RESEARCH PAPER

Recent Progress in Nanoemulsion Drug Delivery Systems: Formulation, Assessment, and Biomedical Applications

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Abstract

Drug delivery systems using nanoemulsions have been developed to overcome the drawbacks of conventional drug administration methods. An excellent summary of the most current developments in the nano-emulsion medication delivery method was given in this article. These submicron emulsions, which are nanoscale, were created to improve the circulation of active medicinal substances to the intended location. An effective material, such as emulsifying agents, is used to stabilize nano emulsions, which are homogenous mixtures of lipid and aqueous phase. The range of the droplet size has been 50–500 nm. The typical technique distinguishes between emulsion, micro-emulsion, and nano-emulsion based on the size and form of the material disseminated throughout. Nanoemulsion improves the pharmacological action of medications and provides a new dose form for those with lower water solubility. Future applications of nano-emulsion include biotechnology, drug therapy, diagnostic testing, and cosmetics. A brief overview of nanoemulsion, its benefits, drawbacks, limitations, types, formulation components, surface active agents (surfactants), preparation techniques, and characterization techniques are all part of this analysis, which pays close attention to the various pharmaceutical uses of nanoemulsion in various fields, including targeted drug delivery, mucosal vaccination, transdermal drug delivery systems, and cancer and tumor therapy.

Keywords: Nano-emulsion, Types of Nano- emulsion, Surfactants, Novel drug delivery, Pharmaceutical Application

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Introduction

Nano-emulsions high opacity at superior droplet volumetric fractions, enhanced incidence of migration or bioavailability, and extended biopharmaceutical shelf life make them suitable for usage in the pharmacy industry. Drug distribution by nano-emulsion is a flexible method. The bioavailability of medications that are less soluble in water can be increased with this novel drug delivery method. Dispersing two incompatible liquids and water to create an isotropic, transparent nano-emulsion that is buffer-stabilized and energetically advantageous. [1] Oils, a surfactant system, water, and medications are all combined to create an isotropic nano-emulsion. These are nanosystems of colloidal particles that act as drug carriers and have a droplet size range. A drug's pharmacological action, bioavailability, and toxic effects are all improved by a nano-emulsion drug delivery technology. Droplets in a nano-emulsion range in size from 50 to 500 nm and are made up of a concentration ratio of oils and surfactant system. When two immiscible liquids are combined with particles smaller than 500 nm, the result is a clear, stable emulsion known as a nano-emulsion. [2] The incorporation of bioactive ingredients into these nanoemulsions guarantees increased bioavailability. It has been demonstrated that nanoemulsion can help a medication's survival time in a bodily system such that a small amount of the drug is required for therapeutic activity. Prior studies have demonstrated that the bioavailability of lipid-soluble medications can be enhanced using nano-emulsion processing. [3]

For a long time, O/W type nano-emulsion formulations have been made; nevertheless, K.L. and Fester have lately examined water in oil type nano-emulsions. Both varieties of nano-emulsion have distinct benefits, including those in cosmeceutical and medicines. [4] In recent years, this kind of dosage form has been widely employed to administer various biopharmaceuticals, such as antibiotics, vaccines, and drugs with DNA encoding. The application of a nano-emulsion medication delivery technology is topical and cosmetic. [5]

The formulation of this system may be administered by oral, ocular, and transdermal channels, which is a significant advantage over conventional dosage forms. [6] In this piece, we attempt to clarify the many manufacturing processes for nano-emulsion, the types of emulsifying agents, and the varied problems that arise during the design and invention of the nano-emulsion delivery system. [7] With the creation of Ostwald, the crucial step in the deterioration of nano-

emulsions, the incredibly small teardrop width guarantees stability against sedimentation and cremation. [8] [Figure No.1]

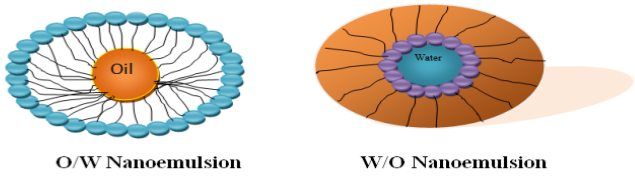

Figure No.1 Structure of Nanoemulsion

Merits [9] [10] [11]

1. It can be used in place of vesicles and medications that are lipid/protein coated.
2. Makes medications more bioavailable.
3. Nano-emulsion is non-irritating and non-toxic.
4. There is more physical stability now.
5. Droplets with a larger surface area and higher absorption are made possible by nano emulsions.
6. A variety of formulations, including foam, cream, oil, and sprays, is created using nano-emulsion.
7. Makes lipophilic medications more soluble.
8. Aids in covering up the smell.
9. A lower amount of energy is required.

Demerits [12]

1. To stabilize nanodroplets, a high ratio of surfactant to co-surfactant must be used.
2. The inability to dissolve rapidly melting liquids.
3. Environmental factors that impact the stability of nanofluids include pH and humidity.

Restrictions to Nano-Emulsion [13] [14]

1. The process of creating nano-emulsion formulations is expensive since it is highly challenging to reduce the size of the droplets, requiring a certain kind of equipment and process system. For instance, creating nano emulsions requires the use of a homogenizer, which is an expensive process. Ultrasound and micro-fluidification (the manufacturing process) therefore require a significant amount of financial assistance.
2. For a longer time, nano-emulsion stability is highly undesired and presents a major problem when preparing the formulation.

Table No.1 Differentiation of Nano-Emulsion, Micro-Emulsion, Emulsion [15] [16] [17] [18]

S.No.	Parameters	Emulsion	Nano-emulsion	Micro-emulsion
1.	**Definition**	The emulsion is a biphasic liquid drug dosage form that allows for the distribution of a restricted number of globules in a different liquid state.	Mixture of gasoline that is isotropic, drug and surfactant system.	Combination of oils and surfactants that is isotropic drug, and system.
2.	**Appearance**	Cloudy	More transparent	Transparent
3.	**Surface area**	Less	High	High
4.	**Energy**	High	Very low	Low
5.	**Droplet size**	0.1-10 µ	50-200nm	200-500nm
6.	**Formation**	Required vigorous shacking	Spontaneous formation	Phase titration and phase inversion
7.	**Viscosity**	More	Very less	Less
8.	**Type**	w/o/w, o/w, o/w/o,w/o	o/w, w/o, bicontinuous	Cylinder/ w, w/o
9.	**Stability**	Thermo-dynamically unstable	Thermo-dynamically and kinetically stable	Thermo-dynamically stable
10.	**Surfactant Concentration**	More	Very less	Less
11.	**Interfacial tension**	High	Ultra low	Low
12.	**Absorption rate**	Slow	Very fast	Fast
13.	**Bioavailability**	Minimum	Maximum	Intermediate
14.	**Permeation**	Minimum	maximum	Intermediate
15.	**Optimization**	Wet gum & dry gum method	Pseudo-ternary phase diagram	Ternary phase diagram

Types of Nanoemulsion

In general, nano-emulsions were classified into three types: bicontinuous, O/W, and W/O. [Figure No.2&3]

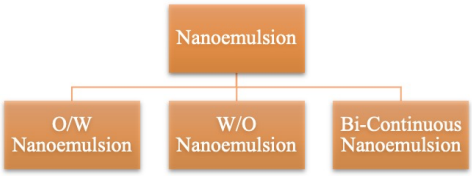

Figure No.2 Types of Nanoemulsion

1. O/W Nanoemulsion; When two immiscible liquids—oil and water—combine with a surfactant present, oil in water nano emulsion is naturally produced. The infraction of this type of nanoemulsion is frequently higher than that of the water-in-oil nanoemulsion. This kind of nano emulsion can be a surfactant system film that, in a droplet circle, produces an oily phase distributed in an aqueous phase, which is a repeating phase. This type of nanoemulsion is often more temporary than W/O Nanoemulsion. [19]

2. W/O Nanoemulsion; A nano-emulsion of the water-in-oil category may be identified by its small liquid particles surrounded by a typical oil phase. In the oil process, they a identified as "revermicelles" with polar head groups of surfactants and fatty acid tails in water droplets. [20]

3. Bi- Continuous Nanoemulsion; Bi-continuous nano-emulsion may be seen since the water and oil process micro-domains are dispersed throughout the system. [21]

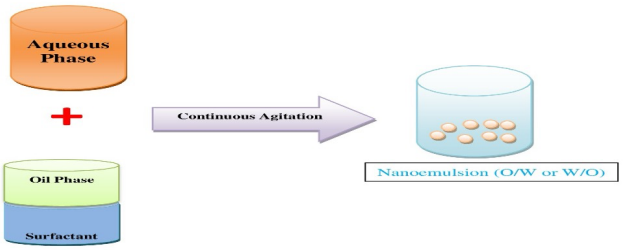

Figure No.3 Preparation of Nanoemulsion (o/w or w/o)

Nano-Emulsion Components

Particle sizes in nano-emulsions range from 10 to 1,000 nm. In their capacity as drug carriers, they lessen the harmful effects of the medication and increase its therapeutic efficacy. Despite being a poor thermodynamic method, it can be stabilized by the addition of a surfactant (emulgent or emulsifier). The continuous phase is another name for the phase of the nano-disseminated emulsion, while the dissolving medium is another name for its other phase. Intermediary and flexible are other names for the micelles.

Three main components make up a nano-emulsion: oil, water, and surfactant. The ideal blend of these ingredients determines the emulsion's consistency and characteristics. [22]

When creating nano-emulsions, the following kinds of components are utilized. Lipids and surface-active ingredients are typically utilized in nano-emulsions, which must be nontoxic, therapeutically acceptable, biodegradable, and biocompatible. [23] [Figure No.4]

Oil Phase

The choice of oily phase is important since it affects the choice of other materials for the nano-emulsion, especially when it comes to O/W nano-emulsion. The oil that has the highest emulsifying ability of the selected candidate medication is usually used as an oily stage in the nano-emulsion composition process, which facilitates drug loading. [23]

Aqueous Phase

The water phase may include protective agents and hydrophilic active substances. Frequently, buffer solutions are employed as the water phase, also known as the aqueous phase. In addition to water as one of its primary ingredients, an aqueous layer is a sample of water that contains certain water-soluble substances. [24]

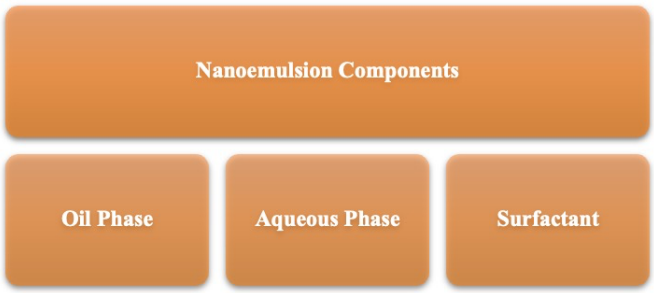

Figure No.4 Nanoemulsion Components

Surfactant

Surfactants have elements in their chemical structure that are both soluble in water and soluble in lipids. Since surfactants are amphiphilic, they reduce the worries about creating a flexible film that can extend across the particles with the proper shape by making dispersion bi continuous stages. [24] A common criterion for classifying surfactants is the hydrophilic-lipophilic balance (HLB), an objective figure that ranges from 0 to 20. The development and strength of the composition are significantly impacted by the surfactants' electronic conductivity. [25]

Cationic Surfactant

The aqueous phase of a cationic surfactant yields amphiphilic cation and negative kinds, such as the halogen variations. Some types of surfactants have a positively charged head. The world of non-ionic and anionic payloads is generally incompatible with the cationic character of the surface-active official, which kills the bacterial and viral epithelium. Among the alkyl trimethylammonium salts found in continuously energized ammonium sulfate cations are cetyltri-methylammonium bromide (CTAB) and cetyltri-methylammonium chloride. [26]

Anionic Surfactant

When the anionic surfactant is added to water, it provides both an amphoteric anion and a positively (Na, k) or ammonium sulfate cation. Among the anionic molecular orbitals of the anionic surface-active substance are phosphate, sulfate, carboxylates, and sulfonate at the cap. [27]

Non-ionic Surfactant

Through polarity and hydrogen-bonding interactions, non-ionic surface-active chemicals can interact with the water's likely hydrophobic interface and hydrate layer to become stable. Being phenol, alcohol, ester, amide, etc., the hydro-lover group is inseparable and is not ionized in water solution. Hydrophilic compounds that include a polyethylene glycol chain remove a sizable amount of these nonionic surface-active chemicals. [27]

Zwitterionic Surfactant

The Zwitterionic surfactant can have co-surfactants, and nanoparticles can be created when both positively and negatively charged groups, or anionic and cationic centers, connect to the same molecule. [28]

Co-Surfactant

Co-surfactant, a surface-active amphoteric reagent, cannot adequately stabilize the emulsion due to the minuscule quantity of the covalent bond. Nonetheless, because it therapeutically improves the surfactant's action, it is advantageous in the creation of nano-emulsion. In general, the co-surfactant can increase the responsiveness of the hydrocarbons area at the interface and further reduce the interfacial stress, increasing the durability of the vehicle. [29]

Co-Solvent

These compounds, which are sometimes referred to as co solvents, interact with a mixture of two or more typically immiscible substances to make them mixable and are added to increase the solvent strength of the primary material. Methanol, ethanol, and water are common cosolvents. The solubility of a co solvent determines its potency. In mixes of various formulations, that is the maximum solute dissolution amount. [29]

Mechanism of Nano-emulsion System

Nano-emulsions are combinations of nanoscale particles that were created to improve the absorption of pharmaceutically active substances. They would be stable crystal anisotropy complexes when two insoluble liquids are emulsified to form a specific phase using an emulsifier, such as a detergent complex like reagent and co-surfactant. The distribution of therapeutically active substances can be improved by using nanoemulsions, which are small-scale emulsions. [30]

The development and formulation of nano-emulsion drug delivery systems are influenced by the following aspects. [31] [32]

1. Deciding which emulsification technology is needed.
2. The fundamental component should be very insoluble in the dispersion medium to stop Oswald from ripening the decentralized process.
3. The nano-emulsion drug delivery method needs a little quantity or concentration of surfactant to function.

Method of Preparation for Nano-Emulsion Drug Delivery System

These Are Some Method of Preparation of Nanoemulsion Drug Delivery System. [33] Figure No.5]

High Pressure Homogenization

The material's tremendous friction and kinetic shear create very thin emulsion particles when two liquids (oily phase and water phase) are pushed together at extremely high pressure (500–5000 psi) through a small input hole. The corresponding watery core of the produced particles has been separated from a liquid, lipid-soluble core. The sole drawback of this high-quality approach is that it uses a lot of resources and raises emulsion temperatures significantly during operation. [34]

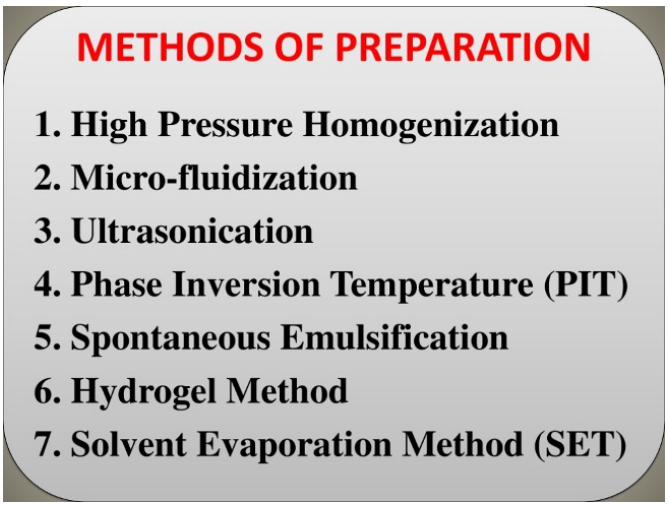

Figure No.5 Method of Preparation for Nano-Emulsion Drug Delivery System

Micro-fludization

Micro-fluidization is a mixing method that makes use of a microfluidified device. In order to use this technology, a high-pre positive displacement pump (500–20,000 psi) is required. This pump pressures the material into a chamber with small channels known as "micro-channels". When the material moves past the channel walls and into the area of occlusion, submicron-sized particles are created. The two materials—the water phase and the oil phase—are mixed and

separated in an internal granulator to create a coarse emulsion. [35]

Ultrasonication

Nano emulsion formulation has been documented in a number of research publications that focus on leveraging the strength of ultrasonic sound to reduce particle size. Another option is to employ a sonotrode with a constant intensity at device pressures higher than the ambient value. The cavitation threshold for ultrasonic waves is known to increase with increasing external pressure, which also makes the bubbles less shaped. [36] But there is also an increase in outside forces that make cavity bubbles more likely to explode. This suggests that the bubble collapses more forcefully and intensely during cavitation than it would under normal strain circumstances. [37]

Phase Inversion Temperature (PIT)

The uniform distribution within this operation is driven by prospective energy from symmetry breaking produced by the flocculating process. [38] The change can be achieved by altering the rotation of the emulsion while keeping the internal temperature constant, or the other way around. [39]

Spontaneous Emulsification

There are many phases involved:

1. The creation of a culturally homogeneous phase that includes a water-soluble surfactant and a lipid-soluble surfactant system in a soluble watery solution. [40]
   The oil/water emulsion was created by infusing the organic layer into the watery medium while stirring mechanically. [41]
2. Under reduced pressure, convection has been used to extract the water-soluble solvent. [42]

Hydrogel Method

The anti-solvent drug renders the solvent component soluble, which is the only difference between these two approaches. Higher shear strengths affect the development of Ostwald and the formation of crystals. [43]

Solvent Evaporation Method (SET)

This process involves combining a medicine and its emulsifying agent with a solvent that isn't the drug itself. The solution vaporizes, causing the drug to precipitate. It is possible to regulate crystallization by applying strong shear pressures with a high-speed stirrer. [44] [45]

Evaluation Parameter

These Systems are Some Evaluation Parameter for Nanoemulsion Drug Delivery. [46] [47] [48]
[Figure No.6]

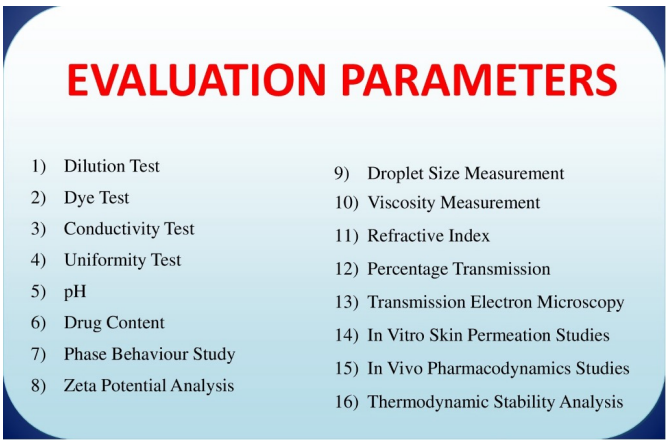

Figure No.6 Evaluation Parameter of Nanoemulsion

Dilution Test

The test concerns the discovery that the dilution of the continuous step had no effect on the stability of the nano emulsion. [49]

Dye Test

The dye test was used to gauge the nanoemulsions color homogeneity. [50]

Conductivity Test

The conductivity of the nanoemulsion was determined using the conduct meter equipment. [51]

Uniformity Test

It displays the droplet's consistent size inside the nano emulsion. [52]

pH

A pH meter was used to determine the Nano-emulsion system's pH. [53]

Drug Content

The drug content's formulation quality was assessed using HPLC and UV spectrophotometric methods. Mostly under UV light, 100 ml of solvent was used to dissolve 10 mg of the drug-loaded nano emulsion. To dilute 1 milliliter of this stock solution, 10 milliliters of solvent must be added. Additionally, the drug concentration was evaluated at the recorded Lambda maximum of the drug molecule. [54]

Phase Behaviour Study

The pseudo ternary phase diagram was used to assess the nano-emulsion system. Additionally, it specifies the field of nanoemulsion systems. [55]

Zeta Potential Analysis

Zeta potential was used to calculate the load on the Nano emulsion droplet's surface. Zetasizer was used to measure the

formulation (0.1 ml), which had been diluted 100 times using double-distilled water. [56]

Droplet Size Measurement

The particle diameter characterization of a nano-emulsion was evaluated using a diffusion technique and a light-scattering analyzer for measuring particle sizes. Furthermore, association spectrometry, which looks at the change in specular reflection caused by Brownian motion, is used to identify it. [57]

Viscosity Measurement

A Brookfield type rotational viscometer was used to measure the viscosity of the nano emulsion at various temperatures and shear rates. [58]

Refractive Index (RI)

Abbe's Refractometer was used to determine the nano emulsion's refractive index. [59]

Percentage Transmission (PT)

Using a UV Spectrophotometer to measure the percentage transmission of created nano-emulsion formulations at the same medicinal molecule's Lambda max. [60]

Transmission Electron Microscopy (TEM)

Nano emulsion systems are analyzed structurally and morphologically using transmission electron microscopy (TEM). [61]

In Vitro Skin Permeation Studies

In vitro drug release from enhanced nanoemulsion was assessed using the diffusion technique. One milliliter of nanoemulsion was transferred from the dialysis tube into 900 milliliters of diffusion medium at 100 rpm and 37 0.5°C (pH 6.4–6.8). [62] The dialyzing medium was regularly refilled with new medium, and dilutions of 5 mL samples were regularly removed to maintain the sink condition. [63] The proportion of all controlled release events was computed using UV analysis to quantify the sample's partial Lambda max of the medication component. [64]

Thermodynamic Stability Analysis

After centrifuging the created nano emulsion for 30 minutes at 1000 RPM, it was tested for phase separation and cremation. [65] The nano-emulsion heating procedure was conducted six times at varying temperatures for at least 48 hours at each of the refrigerator's 4°C to 45°C temps. [66] To ensure that the nano-emulsion is thermodynamically stable, the produced formulations were stored at each temperature for at least 48 hours over three freeze-thaw cycles between -21°C and +25°C. [67] [68] [69]

Nanoemulsion Application

These are Some Application of Nanoemulsion Drug Delivery System. [Figure No.7]

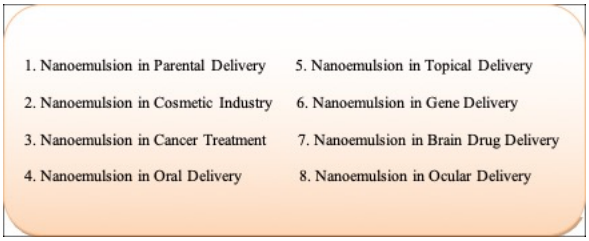

Figure No.7 Application of Nanoemulsion

Nanoemulsion in Parental Delivery

In intravenous administration, nano emulsion has been utilized. This particular route of administration is only required when a droplet scale diameter of less than one micrometer forms. [70] Nutrition involves parental (or injectable) nano emulsion delivery for things like fats, carbs, and vitamins. [71][72][73]

Nanoemulsion in Cosmetic Industry

Due to its aesthetic qualities, such as its low viscosity and transparent functional properties, nano-emulsions with droplet sizes under 200 nm are very attractive for use in cosmetics because they offer a large surface area that facilitates the easy transfer of the active ingredient to the skin. [74] Using nanoemulsion technology, a mini-emulsion of oil-in-water concentration is created that is suitable for lowering transepidermal water loss, enhancing skin safety, and improving medication penetration. [75]

Nanoemulsion in Cancer Treatment

Noisome may be used as a transporter in chemotherapeutics to extend the drug's flow following muscle contractions and to influence the surrounding injections (W/O systems). [76] Additionally, because it is a non-irritating method, it improves the lymphatic penetration of anti-cancer treatments through the skin, which improves the administration of transdermal drugs. [77]

Nanoemulsion in Oral Delivery

The use of nanoemulsions in oral drug administration has shown great promise, especially when it comes to improving the solubility and bioavailability of medications that are not highly soluble in water. [78] [79] [80] the increased surface area for medication absorption due to their tiny droplet size improves therapeutic effectiveness. [81]

Nanoemulsion in Topical Delivery

Topical distribution using nanoemulsion is a cutting-edge medication delivery method that improves the active components' stability, penetration, and bioavailability when administered topically. [82] [83] [84] [85] for

pharmacological, dermatological, and cosmetic uses, nanoemulsions work incredibly well. [86]

Nanoemulsion in Gene Delivery

As potential platforms for genetic modification of liposomes, emulsion systems were developed. [87] Other emulsion genetic manipulation experiments (non-pulmonary route) have shown that the retention of the emulsion/DNA pair is greater than that of the encapsulated transmitter alone. [88] Compared to microcapsules, this continuous emulsion technique generated genes more efficiently. [89]

Nanoemulsion in Brain Drug Delivery

Noninvasive drug administration is a more efficient means of delivering medicine than parenteral or oral methods. Medication caused nasal mucosa to grow. [90] Medicines that target the brain have been linked to a multitude of difficulties, particularly aqueous medicines and more complex molecular concerns. [91] A suitable method for transporting common drugs appears to be useful in overcoming hurdles to their timely arrival into particular locations. [92] As a result, the approach is non-invasive, pleasant, and extremely effective. [93] The mucosal membrane is very efficient because to its low catalyses activity and abundance of fully impermeable areas. Large molecules with a high molar mass. [94] This is because the micro vascular system, which separates the blood-brain barrier from the circulation, is hermetic. Stimulant nano-emulsions can cure Alzheimer's disease, migraine, epilepsy, schizophrenia, Parkinson's disease, and meningitis by targeting the nasal mucosal olfactory area, which is linked to the brain. [95]

Nanoemulsion in Ocular Delivery

Drugs are used to treat eye problems, which are mostly given topically via nano-emulsions we examined ocular delivery, dissolving poorly soluble medicines, improving absorption, and producing a sustained release profile. [96]

Conclusion

The nano-emulsion medication delivery technique has seen considerable usage in the pharmaceutical industry. Nano-emulsions provide several benefits for medication delivery and biological processes. Nano-emulsion proved suitable for numerous routes and so has potential in a variety of applications. This technical invention addresses the issue of few watery soluble pharmaceuticals and may be used for insoluble aqueous medications. Nowadays, nanoemulsions are utilized to selectively administer a variety of medications, including anti-cancer therapies and photo-sensitizers. Overall, all nano-emulsion formulations were proven to be effective, secure, and patient-friendly for pharmaceutical delivery. More study and advancement on nano-emulsions are predicted in the future.

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