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Enhancing Drug Delivery with Nanoemulsion: Current Applications and Future Prospects

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KEYWORDS

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ABSTRACT:

Nanoemulsions are thermodynamically stable, isotropic entities made of two immiscible fluids came to form a single phase, which was then stabilised by emulsifying agents. With droplet sizes ranging from 20-200nm, NEs offer improved delivery of active pharmaceutical ingredients. An outline of the nanoemulsion formulation, preparation procedures, characterisation methods, assessment criteria, and applications is provided in this review. Various techniques, including Microfluidization, Phase Inversion Temperature, High-Pressure Homogenization, Ultrasonication, are discussed. The advantages of NEs, including improved bioavailability, targeted delivery, and stability, are highlighted. The uses of NEs in medicines, cosmetics, and biotechnology are also investigated. With an emphasis on current patents about nanoemulsion formulation, this research aims to present a thorough analysis of NEs, stressing their formulation features, recent developments, and the variety of possible applications for them across several sectors.

1. Introduction

Emulsions comprised of two liquids that are immiscible that combine using a surfactant to stabilise the tension between their surfaces and enables dispersion of single fluid droplet (dispersed phase) in second liquid's continuous phase **[1]**. When two liquids that are immiscible are combined, metastable colloidal formations called emulsions are created **[2]**. A colloidal dispersion with an interior phase and sizes of droplet range from 10nm to 200nm is called a nanoemulsion (NEs). A nano-sized oil droplet serves as interior phase of oil in water (O/W) NEs, where hydrophobic medications are dissolved and their bioavailability is boosted **[3]**. The word "nano" comes from the Greek word for "dwarf". A DNA molecule has a diameter of 2.5nm, a normal sheet of paper is 100,000nm thick, and a blood cell is between 2000 and 5000 nm in size. A nanometre is around 60,000 times smaller than an individual's hair or a virus**[4]**. A type of emulsion known as a nano-emulsion can be clear, translucent (50–200nm), or "milky" (500nm). Unlike microemulsions, which can be both transparent as well as thermodynamically stable, NEs are only kinetically stable. One characteristic that sets nano-emulsions apart is their long-term physical stability; they don't seem to flocculate or coalesce, which can be referred to as "approaching thermodynamic stability" **[5]**. Materials that break down in the dispersion phase can be encapsulated in NEs, which are extraordinarily versatile systems. While hydrophilic components are readily contained using inverse systems, hydrophobic components can often be conveniently encapsulated utilising direct systems (such as oil-in-water NEs) **[6]**. Because of its lower toxicity and capacity to greatly improve the bioavailability of medications, NEs appear to have garnered a lot of interest **[7]**.

The following types of NEs were supposed to occur according to the ingredients:

- NEs with oil droplets disseminated throughout the water phase, water in oil, and NEs containing oil

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droplets scattered throughout continuous oil phase **[8]**.

- Bicontinuous NEs include trace quantities of water and oil scattered throughout the structure.
- W/O/W, or Water in Oil in Water.
- O/W/O, which stands for Oil in Water in Oil **[9]**.

The process of creating a double emulsion usually involves two steps: first, an internal emulsion is created, and then the first emulsion is shadowed by the second emulsion. Because double emulsions require both hydrophilic and lipophilic surfactants to stabilize each oil-water contact, they provide extra stability and production challenges. Degradation and coalescence increase with the diffusion of each stage **[10].**

2. ADVANTAGE OF NANOEMULSION:

- Reduce absorption variability;
- Increase a lipophilic compound's solubility;
- Masking taste
- Administer medications through a diversity of routes, involving topical, oral, & intravenous
- Facilitated the rapid and efficient entry of medications through the skin and colon.
- Reduced drug degradation and loss
- Increased bioavailability
- Increased drug concentration in target areas
- Reduced toxic effects
- Versatility and flexibility
- Improved patient compliance, particularly for cosmetic reasons **[11,12]**.

3. DISADVANTAGE OF NANOEMULSION:

- Large volumes of surfactants and co-surfactants were required for stability.
- Environmental variables like temperature and pH affect NE stability.
- Only use nontoxic surfactants and co-surfactants.
- Limited ability to dissolve high-melting compounds. **[12]**

4. COMPONENTS OF NANOEMULSION:

4.1 Oils: Because it may solubilise lipophilic drug molecules and enhance absorption across lipid barriers, the oil phase is second most significant carrier afterward water **[13]**. Oil has a distinctive property of entering the cell membranes, making it excellent for lipophilic active delivery of drugs. Oil phase influences swelling of surfactant's tail group area. Short chain alkanes show better penetration than long chain alkanes **[14]**.

Components	Examples
Saturated fatty acids	Capric, Lauric, Myristic acid
Unsaturated fatty acids	Oleic acid, linoleic acid and linolenic acid
Fatty acid esters	Ethyl or methyl esters of lauric, myristic and oleic acid

4.2 Surfactants:

Surfactants are used to create thermally stable NEs, which encourage low interfacial tension, in contrast to emulsions that are micronized by external energy. A short-lived emulsion is created when water and oil combine. However, due to the coalescence that occurs among When allowed to stand, the scattered globules cause this mixture to split into two different phases **[15]**. NEs are made from well accepted, safe agent components and contain significant amounts of emulsifiers and surfactants **[16]**. Surfactants that can be of the following types:

Components	Examples
Non-ionic surfactant	Polyoxyl40, Polysorbate80, d-α-tocopherol polyethylene glycol1000succinateSolutol HS-15, Polysorbate20, Polyoxyl40 stearate, hydrogenated castor oil,
Anionic surfactant	Carboxylate groups, Soaps, Sulfo-nates, Divalent ions
Cationic surfactant	Amines, quaternary ammonium compounds

4.3 Cosurfactants:

Cosurfactants are used to improve surfactant performance. Because it has adverse effects at larger concentrations, it should only be used in smaller oils and lipids **[17]**. The surfactant film's stiffness is reduced, its flexibility is increased, and varied curvatures are adopted to create NEs across an expansive composition range **[18]**. Ethanol is one example of a short-chain co-

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surfactant that tends to prolong the NE area of the phase diagram. It functions as a hydro trope and considerably reduces the layer of surfactant tension between the water and oil phases **[19]**.

Components	Examples
Short chain glycols	Propylene Glycol
Medium chain alcohols	Acids or Amines
Short chain alcohols	Ethanol to Butanol

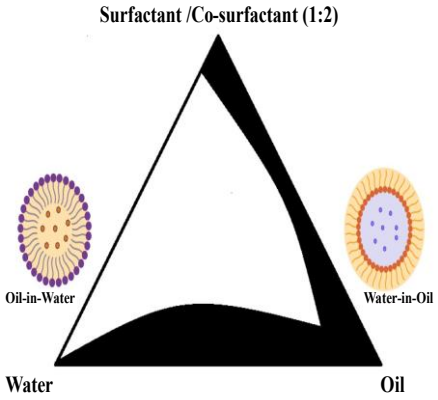
4.4 Aqueous: NEs stability is detected by characteristics of aqueous phase and droplet size, which include pH, ionic concentration, and electrolytes. Phosphate buffered saline, Ringer's Solution, plain water, imitating stomach fluid (pH 1.2), and simulating gastrointestinal fluid (pH 6.8) can all be used as aqueous phases to investigate spontaneous nanoemulsification of NEs. According to the previously described aqueous phase characteristics, when a medication whose solubility depends on pH is added to the system, the pH of the aqueous phase can have a substantial impact on the phase behaviour of NEs **[20]**.

5. FACTORS TO CONSIDER DURING NANOEMULSION PREPARATION

- Surfactants are carefully selected so that ultralow tension at the interface could be a achieved, which is a major need for producing NEs.
- Surfactant concentration needs to be sufficient to stabilise microdroplets and create nanoemulsion.
- The surfactant essential for sufficiently fluid or flexible to enable formation of NEs **[21]**.

6.TERNARY PLOT

The starting concentration of each of constituents is obtained utilising water titration technique at room temperature through creating pseudoternary diagrams **(Figure 1)** of phases in nanoemulsion system. To generate distinct phase diagrams, Numerous weight ratios for emulsifiers and coemulsifiers are employed. The phases in diagrams are carefully investigated by ranging the ratios of coemulsifier to emulsifier as well as emulsifier to coemulsifier. The proportions of oil to emulsifier and coemulsifier mixes are modified for each phase diagram in order to achieve a certain weight ratio of emulsifier to coemulsifier. Water is added drop by drop to oil, emulsifier, and coemulsifier mixes, which are lightly magnetically stirred. Visual observations are made on clear, freely flowing NEs. An artificial ternary phase diagram shows the phase of water on the initial axis, the oil phase on the second, and Smix (emulsifier/coemulsifier) with a predetermined weightiness ratio on the third axis. On the foundation for calculating and constructing pseudoternary phase diagrams, and, most importantly, describes how to select formulations from Phase diagrams for avoiding metastable formulations with the lowest surfactant level in shortest feasible period **[22,23,24,25]**.



(Fig 1): Pseudo ternary phase diagrams

7.METHOD OF PREPARATION:

7.1 High-Energy Methods

High-energy emulsification techniques practice a variety technique to produce extremely powerful mechanical power, resulting in NEs with small droplets. The highly disruptive force needed to separate the water and oil phases and create nanoscale droplets is provided by mechanical devices. NEs are commonly created via high-pressure homogenisers, microfluidizers, and ultrasonicators [**26]**.

7.1.1 High Pressure Homogenisation:

Utilising High-Pressure or piston homogeniser **(Figure 2)**, this approach produces NEs through extremely small sizes of particle (up to 1nm) **[27]**. Two types of liquid (oily & aqueous) can be distributed in a high-pressure homogeniser by driving the mixture via a tiny inlet hole at extremely elevated pressures (50-5000 psi) **[28]**. This makes it possible for the product to experience

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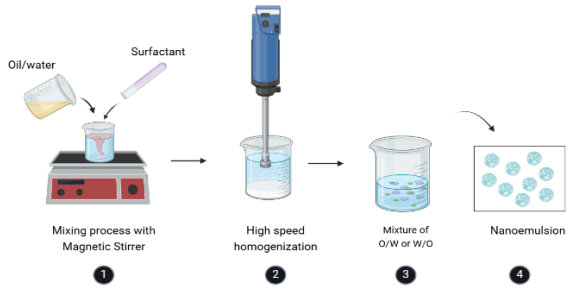
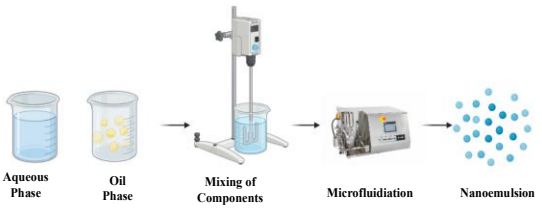
significant hydraulic stress and turbulence, producing very thin emulsion particles. Such devices are more efficient in reducing droplets size in current coarse emulsion than at forming a nanoemulsion by combining oil and water phases. The only disadvantages of this highly successful approach are its high energy utilizing and the emulsion's temperature elevate while processing **[29]**.



(Fig 2): High pressure homogenization for Nanoemulsion

7.1.2 Microfluidization:

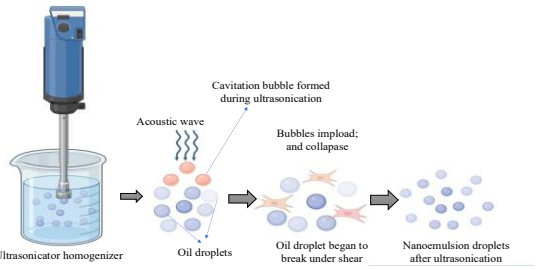
A mixing process that uses a microfluidizer is called micro fluidization **(Figure 3)**. The device utilises high pressure to force the medicinal product via its interaction chamber, generating a very tiny particle in the submicron range **[30]**. The technology is a proprietary microfluidizer-based mixing process. This device drives materials into the interaction chamber, that is made by microscopic networks known to be "microchannels" using a high-pressure pump through positive displacement (500–20,000 psi) **[31]**. High pressure is applied to force the coarse emulsion into an input channel, which is designed to divide it into two streams that quickly collide in an interaction chamber. An interaction chamber's powerful disruptive forces are particularly effective in dissolving droplets and creating microscopic emulsions **[32]**.



(Fig 3): Micro fluidization technique

7.1.3 Ultrasonication:

These devices work by forcing a sample that has to be homogenised via a tube that contains an element that may generate strong ultrasonic vibrations **(Figure 4).** Recently, several studies have examined the key factors affecting the sonication-based production of NEs **[33]**. Kentish and colleagues demonstrated the ability to create NEs from food-grade substances using high-frequency ultrasound **[34, 35]**. The narrow surface exposed the outside tension, resulting in fewer bubbles and increasing the rate of cavitation threshold force within an ultrasonic field. However, increasing the external strain causes a rise in the cavitation bubble's disruption tension. This device also uses a water cover to prevent temperature from rising above its optimal level **[36]**.



(Fig 4): Ultrasonication technique

7.2 Low-Energy Methods.

Low-energy ways of preparing NEs emerged much later than high-energy approaches. The key characteristics of these technologies are the creation of extremely small globules or droplets, as well as the use of minimal energy. These approaches rely on Emulsions undergo

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phase inversion in reaction to compositional or temperature changes **[37]**.

7.2.1 Phase inversion temperature method:

The phase inversion temperature (PIT) approach relies on a heat-sensitive non-ionic surfactant, especially polyethoxylated surfactants [38]. Using an intermediate bicontinuous phase, this form of phase inversion typically comprises a controlled change in emulsion type, that is, from W/O to O/W or vice versa. The PIT technique may be applied to change the temperature and time profiles of certain oil, water, and non-ionic surfactants and oil mixtures in order to create NEs. [37] Ostwald ripening is the most significant problem with this method. At the identical time, a change in composition generates an inversion of phase at fixed temperature by disrupting hydrophilic-lipophilic balance **[40]**.

7.2.2 Phase Inversion Composition (PIC)

Phase inversion composition (PIC) approach involves creating nanoemulsion that utilises phase inversion phenomenon by gradually diluting oil phase by water phase, or vice versa **[41]**. Phase inversion composition, or PIC, approach comparable to PIT technique, except their optimal curvature of surfactant is modified by adjusting systems composition rather than temperature **[42]**. An ionic surfactant-stabilized O/W emulsion, for instance, may phase invert into a W/O emulsion with the addition of salt. Because of the capacity of salt ions to screen electrical charges on surfactant head groups, the packing constraint rises from $p < 1$ to $po > 1$ **[43]**. When this compositional change is exceeded, the structures containing zero curvature split, resultant in the development of small metastable oil in water droplets **[44]**.

7.2.3 Membrane Emulsification

Membrane emulsification has received more attention in recent years. Membrane-based emulsification uses a microporous membrane to form the emulsion drop by drop. A microporous membrane's pores let the continuous state to traverse over its surface while the scattered phase passes through. The four basic elements that affect membrane surface droplet separation are shear (produced with continuous phase movements or membrane movements), tension among two emulsified liquids, buoyancy, and inertia/pressure via flow over membrane's surface. Droplets in the dispersion phase might be emulsions or pure liquids. It serves as an alternative to the shear-force emulsification process. This strategy, in contrast to other approaches (such as high-pressure homogenisation as well as ultrasonication), allows for the regulation of droplet dimension and homogeneity of size. This technique is effective for producing droplets of a specific size. One of the technique's disadvantages is the constrained dispersed phase flow through membrane, which becomes troublesome as the sample size increases **[45,46,47]**.

8.CHARACTERIZATION OF NANOEMULSION:

8.1 Zeta Potential:

The zeta potential and surface charge of various emulsions will be determined by electrophoretic translation of dispersed globules affected by the voltage of the zeta potentiometer. Utilising a cylinder-shaped drilled microelectrophoresis container equipped with platinum-iridium electrodes, the apparatus evaluates the electrophoretic mobility of diluted w/o/w emulsion **[48]** ±20mv is the optimal zeta potential. **[49]**

It is computed using the equation that follows **[50]**.

$\zeta = 4 \Pi \eta \mu / \varepsilon E$

Where ζ is the Zeta potential (mv)

η is the dispersion medium's viscosity (poise).

μ = Velocity of migration (cm/sec)

ε = The dispersion medium's dielectric constant

E stands for potential gradient, which is the voltage applied per electrode distance.

8.2 Particle size and polydispersity index:

Photon correlation spectroscopy (PCS), another name for dynamic light scattering (DLS), is used to study intensity changes in droplet/particle scattering brought on by Brownian motion **[51]**. PCS may examine NEs size of droplet, polydispersity, as well as zeta potential utilising particle size analyser. This instrument additionally calculates polydispersity index, by a cumulative study of dynamic light scattering is utilised to calculate width of

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the size distribution. A dispersion's homogeneity or purity is evaluated by the polydispersity index **[52]**. The z-average particle diameter is estimated via PCS. One unique method of figuring the particle size is laser diffraction.

8.3 Morphology Characterization of Nanoemulsion:

Morphology can be described with utilising an electron microscope or light scattering procedures. The neon laser utilized in the dynamic light-scattering spectrophotometer has a wavelength of 632 nm to detect dynamic light scattering at 90°. Data is processed by computer embedded into the gadget. Here's a full overview of a few popular microscopy techniques for determining morphology:

(1) Scanning electron microscopy (SEM):

SEM can Create high-resolution images of a sample material. SEM pictures having distinct 3D look and useful for determining surface structure **[53, 54]**. SEM is one of the most often utilised research tools nowadays due to its higher magnification, bigger field depth, greater resolution, & simplicity of sample observation. Also, because of limited Number of particle observations in the scanning zone, SEM necessitates limited evaluations of size distribution among numerous samples **[55]**.

(2) Transmission electron microscope (TEM):

The resolution of TEM technology is around 0.2 nm. It is commonly employed in research of materials for biological sciences & science/metallurgy; in both situations, The samples need to be very tiny and strong enough to endure high vacuum within apparatus. The structural and morphological features of NEs are further improved by TEM's outstanding three-dimensional resolution, where may be combined with a variety of analytical procedures. This strategy does, however, have several drawbacks. Certain materials require a significant amount of sample preparation, which includes TEM analysis, which is a laborious process with a limited sample throughput when the material is sufficiently thin to be electron transparent. **[56,57]**.

(3) Atomic force microscopy (AFM):

AFM is revolutionary method which being utilised for investigate size, shape, dispersion, sorption, and aggregation of NEs. AFM is a more recent microscopy technique. Direct observation of individual molecules or atoms as tiny as a few nanometers is possible thanks to AFM's exceptional resolution (±0.1 nm). AFM can be utilised to study properties of structural proteins, liposomes and polysaccharides. Some articles demonstrated the variances between NEs as well as Nano-capsules were created by analysing the structure, morphology, and mechanical characteristics of both the emulsion as well as capsule shells utilising AFM, and they discovered that the outer layer of a droplet of oil solidified with increasing amounts of polyelectrolytes.

8.4 Entrapment efficiency (EE):

EE is an evaluation of nanocarrier's capacity to hold onto a medication or active component while delivering an acceptable amount of constituent to the target location. The formulation technique, formulation component type, & nature of encapsulating bioactive component all significant elements that might affect EE are present in the vesicles. Furthermore, as active ingredient is loaded into the nanoemulsion, particle size continues to expand, lowering the nanoemulsion effective energy. A micro dialysis technique was effectively used to estimate EE for nanocapsules, nanospheres, and NEs **[61,62,63,64]**.

The following is the general equation used to calculate the EE:

EE = W1-W2/W1*100

Where;

W1 is quantity of formulation's active component,

W2 is supernatant's active component content **[65]**.

8.5 Viscosity Determination:

A viscometer is utilised to accomplish this. The amount of each of the surfactant, water, & oil components influence the viscosity of NEs. The tension among water and oil increases as amount of surfactant and cosurfactant is reduced whilst raising proportion of water content decreases viscosity. Viscosity is critical for medicine storage and release effectiveness. Furthermore,

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it is less oily than water-in-oil formulations, nanoemulsion carrier formulations often exhibit reduced viscosities since they are effectively oil-in-water **[66,67]**.

8.6 Conductance measurement:

A conductometer determines the conductivity of a nanoemulsion. This test involves immersing two electrodes in an emulsion while connected to a light & an electric source. If emulsion is of o/w kind, current passes through water, illuminating the lamp as it runs among electrodes. Whenever the emulsion is absent, the lamp does not illuminate due to oil in outermost phase unable to carry out the current **[68]**.

8.7 Dye Solubilization:

In the aqueous phase of the w/o droplet, an aqueous-soluble dye remains soluble even when it is distributed throughout the O/W droplet. While they scatter inside a w/o globule, oil-soluble pigments disintegrate in the oily phase of an o/w globule.

8.8 Dilutability Test:

Unlike w/o, which undergoes phase inversion to convert to o/w nanoemulsion, o/w NEs could be diluted with water. **[69]**.

8.9 pH:

To decrease pH drift or development particles that are suspended on the electrode surface, the pH of a formulation is determined at a specific temperature when sedimentation equilibrium is reached. Neutral electrolytes should not be supplied during the external pH value building process since they will reduce the suspension's physical stability **[70]**.

8.10 In Vivo Bioavailability Studies:

The formulation/preparation is given to the entire live animal in this assessment parameter. Additionally, Blood samples are drawn on a regular basis and then centrifuged. Then, HPLC is utilized to generates content of drug in plasma. The bioavailability of medicine preparation is established by outcomes of both in vivo and in vitro study **[71]**.

9. APPLICATION OF EMULSIONS

Application of Emulsions	Description	References
Oral Drug Delivery	Emulsions improve absorption & dissolution rates, which raise bioavailability, making them a helpful tool for poorly soluble drugs.	**72**
Topical Formulations	Emulsions serve as the base for lotions, ointments, and creams, allowing hydrophilic and lipophilic drugs to be combined for better skin absorption.	**73**
Parenteral Drug Delivery	Emulsions are used to lubricate injection sites and deliver lipophilic medications intramuscularly or intravenously.	**74**
Ocular Drug Delivery	In order to improve medication absorption, retention, and sustained release for more efficient therapy, emulsions are used in ocular systems, such as eye drops.	**75**
Nasal and Pulmonary Drug Delivery	Emulsions are ideal for nasal sprays & inhalable products because they enhance medication absorption via mucosa with longer	**76**

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	release and less discomfort.	
Vaccine Adjuvants	Emulsions strengthen immune responses against antigens by enhancing solubility, enhancing immune cell absorption, and providing controlled release for improved immunological responses.	**77**
Taste Masking	Emulsions can disguise flavour and increase patient compliance by encasing harsh drugs, especially in paediatric formulations.	**78**
Cosmeceuticals	Emulsions improve the stability & penetration into the skin of vitamins, antioxidants, & skin agents by acting as carriers for the active ingredients in cosmeceuticals.	**79**

10.PATENTS RELATED TO NANOEMULSION IN PHARMACEUTICALS

Patent Number	Inventors	Publication Year	Title of Patent (Description)
US20210251948A1	Chunxiao Han, Dublin, CA (US)	Aug. 19, 2021	Nanoemulsion hydrophobic Substances
US20210177754A1	Christopher Keller, Advance, NC (US) et.al	Jun. 17, 2021	Nanoemulsion for oral use
US20220257510A1	Jingjun Huang, Monmouth Junction, NJ (US)	Aug. 18, 2022	COMPOSITIONS FOR NANOEMULSION DELIVERY SYSTEMS
US010738268B2	Daniel Michael Leo, Baltimore, MD(US)	Aug. 11, 2020	CANNABIS NANOEMULSION METHODS
USOO9717676B2	Vladimir Gartstein, Mason, OH (US); William Richard Mueller, Cincinnati, OH (US); Charles Raymond Degenhardt, Cincinnati, OH (US); Hiroshi Oh, Cincinnati, OH (US);	Aug. 1, 2017	AMINO SILICONE NANOEMULSION

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	Steven Daryl Smith, Fairfield, OH (US); Nicholas David OH (US)		
US00987283 2B2	Chien -Chin Wu, Wilmington, DE (US)	Jan. 23, 2018	NES HAVING REVERSIBLE CONTINUOUS AND DISPERSED PHASES
US01207578 8B2	Alireza Roostaee, Sherbrooke (CA); Frederic Picard-Jean, Sherbrooke (CA)	Sep. 03,2024	ANTIMICROBIAL NANOEMULSION
US00925940 7B2	James R. Baker, Jr., Ann Arbor, MI(US); Mark R. Hemmila, Superior Township, MI (US); Stewart C. Wang, Ann Arbor, MI (US); Tarek Hamouda, Milan, MI (US); John J. LiPuma, Ann Arbor, MI (US); Jessica Ann Knowlton, Ypsilanti, MI (US); Paul E. Makidon,Webberville, MI (US); Luz Blanco, Ann Arbor, MI (US); Jeffery V. Groom, II, Utica, MI (US); Anna U. Bielinska,Ypsilanti, MI (US)	Feb. 16, 2016	NANOEMULSION THERAPEUTIC COMPOSITIONS AND METHODS OF USING THE SAME

11.CONCLUSION

To solve the fundamental flaws in the present medicine delivery methods, a new distribution plan might be developed. This review discusses a nanoemulsion technology in depth. The use of emulsions at the nanoscale to enhance the delivery of active pharmaceutical ingredients is known as nanoemulsion. Thermodynamically stable isotropic systems are produced when two immiscible liquids are combined into a single phase using an emulsifying agent, such as a surfactant or co-surfactant. In NEs, droplet diameters usually fall between 20 and 200 nm. The size and shape of the particles scattered throughout the continuous phase are the primary differences between emulsion and nanoemulsion. An overview of the formulation, preparation, characterisation, assessment, and several applications of NEs is given on this page.

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