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Nanoemulsion in Drug Formulation: Methods, Characterization and Therapeutic Applications

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Abstract: *Nanoscale oil-in-water emulsions (NEs) are mixed systems of two non-mixing liquids that are stabilized by emulsifiers or surfactants. They hold significant promise for medical use due to their appealing properties for transporting drugs. NEs have been investigated as carriers for hydrophobic substances through different methods of administration, offering potential enhancements in drug delivery through alternative routes. The primary benefit of nanoemulsion (NE) technology lies in its stability compared to other colloidal carriers. This stability can last from a few hours to several years, depending on the materials chosen and the methods used for preparation. Destabilization of NEs occurs due to changes in droplet size through Ostwald ripening. A major challenge in functionalizing the surface of NEs is maintaining the stability of the oil-water interface during the emulsification process. This review aims to clarify various concepts in the literature related to NE development, component selection, preparation methods, evaluation criteria, and stability concerns, particularly concerning the importance of pseudo-ternary phase diagrams.*

Keywords: Nanoemulsion, drug delivery, nanotechnology, stability, droplet size

I. INTRODUCTION

Nanoemulsions are Colloidal systems that serve as effective drug delivery vehicles, particularly for poor water soluble compounds, utilizing safe grade excipients [1,2]. These formulations consist of nanometre sized droplets dispersed in a continuous liquid phase, enhancing stability and solubility. Additionally, the encapsulation mechanism protects the activity pharmaceutical ingredients from degradation and prolongs its half-life in the bloodstream. This unique structure makes Nanoemulsion a promising approach in drug formulation and delivery [3]. Nanoemulsion are colloidal carrier systems composed of surfactants, water, and oil, characterized by high kinetic stability, low viscosity, and optical transparency [4]. Typically, they feature uniform droplet sizes Under 200nm; However, emulsions with a surfactant content that is low yet still kinetically stable can have droplet sizes up to 500 nm [5,6]. This stability minimizes issues like separation, sedimentation, and creaming, making Nanoemulsions particularly valuable in dermatological applications [7].

In addition to being taken by a variety of similarly varied routes, such as topical oral, intravenous, intranasal, pulmonary, and ophthalmic, Nanoemulsions may be transformed into a number of dosage forms, such as liquids, creams, sprays, gels, aerosols, and foams. They are used as an aqueous foundation for organic deliverables in the cosmetic and pesticide industries because they have a better solubilisation capacity than simple micellar dispersions and more kinetic stability than coarse emulsions.

Their tiny droplet size directly affects their long-term physical stability by thwarting typical destabilisation processes as creaming, sedimentation, and coalescence. Brownian motion is frequently powerful enough to counteract kinetic instability brought on by gravity or viscosity. Parenteral administration Nanoemulsions have been utilised to target certain organs by taking advantage of improved permeability and retention effect, to solubilise and protect pharmaceuticals from harsh environmental conditions (oxidation, pH, hydrolysis), and to circumvent the reticuloendothelial system [8].

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1.1 Emulsion-Microemulsions-Nanoemulsions: -

1.1.1. Emulsion: -

One liquid distributed in another immiscible liquid forms an emulsion, which is a metastable colloidal system. Emulsions need to be mixed mechanically and contain a surface-active substance, such surfactant, to prevent droplets from coalescing. In other words, phase separation happens due to gravity since the average drop size keeps increasing. Numerous variables affect an emulsion's characteristics.

Among the several variables that need to be taken into account when creating an emulsion are the amount and kind of each component related to the composition, the dispersing technique employed, the temperature during the dispersing process, and the mixing order. Emulsions are utilized in a wide range of products, including paints, medications, food, cosmetics, and improved oil recovery [9].

1.1.2. Microemulsion: -

Unlike emulsion, which is hazy, microemulsion is a transparent dispersion. Known as small scale emulsions, it is made up of two immiscible liquids that can be combined to form a single optically isotropic substance. Since microemulsions are liquid solutions that are thermodynamically stable, they do not require a lot of energy to form. In addition, the dispersed phase droplet sizes in microemulsions range from 10 nm to 100 nm. Researchers are becoming interested in microemulsions because of their potential in the petrochemical sector, medication delivery systems, culinary, and pharmaceutical applications, as well as their decreased energy requirements [10].

1.1.3. Nanoemulsion: -

Nanoemulsions have the potential to be extremely helpful in a variety of applications. Since mechanical stirring is necessary for the formation of Nanoemulsions, their stability and properties are dependent on the preparation technique, phase makeup, and component additions made during the emulsification process [11].

One advantage of Nanoemulsions is their comparatively great kinetic stability over a number of years. They can be formed into deformable droplet systems that are extremely homogeneous and monodisperse. They are stable against creaming due to the small droplets and the action of thermal excitations, and they do not coalesce because of their high surface charge [12].

Table no.1: - Difference Between Emulsion, Microemulsion And Nanoemulsions.

Emulsion	Microemulsion	Nanoemulsion
Thermodynamically unstable	Thermodynamically stable	Kinetically stable
Emulsion appear cloudy	Microemulsion are clear	Nanoemulsion are clear and translucent
Emulsion form only after application of large input of energy	Microemulsion form spontaneously	Nanoemulsion for after application of high shear

1.2. Types Of Nanoemulsions Based On Composition: -

1.2.1. Oil in Water (O/W) Nanoemulsions: -

In this oil droplets dispersed in a continuous aqueous phase.

1.2.2. Water in Oil (W/O) Nanoemulsions: -

In this water droplets are dispersed in continuous oil phase

1.2.3. Bi-continuous Nanoemulsions: -

In this oil and water are interdispersed within the system.

1.2.4. Water-in-Oil-in-Water (W/O/W) Nanoemulsions: -

This structure contains water droplets encapsulated within oil droplets, which are then dispersed in another aqueous phase.

1.2.5. Oil-in-Water-in-Oil (O/W/O) Nanoemulsions: -

This configuration features oil droplets encased in water droplets, which are then surrounded by a continuous oil phase [13].

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1.3. Physicochemical Characteristics Of Nanoemulsion: -

Physicochemical characteristics of Nanoemulsions (NEs), such as **stability, visual appearance, and rheology,** are influenced by factors including droplet size, composition, concentration, and surface properties. To ensure NE stability against environmental factors like pH and temperature during storage and usage, it's essential to manage droplet size, surfactant, and oil concentrations. For instance, smaller NEs are less prone to gravitational separation [14]. Additionally, the smaller droplet size increases the surface area-to-volume ratio, enhancing the reactivity of NEs with their environment. Rheology also plays a crucial role, affecting the production, functionality, and storage of NEs, as the viscosity of both dispersed and continuous phases impacts droplet fragmentation during emulsification. These physicochemical properties are fundamental quality parameters that need to be tailored according to specific applications and routes of administration.

II. COMPONENTS OF NANOEMULSION: -

2.1. Oils/Lipids: -

The solubility of the drug in the oil phase is an important criterion for oil selection. Oils are one of the main aids in the development of NE, not only because of their ability to eliminate large amounts of lipophilic drugs, but also because of the increased amount of lipophilic drugs transported through the intestinal lymphatic system. n system, thereby increasing the absorption of drugs from the gastrointestinal tract depending on the molecular shape of the oils [15]. The w/o NEs are better choice for hydrophilic drugs, however lipophilic drugs are preferably solubilized in o/w NEs. Drug loading in the formulation is a very critical design factor in the development of NEs for poorly soluble drugs, which is dependent on the drug solubility in various formulation components. Edible oils are not frequently useful in NE development due to their poor ability to dissolve large amounts of lipophilic drugs. Moreover, the formulation of NEs with oils of low drug solubility would require incorporation of more oil to incorporate the target drug dose, which in turn would require higher surfactant concentration to achieve oil solubilisation. This will finally result in increase in the toxicity of the system. Novel semi-synthetic medium chain derivatives (as amphiphilic compounds) having surfactant properties are progressively and effectively replacing the regular medium chain triglyceride oils [16].

2.2. Surfactants: -

Surfactants reduce surface tension to a minimum to aid the spreading process and create a flexible layer that easily forms around the droplets. Their lipophilic nature provides the correct curvature in the interfacial region for the desired type of NE, I,e for o/w, w/o or bicontinuous [17,18]. Low HLB (3-6) surfactants such as size are considered for the development of NEs, but high HLB (8-18) such as Tweens are preferred when o/w is required. the NE system is the Surfactant used in the production of NE from the following components.

2.2.1. Anionic Surfactant: -

Sodium bis-2-ethylhexylsulphosuccinate (AOT), which is twintailed to stabilise without NEs, is the most often employed surfactant in topical routes [19].

2.2.2. Cationic Surfactant: - Among the most well-known groups of cationic surfactants are quaternary ammonium compounds.

Hexadecyl trimethyl ammonium bromide (CTAB) and didodecyl ammonium bromide (DDAB) are the two most often utilised cationic surfactants. These surfactants are more widely used as disinfectants or antiseptics. Typically, ophthalmic formulations employ these surfactants [20].

2.2.3. Nonionic Surfactant: -

The most utilised products in this category are polyoxyethylene derivatives like Tweens and sorbitan fatty acid esters like Spans [21].

2.2.4. Zwitterionic Surfactant: -

The most often utilised type of zwitterionic surfactant is phospholipid, which has outstanding biocompatibility. These days, amino acids (leucine and isoleucine) are also regarded as safe [21].

2.3. Co-surfactants: -

A cosurfactant is typically required in order to create transient negative interfacial tension, which cannot be accomplished with a single surfactant. When cosurfactant is not present, the surfactant forms an extremely stiff film, which results in NE production across a very small concentration range.

Cosurfactants give the interfacial film the flexibility it needs to absorb the various curvatures needed to create NE across a broad composition range. The o/w interfacial tension cannot be substantially decreased by single chain surfactants to allow for the formation of a NE. Alcohols with medium chains, which are frequently introduced as cosurfactants, have the important impact of further lowering interfacial tension while simultaneously boosting the system's entropy and interface fluidity.

Additionally, they improve the hydrocarbon tail's mobility and the oil's ability to penetrate this area. Additionally, it has been proposed that some oils, such as ethyl esters of fatty acids, function as cosurfactants by entering the surfactant monolayer's hydrophobic chain area. Without the assistance of cosurfactants, certain double chain surfactants including AOT, CTAB, and DDAB, can produce NEs [22].

2.4. Antioxidants, And Preservatives: -

Low toxicity, stability to heat and storage, physical and chemical compatibility, affordability, accessibility, tolerable odour, taste, and colour, as well as a wide range of antibacterial activity, are all requirements for preservatives used in Nanoemulsions.

Since microorganisms can grow in both water and oil, a chosen preservative should achieve an effective concentration in both phases. Because of their potential for toxicity, preservatives are generally avoided when used in parenteral Nanoemulsions. Benzoic acid, sorbic acid, propionic acid, and dehydroacetic acid are examples of acids and their derivatives that can be utilized as antifungal agents in formulations. In ophthalmic, alcohols such as phenoxy-2-ethanol and chlorobutanol are frequently utilized. Broad spectrum preservatives include quaternary ammonium compounds and phenolics. When exposed to air, emulsified oil and lipids can undergo autoxidation; many medications utilized in Nanoemulsions are also extremely vulnerable to oxidative destruction [23].

III. METHOD OF PREPARATION

3.1. High-Energy Nanoemulsion Techniques: -High energy methods deploy strong disruptive forces to produce tiny droplets using mechanical devices such as high-pressure homogenisers, microfluidizers, and ultrasonicates. The kind of equipment utilised, production parameters like temperature and duration, and the properties and makeup of the mixture all affect how big these droplets get. These methods are expensive because they need sophisticated equipment and use a lot of energy. Nonetheless, they provide extensive component options and exact control over droplet size. Large macromolecules like proteins, enzymes, and nucleic acids, as well as thermolabile active components like retinoids, cannot be handled by these techniques [24].

3.1.1. High Pressure Homogenisation: -

This method, which is frequently used to create Nanoemulsions, depends on a number of forces, such as cavitation, severe turbulence, and hydraulic shear. To create Nanoemulsions, a mixture of two liquids-surfactants and co-surfactants is passed through a tiny hole in a piston homogeniser at high pressures (500–5000 psi) [25,26]. First, a sizable volume proportion of the dispersed phase is created in the emulsion, which can then be diluted. A surplus of surfactants can be used to reduce the probability of coalescence. Although high pressure homogenisation is an effective method that can be used in both laboratory and largescale settings, it uses a significant amount of energy and may have negative effects on the components involved due to the temperature increase that occurs during processing [25].

Using High pressure homogeniser Nanoemulsions with particle sizes down to 1 nm are produced by the HPH method.

Influencing factor:

1. The number of cycles (homogenization cycles) (more cycles =smaller droplets)

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2. Viscosity ratio nD/nC of dispersed (nD) and continuous (nC) phases (Average ratios + accepted ratio: $0.05 < nD/nC < 5$) [26,27].

What can be done:
1. O/W Nanoemulsions
2. Oil phase content: 20% vol max [28].
3. Control over droplet size.

Constraints:
1. Low productivity
2. Production of heat which can degrade some components
3. O/W Nanoemulsions only.

Benefits:
1. The most widespread method of Nanoemulsion preparation.
2. An ability to control the size of droplets
3. Ability to use in various fields (pharmaceuticals, cosmetics, food)

The HPH method enables the control of droplet size but in terms of productivity, it has a disadvantage and heat management which is considered as a disadvantage. However, it is one of the common techniques employed in the fabrication of Nanoemulsion with its own merits [29].

3.1.2. Microfluidization: -

To create fine Nanoemulsions, this mixing method makes use of a high-pressure displacement pump (3,45–137,89 MPa).

When liquids (water and oil) from two opposing microchannels clash at a shared impingement location, high pressure is created that causes extreme shear. The interaction chamber microfluidizer is repeatedly passed through with crude emulsion until the droplets reach the required size [25].

Crude emulsion is filtered in a nitrogen environment to eliminate bigger droplets in order to produce droplets of the Nanoemulsions inner phase that are homogeneous in size [28].

As the pressure of homogenization increases, or by increasing the number of passages through microchannel devices, increasing the concentration of surfactant, and decreasing the ratio of dispersed and continuous phase viscosities, the droplet size of the dispersed phase of Nanoemulsions produced in Microfluidizers decreases [30]. Largescale Nanoemulsion preparation is not a good fit for microfluidization, and it is highly expensive [31, 32].

3.1.3. Sonication: -

Kinetically stable Nanoemulsions can be made by ultrasonic homogenization or sonication. The ultrasonic homogenizer's sonicator probe creates mechanical vibration and cavitation when it comes into contact with liquids that are dispersed with surfactants and cosurfactants.

This provides the energy input required for the creation of tiny droplets. Nanoemulsions are frequently produced on a small scale via sonication, also known as ultrasound processing. But caution needs to be exercised to avoid coalescence caused by shear [33,34]. As the time of ultrasonic homogenization, power levels, and surfactant concentration increase, the dispersed phase particle size in Nanoemulsions created by sonication decreases [30]. Optimizing the design of ultrasonic reaction chambers, operating conditions, and product formulation (e.g., surfactant concentration and oil phase type and content) are required to reach a dispersed phase droplet size of 20 nm [35]. The primary drawback of sonication is its unsuitability for producing large quantities of Nanoemulsions [29].

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3.1.4. Jet Disperser: -

In a jet disperser, multiple jets of crude emulsion from opposing bores collide in a manner distinct from that in a microfluidizer. The bore diameters in jet dispersers typically range from 0.3 to 0.5 mm. An “orifice plate” serves as a basic design for a homogenizing nozzle, facilitating the energy dispersion of the emulsion jet. Droplet disruption primarily occurs due to the laminar elongation flow ahead of the bores. Unlike radial diffusers, the nozzle functions as a microfluidizer. Both jet dispersers and orifice plates have no moving components, enabling them to operate at high pressures of 300-400 MPa [34, 36].

3.1.5. High-Amplitude Ultrasonic Method: -

This technique serves as an alternative to high-pressure homogenization. The forces needed to create Nanoemulsions are produced through ultrasonic cavitation, which generates violent and unevenly collapsing vacuum bubbles. Micro-nozzles are used to disperse and reduce droplets to the nanometer scale. This method has proven effective for producing small amounts of pharmaceutical Nanoemulsions and liposomes. Traditional ultrasonic technology typically functions on the principle of operating with either small amounts at high amplitude or large amounts at low amplitude, without the ability to combine these processes at high amplitude for larger volumes. Although the method shows promise, its use is largely restricted to laboratory settings [29].

3.1.6 Piston Gap Homogenizer: -

Piston gap homogenizers operate based on the principles of colloid mills. A coarse emulsion is forced through a narrow gap (approximately 10 µm wide) located between a stationary stator and a rapidly rotating rotor. The reduction in particle size occurs due to the high shear, stress, and grinding forces produced by the interaction between the rotor and stator. The maximum droplet size can be determined by setting the dissipation gap to the desired measurement, indicating that no yield will be achieved unless the emulsion is processed to a size that is equal to or smaller than the gap between the rotor and stator [37].

3.2. Low Energy Emulsification Method: -

Nanoemulsions prepared by low energy emulsification methods were developed after studying cumulative behaviour of oil, surfactants, cosurfactants, drug, aqueous component, hydrophilic lipophilic balance of utilized oil surfactant blend, and operative temperature [38]. Low energy methods include spontaneous emulsification [39], phase inversion [40] and the less utilized catastrophic phase inversion method [41]. A key character of these methods is utilization of energy stored in the system to produce ultra-fine droplets. Low energy methods are sometimes limited by oil type and emulsifiers that can be used.

3.2.1. Spontaneous Emulsification: -

The process of spontaneous emulsification is similar to the Nanoprecipitation technique used to create polymeric nanoparticles. But oil is utilized in place of polymer. The process comprises the manufacture of two phases: an oil soluble surfactant like Span, a somewhat water miscible organic solvent like acetone or ethyl acetate, and an organic or oil phase like mygliol containing a medication. To create tiny nanoscale emulsions, the organic phase is added dropwise to the aqueous stirring phase (but the opposite, that is, adding water to oil, is also possible in the case of W/O emulsions) [8].

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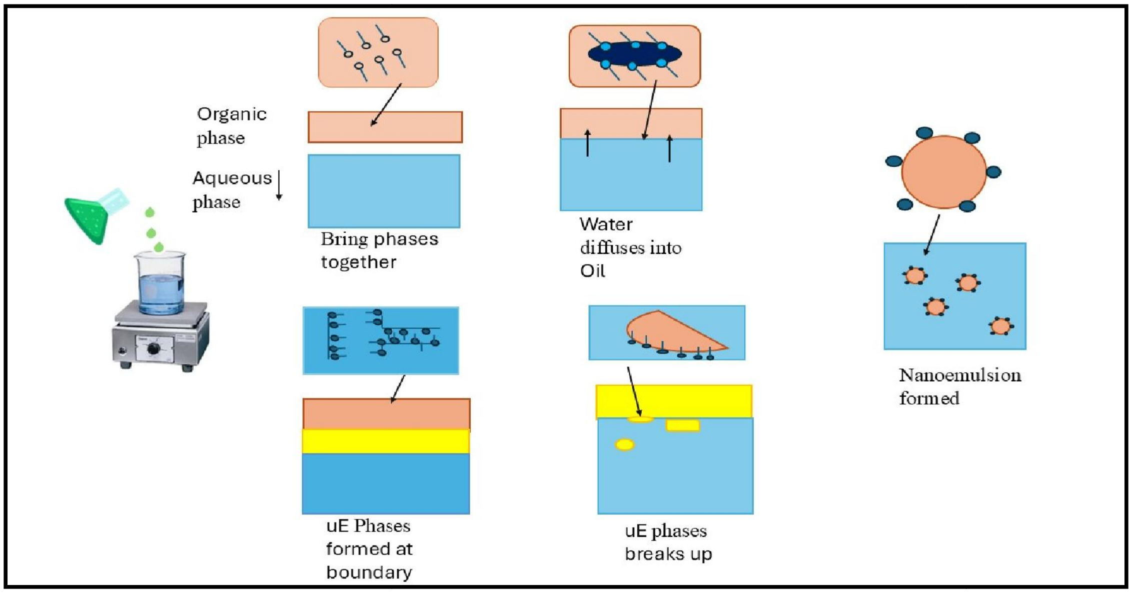

Fig no. 1: - Spontaneous emulsification [13].

3.2.2. Method Of Phase Inversion: -

By taking advantage of variations in the aqueous/oil solubility of surfactants in response to temperature fluctuations, phase inversion temperature (PIT) techniques create Nanoemulsions. Through the use of an intermediate bicontinuous phase, a W/O emulsion can be orderly converted to an O/W emulsion or vice versa. An oil, water, and surfactant mixture is often heated over a predefined temperature, known as PIT (depending on the formulation blend used), and quickly cooled afterward. Phase inversion results from the opening and reversal of the interfacial structure brought on by a change in temperature from low to high. Rapid quenching that follows causes the interfacial structure to close once more, trapping water or oil. The process is bottom-up, and because of the extensive surfactant covering, the nascent droplets stay stable for a long time. Because heat input is required, PIT techniques may prohibit the use of thermosensitive medications. Good solubility of the medication, oil, surfactant, and water is also necessary for a smooth phase transition [8].

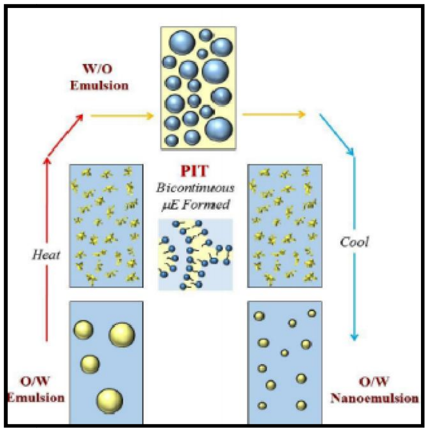

Fig no.2: - Method of phase inversion (PIT) [13].

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3.2.3. Solvent Evaporation Technique: -

This technique involves combining a mixed drug with an organic solvent and a suitable surfactant to create an O/W emulsion by mixing it into a uniform phase. Subsequently, the organic solvent is removed through vacuum, heating, or at room temperature, leading to the formation of drug-loaded microspheres, which are then processed through centrifugation or filtration. A schematic illustration of this method is presented in Fig. **(**3**)** [42]. The volume of the emulsion, the viscosities of the emulsion and its phases, the kind and concentration of the surfactant, temperature, and the size and size distribution of the droplets of the disperse phase are some of the numerous variables that influence the choice of emulsifying device.

The emulsification formulation parameters need to be tuned in order to produce the intended Nanoemulsions. These variables include temperature and emulsification time, flow rate, pressure, interface density, and rotational speed [43]. The removal of the organic solvent from the NEs during preparation is the main disadvantage of this approach [44].

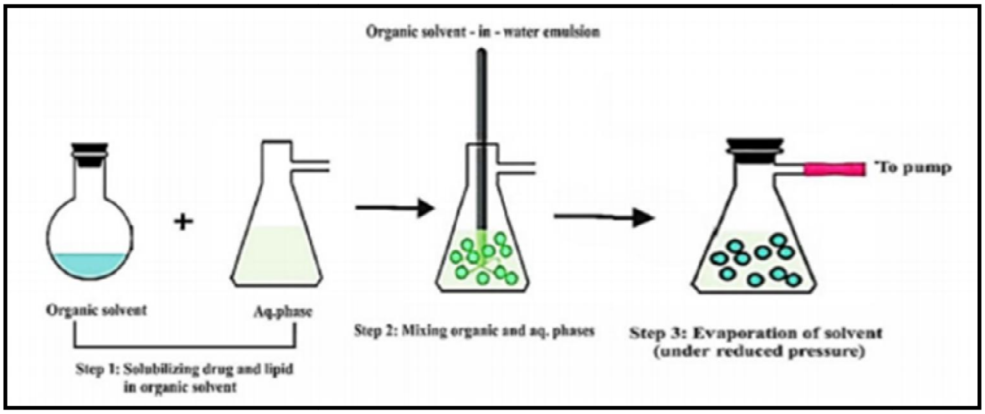

Fig no. 3: - Solvent evaporation technique [13]

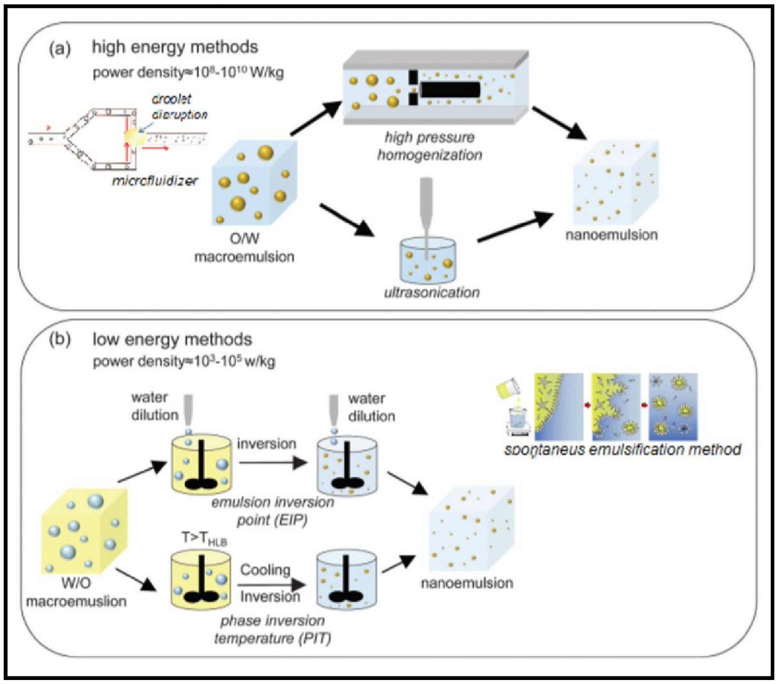

Fig no. 4: - Overview of high energy and low energy method for preparation O/W Nanoemulsion [45].

Table no. 2 : - Method Used For Preparation Of Nanoemulsion.

Techniques	**Emulsifier/surfactant**	**Active ingredient**	**Size distribution (nm)**	**Reference**
High-pressure homogenization	Tween 20, 40, 60 and 80, sodium caseinate	β-Carotene, α-tocopherol	132–178, 391	[46,47]
Ultrasound	Pluronic F68, Poloxomer, Tween 80, Span 80, lechithin, sodium dodecyl sulfate	2-(Butyl amino)-1-phenyl-1-ethanethiosulfuric acid	380, 200–251, 40,	[48,49,50]
Solvent displacement technique	Pluronic F68	_	185–208	[51]
Phase inversion temperature	Brij30, polyoxyethylene 4-lauryl ether, polyoxyethylene 4-lauryl ether	_	80–120, 50–130, 29–80	[52,53,54]
Spontaneous emulsification	Lecithin, Tween 20, 80, Span 85	Carbamazepine, quercetin or methylquercetin	150–212, 300, 171	[55,56]

IV. EVALUATION PARAMETERS

4.1. Dye Solubilization: -

A water-soluble dye is solubilized within the aqueous phase of the w/o globule but is dispersible in the o/w globules and vice versa [57].

4.2. Dilution Test: -

While w/o NEs are not diluted with water and undergo phase inversion into o/w NE, o/w NEs can be calculated by diluting with water. Due to water being the internal or dispersal phase, w/o NEs are not very conducting but o/w NEs are at low volume fractions, a significant increase in conductivity was seen in some w/o NE systems; this phenomenon is known as "percolative behaviour," or the exchange of ions between droplets prior to the creation of bicontinuous structures [58].

4.3. Measurement Of Viscosity: -

A Brookfield type viscometer can be used to measure the viscosity of NEs at various shear rates and temperatures.
The samples for the measurement and the testing room temperature must be kept constant [58]. When assessing NEs' flow characteristics, their viscosity is helpful.

4.4. Polydispersity: -

Photon correlation spectroscopy, utilizing a He-Ne laser at a temperature of 25 °C, is employed to measure the average size and polydispersity index of formulations. The polydispersity of Nanoemulsions (NEs) is particularly valuable for evaluating the uniformity of droplets within these formulations [59, 60].

4.5. Tension Over The Interface: -

By measuring the interfacial tension, one may investigate the creation and characteristics of NEs. Interfacial tension at extremely low values is associated with phase behaviour, especially when middle phase NEs or the surfactant phase are present and in balance with the aqueous and oil phases. It is possible to measure the ultra-low interfacial tension of NEs using spinning-drop device [57].

4.6. Transmission Electron Microscopy (TEM): -

Transmission electron microscopy was used to analyse the Nanoemulsions structure and morphology. The size and structure of the Nanoemulsion droplets were depicted using a combination of diffraction modes and bright field imaging at different magnifications. To make observations, a drop of the Nanoemulsion was applied straight onto a holey film grid and allowed to dry after being examined [61].

4.7. Drug Content: -

The drug content was quantified using the reverse phase HPLC method with a C18 column [62].

4.8. Zeta Potential

The zeta potential technique measures the surface charge characteristics and long-term physical stability of Nanoemulsions.This was accomplished using a Zeta PALS instrument.

Measurements were taken from diluted Nanoemulsion formulations [63], with values determined based on the electrophoretic mobility of the oil droplets. A minimum zeta potential of ±20mV is considered optimal.

4.9. Percentage Transmittance: -

The percentage transmittance of the Nanoemulsion formulations was assessed spectrophotometrically with a UV-VIS Spectrophotometer [64].

4.10. In Vitro Skin Permeation Studies: -

In vitro skin permeation studies were conducted using the Keshary Chien-diffusion cell on abdominal skins sourced from male rats weighing 250±10 g. The setup included a recirculating water bath and 12 diffusion cells.

The skins were positioned between the donor and receiver chambers, which were filled with fresh water containing 20% ethanol, set at 37°C, and continuously stirred at 300 rpm. The formulations were introduced into the donor chamber. At intervals of 2, 4, 6, and 8 hours, 0.5 ml samples were extracted from the receiver chamber for gas chromatography analysis and replaced with equal volumes of fresh solution [65]. Each test was repeated three times, with cumulative corrections made to ascertain the total drug amounts that permeated at each time point. The cumulative drug amounts permeated through rat skins over time were plotted, and the steady state permeation rates were derived from the slope of the linear section of the cumulative amounts plotted against time per unit area.

4.11. Phase Behaviour Investigation: -

This research focuses on the characterization and optimization of components, including surfactant, oil phase, and aqueous phase. It is particularly important for Nanoemulsion formulations created using the phase inversion temperature method and the self emulsification method, aiming to identify the Nanoemulsions phase and its dispersibility.

The study involves combining different ingredients of the Nanoemulsion in varying concentrations within glass ampules and thoroughly homogenizing them at a specific temperature for a set period until equilibrium is reached. Anisotropic phases can be recognized using polarized light [66].

4.12. Particle Size Evaluation: -

The formulated Nanoemulsion should undergo assessment to determine its hydrodynamic particle size and the distribution of these particle sizes. Generally, dynamic light scattering (DLS) is utilized to measure the particle size and to analyse the distribution of particle sizes within Nanoemulsions [66].

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4.13. pH: -

The pH of the formulation was assessed using a pH meter [67,68]. The values were measured directly from the samples with a calibrated potentiometer (Inolab pH 720, WTW, Germany) at room temperature, and the measurements were conducted three times for accuracy.

V. STRATEGIES FOR PREVENTING INSTABILITY IN NANOEMULSIONS

Creaming], flocculation, coalescence, and Ostwald ripening are some of the primary causes of Nanoemulsion instability. Ostwald ripening is the primary mechanism of Nanoemulsion instability among them, as the usage of non-ionic surfactants and the small size of the Nanoemulsion minimise the remaining issues. The quicker diffusion rate of tiny droplets prevents the Nanoemulsion from creaming. The attraction of droplets and the flocculation of the emulsion are caused by Vander wall force. However, non-ionic surfactant in Nanoemulsion does not produce any form of attractive force, hence flocculation does not happen. The small size of the Nanoemulsion prevents swelling because these small exhibit high curvature and Laplace pressure that opposes the diffusivity of large droplets.

The coalescence of Nanoemulsion droplets can be prevented by thick layers of adsorbed surfactant film on the droplet interface. The only problem with instability in a Nanoemulsion arises from the arrival of Ostwald. Upon reaching the Ostwald, small droplets with a high radius of curvature turn into large droplets with a small radius of curvature. When two drops are spread, become one large drop. Therefore, after long-term storage, the droplet distribution changes to large sizes, and the Nanoemulsion becomes opaque.

Ostwald ripening has been shown to be a problem when the formulation is administered. Several theories have been proposed to explain Ostwald ripening, among them the LSW theory that directly explains the factors involved in Ostwald ripening.

Tadros et al showed that the addition of a small volatile oil (squalane) can reduce the diffusion of small oil droplets from small to small to large steam. Another method to prevent the result of Ostwald ripening is to add a polymeric gel to the interface, which increases the elasticity of the grains and further reduces the result of Ostwald ripening [69].

The effect of surfactant mixing ratio on Nanoemulsion stability when phase shift method is used as Nanoemulsion preparation method. The formation of O/W Nanoemulsions was studied by the PIT emulsification method in water/mixture/oil of non-ionic surfactant systems. The lipophilic liquid-water properties were modified by mixing polyoxyethylene 4-lauryl ether (C12E14) and polyoxyethylene 6-lauryl ether (C12E6). Accumulation was performed in samples with constant oil concentration (20% by weight) by rapid cooling from the HLB temperature corresponding to 25 °C. Nanoemulsions with droplet radii of 60 to 70 nm and 25 to 30 nm obtained a total surfactant concentration of 4 and 8 wt.% respectively. Nanoemulsion with surfactant ratio of 8% showed the best stability compared to Nanoemulsion with surfactant concentration of 4% [70].

In another study, successfully demonstrated the effect of process changes on the size of small Nanoemulsion, resulting in increased Nanoemulsion stability. In this work, they studied the structure and stability of n-decane in an aqueous Nanoemulsion produced by the PIT method using polyoxyethylene lauryl ether as a surfactant. The result of this work clearly shows that the changes in the process such as heating and cooling of the heating of the composition and the final temperature when the mixture is cooled after the phase change [71].

In another study, the effects of surfactant concentration and surfactant concentration on the processes of droplet dissolution and mixing in the formation of a decane Nanoemulsion in water in a high-pressure homogenizer were investigated. Food proteins, phosphatidylglycerol and phosphatidylcholine were used as surfactants at different concentrations and the droplet size was controlled for each formulation. It was found that for proteins, the increase of droplet volume with time is linear, indicating the Ostwald ripening process. Although was introduced upon storage at the lowest concentration of phospholipids used, no concentrations were found in the emulsifier concentration, indicating that the phospholipid interfaces were designed to prevent staining with [72]. Surfactant mixtures have been shown to increase stability compared to a single surfactant by Porras M [73]. It was also shown that the stability of the

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electronic and spatial solutions can be controlled by the electrical double charge and the thickness of the droplet surface layer formed by the nonionic emulsifier [74].

VI. PREVENTION OF OSTWALD RIPENING

Theoretically, using an oil phase with minimal aqueous solubility can indefinitely prevent Ostwald ripening. However, this is often impractical, so lipid blends of medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) are typically used to enhance formulation complexity and inhibit Ostwald ripening. One effective strategy is the trapped species method, which involves encapsulating a prone dispersed phase within a phase that resists Ostwald ripening. The internal osmotic pressure from the trapped species counteracts Laplace pressure, thereby slowing down the coarsening of the Nanoemulsion [75]. Research by Delmas et al. demonstrated that adding wax to a standard oil blend of mono-, di-, and triglycerides can completely halt Ostwald ripening of Nanoemulsions, even at elevated temperatures [76]. While the trapped species method effectively reduces Ostwald ripening, it restricts the potential for size reduction because the immobile species within the droplet limits this process. To address this limitation, another technique called evaporation ripening has been developed. In this approach, an oil-in-water (O/W) emulsion is created using an oil phase that often contains a polymer dispersed in a highly volatile solvent. When this system is heated, the solvent evaporates, leaving behind concentrated polymer droplets. The evaporation of the volatile solvent creates a constant sink that overcomes the internal osmotic pressure from the dense polymer droplets, allowing the emulsion to become finer over time and effectively preventing Ostwald ripening for extended periods [77]. Additionally, Nam et al. demonstrated that O/W Nanoemulsions can be successfully stabilized against Ostwald ripening by using surfactants that create a physically robust interphase. They employed an amphiphilic block copolymer, poly(ethylene oxide)-poly(ε-caprolactone) (PEO-b-PCL), which is soluble in the oil phase at higher temperatures but recrystallizes upon returning to ambient temperature, thus inhibiting size growth from Ostwald ripening [78].

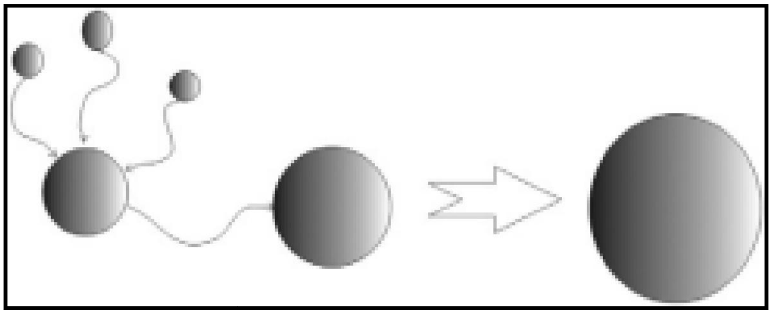

Fig no. 5: - Pictorial depiction of how Ostwald ripening leads to growth of droplet size [8].

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VII. APPLICATIONS OF NANOEMULSION

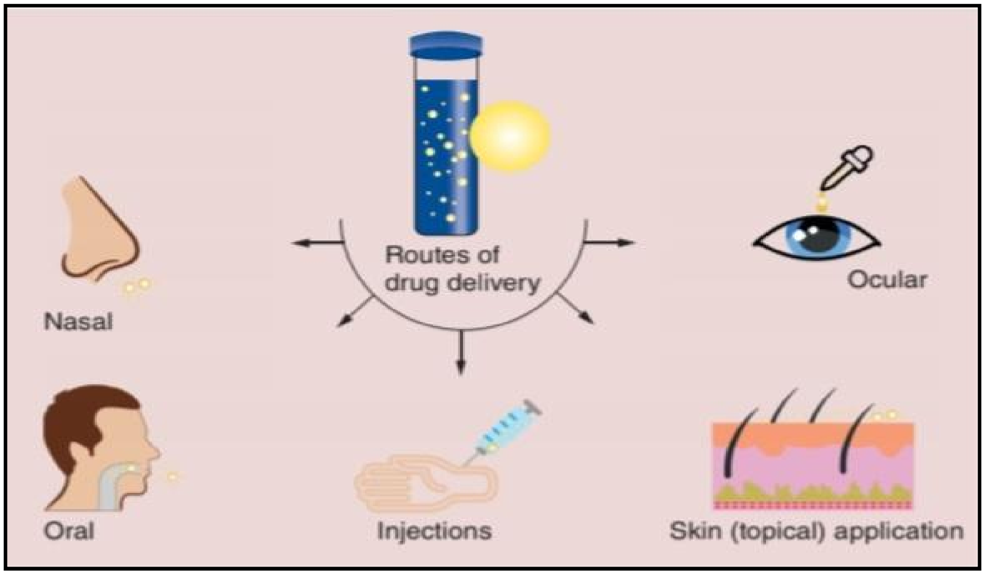

Fig no. 6: - Applications of nanoemulsions in route of drug delivery system [79].

Delivery of Drugs: -

I. Ocular Delivery: -

Oil in water emulsion improves topical lipophilic medication distribution to the eye. Unquestionable, lipophilic drug-loaded oil in water (o/w) ocular emulsions offer a better balance between ocular bioavailability enhancement and patient comfort after topical instillation into the eye. For instance, pilocarpine, cyclosporine A, piroxicam, and indomethacin [80].

II. The Nasal Route: -

The nasal route has drawn a lot of interest since it has several benefits over parenteral and oral administration, particularly because it bypasses the liver. By solubilizing the medication in the inner phase of an emulsion, Nanoemulsions improve absorption and extend the period that emulsion droplets are in contact with the nasal mucosa [80].

III. Oral Route: -

Availability of water-soluble drugs is low due to low dissolution rate. Therefore, o/w Nanoemulsion for these drugs increases solubility, absorption and bioavailability after oral administration [81].

IV. Topical Route: -

This substance can penetrate the skin layer in three ways. To improve drug targeting and control the distribution of drugs through blood and lymphatic vessels. Nano-sized emulsion has the ability to penetrate skin pores and achieve systemic delivery. Nanoemulsion is considered a useful method with advantages such as low preparation cost, stability during storage, absence of organic solvent and thermodynamic stability [81].

V. Injectable route: -

Nanoemulsions have different applications. It is used to transport drugs with lower bioavailability and lower therapeutic index. Chlorambucil, a lipophilic anticancer agent, has been administered parenterally as a Nanoemulsion (produced using ultrasound and high homogenization) for the treatment of ovarian and breast cancer [82].

VI. Cosmetics: -

Because of their lipophilic interior, which makes them more suited for transporting lipophilic compounds than liposomes, Nanoemulsions are significant as potential vehicles for the dispersion of active ingredients in specific skin

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layers and for controlled delivery in cosmetics. Nanoemulsion are suitable for use in cosmetics since they are non-toxic and easy to apply to the skin. Additionally, there is no sedimentation, flocculation, or creaming that resembles macro emulsions. The effect of possible irritation brought on by surfactants can be prevented during manufacture by employing high-energy equipment [83].

VII. Oil Industry

Oil field chemical-containing Nanoemulsions are frequently employed for flow assurance, well treatments (such as acidizing and scaling inhibition), and deposit removal or cleanup. The EOR mechanism, which aids in the recovery of residual oil from the reservoir rock, is most significantly impacted by Nanoemulsion. Because the Nanoemulsions' droplet size is smaller than the pore throats in gravel packs and reservoir matrix rock, they have good penetration and infectivity without filtration.

Therefore, the two phases are not affected by gravity-driven separation because of their different densities. The use of materials, advancements, tools, and techniques in Nanoemulsion, where the critical length scale is roughly 1-100 nm, is represented. According to the proposed physicochemical characteristics of the Nanoemulsion, capillary forces effectively recover the trapped residual oil that was discovered in the reservoir rocks following primary and secondary recovery [84].

VIII. Targeted Drug Delivery:

Targeted drug delivery systems aim to deliver therapeutic agents specifically to the site of action, minimizing side effects and improving treatment efficacy. Nanoemulsions can be engineered for site-specific delivery in the following ways:

Ligand Targeting: - Surface modification of Nanoemulsions with specific ligands (e.g., antibodies, peptides, or small molecules) can direct the drug to specific cell receptors or tissues. This approach is particularly useful for targeting cancer cells or inflamed tissues [85].

Passive Targeting: -

Due to their small size, Nanoemulsions can passively accumulate in specific tissues through the Enhanced Permeability and Retention (EPR) effect—a phenomenon seen in tumours and inflamed tissues. This allows for high local drug concentrations with minimal systemic exposure [85].

IX. Smart Delivery Systems: -

Smart drug delivery systems are designed to respond to specific stimuli (e.g., pH, temperature, enzymes, or external magnetic fields) to release the drug in a controlled manner. Nanoemulsions can be incorporated into such systems for more precise and controlled drug release [85].

X. Gene Delivery: -

Nanoemulsions are used to deliver plasmid DNA, siRNA, or CRISPR-related components to specific cells. Their lipid composition allows for the incorporation of nucleic acids and facilitates their release inside target cells [86].

XI. Reduced Toxicity: -

Nanoemulsions can reduce the toxicity associated with gene delivery by providing a safer vehicle compared to viral vectors, which can have immunogenic and safety concerns [86].

XII. RNA-Based Therapies: -

mRNA Vaccine Delivery: The development of mRNA vaccines (like the Pfizer-BioNTech and Moderna COVID-19 vaccines) has underscored the role of lipid nanoparticles, a form of Nanoemulsion, in stabilizing and delivering mRNA into cells. Nanoemulsions protect mRNA from enzymatic degradation and facilitate its release into cells, where it can be translated into proteins [87].

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VIII. NANOEMULSION IN CLINICAL TRIALS.

Table no.3: - Nanoemulsion in clinical trials.

Condition	Encapsulated Drug	Clinical trial phase	Route	Sponsor	Clinical trials, gov identifier
Osteoarthritis	Diclofenac	II (completed)	Topical	Pharmos	NCT00484120
Women (menopause) libido	Testosterone	II (not completed)	Transdermal	University Potiguar	NCT02445716
Multiple actinic keratosis	Aminolevuli-nic acid	IV (Completed)	Topical	Joint Authority for Paijat-Hame ¨ Social and Health Care	NCT02685592
Lentigo maligna	5-Aminolevulinic acid	IV (completed)	Topical	Joint Authority for Paijat-Hame ¨ Social and Health Care	NCT0268559
Leukemia	Propofol	II, III	Intravenous	Cristália Produtos Químicos Farmacêuticos Ltd	NCT0132607

IX. DISADVANTAGES

1. Stabilising the nanodroplets requires the use of a high concentration of surfactant and cosurfactants [90].
2. One significant problem storage of Nanoemulsion formulations. The cosmetics industry has noted that the delivery of Nanoemulsions is expensive [90].
3. The stability of Nanoemulsions is influenced by environmental conditions such as pH and temperature [91].
4. Limited ability to dissolve materials with high melting points [91].
5. The Oswald ripening effect leads to the instability of Nanoemulsions [21].

X. LIMITATIONS OF NANOEMULSION

1. Despite the fact that this plan offers buyers amazing focal points as a delivery system, the limited use of Nanoemulsion formulation is occasionally caused by the smaller size of the beads. The following are some Nanoemulsion restrictions [92].
2. Because the size reduction of beads is problematic and necessitates the use of unusual tools and techniques, the production of Nanoemulsion formulation is an expensive process. The homogeniser arrangement, for example, is an expensive process. Again, microfluidization and ultrasonication require significant financial backing [91].
3. Food Nanoemulsions can reduce the dosage and increase the effectiveness of bioactive compounds, and improve general food properties such as texture, taste and stability. However [93], Nanoemulsions are thermodynamically unstable systems that can be degraded in various physical or chemical processes [94].
4. Decreasing the droplet size in Nanoemulsions usually increases stability to separation and aggregation but decreases chemical stability due to increased contact between oil phases and water phase [95].

XI. CONCLUSIONS

Nanoemulsions are versatile and promising systems for drug delivery due to their ability to enhance the bioavailability, stability, and controlled release of lipophilic drugs. Their small droplet size offers kinetic stability and prevents common destabilization issues such as coalescence and creaming. These systems are especially advantageous for oral, topical, and parenteral drug delivery, targeting specific sites with precision and reducing side effects. Applications extend to cosmetics, antimicrobial agents, and gene therapies, with their adaptability across various delivery routes being a key advantage. Despite challenges like the high cost of production and stability issues such as Ostwald ripening, the development of Nanoemulsions has opened new pathways for the effective formulation of poorly soluble therapeutic agents. The field of Nanoemulsion research is expected to grow with advancements in emulsification techniques and the development of cost-effective and scalable methods.

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