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Overview of Nanoemulsion

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ABSTRACT
A novel drug delivery system has been developed to address the limitations of conventional drug delivery methods. This comprehensive review explores the nanoemulsion system. The interest in nanoscale emulsions has considerably grown in recent decades as a consequenceof their specific attributes such as high stability, attractive appearance, in addition to high performanceand sensorial advantage. In fact, it nanoemulsions are one of the major popular formulationssystems in the pharmaceutical and cosmeceutical fields.Nanoemulsions are colloidal dispersion systems that are thermodynamically stable, composed of two immiscible liquids mixed along with emulsifying agents. These come across as ultrafine dispersions whose differential drug loading; viscoelastic as well as visual properties can cater to a wide range of functionalities including drug delivery. However, there is still relatively narrow insight regarding development, manufacturing, fabrication and manipulation of nanoemulsions which primarily stems from the fact that conventional aspects of emulsion formation and stabilization only partially apply to nanoemulsions.This review provides insights into the formulation methods, characterization techniques, evaluation parameters, and diverse applications of nanoemulsion, offering a fundamental understanding of this innovative drug delivery system.
Keywords: *Nanoemulsion, novel drug delivery, emulsifying agents etc.*

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I. INTRODUCTION

Nano-emulsions are a new type of emulsion which can be defined as an emulsion with uniform and extremely small droplet sizes. The term "Nanoemulsion" states to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules.[1-2]

They naturally have a mean droplet diameter of around 500 nm, resulting in a clear or hazy appearance. This contrasts coarse emulsions with larger droplets, giving them a milky white color due to light scattering. While the terms nanoemulsion, submicron emulsion, and mini emulsion are sometimes used interchangeably, it's significant to note that nanoemulsion should not be confused with microemulsion. Despite having a similar droplet size range as microemulsions, nanoemulsions vary significantly in their structure and long-term thermodynamic stability.[3]

Nanoemulsions can be formulated into various dosage forms, including liquids, creams, and sprays, gels, aerosols, and foams. They can be administered through different routes, such as topical application, oral ingestion, intravenous injection, intranasal delivery, pulmonary inhalation, and ocular application. Compared to simple micellar dispersions, nanoemulsions have a higher capacity for solubilization and exhibit greater kinetic stability than coarse emulsions. They have found applications in industries like cosmetics and pesticides, serving as aqueous bases for delivering organic compounds.[4]

The small droplet size of nanoemulsions contributes to their long-term physical stability, preventing issues like creaming, sedimentation, and coalescence that commonly occur in larger emulsion droplets. The strong Brownian motion exhibited by the small droplets helps counteract gravity and viscosity-induced kinetic instability. In the case of parenteral administration, nanoemulsions have been used to solubilize and protect drugs from harsh environmental conditions, such as oxidation, pH changes, and hydrolysis. They can also be utilized to target specific organs by taking advantage of the enhanced permeability and retention effect or to evade the reticuloendothelial system.[5]

TYPES OF NANOEMULSION

1. **Water-in-oil (W/O) nanoemulsions:** Nanoemulsions in which water droplets are dispersed in continuous oily phase.[6]
2. **Oil-in-water (O/W) nanoemulsions**: Nanoemulsions in which oil droplets are dispersed in continuous aqueous phase. [7]
3. **Bi-continuous nanoemulsions:** Nanoemulsions in which micro domains of oil and water are interdispersed within the system i.e. O/W/O and W/O/W[8]Bi-continuous or multiple emulsion systems contain consistent continuous networks of both oil and water phases. Surfactants or co-surfactants steady the bi-

continuous nanoemulsion. This type of system finds applications in pharmaceuticals and controlled drug delivery.[9]

4. **Pickering nanoemulsion:** Pickering nanoemulsionsdepend on solid particles adsorbed at the oil-water interface for stabilization. These particles act as emulsion stabilizers, preventing droplet coalescence. Pickering nanoemulsions have gained attention due to their potential for natural and biocompatible stabilization.[10]

5. **Microemulsion:** Microemulsions are thermodynamically stable, clear systems consisting of oil, water, surfactants, and co-surfactants. Droplets in microemulsions are typically smaller than those in nanoemulsions, reaching from a few nanometers to tens of nanometers. Microemulsions possess outstanding solubilization capabilities and find wide usage in drug delivery and enhanced oil recovery.[11]

ADVANTAGES OF NANOEMULSION

1. Nanoemulsions can be designed to target exact sites or tissues in the body, letting for exact drug delivery and reduced systemic side effects.
2. Nanoemulsions provide desirable sensory attributes, such as a non-greasy texture and transparency, making them fit for cosmetic and personal care applications.
3. Nanoemulsion formulations can protect active ingredients from degradation, oxidation, or interactions with external factors, such as light or heat.[12]
4. Nanoemulsions are thermodynamically stable system and the stability allows self-emulsification of the system.
5. Nanoemulsion has a transparent and fluidity property which improves the patient compliance and ease of administration due to the absence of any thickening agent and colloidal particles.[13]
6. Drug absorption variability can be reduced.[14]
7. Nanoemulsions can deliver both type of drugs i.e. hydrophilic and lipophilic.
8. Nanoemulsion also enhances permeability of drug into skin. [15]

DISADVANTAGES OF NANOEMULSION

1. For stabilizing the nano-droplets, it requires large concentration of surfactant and co- surfactant.[16]
2. Limited solubilizing capacity for high-melting substances. 3. The surfactant must be nontoxic for using pharmaceutical applications.[17]
3. Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and co-surfactants.[18]

LIMITATIONS OF NANOEMULSION

1. The manufacturing of nanoemulsion formulation is an expensive process because of their nano size requirement.
2. Reduction of droplets is very hard as it required a special kind of instruments and process methods. Stability of nanoemulsion is quite unacceptable and creates a big problem during the storage of formulation for the longer time unacceptability of nanoemulsion formulations. Ostwald ripening is the main factor associated with less availability of surfactant and cosurfactant required for the manufacturing of nanoemulsion.
3. Energy-intensive manufacturing process.
4. Sensitivity to environmental factors.
5. Need for specialized equipment and expertise.[19]

COMPONENTS OF NANOEMULSION

Nanoemulsions consist of two primary components: an oil phase and an aqueous phase, along with surfactants or co-surfactants that act as stabilizers. The composition of a nanoemulsion can vary based on the specific application and desired properties.

1. **Oil Phase:** The oil phase typically includes hydrophobic liquids, either single oils or a combination of different hydrophobic liquids. Examples include natural oils like vegetable oils, mineral oils, essential oils, or synthetic oils. The selection of the oil phase depends on factors such as the solubility of active ingredients, desired properties (e.g., viscosity, stability), and the intended application.[20]
2. **Aqueous Phase:** The aqueous phase contains of water or a water-based solution. It helps as the medium for dispersing the oil phase and other water-soluble components. The aqueous phase may also include additional water-soluble active ingredients, salts, or other components based on the specific formulation requirements.[21]
3. **Surfactants:** Surfactants play a vital role in steadying the nanoemulsion by reducing the interfacial tension between the oil and water phases. Typically, surfactants are amphiphilic molecules with both hydrophilic and hydrophobic regions. They can be classified as primary surfactants or emulsifiers, which help stabilize the droplets by forming a protective layer around them. Additionally, secondary surfactants or co-surfactants are

often used in combination with primary surfactants to further enhance stability and improve formulation characteristics.[22]

4. **Co-surfactants:** Co-surfactants are optional components utilized in some nanoemulsion formulations to optimize stability and properties such as droplet size, viscosity, and texture. Co-surfactants can enhance the solubility of lipophilic components, improve the emulsification ability of surfactants, and contribute to the overall stability of the nanoemulsionsystem.[23]

5. **Preservatives, antioxidants, and chemoprotectants:** Preservatives used in nanoemulsion need to fulfill certain requirements, including low toxicity, heat and storage stability, compatibility with the formulation, affordability, easy availability, pleasant Odor, taste, and color, as well as possessing a wide antimicrobial spectrum. It is important to consider that microorganisms can survive in both the oil and water phases of the nanoemulsion, so the chosen preservative must be able to reach effective concentrations in both phases. [24]

FACTORS TO BE CONSIDER FOR PREPARATION OF NANOEMULSION SYSTEM

1. Selection of appropriate emulsifying system (surfactant) such that an ultra-low interfacial tension may achieved which is primary need to produced stable nanoemulsion system.
2. Specific composition is required to avoid Oswald ripening the dispersed phase should be highly insoluble in the dispersed medium.
3. Optimum concentration of surfactant is required to stabilize the nanoemulsion.

FORMULATION OF NANOEMULSION

1. High-Pressure Homogenization

High-pressure homogenization is a method used to prepare nanoemulsions. A high-pressure homogenizer or piston homogenizer is employed in this technique to produce nanoemulsions with remarkably small particle sizes, reaching as low as 1nm. The process involves forcing a mixture of two liquids (oily phase and aqueous phase) through a small inlet orifice at very high pressure (ranging from 500 to 5000 psi). This intense pressure generates turbulence and hydraulic shear, resulting in the formation of extremely fine emulsion particles. The particles consist of a liquid, lipophilic core surrounded by a monomolecular layer of phospholipids that separate it from the surrounding aqueous phase. High-pressure homogenization is highly efficient, but it consumes a significant amount of energy and can cause an increase in the emulsion's temperature during processing.[26]

2. Ultrasonication

Ultrasonication is a commonly used technique in the preparation of nanoemulsions. It involves the application of high-frequency ultrasound waves to an emulsion, typically in the range of 20 to 100 kHz. Ultrasonication utilizes the phenomenon of acoustic cavitation, which refers to the formation, growth, and collapse of microscopic bubbles in a liquid subjected to ultrasound. In ultrasonication, the high-intensity ultrasound waves create alternating high-pressure and low-pressure cycles in the emulsion. In regions of low pressure, the liquid experiences negative pressure, causing the formation of small bubbles or voids. These bubbles grow rapidly during the low-pressure phase and then implode or collapse during the high-pressure phase. The collapse of these bubbles generates intense local energy, resulting in several physical effects, including microstreaming, shockwaves, and high shear forces. These effects induce the disruption and breakup of larger droplets into smaller droplets, leading to the formation of a nanoemulsion with reduced droplet size.[27]

Probe sonication, also known as tip sonication or direct sonication, is a technique used in the preparation of nanoemulsions and other dispersed systems. It involves the use of an ultrasonic probe, also known as a sonicator or ultrasonicator, to apply high-frequency sound waves directly to the sample. In probe sonication, the ultrasonic probe is immersed directly into the liquid sample, typically contained in a suitable vessel such as a beaker or test tube. The probe generates high-frequency sound waves, usually in the range of 20 to 100 kHz, which propagate through the liquid. As the sound waves pass through the sample, they cause alternating high-pressure and low-pressure cycles, resulting in the formation and collapse of microscopic bubbles, a phenomenon known as acoustic cavitation. The collapse of these bubbles generates localized energy in the form of shockwaves, microstreaming, and high shear forces.[28]

3. Low Energy Emulsification

Low-energy emulsification is a technique used to prepare oil-in-water (o/w) nanoemulsions. It capitalizes on the physicochemical properties of these systems by taking advantage of the phase transition that occurs during the emulsification process.[29]

4. Spontaneous Emulsification

Spontaneous emulsification involves three main steps. First, a homogeneous organic solution consisting of oil and a lipophilic surfactant is prepared in a water-miscible solvent along with a hydrophilic surfactant. Next, the organic phase is injected into the aqueous phase while under magnetic stirring, resulting in the formation of an oil-in-water (o/w) emulsion. Finally, the water-miscible solvent is removed through evaporation under reduced pressure.[30]

5. Solvent Evaporation Technique

This technique involves preparing a solution of the drug and subsequently emulsifying it in a nonsolvent liquid. The evaporation of the solvent leads to the precipitation of the drug. By employing high shear forces using a high-speed stirrer, crystal growth, and particle aggregation can be controlled during this process.[31]

6. Membrane Emulsification

Membrane emulsification employs a porous membrane as a dispersion device. The emulsion is forced through the membrane pores, resulting in the formation of droplets of a smaller size. This technique offers control over droplet size by manipulating the membrane properties. [32]

7. Hydrogel method

The Hydrogel Method is a technique used for nanoemulsion preparation that is similar to the solvent evaporation method. The main difference between the two methods lies in the solvents used. In the Hydrogel Method, the drug solvent is miscible with the drug anti-solvent. This miscibility allows for the formation of a hydrogel matrix. In the Hydrogel Method, the drug and anti-solvent are mixed to form a hydrogel. The hydrogel acts as a template or matrix for the formation of the nanoemulsion. The drug is encapsulated within the hydrogel, and the nanoemulsion is formed by incorporating the hydrogel into an aqueous medium.[33]

8. Micro fluidization

The instrument for formulating nanoemulsion is calleda microfluidizer. The first generation microfluidizerwas designed by the Arthur D. Little Co., but waslater taken over by the Microfluidics Corp.[34]

Formulating by micro fluidization demands the use ofhigh-energy inputs and powerful equipment to produceultrafine emulsions at much lower surfactant-tooilratio (SOR < 0.1). High pressure is used todrive the fluid through specifically configured microchannels,and a combined effects of shear, impact andcavitation superbly emulsifies the fluid 35. The processbegins when the mixture of the water phase andoil phase is forced into an inline homogenizer to producea course emulsion. The resultant emulsion isthen forced into an interaction chamber lined withmicro channels by a high-pressure positive displacementpump (500–200 psi). The flow of the emulsionthrough an impingement area then turns the viscousmixture into very fine submicron or nano-sized droplets,to finally achieve a stable nanoemulsion.Smaller size emulsions can be produced by increasingthe pressure up to approximately 700 MPa. It is thought thata microfluidizer is more efficient in producing higherquality nanoemulsions showing smaller and narrowerparticle size distributions as compared to the HPH.[36, 37]Towbin et al. used a MicrofluidizerVR Processor to prepare a nanoemulsion containing ananti-inflammatory agent, i.e. aspirin. Data from the crotonoil-induced (CD-1) mouse ear oedema modelexhibited reduced inflammation based on ear lobethickness, as well as an accumulated auricular cytokinelevels as biomarkers for inflammation.[38]

9. Phase inversion method

In phase transitionmethod, the adequate phase transitions is obtainedby changing the composition of oil and aqueousphase at constant temperature or also by changing thetemperature at constant composition. This method isbased on principle of the changes of solubility ofpolyoxyethylene type surfactant with temperature.This surfactant becomes lipophilic as increase intemperature because of dehydration of polymerchain. At low temperature, the surfactant monolayerhas a great positive spontaneous curvature formingoil swollen micellar solution phase.[39]

10. Self-emulsification methods

This methodprepares nanoemulsion at room temperature withoutany use of organic solvent and heat. In this method,small droplet size of 50nm can be generated by stepwise addition of water into solution of surfactant inoil, with gentle stirring and at constant temperature. [40]

11. Brute force method

This method includes utilization of brute forces for breaking the oil droplets into the nano range. Instruments that have been utilized for formulation of nanomeulsions include high pressure homogenizer, high speed mixer, small pore membrane and high frequency ultrasonic device. Nanoemulsion properties like its small size, optical transparency and high kinetic stability is not only dependent upon the composition of variables but also on the processing variables like emulsification time, degree of mixing, energy input and emulsifying path. High-pressure homogenization and micro fluidization methods are employed at both industrial and laboratory scale for attaining very small size of nanoemulsion by utilizing high pressure equipment.[41]

CHARACTERIZATION OF NANOEMULSION

1. Droplet size analysis particle size distribution

Dynamic Light Scattering (DLS), also known as photon correlation spectroscopy or quasi-elastic light scattering, is a technique used to rapidly determine the size distribution profile of small particles in suspensions

or polymers in solution. By analyzing the intensity fluctuations in the scattered light from particles illuminated by a laser, DLS can calculate the particle size based on the Brownian motion, using the Stokes-Einstein equation. This method provides a quick and effective evaluation of the size and size stability of nanoemulsions during storage.[42]

2. Zeta potential

Zeta potential refers to the electrokinetic potential in colloidal systems. It represents the potential difference between the dispersion medium and the stationary fluid layer attached to the dispersed particle. In colloidal chemistry, a zeta potential value of ±30 mV is often considered as a threshold to differentiate between low-charged and highly-charged surfaces. The zeta potential value indicates the level of repulsion between similarly charged particles in the dispersion, thereby affecting colloidal stability. Higher zeta potentials (positive or negative) confer electrical stability and resist aggregation, while lower zeta potentials lead to attraction, resulting in flocculation or coagulation. In summary, zeta potentials ranging from 0 to ±30 mV indicate instability, whereas zeta potentials exceeding ±30 mV indicate stability.[43]

3. Transmission Electron Microscopy

TEM (Transmission Electron Microscopy) is a valuable characterization technique for nanoemulsions. It allows for high-resolution imaging of the nanoemulsion droplets, providing information about their size, shape, and internal structure. TEM helps in assessing the uniformity and stability of the droplets, as well as the distribution of encapsulated nanoparticles or active ingredients. It aids in understanding the morphology and interfacial properties of nanoemulsions, supporting their formulation optimization and performance evaluation.[44]

4. FESEM (Field-Emission Scanning Electron Microscopy)

FESEM (Field-Emission Scanning Electron Microscopy) is a powerful imaging technique used for the characterization of nanoemulsions. It provides high-resolution, three-dimensional images of the emulsion droplets, allowing for the examination of their surface morphology and structure. FESEM also enables the investigation of the distribution and localization of nanoparticles or active ingredients within the nanoemulsion. It aids in understanding the interfacial characteristics and particle arrangements, providing valuable insights for the development and optimization of nanoemulsion formulations.[45]

5. Atomic force microscope (AFM)

AFM (Atomic Force Microscopy) is a relatively recent technique utilized to investigate the surface morphology of nanoemulsion formulations. In this technique, nanoemulsions are first diluted with water, and the diluted nanoemulsion is then drop-coated onto a glass slide. The coated droplets are subsequently dried in an oven and scanned using AFM at a scan rate of 100 mV/s.[46]

6. Dye solubilization

A water-soluble dye has the ability to disperse within an oil-in-water (O/W) globule, while it dissolves in the aqueous phase of a water-in-oil (W/O) globule. Conversely, an oil-soluble dye can disperse within a W/O globule but is soluble in the oily phase of an O/W globule. When a water-soluble dye is added to an O/W nanoemulsion, it uniformly incorporates the color throughout the emulsion. However, in a W/O emulsion, the dye remains in the dispersed phase, resulting in uneven distribution of color. This phenomenon can be observed through microscopic examination of the emulsion, revealing the different behaviors of water-soluble and oil-soluble dyes in O/W and W/O nanoemulsions, respectively.[47]

7. Thermodynamic stability studies

Thermodynamic stability investigations are typically conducted in a three-step process. Initially, a heating-cooling cycle is performed to evaluate the impact of temperature variations on the stability of the nanoemulsion. The nanoemulsion is subjected to six cycles alternating between refrigeration temperature (4°C) and room temperature (40°C), with each temperature being maintained for at least 48 hours. Formulations that demonstrate stability under these temperature conditions proceed to the next step: a centrifugation study. In this study, the formulated nanoemulsions are centrifuged at 5000 rpm for 30 minutes to assess for any signs of phase separation, creaming, or cracking. Those formulations that exhibit no indications of instability then undergo a freeze-thaw cycle. In this third step, the nanoemulsion formulations are subjected to three freeze-thaw cycles, with temperatures ranging from -21°C to +25°C. Formulations that remain stable throughout this cycle are considered to have good stability. [48]

8. Determination of viscosity

Viscosity assessment plays a crucial role in the physicochemical characterization of nanoemulsions. Several instruments are utilized for measuring viscosity, including the Ostwald viscometer, Hoeppler falling ball

viscometer, Stormer viscometer, Brookfield viscometer, and Ferranti-Shirley viscometer. Among these options, the Brookfield viscometer is commonly preferred for assessing the viscosity of nanoemulsions. The viscosity determination helps determine whether the system is an oil-in-water (O/W) or water-in-oil (W/O) emulsion. Low viscosity indicates an O/W type, while high viscosity suggests a W/O type system. Accurate viscosity measurements contribute to the understanding of the emulsion's composition and behaviour.[49]

9. Refractive index

The refractive index is a crucial parameter that indicates how light propagates through a medium and influences the transparency of a nanoemulsion. It is defined as the ratio of the speed of light (c) in a reference medium to the phase speed of light (vp) in the medium: n = c/vp. The refractive index of a nanoemulsion can be determined using an Abbe-type refractometer at a temperature of 25±0.5°C. A drop of the nanoemulsion is placed on a slide, and its refractive index is compared with that of water (1.333). If the refractive index of the nanoemulsion is equal to that of water, it indicates that the nanoemulsion possesses a transparent nature. This measurement helps assess the optical properties and transparency of the nanoemulsion system.[50]

10. Percentage Transmission

The transparency of a formulated nanoemulsion can be assessed by measuring it's percent transmittance at a specific wavelength using a UV spectrophotometer, with distilled water as a reference. If the nanoemulsion demonstrates a percent transmittance exceeding 99%, it is regarded as having a transparent nature. This indicates that the nanoemulsion allows a significant amount of light to pass through without significant absorption or scattering, implying good optical clarity.[51]

11. pH and osmolarity measurements

A pH meter is utilized to measure the pH of a nanoemulsion, while a microosmometer is employed to determine the emulsion's osmolarity using the freezing point method. To perform the osmolarity measurement, a volume of 100 µl of the nanoemulsion is transferred into a microtube, and subsequent measurements are conducted. These characterization techniques provide essential information about the pH level and osmolarity of the nanoemulsion, aiding in understanding its physicochemical properties and potential applications.[52]

12. Fluorescence test

Several oils exhibit fluorescence when exposed to UV light. When a water-in-oil (W/O) nanoemulsion is observed under a microscope with fluorescence lighting, the entire field of view will emit fluorescence. However, in the case of an oil-in-water (O/W) nanoemulsion, fluorescence will appear as distinct spots or localized areas. This phenomenon can be used as a visual indicator to differentiate between W/O and O/W nanoemulsions based on their fluorescence patterns when illuminated with UV light.[53]

13. In vitro drug release studies

In vitro, drug release studies are conducted to estimate the performance of a drug formulation in vivo. The release rate of the drug in vitro is typically investigated using a USP dissolution apparatus. A nanoemulsion or dried nanoparticles containing an equivalent of 10 mg of the drug are dispersed in a buffer and introduced into dialysis membrane pouches, which are then placed in a flask containing buffer solution. The study is conducted at a temperature of 37±0.5°C with stirring at a speed of 50 rpm. At specific time intervals, samples are withdrawn and replaced with the same volume of fresh dissolution medium. These samples are appropriately diluted, and their absorbance is measured using spectrophotometry at a designated wavelength. The absorbance values of the collected samples are then used to calculate the percentage of drug release at different time points by referencing a calibration curve.[54]

14. Differential scanning calorimetry (DSC)

DSCprovides information on the interactions of differentcomponents and polarization microscopy usingcrossed polarizers is employed to confirm isotropicityof the formulation.[55]

15. Flocculation and creaming

Flocculation consistsof the joining together of globules to form largeclumps or floccules,which rise or settle in theemulsion more rapidly than the individual globules.The rising up or settling down of dispersed globulesto give a concentrated layer is known as creaming.Thus, flocculation leads to creaming. Flocculation andcreaming is determined by visual inspection of storedsample.[56]

16. Entrapment efficiency

Entrapment efficiency (EE) is used to estimate the efficacyof a nanocarrier to retain the drug/active ingredient,to ensure delivery of an adequate amount of thecomponent to the targeted site. Key factors thatcan have a profound

impact on EE include the techniqueof formulation, type of formulation ingredientsand nature of the encapsulated bioactive compound inthe vesicles. Moreover, particle size tends toexpand with higher loading of the active ingredientinto the nanoemulsion, thus reducing EE of thenanoemulsion. The estimation of EE was successfullydemonstrated using a micro dialysis technique for nanocapsules,nanospheres and nanoemulsions.Other strategies for estimating EE of different nanocarriersinclude gel filtration, dialysis bag diffusion, ultrafiltrationand ultracentrifugation. EE estimation by gelfiltration is in actual, a type of exclusion chromatography.An aqueous suspension of porous gel particles isused to separate the nanoparticles according to theirmolecular weight. Dialysis, on the other hand, can isolatenanoparticles from a mixture of other nanoparticlesor free drugs. The free active ingredient diffuses out ofthe dialysis bag, while the nanoparticles are retainedwithin. In contrast, the centrifugation technique separatesfree molecules from the micelles based on theirdifferent ability to traverse membrane of a certain poresize during centrifugation. The general equationto determine the EE is as follows.[57-58]:

$EE = W1\text{-}W2/W1 \times 100$

where W1 is the amount of active ingredient added inthe formulation and W2 is the amount of active ingredientin the supernatant.

17. Fourier-transform infrared spectroscopy (FTIR) spectral analysis

FTIR analysis can be carried out for the assessment of drug excipient interaction, polymerization, crosslinking as well as drug loading in the formulation. It is also used for identifying the functional groups with their means of attachment and the fingerprint of the molecule. At low temperature a molecule exists in ground state and on absorbing the radiant energy, they get excited to higher energy states. IR spectroscopy is based on determining this energy difference (ΔE) between the excited and ground states of the molecule. For performing FTIR, sample can be prepared by employing suitable method such as potassium bromide pellet method, Nujol mulls and then sample is scanned in FTIR at moderate scanning speed between 4000- 400 cm-1. Srilatha et al. conducted FTIR studies on pure drug and glipizide nanoemulsion and reported absence of drug excipient interactions (hence compatibility of drug and excipient) as all the characteristics peaks of drug appeared at same point in formulation.[59]

18. Dispersibility studies

Dispersibility studies for evaluating the efficiency of self-emulsification of nanoemulsion are carried out by using a standard USP XXII dissolution apparatus 2.1 ml of each formulation is incorporated into 500 ml of distilled water maintained at 37±0.5°C. A standard stainless steel dissolution paddle rotates at 50 rpm for providing gentle agitation. In vitro performance of the nanoemulsion formulations is evaluated visually by using a grading system described below. Grade A nanoemulsions form rapidly within 1 min and appear to be clear or bluish. Grade B nanoemulsions form rapidly but are slightly less clear emulsions appear to be bluishwhite. Grade C nanoemulsions are fine milky emulsion that form within 2 min. Grade D are those dull, greyishwhite emulsions that has a little oily appearance and are slower to form (>2 min). Grade E nanoemulsions display either poor or negligible emulsification with large oil globules present on the surface.[60]

19. Dilutability test

The rationale of dilution test is that continuous phase can be added in larger proportion into a nanoemulsion without causing any problem in its stability. Thus O/W nanoemulsions are dilutable with water but W/O nanoemulsions are not and go through a phase inversion into O/W nanoemulsion. The W/O nanoemulsion can be diluted with oil only. Laxmi et al. performed dilutability test on nanoemulsion by diluting it with water and observed no sign of phase inversion and precipitation thus claiming their nanoemulsion formulation to be stable[61.]

20. Conductance measurement

The O/W nanoemulsions are highly conducting because they have water in external phase whereas W/O nanoemulsions are not conducting as they have water in internal or dispersal phase. Electrical conductivity measurements are very much beneficial for determining the nature of the continuous phase and for detecting phase inversion phenomena. At low volume fractions, increase in conductivity of certain W/O nanoemulsion systems was observed and such kind of behaviour is deduced as an indicator of a percolative behaviour or ions exchange among droplets prior to the development of bicontinuous structures. Dielectric measurements are a great means of exploring the structural and dynamic features of nanoemulsion systems. Conductometer is employed for determining the conductance of nanoemulsion. For carrying out conductance measurement, a pair of electrodes is attached to a lamp and an electric source is immersed into an emulsion. When the emulsion is O/W type then water will conduct the current and lamp will glow because of passage of current among connecting electrodes. The lamp will not glow if it is water in oil emulsion as oil in external phase does not conduct the current.[62] Harika et al. performed conductivity test on amphotericin B nanoemulsion using an

electroconductometer. They reported conductivity of the formulations in the range of 454.2-552.3 μS/cm and concluded the system to be O/W on the basis of electroconductivity study.[63]

21. Interfacial tension

By measuring the interfacial tension, the formation and the properties of nanoemulsion can be investigated. Ultra-low values of interfacial tension correspond to phase behaviour, mainly the coexistence of surfactant phase or middle-phase nanoemulsions with aqueous and oil phases in equilibrium. For determining ultralow interfacial tension spinning-drop apparatus is used. Interfacial tensions are obtained by measuring the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.[64]

APPLICATIONS OF NANOEMULSION

Nanoemulsions could be and have been applied in various aspects of drug delivery including: cosmetics and transdermal delivery of drug, cancer therapy, vaccine delivery, prophylactic in bio-terrorism attack, non-toxic disinfectant cleaner, cell culture technology, formulations for improved oral delivery of poorly soluble drug, ocular and optic drug delivery, intranasal drug delivery, parenteral drug delivery and pulmonary delivery of drugs.[65]

1. Parenteral administration

Parenteral administration of medications with limited solubility, particularly via the intravenous (IV) route, is a significant concern in the pharmaceutical industry due to poor drug delivery to specific target sites. Nanoemulsion formulations offer advantages over macroemulsion systems when administered parenterally, as the small particle size of nanoemulsions leads to slower and more sustained excretion from the body compared to emulsions with larger particles. This results in longer duration of action. Parenteral delivery can be achieved using either oil-in-water (o/w) or water-in-oil (w/o) nanoemulsions. Various nanoemulsion systems described in the literature show potential for parenteral administration, with consideration given to surfactant toxicity and the suitability of parenteral use.[66]

2. Oral delivery

Nanoemulsion formulations offer several advantages for oral drug delivery compared to traditional formulations. They have the potential to increase the clinical effectiveness and absorption of medications, while reducing drug toxicity. Nanoemulsions have shown promise as a delivery system for various medications, including steroids, hormones, diuretics, antibiotics, and peptides. Peptides and proteins, which are highly potent and targeted in their physiological effects, are often challenging to deliver orally. Conventional formulations have low oral absorption rates (below 10%) for these molecules. Nanoemulsions have the potential to improve the oral bioavailability of protein drugs, reducing the reliance on parenteral administration.[67]

3. Topical administration

Topical drug administration offers advantages such as bypassing hepatic first-pass metabolism and enabling direct application to the affected skin or eyes. In the case of prostaglandin E1 administration, both oil-in-water (o/w) and water-in-oil (w/o) nanoemulsions were tested in a hairless mouse model. The nanoemulsions were formulated using oleic acid or Gelucire 44/14 and stabilized with a surfactant mixture of Labrasol and PlurolOleique CC 497. Although the o/w nanoemulsion demonstrated enhanced drug delivery rates, the penetration rates of both systems were deemed insufficient for practical application. Additionally, a lecithin/IPP/water nanoemulsion was used to deliver indomethacin and diclofenac transdermally. Through FTIR spectra and differential scan calorimetry (DSC), it was observed that the IPP organogel altered the lipid composition in the mammalian stratum corneum after one day of incubation.[68]

4. Ocular and pulmonary drug delivery

Topical administration is the primary method for delivering drugs to treat eye disorders. In ocular delivery, researchers have investigated o/w nanoemulsions to address challenges such as poor solubility, increased drug absorption, and achieving sustained release. Nanoemulsions containing pilocarpine were formulated using ingredients like lecithin, propylene glycol, and PEG 200, with IPM as the oil phase. These formulations exhibited favorable properties such as a suitable refractive index and low permeability, making them well-suited for ophthalmic applications. Additionally, a non-ionic fluorocarbon surfactant was utilized to stabilize a water-in-HFA propellant nanoemulsion designed for pulmonary delivery. [69]

5. Nanoemulsions in Biotechnology

Enzymatic and biocatalytic processes often utilize aqua-organic or purely organic media, including biphasic systems. Pure polar media can lead to the denaturation of biocatalysts. However, using water-resistant media offers several advantages including it exhibit increased solubility in non-polar reactants, Experience

thermodynamic equilibrium modifications that promote condensation reactions, show improved thermal stability, enabling reactions to be conducted at high temperatures.[70]

6. Nanoemulsions in Cell Culture Technology

Cellcultures are used for in vitro assays or to producebiological compounds, such as antibodies orrecombinant proteins. To optimize cell growth, theculture medium can be supplemented with a numberof defined molecules or with blood serum. Theadvantages of using nanoemulsions in cell culturetechnology are better uptake of oil-solublesupplements in cell cultures; improve growth andvitality of cultured cells, and allowance of toxicitystudies of oil-soluble drugs in cell culture.[71]

7. Cosmetic Applications

Nanoemulsions haveattracted considerable attention for application inpersonal hair products. They were found useful for anoptimized dispersion on skin and controlled delivery
of cosmetics. They are easily valued in skin carebecause of their good sensorial properties and theirbiophysical properties especially hydrating power.[72]

8. Nanoemulsion in Mucosal Vaccine

Nanoemulsionsare utilized to deliver either recombinant proteins or inactivated organisms toa mucosal surface toproduce an immune response. The 1st application, aninfluenza vaccine and an HIV vaccine, can proceed toclinical trials.The nanoemulsion needs proteinsapplied to the mucosal surface to be adjuvant and itfacilitates uptake by antigen-presenting cells.Additional research is ongoing to complete verifyconcept in animal trials for other vaccines includingHepatitis B and anthrax20 Mice and guinea pigsintranasally immunized by the application ofrecombinant HIV gp120 antigen mixed innanoemulsion which demonstrated robust serum antigp120IgG, as well as bronchial, vaginal, and serumanti- gp120 IgA in mice[73]

9. As Antimicrobial

Antimicrobial nanoemulsions areo/w droplets, ranges from 200 to 600 nm. They arecomposed of oil and water and are stabilized byalcohol and surfactants. Nanoemulsion has a broad-spectrumactivity against bacteria (e.g. E. coil,Salmonella s, S. aureus), enveloped viruses (e.g.HIV, Herpes simplex), fungi (e.g. Candida,Dermatophytes), and spores (e.g. anthrax).Nanoemulsion can attain a level of topicalantimicrobial activity that has only been previouslyachieved by systemic antibiotics.[74]

10. Nanomeulsions in food industry

Nanomeulsionscan be used in the food industry to design smart foods with ingredients that are otherwise difficult to incorporate due to low-water solubility; an example is b-carotene, a pigment responsible for color in vegetables like carrots possessing important health benefits. Nanoemulsions in the food industry have explored the preparation and stability of flavored nanoemulsions using low energy methods.[75]

11. Nanoemulsions as building blocks

Nanoemulsions can be used as building blocks for the preparation of more complex materials through exploitation of their small size and high surface area which enable easy decoration of a liquid–liquid surface with functional moieties such as designer macromolecules.[76]

12. Nanoemulsion in the treatment of various other disease condition

Pharmos (US-based company) has developed nanoemulsion topical diclofenac cream as potential treatment for osteoarthritis pain. A topical application of nanotechnology has already demonstrated excellent targeted delivery of lipophilic drug to muscle and joints in animal model. Nanoemulsion also used to treat many more diseases. [77]

II. FUTURE PROSPECTIVES

Nanoemulsions have gained popularity over the past decadebecause of their exceptional properties such as high surface area,transparent appearance, robust stability and tunable rheology.The most widely used preparation methods for nanoemulsionsinclude high energy methods such as high-pressure homogenizationand ultrasonication, and low energy methods such as phaseinversion temperature and emulsion inversion point. Emergentsynthesis techniques are bubble bursting at liquid/air interface,evaporative ripening and micro fluidization. There is little understandingof the possible industrial relevance of many of theseapproaches as the physics of nanoemulsion formation is stillsemi-empirical and rational scale-up procedure have not beenwidely explored.However, current research has not

explored the idea of designing polymers that can be used asemulsifier for the preparation of stable nanoemulsions. Polymerscan be tuned from being hydrophobic to hydrophilic which canresult in rich properties, including tunable rheology and stability.Due to their small size, molecules sitting at the interface ofnanoemulsions experience higher curvature which will greatlyinfluence self-assembly at the interface.[78.]

Nanoemulsions can alsoserve as a model system to enhance understanding of colloidalassembly and rheology of complex emulsion systems. They canbe readily density matched, selectively dyed for visualization,and made magnetic field responsive. Their liquid interfaces aredynamic, which expands the richness of their soft matter physicalproperties.Leveraging the high surface area of nanoemulsions,researchers have used them extensively in drug delivery, and inthe food, cosmetics and the pharmaceutical industries. Whilenanoemulsion applications within these industries look promisingand there is a need for continued research in these areas, many other potential uses, such as enhanced oil recoveryortissue engineering, are relatively unexplored.With the growing interest in herbal drug formulations, nanoemulsions hold great potential as a delivery platform for challenging phytopharmaceuticals. The future of nanoemulsions relies on the innovative formulation approaches that leverage their advantages to address issues related to drug absorption, permeation, and stability, both for conventional and herbal drugs.[79]

III. CONCLUSION

Nanoemulsions are widely used in pharmaceutical systems. Nanoemulsion formulation offers several advantages such as delivery of drugs, biological or diagnostic agents. The most important application of nanoemulsion is for masking the disagreeable taste of oily liquids. Nanoemulsion may also protect the drugs, which are susceptible to hydrolysis and oxidation.

Recently, Nanoemulsions are receiving great attention as drug carrier for improving the delivery of neutron capture therapy agents, various anticancer drugs and pharmaceutical ingredients. The Nanoemulsion formulations which are formulated is found to be transparent because its particle size in nm and these formulations contains oil, surfactants, and co-surfactants. Overall, nanoemulsion formulations offer effective, secure, and patient-compliant delivery methods for pharmaceuticals. They also hold the potential for overcoming absorption challenges and enhancing the miscibility of phytopharmaceuticals with cell membrane lipids. The stability of nanoemulsion formulations can be enhanced by controlling factors such as surfactant and co-surfactant types and amounts, oil phase variations, formulation techniques, and process variables. It is expected that further research and development will be carried out in the future regarding nanoemulsion. From this review we can conclude that nanoemulsion offers different routes to deliver the formulation. It offers multiple advantages for less soluble drugs. It is also effective in targeted and controlled delivery of the drug.

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