

Nanoemulsion : Comprehensive Review

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Abstract: *In pharmaceutical formulations, nanoemulsions are practical in the nanometer range. They have the ability to encapsulate drugs that are poorly soluble in water due to their hydrophobic nature and also consist of safe gradient excipients, making them safer and more stable for drug delivery. The treatment of cancer has been a problem for several decades, because the drugs developed to treat this disease have not always succeeded or even failed, mainly due to low solubility and non-specific toxicity. This problem can be solved with a nanoemulsion, because it not only solves the water solubility problems, but also provides a specific target for cancer cells. This chapter provides an overview of nanoemulsions and various approaches to prepare nanoemulsions, which include high energy approaches such as microfluidizer high pressure valve homogenization, ultrasonic homogenization. For low-energy approaches, the phase inversion composition, phase inversion temperature, and emulsion inversion point for spontaneous emulsification are discussed in detail.*

Keywords: nanoemulsion, production approaches, applications.

I. INTRODUCTION

This review article provides detailed information on various formulations and approaches used to prepare nanoemulsions. Emulsions can be oil-in-water (O/W), water-in-oil (W/O) and oil-in-oil (O/O) types. An emulsifier is also used as a third component, which plays an important role in dispersing two immiscible liquids (continuous phase and dispersed phase). Emulsions are heterogeneous systems that are classified based on the nature of the emulsifier used and the structure of the system formed. Different structures of emulsion system include nanoemulsions, microemulsions, mixed, double and multiemulsions. Today, nanoemulsions have promising medical applications such as anticancer activity and antimicrobial activity.

The most critical factor in emulsions is their degradation processes. Ostwald ripening, creaming, phase inversion, sedimentation, flocculation, coalescence and are different degradation processes related to the instability of the emulsion formed. Some of these are microbial contamination, oxidation and adverse storage conditions types of chemical instability. Emulsions are characterized by various methods such as fluorescence test, dye test, dilution test, sphere size analysis, conductivity, accelerated stability and macroscopic examination. Emulsions have a wide range of applications in everyday life. The concept of emulsions is widely used in various industries. Emulsions have different applications: agricultural chemicals (emulsion concentrates and pesticides, self-emulsifying oils), oils (oil-based and oil varnish dispersions), foodstuffs (candy, dairy products, baked goods, meat products and drinks), paints (latex emulsions). and alkyd resin-based products), pharmaceutical products (anesthetics, creams, chemotherapy, creams), cosmetics (skin care products and hair products), personal care products (emulsions, creams), dry cleaning products and others..[1-5]

II. TYPES OF NANOEMULSION

W/O, or water in oil nanoemulsion: A droplet of water was distributed in a continuous phase of oil during a nanoemulsion.[6]

O/W or oil in water nanoemulsion: Oil droplets were dispersed in a continuous phase of water during a nanoemulsion.

Bi-continuous Nanoemulsion: In this process, the surfactant was soluble in both the water and the oil phases, and the droplet was distributed in both. [7]



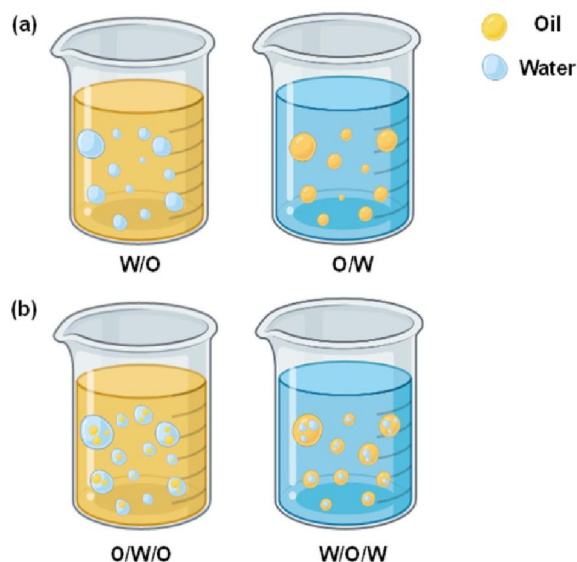


Fig. 1. Types of Emulsion

III. CHARACTERIZATION OF NANOEMULSION

Various characterization parameters of NE include transmission electron microscopy, NE droplet size analysis, viscosity determination, refractive index, in vitro skin permeation studies, skin irritation test, in vivo efficacy study, thermodynamic stability studies and surface properties. NOT surface charge. droplets have a significant effect on the stability of the emulsion system and on the in vivo localization and removal of the droplets. The inset shows the microscope image at a higher magnification. NE droplets were in the size range of 25–40 nm and some particle aggregates were in the size range of 100–150 nm.[8]



Fig. 2. Characterization of Nanoemulsion and the types



IV. ADVANTAGES OF NANOEMULSIONS OVER OTHER DOSAGE FORMS

1. Eliminates variability in absorption
2. Increases the rate of absorption.
3. Helps in solubilizing lipophilic drug.
4. Provides aqueous dosage form for water insoluble drugs.
5. Increases bioavailability.
6. Various routes like topical, oral and intravenous can be used to deliver the product.
7. Rapid and efficient penetration of the drug molecule.
8. Helps in taste masking.
9. Provides protection from hydrolysis and oxidation as drug in oil phase in o/w emulsion
10. Less amount of energy required
11. Liquid dosage form increases patient compliance
12. Nanoemulsions are thermodynamically stable systems and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.
13. Nanoemulsions carry both lipophilic and hydrophilic compounds.
14. Use of Nanoemulsion as delivery systems improves the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.[9].

V. METHOD OF PREPARATION

Nanoemulsions can be created in a number of ways, including combining high- and low-energy emulsification techniques. High energy mixing, ultrasonic emulsification, high homogenization, including microfluidics and membrane emulsification are at the forefront of high-energy approaches. Phase inversion temperature method, emulsion inversion point method and so on spontaneous emulsification are three low-energy emulsification techniques. Inverse nanoemulsions can be organized into ultraviscous systems using a combined technique that combines high- and low-energy emulsion. The main advantages and disadvantages of various nanoemulsion preparation techniques are reviewed and, consequently, future applications of nanoemulsions are considered. [10]

The self-nano emulsification method:

The self-emulsification approach allows the creation of nanoemulsions without affecting the surfactant and natural curvature. Nanosized emulsion droplets are produced by rapid diffusion of surfactant and/or cosolvent molecules from the dispersed phase to the continuous phase, resulting in turbulence. The spontaneous emulsification method is another name for the self-emulsification technique. SNEDDS has a lower lipid content and more hydrophilic surfactants (cosolvents), which support the self-emulsification phenomenon. [11] The term "SNEDDS" refers to an isotropic mixture of oil, surfactant, surfactant, and drug. In the presence of aqueous fluids, this mixture forms a thin and optically transparent O/W nanoemulsion by slight acceleration due to gastric and intestinal digestive movements. Diffusion of hydrophilic cosolvent or surfactant from the organic phase to the aqueous phase and negative free energy formation of nanoemulsion under transient negative or ultralow interfacial tension are the two most commonly reported mechanisms for nanoemulsion formation by SNEDDS. SNEDDS is also the most popular and most an optimistic delivery route for hydrophobic drugs with low bioavailability. Distribution of bioactive food ingredients has also been done with SNEDDS. [12].

VI. FORMULATION OF NANOEMULSION

The main components involved in the formulation of nanoemulsion could be explained as follows.

Aqueous phase: Water is usually used as the aqueous phase in nanoemulsion preparation. Polar compounds can contain proteins, carbohydrates, minerals, co-solvents, acids and bases. The concentration and type of components they use determine the ionic strength, pH, polarity, rheology, density, refractive index, interfacial tension, and phase behavior of the aqueous phase, and this directly affects phase formation, physicochemical properties, and stability. nanoemulsion is formed.



Oil phase: The physicochemical properties of the oil phase determine the stability, formation and properties of the nanoemulsion. The physicochemical properties of the oil phase can be viscosity, polarity, density, water solubility, interfacial tension, refractive index, phase behavior and its chemical stability. The oil phase is usually selected from non-polar components such as monoacylglycerols, triacylglycerols, free fatty acids, diacylglycerols, essential oils, flavor oils, mineral oils, waxes, fat substitutes and others.

Stabilizers: To avoid nanoemulsion degradation processes such as coalescence flocculation, Ostwald ripening and gravitational separation, various stabilizers are used to improve their stability.

Emulsifiers: The emulsifier is able to promote the breakup of the droplets, and the adsorption of the droplets on the surface prevents the formation of droplets from aggregates. Therefore, the choice of emulsifiers plays an important role. In high-energy methods, small droplets are formed because the emulsifier causes disruption of the droplets reducing the surface tension. In low energy methods, the emulsifier is able to produce a low interfacial tension, which causes the spontaneous formation of small droplets in solutions and under certain environmental conditions. Small molecules are classified as nonionic, ionic, and zwitterionic based on their electrical properties.[13-19]

VII. APPLICATIONS

In various fields, more attention is being paid to the research of nanoemulsions for potential applications. If nanoemulsions are prepared immediately before use, the use of nanoemulsions is quite effective. The direct use of nanoemulsions in medicine has brought many benefits, but food technology and agrochemicals have not yet been fully developed. The development of nanocarriers has helped to treat many diseases. Some anti-inflammatory, anticonvulsant, antibiotic and antihypertensive drugs have been dissolved in nanoemulsions for use. Drugs dissolved in nanoemulsions have been studied in cancer treatment and HIV/AIDS treatment. Many other studies on nanoemulsions such as applications such as general antimicrobial activity, anthrax vaccine, schistosomicidal compound efficacy, Ebola virus inactivation, intestinal absorption of three model drugs, and others. [20]. A revolution in the targeted treatment of many cancers has occurred thanks to nanoemulsions that enable targeted delivery. Tumors can be removed without affecting healthy tissues and this improves the effectiveness of cancer drugs. They tolerate multidrug resistance, increase the specificity and efficiently deliver the therapeutic agent. Folic acid receptors have been studied to target therapeutic compounds directly to cancer cells. However, nanoemulsions are being studied for cancer treatment, detection and prevention, their long-term effects and exact doses for cancer treatment have not yet been studied[21]. Nanoemulsions are used in the fuel combustion process to improve engine efficiency. To improve combustion properties, a water-diesel nanoemulsion was prepared by mixing water with nano-AI additives in different proportions. The surfactant used was Triton X-100. The emulsion formed was in the nanometer range and zeta potential values were neutral at the water-diesel interface. Furthermore, the mixture was thermodynamically stable. The authors suggest that the prepared nanoemulsion fuels should be further tested for their fuel properties and engine performance to ensure their effective use as a future sustainable fuel alternative.[22]

Experimental Designs For Optimization:

The desired response can be correlated with the variables using polynomial equations, which can be done through statistical analysis of the results. The purpose of the experimental design is to find out how two qualitative independent variables - the type of oil and the type of lipophilic emulsifier - affect the final result. The four references on the left and right are from the same research group. The amounts of oil, surfactant, and cosurfactant in the formulation are three independent factors evaluated in the inclusion. retinol itself into the nanoemulsification formulation, while average droplet size, turbidity, and dissolution rate are the four response variables. [23] The system is optimized for a 30 min dissolution rate using three opposing responses as a limit. The response equations are provided. In the response surface technique, six response factors are analyzed and more information is provided. [24] Comparative evaluation process for the characterization of nanoemulsions using ultrasound technology. The creation of nanoemulsions is covered with a comprehensive discussion of the application of experimental design. In low-energy emulsification, the phase inversion composition method is applied and the effect of composition factors was compared. The droplet size response surface was reduced separately, first with respect to formulation variables and then with respect to formulation variables. The



results show that there is an optimal surfactant mixing ratio, or in other words an optimal HLB, where the higher the ratio of oil to surfactant, the larger the droplet size. The optimum mixing speed is found for the production variables of addition and mixing speed, which are minimal but still important. effect Nanoemulsions produced by the phase inversion composition method in the ionic surfactant system are subjected to an experimental design optimization method. The combination used has an ideal surfactant ratio and again, the higher the ratio of oil to surfactant, the larger the droplet size. Again, production factors have little or no effect on drop size. Authors and other unpublished observations of nanoemulsions made at the phase inversion temperature support the idea that production factors such as cooling rate and stirring do not significantly affect droplet size. Articles using experimental designs generally conclude that this methodology is an excellent tool to study the preparation of nanoemulsions. [25] Optimization phase behavior studies: When using so-called condensation or low-energy emulsification methods, phase behavior studies are often important to optimize nanoemulsion properties, since the phases involved in emulsification are crucial to obtain nanoemulsions with small droplet sizes and low polydispersity. However, when cutting methods are used, there is no compositional emulsification path and only the phases of the final composition are important. Recent reviews discuss in great detail the importance of phase behavior, particularly the crossing of microemulsion (double image, D) or lamellar liquid crystal phase regions during emulsification. [26] This conclusion was experimentally proven in some recent preliminary studies, including studies that prepared nanoemulsions using the phase inversion temperature (PIT) method, the phase inversion composition (PIC) method [27] or the self-emulsification technique. The only microemulsions believed to be suitable for self-emulsification are bicontinuous (D) or O/W microemulsions. Lamellar liquid crystal the compounds do not self-emulsify on dilution, possibly due to the viscosity of the lamellar phase. [28] When comparing data and results, it is often claimed that slow addition of water to a laminar liquid can produce nanoemulsions, while rapid dilution can produce emulsions with larger droplets (as in self-emulsification methods). [39] When an aqueous phase is added, the emulsification pathway through the micellar cubic liquid crystalline phase produces very small droplet size nanoemulsions in the ionic surfactant system. In reality, the requirements for the production of O/W nanoemulsions with the smallest possible droplet size and consequently low polydispersity are often stated as follows: "When emulsifying by phase inversion temperature or composition methods, aqueous continuous phase, O/W or bicontinuous, where the whole oil is dissolved, must be passed just before the final into the two-phase region where nanoemulsions are formed. These formulation conditions are necessary, but not sufficient, because preparation factors such as the rate of addition of the aqueous phase in the PIC method or the cooling rate in the PIT method also affect how quickly the oil is incorporated or aggregated in the existing water continuous phase nanoemulsion. drops [30] Optimization by selectively changing parameters: Factors whose effects on nanoemulsion properties are often studied are classified as compositional or manufacturing variables. Composition variables have a greater effect than production variables on emulsification in low-energy methods, but the influence of production variables is crucial in shear emulsification. Examples of recent studies on the optimization of shear produced nanoemulsions include analyzes of the effects of various factors and the relationships between drop size and these factors. [31] A high-pressure microfluidizer is used to emulsify the food system, while surfactant and other polymers are used to stabilize the emulsions. We study the processes of fracture and melting, taking into account the role of stabilizers. [32] By subjecting the crude emulsion to the subcritical conditions of water, the production of nanoemulsions is optimized. Optimization (temperature) was analyzed by carefully varying the composition parameters (surfactant and oil content) and the production parameter. Small sizes, 40 nm, are obtained by this method. The ratio of surfactant oil and thus, the ratio of surfactants when using a combination of surfactants is a factor whose influence is often studied in alternative condensation processes. Several well-known references in the recent bibliography show optimization by selectively changing the parameters of nanoemulsions prepared by the phase inversion temperature method. When the droplet size is examined in relation to the oil to surfactant ratio, it is clear that the higher the oil to surfactant ratio, the larger the droplet size. However, if one examines the droplet size in relation to the mixing ratio of surfactants, it is strikingly clear that in the preparation of nanoemulsions On cooling from the HLB temperature, the droplet size does not depend on the surfactant mixing ratio. There are also several of them



VIII. MORPHOLOGICAL STUDY OF NANOEMULSION

The morphological study of nanoemulsion is carried by using transmission electron microscopy (TEM). In TEM, a beam of electron is incident on a thin foil specimen and passed through it. On interacting with the specimen, these incident electrons transform into unscattered electrons, elastically scattered electrons or inelastically scattered electrons. The distance among the objective lens and the specimen and among the objective lens and its image plane regulates the magnification. The electromagnetic lenses concerted the unscattered or scattered electrons and cast them onto a screen that produce amplitude-contrast picture, a phase-contrast image, electron diffraction, or a phantom picture of distinct darkness, which is dependent upon the density of unscattered electrons. Bright field imaging at increasing magnification in combination with diffraction modes used for disclosing the size and form of nanoemulsion droplets. For performing TEM, few drops of nanoemulsion or a suspension of lyophilized nanoparticles is prepared in double distilled water and are placed onto holey film grid and immobilized. Excess solution has to be wicked off from the grid following immobilization and stained. The stained nanoparticles are then examined at particular voltage. Singh et al. studied surface morphology characteristics of primaquine nanoemulsion by TEM analysis and reported spherical shape of primaquine nanoemulsion with smooth surface.

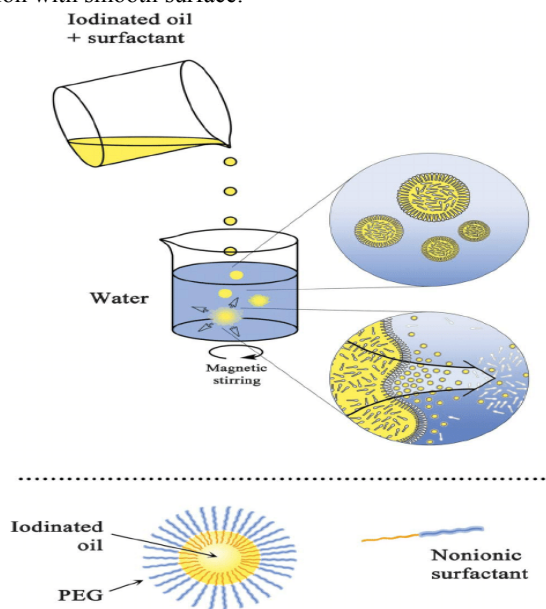
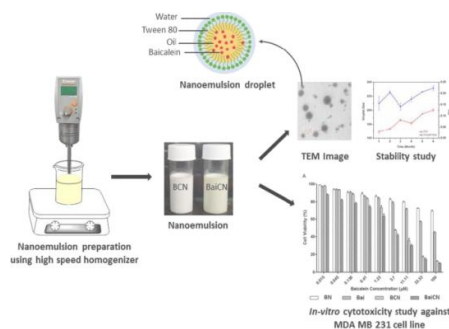


Fig. 3. Morphological study of Nanoemulsion

IX. STABILITY STUDIES

Stability studies are performed for assessing stability of the drug substance under the influence of a various environmental factors like temperature, humidity and light. The stability studies of nanoemulsion are carried out after storing the formulation for 24 mo in dispersed and freeze-dried state as per International Conference on Harmonisation guidelines. The storage conditions followed are ambient ($25 \pm 2^\circ / 60 \pm 5\%$ RH), refrigeration ($5 \pm 3^\circ$) and freeze ($-20 \pm 5^\circ$). The requisite volume of nanoemulsion is stored in glass bottles and is tightly sealed. Samples are withdrawn at predefined time interval and analysed for the characteristics such as particle size, loading and EE and in vitro drug release profile. Singh et al. performed stability studies on nanoemulsion and observed that no change in viscosity, drug content and particle size when the formulation was stored for 3 mo at $25^\circ / 60\%$ RH and $30^\circ / 65\%$ RH.





XII. EQUIPMENT USE IN NANOEMULSION

Beaker
Stiring rod
Mortar and pestle
Electronic Weighing balance
Butter paper, etc.



Fig. 6. Beaker

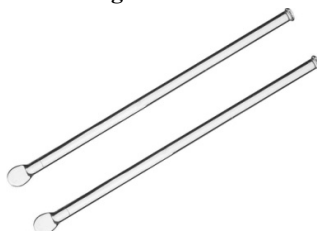


Fig. 7. Stiring rod



Fig. 8. Mortar pestle



Fig. 9. Electronic Weighing balance.



Fig. 10. Butter paper



XIII. CONCLUSION

Nanoemulsions have gained great popularity and attention in the last decade due to their extraordinary properties such as appearance, transparent stable stability, large surface area and tunable rheology. The best-known nanoemulsion preparation methods are high-energy methods such as high-pressure homogenization, microfluidizers, and ultrasonic homogenization, and low-energy methods such as spontaneous emulsification, phase inversion composition, phase inversion temperature, and emulsion inversion point. Nanoemulsions are considered one of the most promising systems to improve the bioavailability, solubility and functionality of non-polar active ingredients. In the food industry, these systems are used for inclusion lipophilic functional compounds for the development of innovative foods.

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