emulsions, liposomes, and solid nanoparticles, have been refined for various respiratory disorders in recent years, and some have received clinical permission to enter the pharmaceutical market. Alveofact R is a liposome formula that was approved in 1980 as a synthetic lung surfactant, demonstrating the potential of lipid-based nanoparticles to operate as surfactants. Its primary purpose is to prevent or cure respiratory distress syndrome in premature newborns with undeveloped lungs [50]. Nanoemulsions achieve a relatively uniform

drug dose distribution among alveoli, improved drug solubility from its own aqueous solubility, and sustained drug liberation, which decreases dosing recurrence, improves patient compliance, reduces side effects, and the possibility for drug internalization by cells [9]. There are only a few published studies that show how NEs can be used to deliver drugs into the lungs. When compared to suspensions, NEs have a high aerosolization act following nebulization because they operate as solutions with a large fine particle fraction (FPF). When compared to the commercially available suspension-based budesonide, Pulmecort Respules [51], the nanoemulsification of budesonide demonstrated a considerable improvement in aerosolization capacity. Ibuprofen O/W NE mists have also been utilized to treat inflammatory illnesses such as asthma [50]. To guard against Mycobacterium tuberculosis, electrostatic interaction was exploited to prepare NEs as a carrier for oligonucleotides (pulmonary immunization). The pulmonary immunization was done utilizing cationic submicron emulsions to transfer DNA to the lungs [51]. Cyclosporine A (CsA) has been utilized as an anti-inflammatory (asthma and other respiratory inflammations), antifungal, and antiparasitic medication, but it is not widely used in clinical practice due to its poor solubility and oral absorption [52].However, when CsA dry emulsions (lipid-based powder) were coupled with a lactose carrier, the dissolving behavior of CsA was improved by 4500-fold, resulting in a dispersion suited for inhalation therapy [53]. In 2014, Nesamony et al. produced an O/W nanoemulsion that may be inhaled to transport water-insoluble materials into the lungs. The formulations were tested in vitro for cytotoxicity using NIH 3T3 cells, and ibuprofen was employed to determine the formulation's ability to deliver a weakly water-soluble medication [54]. Drug delivery system by intranasal route has now been established as a credible alternative to parenteral and oral drug administration. The nasal mucosa has shown to be a therapeutically useful conduit for the delivery of systemic medicines, as well as a convenient means to circumvent the barriers to direct drug entrance to the target site [55]. This approach is mostly used to treat nasal and paranasal sinus ailments, such as nasal congestion, infections, and sinusitis [56]. This method is also painless, non-invasive, and long-lasting. Reduced enzymatic activity, increased imminoactive sites, and moderate permeability properties of epithelial tissue make this pathway important [57]. That biocompatible o/w nanoemulsions and nanoemulsion-based hydrogels produced and structurally described as carriers of lipophilic chemicals could be used to deliver vitamin D3 and curcumin. These nanoemulsions and nanoemulsion-based gels have the potential to be a viable option for intranasal administration of a variety of lipophilic bioactive molecules [58]. There are several issues with targeting drugs to the brain; however, the nasal route is another alternative strategy for the treatment of CNS disorders. Drugs' hydrophilic properties and high molecular weight, as well as the blood brain barrier, reduce drug viability in the brain. However, the olfactory pits of the nasal cavity are considered an immediate route and connection between brain and nose. By employing nanoemulsions laden pharmaceuticals, scientists have been able to cure a variety of diseases and conditions such as Alzheimer's disease, migraine, depression, schizophrenia, Parkinson's disease, meningitis, and others [59]. For sustained effect, Bhanusha-Liet al developed intranasal nanoemulsion and gel formulations for rizatriptan benzoate. Thermo-triggered muco adhesive nanoemulsions were created using a variety of mucoadhesive agents [9]. Another benefit of this method over parenteral and oral administration is that it bypasses the liver. Nanoemulsions improve drug absorption by solubilizing the drug in the emulsions inner phase and extending the contact period between nanoemulsion droplets and the epithelium of the nasal cavity. Examples include the incorporation of a lipid-soluble renin inhibitor into an O/W emulsion, as well as the delivery of insulin and testosterone [38]. The bioavailability of the highly lipophilic calcium channel blocker nitrendipine, which is used to treat hypertension, was improved in a NE formulation and administered through the nasal cavity [60]. Nanoemulsion is currently being employed for vaccination via an intranasal drug delivery system, which is a critical application since it enhances nanocarrier contact with nasal mucosae and directs antigen to lymphoid tissues [9]. The first applications, an HIV vaccine and an influenza vaccine. The nanoemulsion aids the absorption of antigen-presenting cells in the applied protein's nasal cavity. Animal trials were utilized in additional research to

prove various vaccines, such as Hepatitis B and anthrax20, and intranasally immunizing mice and guinea pigs with recombinant HIV gp120 antigen combined in nanoemulsion resulted in robust serum anti-gp120 IgG[23]. As a result, using NE in the systemic distribution of hydrophobic medicines via the nasal route could be a viable strategy to avoid some of the drawbacks of intravenous injections [7].

**3- Parenteral Delivery /Injectable NEs**

Because infusing pure oil at 1-g olive oil/kg into the circulation as a nutritional source is lethal, the first trial of intravenous administration of olive oil to a dog in the 17th century resulted in embolism and death. Intralipid, Europe's first safe lipid-based intravenous nutritional nanoemulsion, was approved in 1962 [61]. Intralipid injections of essential fatty acids are still marketed and used for calories in patients who are malnourished or sick. It's made up of % phospholipids from egg yolks, 20% soybean oil, 2.25 % glycerin, and water. Even though Intralipid was approved and marketed for therapeutic use, hypersensitivity has been reported in a small percentage of patients who are allergic to egg and soybean protein [62]. Many uses of NEs have been studied, with cancer diagnostics and therapy being a significant target for the utilization of drug-delivery systems because Nanoemulsion formulation is efficient and non-harmful. Nanoemulsion particles must have a droplet size of less than 1 micrometer for intravenous administration, and nanoemulsion has this benefit. Parenteral (or injectable) administration of nanoemulsion is used for a variety of purposes, including nutrition (fats, carbohydrates, vitamins, and so on) [63]. Lipid nanoemulsions have been extensively studied for drug delivery via parenteral injection, and both O/W and W/O nanoemulsions can be employed for this purpose. However, nanoemulsions are removed more slowly and so have a longer residence time in the body [64].According to Khalil's findings, the formation of NE composed of 10% oleic acid with an infinite dilution capacity and a high surfactant to cosurfactant ratio (3: 1) is critical for improving the solubilization capacity of a potent antitumor benzimidazole derivative, a poorly water-soluble active ingredient that is suitable intravenous delivery system [65].

**4- Ingestible NEs**

Because Nanoemulsions contain very small droplets (r 100 nm), they can considerably increase the bioavailability of encapsulated lipophilic compounds, they have various applications in the food, beverage, and pharmaceutical industries as delivery methods. It's crucial to think about particle features like size and interfacial properties, which have a big impact on how nanoemulsions behave in the digestive tract. Several enzymes in the digestive system can break down and modify pharmaceutical medications, reducing their bioavailability, but integrating them into an oil matrix with the help of nanoemulsion can protect them from digestion [66]. There are also numerous other hurdles, such as pH changes and other GI tract contents, such as protein and lipids released from food, which might interact with orally delivered medications [67 ]. As a result, it is critical to protect ingested drugs from endogenous influences. By prolonged lodging in the GI tract and initiating intestinal lymphatic transportation, NE formulations can improve absorption and effectiveness of orally delivered drugs [68]. The interaction of lipophilic drugs with chylomicrons has the potential to stimulate the intestinal lymphatic route, which is critical for avoiding liver damage [69].Wang and his colleagues and Young and his team demonstrated that orally delivered curcumin-loaded NEs improved the anti-inflammatory impact of curcumin when compared to curcumin in a surfactant solution in an invivo study of orally administered curcumin-loaded NEs [70& 71]. Another example is the fact that primaquine-loaded NEs have better antimalarial activity when given orally at a 25% lower dose than free primaquine [72]. Another study found that using a nanoemulsion as a drug delivery technology is a viable option for alternative docetaxel therapy [73]. There are several considerations and barriers to overcome in order to improve the therapeutic usage of NE as a drug delivery mechanism [7].A recent comparative research of Vitamin D (VD) and VD nanoemulsion administration to Vitamin D deficient male albinos found that the VD nanoemulsion treatment resulted in a significant rise in testicular levels of GSHPX, CAT, and SOD, as well as a decrease in MDA. VD nanoemulsion

was found to be more effective than VD supplementation alone [74&75].

Table below shows several types of drugs naoemulsion that used to perform several purposes as treatments.

**Table 2: Examples of parenteral nanoemulsions [30 ]**

| Drugs | Dispersed phase | surfactant | purpose |
|---|---|---|---|
| Carbamazepine | Castor oil, MCT | Soy lecithin, Polyoxyl 35, castor oil, Tween 80 | increase solubility |
| Docetaxel | Stearyl amine and Oleic acid, | Egg lecithin | Poor solubility, hydrolytic instability, and drug-induced side effects |
| Thalidomide | Castor oil, soyabean oil MCT and olive oil. | Twee 80 | Control poor solubility |
| Primaquine | Miglylol 812 | Pluronic F68 | Dose reduction, reduced toxicity and improved bioavailability, |
| Insulin | Self assembling Protein complex | Poly vinyl alcohol | Protection against enzymatic degradation |
| Fisetin | Miglylol 812, soybean oil, ethyl oleate | Labrasol, Lipoid E80 | Improved pharmacokinetics and anti- tumor activity |
| Paclitaxel and Sulforhodamine B | Vitamin E | TPGS | Long circulation half lives increase Theranostic capability |
| Clotrimazole | Soybean oil | Pluronic F68, cremophor, Tween 20, tween 80 | Increased bioavailability |
| Paclitaxel and ceramide | Pine nut oil | Lipoid-80 | Increased cell absorption |

## Conclusion

Nanoemulsions are characterized by minuscule droplet sizes that must be in the submicron range. Despite the numerous limitations of NEs, their industrial development and production could be highly promising, providing a time-saving combination of NE preparation simplicity and the low cost of their constituents. Several factors must be taken into account, including the careful selection of ingredients, including emulsifiers and the oil phase, to address safety problems such as hypersensitivity. The ease of large-scale synthesis, storage, and stability must all be considered with the application in mind. The advancement of NE technologies will necessitate a thorough understanding of the link between NE formulation science and the many physiological difficulties that come with their use. Transdermal, aerosolized, parenteral, and ingestible NEs are some of the medicinal applications. Continued research into methods for developing ever more complex NEs is critical for enhancing the likelihood of clinical translation of NEs for a wide range of applications.

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# مستحلب النانو كمنصة جديدة لنظام توصيل الدواء وطرق التحضير والتطبيق الطبي الحيوي

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**الخلاصة:**

تعد تقنية النانو ، وخاصة مستحلبات النانو ، موضوعًا أساسيًا أثار اهتمام الباحثين على مر السنين. تتميز هذه الجزيئات المهمة ببنية صلبة كروية ، وسطح ذات شحنة سالبة غير متبلورة محبه للدهون ، و ذات حجم قطيرة صغير ، ومساحة كبيرة ، وكلها تساهم في المستقبل الواعد لطب النانو وأهميتها في مجموعة متنوعة من القطاعات. تم تلخيص مزايا وعيوب ومكونات مستحلبات النانو وكذلك تمت دراسة طرق التحضير والتوصيف والتقييم بالاضافه الى تطبيقاتها كنظام لتوصيل الدواء في ورقة المراجعة هذه. هناك طريقتان مختلفتان لتحضير مستحلبات النانو: طريقة الطاقة العالية و طريقة الطاقة المنخفضة. في طرق الطاقة العالية ، يتم وصف التجانس عالي الضغط ، والتسييل الدقيق بالموجات فوق الصوتية ، والاستحلاب التلقائي بدقة. تؤكد مناهج الطاقة المنخفضة على درجة حرارة انقلاب الطور ، وتكنولوجيا تبخير المذيبات ، وتقنيات الهيدروجيل. يجب تفضيل الإجراءات منخفضة الطاقة على الأساليب عالية الطاقة لأنها تستخدم طاقة أقل ولا تتطلب استخدام أدوات محددة. يعد التطبيق عبر الجلد والمستحلبات نانوية الرذاذة والمستحلبات النانوية القابلة للابتلاع والتقنيات الوريدية هي الخطوط الأساسية الاربعة للاستخدامات الطبية الحيوية لمستحلبات النانو كإستراتيجية توصيل. للتلخيص ، هذه الاستراتيجيات الجديدة واعدة للغاية ، ولكن هناك حاجة إلى مزيد من البحث لفهم العلاقة بين صياغة مستحلبات النانو والمشكلات الفسيولوجية والمرضية المرتبطة بالإعداد والتوصيف وطرق الإدارة المتنوعة.

**الكلمات المفتاحية**:المستحلب النانوي ، التوتر السطحي ، التوافر الحيوي ، المستحلبات نانوية عبر الجلد ، المستحلبات نانوية الرذاذة ، المستحلبات نانوية بالحقن والمستحلبات نانوية القابلة للابتلاع.