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A COMPREHENSIVE REVIEW OF "NANOEMULSION"

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ABSTRACT

Nanoemulsions are form of novel drug delivery system (NDDS) which is used to increase the solubility and stability which results in the increase of bioavailability of medications that are not highly water soluble. Nanoemulsions are submicron sized emulsions which work as medication carriers for enhancing the delivery of therapeutic substances. Droplet size of nanoemulsion ranges from 20 to 200nm. These are thermodynamically stable isotropic systems made up of two immiscible liquids which are mixed up with surfactants and co-surfactant (emulsifying agents) to reduces the surface and interfacial tension. Nanoemulsions are prepared by using two methods these are high energy methods and low energy methods. A variety of analytical methods are described to evaluate droplet size, stability, and interaction with biological systems in the context of nanoemulsion assessment. It includes physical and chemical instabilities along with thermodynamic stability. Nanoemulsions have potential use in cosmetics, diagnostics, medicinal treatments, and biotechnology. Commercial products, marketed products and patented nanoemulsion are also discussed.

KEYWORDS: Nanoemulsion, Novel Drug Delivery System (NDDS), Droplet size.

INTRODUCTION

Nanoemulsions are form of Novel Drug Delivery System (NDDS). They are the novel formulation which are designed to improve the administration of those drugs which are poor with their water solubility.[1] There are many new drugs designed which have an issue with their low solubility and leads to the poor absorption of the drug.[2] Natural plant compounds have limited therapeutic efficiency due to their low water solubility, bioavailability, stability, metabolism, active efflux mechanism, and first-pass metabolic effects.[3] NDDS and nanoemulsion serves as a framework or guide for development of different type of drug delivery systems. On other hand there are many limitations of traditional drug delivery methods, this method or system might be ineffective for transporting certain body parts. Researcher and scientists have been used the various ways to enhance the bioavailability, permeability, drug solubility and

sustainability.[4] To deal with these difficulties novel drug delivery system and carriers should try to satisfy important needs such as delivers medicine in a controlled manner coordinated with the body's demands throughout therapy.[5] According to pharmaceutical research, adding poorly water-soluble medicines into emulsion-based delivery system can significantly increase their bioactivity, making them more effective in therapeutic uses.[6] Novel drug delivery systems, like nanocarrier technology, have successfully addressed the physicochemical and pharmacokinetic challenges associated with phytochemicals. These advancements improved controlled release and improved the effectiveness of biological agents. This discovery highlights nanomedicine's promising future as a treatment option for a wide range of chronic illnesses.[7]

EMULSION

An emulsion is a mixture of two liquids that don't mix, where one liquid is spread as droplets throughout the other. The liquid surrounding the droplets is called the continuous or external phase, while the liquid forming the droplets is called the dispersed, internal, or discontinuous phase.[8] Emulsions being used in a wide variety of industries, from the food we eat to the medicines we take, as well as in farming, cosmetics, and even the petroleum industry.[9] Emulsions aren't just water and oil; they can also include solids or gases. They are naturally unstable because oil and water don't like to mix. However, some emulsions are stable due to tiny droplet sizes and a protective film around the droplets.[10]

CLASSIFICATION OF EMULSION

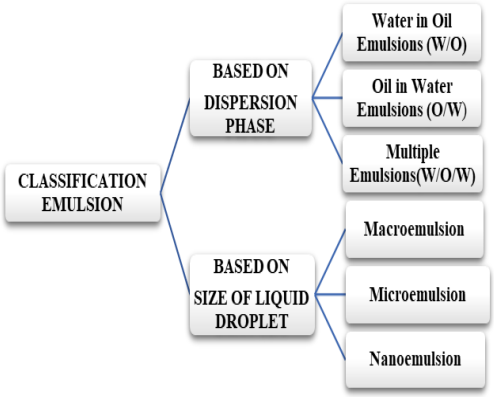

Fig. no. 1: Classification of Emulsion.[11]

BASED ON THE DISPERSION PHASE

- **Water in oil emulsions (w/o)** are characterized by water droplets being dispersed within a continuous oil (hydrophobic) phase.[12]
- **Oil in water emulsions (o/w)** oil is the dispersed phase, and water is the continuous phase.
- **Multiple emulsions (w/o/w)** which are stabilized by both hydrophilic and hydrophobic surfactants, are complex systems containing small droplets within larger droplets, all dispersed in a continuous phase, such as water droplets within oil droplets suspended in water (W/O/W).[13]

BASED ON SIZE OF LIQUID DROPLET.[11]

- **Macroemulsion** 0.2 to 50 micro-meter (µm)
- **Microemulsion** 0.01 to 0.2 micro-meter (µm)
- **Nanoemulsion** 20 to 200 nanometers. (nm)

NANOEMULSION

Nanoemulsions are kinetically stable dispersions of two immiscible liquids, such as oil and water, with nanometer-scale droplets.[14,15] The droplet size of nanoemulsions typically falls within the range of 20 to 200 nanometers, typically around 100 nm, giving them unique properties like high surface area and optical transparency. Nanoemulsions can be oil-in-water (O/W) or water-in-oil (W/O). They are created using high and low-energy methods like high-pressure homogenization and ultrasonication. These emulsions enhance drug solubility, stability, and delivery, finding applications in drug delivery, cosmetics, and food industries.[14,16] Nanoemulsions are versatile templates for creating polymer latex particles and nanoporous polymeric solids. In the pharmaceutical field, nanoemulsions composed of safe ingredients are used to develop oral drug delivery systems. These emulsions are also known by various names, including miniemulsion, ultrafine emulsions, and submicron emulsions, highlighting their small size and unique properties.[17]

Surfactants play a crucial role in emulsions by reducing the surface tension between the two liquids that don't mix. This reduction in surface tension prevents the emulsion from breaking down, as the system naturally tries to minimize its energy. Surfactants essentially create a barrier, stopping the droplets from merging together (coalescence) and helping to keep the emulsion stable.[18] Phase behaviour studies indicate that droplet size in nanoemulsions is controlled by the surfactant phase structure, whether it's a continuous microemulsion or lamellar structure, at the point of inversion caused by temperature or composition changes. Research on nanoemulsion formation using the phase inversion temperature method demonstrates a link between the smallest possible droplet size and the complete dissolving of the oil within a microemulsion's bicontinuous phase. This relationship holds true regardless of whether the initial phase equilibrium consists of a single phase or multiple phases.[19] To obtain small sized nanoemulsions, it is important to apply an appropriate stirring rate and to stay in the cubic liquid crystal phase with sufficient time to mix all the oil into the liquid crystal.[20]

ADVANTAGES OF NANOEMULSION[19,21]

1. **Higher surface area and free energy:** Because of their tiny droplets, nanoemulsions boast a large surface area and high energy state, making them highly effective for applications like drug delivery.
2. **Stability:** Nanoemulsions resist separation and remain uniform, avoiding issues like creaming, flocculation, coalescence, and sedimentation**.**
3. **Versatility in Formulations:** Nanoemulsions offer versatility in product development, allowing for formulations like foams, creams, liquids, and sprays.
4. **Non-toxic and Non-irritant:** Their safety profile, being non-toxic and non-irritant, makes them appropriate for use on skin and mucous membranes.
5. **Oral Administration:** If the formulation contains biocompatible surfactants, they can be administered orally.
6. **Suitability for Human and Veterinary Therapeutic Purposes:** The cell-friendly nature of nanoemulsions makes them a good option for developing human and animal treatments.
7. **Better Uptake in Cell Cultures:** Nanoemulsions boost the absorption of oil-soluble supplements by cells in culture, which supports better growth and facilitates effective safety studies for oil-soluble drugs.
8. **Substitute for Liposomes and Vesicles:** As a replacement for liposomes and vesicles, nanoemulsions can create lamellar liquid crystalline phases that surround their droplets.

9. **Enhanced Skin Penetration**: The tiny size of nanoemulsions allows them to bypass the skin's uneven surface, leading to improved penetration of active ingredients.
10. **Primary Step in Nanocapsules and Nanospheres Synthesis**: Nanoemulsions are essential for creating nanocapsules and nanospheres using techniques like nanoprecipitation and interfacial polycondensation.
11. **Enhanced bioavailability:** Nanoemulsions significantly improve the solubility and absorption of fat-soluble substances, which is especially beneficial for poorly soluble drugs. This enhanced absorption can lead to better treatment outcomes, even with lower doses of medication.
12. **Targeted delivery**: Nanoemulsions can be engineered to deliver drugs directly to specific tissues or cells, improving treatment effectiveness and minimizing side effects. This targeted approach is particularly valuable in cancer therapy and other specialized treatments.
13. **Biocompatibility**: Because many of the ingredients used in nanoemulsions (like natural surfactants and oils) are highly biocompatible, they are safe and suitable for use in both pharmaceutical and cosmetic products.
14. **Flexibility in administration routes**: Nanoemulsions can be tailored for different delivery methods, such as oral, topical, and injectable, which broadens their applications in healthcare and advances therapeutic approaches.

DISADVANTAGES OF NANOEMULSION [19,21]

1. **Limited capacity for hydrophilic compounds:** Nanoemulsions are great at carrying fat-soluble molecules, but their ability to handle water-soluble ones isn't as good as other delivery systems, like liposomes. This can be a problem when a formulation needs to include water-based ingredients.
2. **High energy requirements**: Nanoemulsion production often relies on energy-intensive techniques like high-pressure homogenization and ultrasonication. These methods can be costly and may not be feasible for large-scale manufacturing. Furthermore, the heat generated during these processes could degrade fragile molecules.
3. **Thermodynamic instability**: While nanoemulsions are more stable than traditional emulsions, they can still degrade over time, especially when exposed to changing temperatures, pH levels, or salt concentrations. Poor formulation or inadequate stabilization can lead to separation or droplet merging.
4. **Potential Toxicity:** The potential toxicity or irritant properties of certain surfactants in nanoemulsions can restrict their applicability.
5. **Complex Formulation:** Achieving the right balance of ingredients to create a stable nanoemulsion can be challenging and requires precise formulation techniques.
6. **Storage Stability:** Despite their typical stability, nanoemulsions can degrade over time due to temperature, pH, or other environmental changes.
7. **Regulatory Hurdles:** Due to potential safety and long-term health concerns, the application of nanoemulsions in food and drug products might encounter regulatory obstacles.

COMPONENTS OF NANOEMULSION

The basic components which are used to formulate nanoemulsions are as follows:

1. Oil phase
2. Aqueous phase
3. Surfactant
4. Co-surfactant
5. Preservatives

6. Antioxidants and chemo protectants
7. Additives

1. Oil phase

Nanoemulsions are colloidal system in which the size ranges from 20-200 nm in oil in water emulsion. It helps to improve the efficacy of lipophilic drugs, vitamins or organic compounds. The selection of lipids or oils for use in nanoemulsions is primarily based on the solubility of the drug.[22] The oil plays a crucial role in maximizing solubilizing capacity for a selected drug candidate in nanoemulsion formulations, offering a vital approach with high drug loading ability. Both naturally and synthetically occurring mixtures of oils and fats, primarily triglycerides, contain long-chain fatty acids.[23] Triglycerides are classified as long-chain triglycerides (LCT), medium-chain triglycerides (MCT), or short-chain triglycerides (SCT) based on the length of their fatty acid chains. Triglycerides, particularly those with short chains (12 carbons), play a crucial role in reducing unsaturation levels and preventing oxidative degradation. The choice of oil phase is influenced by the solubility of the drugs being used, which is essential for forming nanoemulsions. Oil is vital for facilitating the delivery of drugs into intracellular compartments, which is important for improving the water solubility of drugs with low water solubility.[19] McClements and Xiao studied how the composition and droplet size of curcumin nanoemulsions affect their bioavailability. Bio-relevant tests showed that nanoemulsions formulated with long-chain triglycerides (LCT) and medium-chain triglycerides (MCT) resulted in higher systemic availability compared to those made with short-chain triglycerides (SCT), as LCT and MCT nanoemulsions were digested less extensively.[6]

Table no. 1: List of Oils.[21]

Name	Chemical Name
Witepsol	90:10 % w/w c12 Glyceride tri: diesters
Myritol 318	C8/C10 triglycerides
Isopropyl Myristate	Myristic acid isopropyl ester
Captex 355	GlycerylTricaorylate/Caprate
Captex 200	Propylene Dicaprylate/Dicaprate Glycol
Captex 8000	GlycerylTricaprylate (Tricaprylin)

2. Aqueous phase

The continuous phase in a nanoemulsion distributes the dispersed phase uniformly, maintaining its stability and solubility. It facilitates the dissolution of hydrophobic substances in aqueous systems, enhancing the formulation's stability. The viscosity of the continuous phase can be customized for various applications, such as topical formulations or oral suspensions. It also collaborates with surfactants to decrease surface tension, creating stable droplets for uniform distribution and consistent delivery of encapsulated substances.[19]

3. Surfactant

Surfactants, molecules or ions, adsorb at interfaces to alter interfacial properties, controlling interfacial phenomena. They are crucial for nanoemulsion preparation, lowering energy barriers, increasing wetness, and enhancing drug solubility by solubilization, thereby increasing dissolution rate.[24] Surfactants have distinctive structures that feature both hydrophobic (non-polar) and hydrophilic (polar) components.[25] It works as a self-Nanoemulsifying, self-emulsifying, and self-Micro emulsifying agent, able to dissolve poorly water-soluble drug. Non-ionic surfactants have a good balance between water-loving and oil-loving properties, which is important for making nanoemulsions. However,

using too much surfactant can be harmful due to chemical toxicity, so safety is a major concern when choosing surfactant Non-ionic surfactants are generally more stable and safer than ionic ones because they are non-toxic and maintain their structure well under different conditions.

CLASSIFICATION OF SURFACTANTS[25]

- **Anionic surfactant:** Contain negative charge.
- **Cationic surfactant:** Contain positive charge.
- **Amphoteric surfactant:** Contain both negative positive charges.
- **Non-ionic surfactant:** Does not contain any charge.

Table no. 2: List of Surfactants.[21]

Name	Chemical Name
PlurolOleique CC	Polyglyceryl-3 oleate
Labrafil M 1944	Oleoyl macrogol-6 glycerides
Tween 80	Polyoxyethylene (20) sorbitanmonooleate
Labrasol	Caprylocaproyl macrogol-8 glycerides
Cremophor RH 40	Polyoxly 40 hydrogenated castor oil
Tween 20	Polyoxyethylenesorbitanmonolaurate

4. Co-surfactant

When a surfactant alone is inadequate, a co-surfactant can assist reduce oil-water tension and generate a stable nanoemulsion, resulting in a stable solution.[26] Co-surfactants, single-chain molecules, help maintain fluidity at interfaces and prevent rigidity by interacting with surfactants, oil, and water. They create a monomolecular layer, separating components and ensuring stability. Co-surfactants are crucial in Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) to prevent unwanted interactions between oil and water, ensuring effective drug delivery.[19]

Table no. 3: List of Co-surfactants.[24]

Name	Chemical Name
Propylene glycol	1,2 propanediol
Transcutol P	Diethylene glycol monoethyl ether
Ethylene glycol	Ethane 1,2 diol

5. Preservatives

Nanoemulsions require preservatives with low toxicity, stability, compatibility, affordability, availability, and acceptable sensory properties. They should have a broad antimicrobial spectrum to target microorganisms in both oil and water phases. Parenteral nanoemulsions often avoid preservatives due to potential toxicity. Acids and derivatives are commonly used for antifungal applications, while alcohol-based preservatives are used in ophthalmic formulations. Broad-spectrum preservatives like phenolics and quaternary ammonium compounds ensure stability and safety in nanoemulsion formulations.[27]

6. Antioxidants and chemo protectants

To prevent oxidation in nanoemulsions, synthetic lipids that lack sensitive acyl groups can be used, but this is not always practical. As a result, antioxidants are often added to enhance oxidative stability. Antioxidants work in different ways: **reducing agents** (e.g., ascorbic acid, sodium bisulfide, metabisulfite, thiourea, and sodium formaldehyde) neutralize oxidizing agents; **blocking agents** (e.g., ascorbic acid esters, butyl hydroxytoluene, and tocopherols) prevent oxidation reactions; and **synergists** (e.g., ascorbic acid, citric acid, phosphoric acid, and tartaric acid) enhance the

effectiveness of other antioxidants. Since nanoemulsions are typically transparent, they allow visible and UV light to penetrate the oil layers, which can accelerate photodegradation of drug molecules. To counter this environmental degradation, chelating agents, pH stabilizers, and UV protectants are sometimes included in formulations to protect the product's stability and efficacy.[28]

7. Additives

Nanoemulsions can be made more stable by adding specific additives that help improve their ability to stay intact and effective over a long period. These additives ensure the nanoemulsion remains in good condition during storage, preventing issues like separation or degradation.[29]

Table no. 4: List of Preservatives, Antioxidants, Additives.[30]

Components	Examples
Preservatives	Benzalkonium Chloride (0.01%w/v) and Propyl Paraben
Antioxidants	α-tocopherol and Ascorbic acid
Additives	Maltose and Sucrose

FACTORS AFFECTING THE CHOICE OF EXCIPIENTS FOR NANOEMULSION

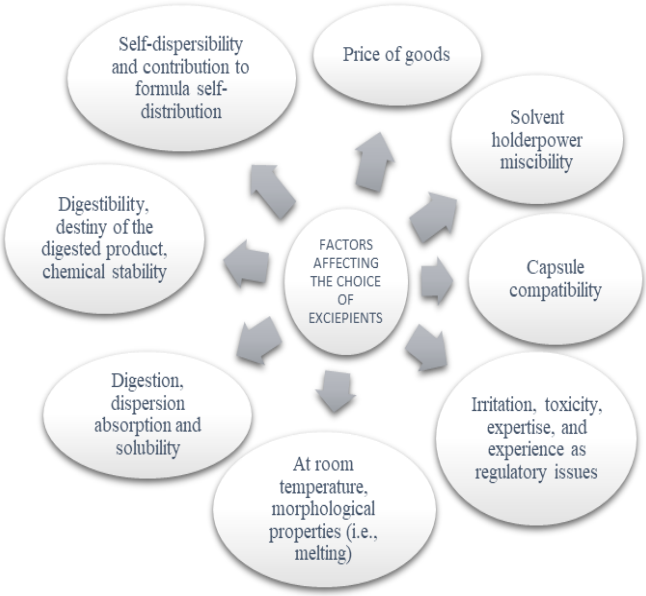

Fig. no. 2: Factors Affecting the Choice of Excipients for Nanoemulsion.[31]

METHOD OF PREPARATIONS[19,32,33]

Nanoemulsions can be prepared using two main approaches: high-energy methods and low-energy methods, each with distinct techniques and applications. By using a combined method that includes both high-energy and low-energy emulsification, it is possible to create reverse nanoemulsions in very thick systems.

HIGH-ENERGY METHODS

These methods use mechanical energy to reduce larger droplets into tiny nanoscale droplets. They need special equipment and a lot of energy. Some common techniques are:

- **High-energy stirring:** By applying strong mechanical stirring
- **Ultrasonic emulsification:** Employing ultrasound waves to create small droplets.
- **High-pressure homogenization:** Pushing the mixture through tight spaces under high pressure

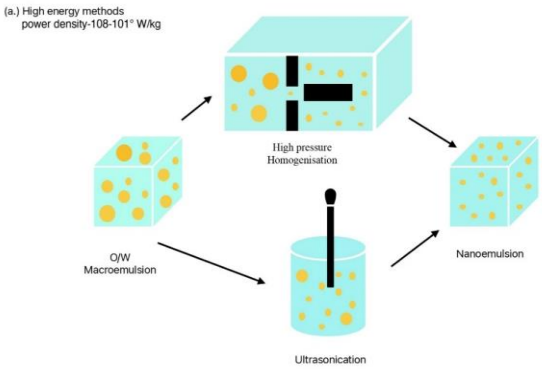

Fig. no. 3: High Energy Methods.[32]

Microfluidics and membrane emulsification: Using small-scale devices to accurately manage how droplets are formed.

LOW-ENERGY METHODS

These methods use the chemical energy stored in the components or environmental changes to form nanoemulsions. Techniques include.

Phase inversion temperature (PIT): Adjusting the temperature to modify the properties of surfactants and trigger emulsification.

Emulsion inversion point (EIP): Introducing water to switch the emulsion's phase.

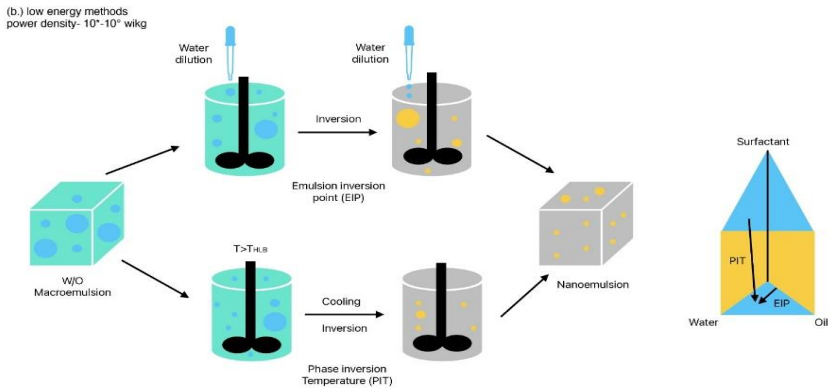

Fig. no. 4: Low Energy Methods.[32]

Spontaneous emulsification: Allowing droplets to form naturally due to changes in composition or conditions like pH or ionic strength.

CHARACTERIZATION OF NANOEMULSION

Different characterization nanoemulsion include parameters transmission for electron microscopy, nanoemulsion droplet size analysis, viscosity determination, refractive index, in vitro skin 2, permeation studies, skin irritation test, in vivo efficacy study, thermodynamic stability studies, and surface characteristics. The surface charge of the nanoemulsion droplets has a marked effect on the stability of the emulsion system and the droplet in vivo disposition

and nanoemulsion droplets were in the size range of 25-40 nm with some particle aggregates in the size range of 100-150 nm.[34] The size distribution of nanoemulsion droplets can be measured using either light scattering techniques or electron microscopy. This method is considered one of the best ways to predict the stability of nanoemulsions.[35]

1. **Conductance Measurement:** In oil-in-water (O/W) nanoemulsions, where water is the external phase, they conduct electricity well. In contrast, water-in-oil (W/O) nanoemulsions do not conduct electricity as effectively because water is the internal or dispersed phase. Measuring electrical conductivity is very helpful for identifying the type of continuous phase and detecting any phase changes.[30,36] A sudden rise in conductivity was noticed in some water-in-oil (W/O) nanoemulsion systems at low volume fractions. This behaviour is thought to indicate "percolative behaviour," which refers to the exchange of ions between droplets before bicontinuous structures are formed. Dielectric measurements are an effective way to investigate both the structure and dynamic characteristics of nanoemulsion systems.
2. **Dilutability Test:** Oil-in-water (O/W) nanoemulsions can be diluted with water, while water-in-oil (W/O) nanoemulsions cannot. W/O nanoemulsions can also transform into O/W nanoemulsions through phase inversion.[34]
3. **Polydispersity:** The average sizes and polydispersity index of the samples were determined using Photon Correlation Spectroscopy. These measurements were conducted at 25°C with a helium-neon (He-Ne) laser.[30]
4. **Dynamic Light-Scattering measurements:** The dynamic light scattering (DLS) measurements are conducted at a 90° angle using a DLS spectrophotometer that employs a neon laser with a wavelength of 632 nm. The data is processed by the instrument's built-in computer.[37]
5. **Dye Solubilization:** A water-soluble dye is dissolved in the water phase of a water-in-oil (W/O) globule but can be dispersed in an oil-in-water (O/W) globule. Conversely, an oil-soluble dye is dissolved in the oil phase of an O/W globule but can be dispersed in a W/O globule.[30,37]
6. **Phase analysis:** To identify the type of nanoemulsion that has formed (either oil-in-water or water-in-oil), the phase system is determined by measuring the electrical conductivity with a conductometer.[36]
7. **Transmission Electron Microscopy (TEM):** The morphology and structure of the nanoemulsion were examined using transmission electron microscopy. A combination of bright field imaging at increasing magnifications and diffraction modes was employed to reveal the shape and size of the nanoemulsion droplets. To make observations, a drop of the nanoemulsion was placed directly on a holey film grid and examined after it had dried.[30]
8. **Viscosity measurement:** The viscosity of nanoemulsions with various compositions can be measured at different shear rates and temperatures using a Brookfield-type rotary viscometer. The sample chamber of the instrument should be kept at a temperature of 37 ± 0.2°C using a thermobath, and the samples need to be immersed in it prior to testing.[30]
9. **pH:** The pH of the formulation was checked using a pH meter.[37]
10. **Interfacial Tension:** The formation and characteristics of nanoemulsions can be analyzed by measuring interfacial tension. Very low interfacial tension values are linked to phase behaviour, especially the presence of surfactant phases or middle-phase nanoemulsions that are in equilibrium with both aqueous and oil phases. A spinning-drop apparatus can be used to measure very low interfacial tension. The interfacial tension is determined by analyzing the shape of a drop of the low-density phase as it rotates within a cylindrical capillary filled with the high-density phase.[34]
11. ***In Vitro* Skin Permeation Studies:** In vitro skin permeation studies were conducted using a Keshary-Chien diffusion cell on abdominal skin obtained from male rats weighing 250 ± 10 grams. The setup included a recirculating water bath and 12 diffusion cells. The skin samples were placed between the donor and receiver chambers of vertical diffusion cells. The receiver chambers contained freshly prepared water with 20% ethanol and were maintained at 37°C, with continuous stirring at 300 rpm. The formulations were added to the donor chamber,

and at intervals of 2, 4, 6, and 8 hours, 0.5 ml of the solution from the receiver chamber was taken out for gas chromatography analysis, immediately replacing it with an equal volume of fresh solution. Each experiment was repeated three times.[35]

12. **Zeta potential:** The Zeta PALS instrument measures zeta potential. It is used to measure the charge on the droplet's surface in nanoemulsion.[38]
13. **Determination of Encapsulation Efficacy:** A specific amount of the formulation is weighed and dispersed in an organic solvent using ultrasonic methods to determine the drug content. The drug is then extracted into a suitable buffer solution. By analyzing the extract spectrophotometrically at its maximum absorbance wavelength (λmax) and comparing it to appropriate dilutions against a blank, the drug content is calculated. These measurements are used to determine the drug's entrapment efficiency (EE) and loading efficiency (LE). Loading efficiency (LE) is defined as the drug content in the final product (mg) divided by the total product weight (mg), multiplied by 100.[39] On the other hand, drug entrapment efficiency (EE) is defined as the drug content in the final product (mg) divided by the total amount of drug added (mg), multiplied by 100. Additionally, drug content can also be evaluated using reverse-phase high-performance liquid chromatography (HPLC).[40]
14. **Percent Transmittance:** The percent transmittance of a prepared formulation is determined using a UV spectrophotometer at a specified wavelength, with distilled water serving as the blank. A nanoemulsion is considered transparent if it's percent transmittance exceeds 99%. Harika and Debnath reported a nanoemulsion of amphotericin B with a percent transmittance greater than 97%.[16]
15. **Fluorescence Test:** Many oils exhibit fluorescence when exposed to UV light. When an oil-in-water (o/w) type nanoemulsion is viewed under a microscope and illuminated with UV light, the fluorescence manifests as spots rather than covering the entire field. Conversely, in the case of water-in-oil (w/o) emulsions, the fluorescence appears differently.[38]

INSTABILITIES IN NANOEMULSION [19,21,37]

PHYSICAL INSTABILITIES

1. **Coalescence:** Coalescence is an irreversible process in which dispersed droplets merge to form larger droplets. This process continues until the emulsion breaks apart, resulting in a complete separation of the oil and water phases. Coalescence occurs when emulsion droplets can overcome the repulsive energy barrier and come close together. Once they reach this proximity, their stability against coalescence largely depends on the strength of the interfacial film that separates them. The coalescence process starts with the drainage of the continuous phase liquid films between the oil droplets as they get closer and begin to distort, ultimately leading to the rupture of the film. Droplets are protected against coalescence by rigid, closely packed elastic films created by specific emulsifier mixtures, as well as thick multi-layered films formed by various polymers, which are highly resistant to film rupture.
2. **Ostwald Ripening:** Ostwald ripening is a process where larger droplets grow at the expense of smaller ones in emulsions with smaller droplets (less than 600 nm) due to the Kelvin effect. This occurs when smaller droplets have higher solubility due to their reduced radius. When these droplets dissolve, their molecules diffuse through the continuous phase, causing larger droplets to grow and increase average droplet size. Ostwald ripening is a key mechanism behind the instability of oil-in-water emulsions and perfluorocarbon emulsions. To prevent Ostwald ripening, add an immiscible secondary oil, use less soluble hydrophobic oils, insoluble additives, surfactants, and polymers that increase the viscosity of the external phase.

3. **Flocculation:** Flocculation is a weak, reversible interaction between emulsion droplets that are separated by trapped continuous phase. Each cluster of droplets, known as a floccule, acts as a single kinetic unit while still maintaining the individuality of each droplet within it. Floccules can be easily redispersed with gentle agitation, such as shaking the container. The likelihood of flocculation can be minimized by using an appropriate emulsifier. While the presence of adsorbed emulsifiers can significantly prolong the timescale between flocculation and coalescence, flocculation is generally seen as undesirable. This is because floccules tend to rise more quickly under the influence of gravity compared to individual emulsion droplets.
4. **Creaming:** Creaming is a process where droplets separate due to gravity, forming a concentrated emulsion. This happens in dilute emulsions with large droplets, especially if there is a density difference between oil and water phases. Oil-in-water emulsions have oil droplets rising to the surface, creating an upper cream layer, while water-in-oil emulsions have water droplets settling to form a lower layer. Creamed emulsions can be returned to their original state with gentle agitation, but this can be unappealing and insufficient dose for patients. To reduce creaming, emulsions with smaller droplet sizes and thickening the external phase with viscosity modifiers can be prepared. However, adjusting density to minimize the difference between phases has not been widely explored.
5. **Emulsion Inversion:** Emulsion inversion occurs under specific conditions, such as changes in emulsifier solubility or interactions with additives. For instance, non-ionic surfactants may shift from being water-soluble at lower temperatures to oil-soluble at higher temperatures, causing phase inversion from oil-in-water (o/w) to water-in-oil (w/o) emulsions. This temperature-dependent inversion is utilized in the low-energy preparation of nanoemulsions. Additionally, emulsion inversion can be triggered by additives; for example, a sodium salt-stabilized o/w emulsion may invert to w/o upon the addition of divalent ions like calcium (Ca^{2+}), which form calcium salts that stabilize w/o emulsions.
6. **Cracking**: Cracking of an emulsion refers to the separation of the dispersed phase into a distinct layer. While a creamed emulsion can be reconstituted through shaking or agitation, a cracked emulsion cannot be restored, indicating permanent instability. The cracking of an emulsion may occur due to: microorganisms, the introduction of a common solvent that is miscible with both the oily and aqueous phases, the addition of an emulsifier with an opposing nature.

CHEMICAL INSTABILITIES

Chemical instability in emulsions arises when the components are not chemically inert under emulsification conditions. It is essential to understand the chemical properties of all components before selection. Particular attention must be given to pharmaceutical oils, which are prone to oxidation by atmospheric oxygen or microbial contamination, leading to unpleasant odors and tastes as they become rancid. Antioxidants and preservatives can be added to mitigate these effects. Polymeric emulsifiers may degrade through hydrolysis or microbial activity, resulting in reduced emulsification power and consistency. Additionally, interactions between emulsifying agents and other components can disrupt emulsifying properties, potentially causing the emulsion to break down. POE non-ionic emulsifiers can form hydrogen bonds with phenolic preservatives, leading to reduced preservation effectiveness and a loss of emulsifying power. Ionic emulsifiers are typically incompatible with materials of opposite charge. For example, when cationic substances like surfactants or drugs (e.g., cetrimide or neomycin sulphate) are added to creams containing an anionic emulsifier like sodium lauryl sulphate, the cream's consistency deteriorates during storage. This occurs because the lamellar structures in the continuous phase are disrupted due to suppressed repulsive forces.

THERMODYNAMIC STABILITY STUDIES[21,27]

The thermodynamic stability of drug-loaded nanoemulsions was evaluated following stress tests, as reported.

1. **Centrifugation:** Nanoemulsion formulations were centrifuged at 3500 rpm, and those that did not exhibit any phase separation were selected for the freeze-thaw stress test.
2. **Heating Cooling Cycle:** Nanoemulsion formulations underwent six cycles of temperature changes between refrigeration (4°C) and 45°C. The stable formulations were then tested using centrifugation.
3. **Freeze Thaw Cycle**: In this study, the formulations underwent three freeze-thaw cycles between 21°C and +25°C while maintained under standard laboratory conditions. These experiments were conducted over a period of three months.

Three batches of formulations were stored at higher temperatures of 30°C, 40°C, 50°C, and 60°C with normal humidity. Samples were taken at regular times—specifically at 0, 1, 2, and 3 months—and tested for drug content using a special HPLC method that indicates stability.

APPLICATION[30,41,42,43]

1. Nanoemulsion is used as a mucosal vaccine.
2. Nanoemulsion is widely used in cell culture technology.
3. Nanoemulsions are currently being utilized to improve the oral delivery of drugs with poor solubility.
4. Nanoemulsions are used in the treatment of various other diseases like Dermatological Diseases, Bacterial Infections, Ophthalmic and Pulmonary Conditions.
5. It is as a vehicle for transdermal delivery.
6. It is used as nontoxic disinfectant cleaner.
7. In these days, nanoemulsions are widely used in cancer therapy and also in targeted drug delivery system.
8. It is also used in cosmetic and food industries.

COMMERCIAL PRODUCTS AVAILABLE

Table no. 5: Commercial Products Available.

Serial no.	Drug name	Carrier used	Method used	Activity	Reference
1.	Cyclosporine	Lipid-based carrier	High-pressure homogenization	Immunosuppressive therapy	44
2.	Dexamethasone	Polymeric nanoparticles	Micro fluidization	Anti-inflammatory therapy	45
3.	Ibuprofen	Lipid-based carrier	Ultrasonication	Anti-inflammatory and pain relief	46
4.	Prednicarbat	Phyto sphingosine	High-Pressure Homogenization	Atopic Dermatitis	47
5.	Celecoxib	Propylene-mono caprylic ester	Low-Energy Emulsification	Evaluation of stability	48
6.	Celecoxib	Diethylene glycol	Spontaneous Emulsification	Arthritis and osteoarthritis	49

MARKETED PRODUCTS AVAILABLE OF NANOEMULSION[50]

Table no. 6: Marketed Products Available.

S.no.	Product Name	API	Manufacturer	Use
1.	Etomidate lipuro	Etomidate	B. Braun Melungeon	Anaesthetic
2.	Limethason	Dexamethasone	Mitsubishi pharmaceutical	Steroid
3.	Restasis, gengraf	Cyclosporine	Allergen, Abbott	Immunosuppressant
4.	Liple	Alprostadil palmitate	Mitsubishi pharmaceutical	Vasodilator, platelet inhibitor
5.	Ropion	Flurbiprofen axtil	Kaken pharmaceutical	NSAID
6.	Norvir	Ritonavir	Abbott	Antiretroviral

PATENTED NANMOEMULSION FORMULATIONS [51]

Table no. 7: Patented Nanmoemulsion Formulations.

Patent application title	Patent application no.	Date (dd/mm/yy)
Topical compositions and methods of detection and treatment	20120039814	16/02/2012
Methods of using nanoemulsion compositions having antiinflammatory activity	20110200657	18/08/2011
Method for the preparation of nanoparticles from nanoemulsion	20110135734	09/06/2011
Perfluorocarbon nanoemulsion containing quantum dot nanoparticles and method for preparing the same	20100233094	16/09/2010
Oil-in-water nanoemulsion, a cosmetic composition	20090208541	20/08/2009

CONCLUSION

Nanoemulsions generally used for increasing the stability of drugs that are poorly water soluble. They have higher solubility and bioavailability, making them suitable for targeted distribution and oral administration. Their distinct properties, including as stability, large surface area, and formulation diversity, make them appropriate for a wide range of applications in medicine, cosmetics, and other industries. However, the widespread use of nanoemulsions confronts obstacles such as limited capacity for water-loving compounds and high production energy costs. To solve these challenges, further research and development are required to maximize their advantages while overcoming present limits. With further research, nanoemulsions have the potential to greatly enhance drug delivery methods, having a significant influence in the medical, cosmetics, and other relevant industries.

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