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A review on nano emulsions in Novel Drug Delivery Systems (NDDS)

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Abstract
Nanoemulsions are advanced drug delivery systems that consist of fine oil-in-water or water-in-oil dispersions stabilized by surfactants, with droplet sizes ranging from 20-200 nm. These nano-scaled emulsions have garnered substantial interest due to their potential to improve the solubility, stability, and bioavailability of poorly soluble drugs. This review aims to explore the formulation techniques, evaluation parameters, and advantages of nanoemulsions in novel drug delivery systems (NDDS). It delves into the methods used to prepare nanoemulsions, their physicochemical characterization, and their therapeutic applications, highlighting their significant impact on enhancing drug delivery.

Keywords: Nanoemulsion, NDDS, microfluidization, ultrasonication, cancer treatment

Introduction
Nano-emulsions have significant potential in the pharmaceutical sector due to their high opacity at optimal droplet volumetric fractions, enhanced bioavailability, and extended biopharmaceutical shelf life [1]. As a versatile drug delivery system, nano-emulsions improve the bioavailability of poorly water-soluble drugs. This technique involves dispersing two immiscible liquids into an isotropically transparent nano-emulsion, which is energetically favorable and stabilized by a buffering mechanism [2]. A nano-emulsion is an isotropic mixture comprising oils, a surfactant system, water, and drugs, forming one of the colloidal particles nanosystems with droplet sizes ranging from 50 to 500 nm, acting as carriers for drug materials [3, 4]. This delivery system not only enhances the bioavailability and pharmacological action of drugs but also reduces their toxic effects [5]. The structure and composition ratio of oils and surfactants in nano-emulsions are illustrated in figure 1[6].

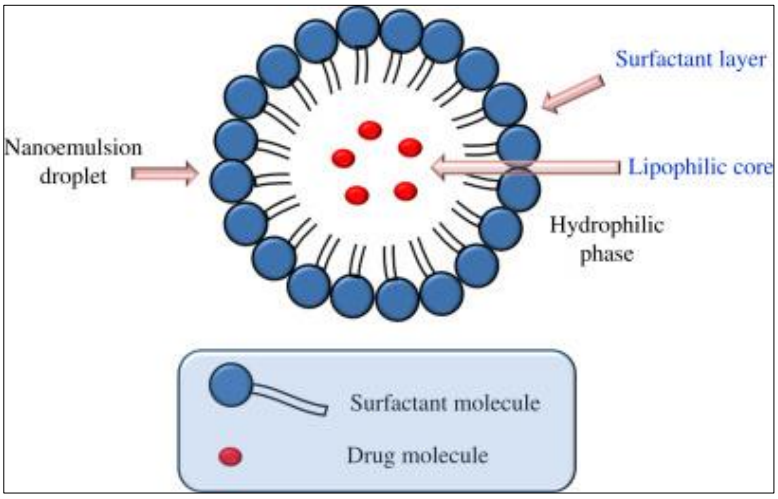

Fig 1: Nanoemulsion structure

Nano-emulsions are transparent, stable emulsions composed of two immiscible liquids with particle sizes smaller than 500 nm. Formulating bioactive substances in nano-emulsions ensures greater bioavailability [7]. Research has shown that nano-emulsions can prolong a drug's presence in the body, necessitating a smaller dose for therapeutic effectiveness. Studies indicate that processing with nano-emulsions can enhance the bioavailability of lipid-soluble drugs [8].

While oil-in-water (O/W) nano-emulsions have been prepared for a long time, recent studies by K.L and Fester have focused on water-in-oil (W/O) nano-emulsions. Both types offer advantages in pharmaceuticals and cosmeceuticals [9].

Nano-emulsions are increasingly employed for delivering a range of biopharmaceuticals, including vaccines, DNA-based drugs, and antibiotics. This drug delivery system is also used in cosmetic and topical preparations. One significant advantage of nano-emulsions is their ability to be administered through various routes, including oral, ocular, and transdermal. This article explores different aspects of nano-emulsion manufacturing, including the selection of emulsifying agents and the challenges in designing and innovating nano-emulsion delivery systems. The extremely small droplet size of nano-emulsions ensures stability against sedimentation and creaming, addressing the Ostwald ripening process, which is key to nano-emulsion degradation [10].

MERITS [11-13]

- Can be used as a substitute for lipid/protein-coated medicaments and vesicles.
- Enhances the bioavailability of drugs.
- Non-toxic and non-irritating.
- Improved physical stability.
- Provides droplets with a wider surface area, leading to increased absorption.
- Can be developed in various formulations such as foams, creams, oils, and sprays.
- Improves the solubility of lipophilic drugs.
- Helps in masking odors.
- Requires less energy for preparation.

Disadvantages of nano-emulsion [14-15]

- Requires a high ratio of surfactant and co-surfactant to stabilize nanodroplets.
- Poor solubilizing ability for fast-melting liquids.
- Stability is affected by atmospheric variables such as humidity and pH.

Limitations of nano-emulsion [16-17]

- The production of nano-emulsion formulations is expensive due to the difficulty in minimizing droplet size, requiring specialized instruments and processes. For example, the homogenizer, necessary for nano-emulsion formulation, is costly. Additionally, manufacturing processes like microfluidization and ultrasound require substantial financial investment.
- Nano-emulsion stability is generally undesirable, posing a significant challenge during long-term preparation and storage.

types of nano- emulsion

Nano-emulsions are commonly classified into three types: oil-in-water (O/W), water-in-oil (W/O), and bi-continuous nano-emulsions [18].

O/W Nano-Emulsion

An oil-in-water nano-emulsion is created by mixing two immiscible liquids (oil and water) in the presence of a surfactant. This type of nano-emulsion typically has a higher fraction than water-in-oil nano-emulsions. In an O/W nano-emulsion, the surfactant system forms a film that disperses the oily phase within the aqueous phase, which acts as the continuous phase, resulting in droplets. Generally, this form of nano-emulsion is more transient compared to water-in-oil nano-emulsions [19].

W/O Nano-Emulsion

A water-in-oil nano-emulsion can be identified by its small liquid particles surrounded by a continuous oil phase. These are referred to as "reversed micelles," where the polar head groups of surfactants are positioned in the oil phase with fatty acid tails in the water droplets [20].

Bi-Continuous Nano-Emulsion

In a bi-continuous nano-emulsion, the micro-domains of oil and water are interspersed within the system. This creates a structure where both oil and water phases are continuous and intertwined [21].

Components of nano-emulsion

Nano-emulsions, with particle sizes ranging from 10 to 1,000 nm, serve as drug carriers that enhance clinical effectiveness and minimize toxic effects. Although thermodynamically unstable, the presence of a surfactant can stabilize them. The phase in which the nano-emulsion is dispersed is known as the continuous phase, while the other phase acts as the dissolution medium. Micelles within the emulsion are often referred to as intermediary or flexible. Nano-emulsions primarily consist of three components: oil, water, and surfactant. The properties and consistency of the emulsion depend on the optimal combination of these ingredients. Generally, lipids and surface-active agents used in nano-emulsions must be nontoxic, clinically acceptable, biodegradable, and biocompatible [22-24].

Oil Phase

Selecting the appropriate oily phase is crucial because it affects the choice of other nano-emulsion components, especially in oil-in-water (O/W) nano-emulsions. Typically, the oil with the highest emulsifying capacity for the selected drug is used to aid in drug loading within the nano-emulsion [25].

Aqueous Phase

The water phase, often referred to as the aqueous phase, may include hydrophilic active ingredients and protective agents. Buffer solutions are commonly used as the water phase. This layer contains water-soluble compounds, with water as one of its main constituents [26].

Surfactant

Surfactants contain both water-soluble and lipid-soluble elements in their chemical structure, making them amphiphilic. This property allows them to create a bi-continuous phase by forming a flexible film that can expand around the particles, achieving the ideal geometry. Surfactants are often classified based on their hydrophilic-lipophilic balance (HLB) value, a numerical scale ranging from 0 to 20. [27].

Surfactants and Their Electronic Conductivity

The electronic conductivity of surfactants plays a crucial role in determining the formation and stability of compositions. Surfactants can be categorized based on their charge into cationic, anionic, non-ionic, and zwitterionic types [28].

Cationic Surfactant

Cationic surfactants are found in aqueous phases and contain a positively charged head group. They typically include amphiphilic cations like halogen variants, which are effective against bacterial and viral membranes. However, they are generally incompatible with non-ionic and anionic payloads [29]. Examples include alkyl trimethylammonium salts such as cetyltrimethylammonium bromide (CTAB) and cetyltrimethylammonium chloride, which feature ammonium sulfate cations that are constantly charged [30].

Anionic Surfactant

Anionic surfactants are introduced with water and feature a negatively charged head group, often with sodium (Na), potassium (K), or ammonium sulfate cations, paired with an anionic group such as phosphate, sulfate, carboxylate, or sulfonate. These surfactants have anionic molecular orbitals at their head [32].

Non-Ionic Surfactant

Non-ionic surfactants interact stably with water through hydrophobic interfaces and hydrate layers via polarity and hydrogen bonding. They do not ionize in aqueous solutions and have a non-separable hydrophilic group, which can be phenol, alcohol, ester, amide, etc. Many non-ionic surfactants contain a polyethylene glycol chain in their structure [33].

Zwitterionic Surfactant

Zwitterionic surfactants contain both anionic and cationic centers within the same molecule, making them amphoteric. Their dual-charged nature, with both positive and negative groups, allows them to create nanoparticles.

Each type of surfactant plays a distinct role in nano-emulsion formulations, influencing their stability and effectiveness as carriers for various applications [34].

Co-Surfactants

Co-surfactants, despite their small quantities, play a crucial role in nano-emulsion development. They are typically amphoteric surface-active agents that enhance the therapeutic function of surfactants, although they do not provide adequate emulsion stabilization alone. Co-surfactants effectively reduce interfacial tension and improve the responsiveness of hydrocarbon regions at the interface, thereby enhancing the overall stability of the formulation [35].

Co-Solvents

Co-solvents are compounds added to improve the solvent strength of a primary material by making normally immiscible substances mixable. They facilitate the dissolution of solutes and are often used in combination with other substances. Common co-solvents include methanol, ethanol, and water, chosen based on their solubility characteristics and ability to enhance the dissolution capacity of the primary solvent in various formulations [36].

Method of preparation for nano-emulsion drug delivery system

Nano-emulsions are stable, transparent mixtures consisting of two immiscible liquids with particle sizes under 100 nm [37]. Here are some common methods for preparing nano-emulsion drug delivery systems: [38].

High-Pressure Homogenization

In this method, two liquids (oil and water phases) are forced together at very high pressures (500–5000 psi) through a small orifice. This intense process creates extremely fine emulsion particles due to high friction and kinetic shear. The lipid-soluble core of the particles is separated from the aqueous core. This technique produces high-quality emulsions but requires significant resources and results in a considerable temperature increase during the process [39].

Microfluidization

Microfluidization involves using a device called a microfluidizer. A high-pressure positive displacement pump (500 to 20,000 psi) forces the substance through tiny channels, or "micro-channels," creating submicron-sized particles as the material passes through. Initially, the oil and water phases are mixed in an internal chamber to form a coarse emulsion [40].

Ultrasonication

Numerous studies document the use of ultrasonic sound waves to reduce particle size in nano-emulsion formulations. This method can also involve continuous sonotrode intensity at pressures above atmospheric levels. [41] Increased external pressure raises the cavitation threshold of ultrasonic waves and reduces bubble formation, but it also strengthens the collapse of cavitation bubbles, making them more intense [42].

Phase Inversion Method

This method leverages the potential energies from symmetry breaking caused by the flocculation mechanism to achieve uniform distribution. The emulsion's phase can be inverted by altering the temperature or other conditions [43].

Spontaneous Emulsification

This method involves several steps

1. Creating a homogeneous phase consisting of oils and a lipid-soluble surfactant in a soluble aqueous solution with a water-soluble surfactant [44].
2. Infusing the organic layer into the aqueous medium with mechanical stirring to form an oil/water emulsion.
3. Removing the water-soluble solvent through convection under reduced pressure [45].

Solvent Evaporation Technique (SET)

In SET, the drug is mixed with an emulsifying agent in a substance that is not a solvent for the drug. The drug precipitates as the solution evaporates. High-speed stirring creates significant shear forces to control crystallization [47].

Hydro-gel Method

This method is similar to SET, but the anti-solvent makes the solvent ingredient soluble. Higher shear forces impact crystal growth and Ostwald maturation [48].

Evaluation parameter

Droplet Size Measurement

The particle size is measured using a light-scattering analyzer and a diffusion method. This process characterizes the particle diameter. Additionally, association spectrometry is employed to study the variations in specular reflection caused by Brownian motion [49].

Viscosity Determination

The viscosity of a nano-emulsion is analyzed using a Brookfield-type rotary viscometer. This analysis is performed at various shear rates and temperatures to obtain accurate measurements.

Drug Content
To determine the drug content in the formulation, UV spectrophotometric and HPLC techniques are used. For analysis, 10 mg of the drug-loaded nano-emulsion is dissolved in 100 ml of solvent, typically under UV conditions. Subsequently, 1 ml of this stock solution is diluted with 10 ml of solvent, and the drug concentration is measured at the drug's specific Lambda maximum.

pH
The pH of the nano-emulsion system is measured using a pH meter to ensure proper formulation conditions.

Refractive Index
The refractive index of the nano-emulsion is calculated using an Abbe refractometer.

Zeta Potential Analysis
The surface charge of the nano-emulsion droplets is determined by measuring the Zeta potential. For this analysis, 0.1 ml of the formulation is diluted 100 times with double-distilled water and measured using a Zetasizer [50].

Percentage Transmission
The percentage transmission of nano-emulsion formulations is measured spectrophotometrically using a UV spectrophotometer at the same Lambda max as the drug molecule.

Conductivity Test
The conductivity of the nano-emulsion is measured using a conductometer system to assess its ionic properties.

Dilution Test
This test evaluates the stability of the nano-emulsion when the continuous phase is diluted, ensuring that the emulsion remains stable under such conditions.

Dye Test
The dye test is used to measure the color uniformity of the nano-emulsion, ensuring consistent distribution of the dye throughout the formulation.

Uniformity Test
The uniformity test assesses the consistency in the size of droplets within the nano-emulsion, ensuring that all droplets are of uniform size.

Thermodynamic Stability Analysis
To evaluate the thermodynamic stability of the nano-emulsion, the formulation is subjected to centrifugation at 1000 RPM for 30 minutes to check for phase separation and creaming. Additionally, the nano-emulsion undergoes a heating process, being cycled six times between 4 °C and 45 °C, with storage at each temperature for no less than 48 hours. The formulation is also subjected to three freeze-thaw cycles between -21 °C and +25 °C, with storage at each temperature for no less than 48 hours, to verify its stability.

***In vitro* Skin Permeation Studies**
The improved nano-emulsion (NE) *in vitro* drug release was evaluated using the diffusion method. A dialysis tube containing 1.0 ml of NE was placed in 900 ml of diffusion medium at 100 rpm and 37±0.5 °C (pH 6.4 - 6.8 phosphate buffer). To maintain sink conditions, 5 ml samples were regularly taken from the diffusion medium, and the removed volume was replaced with fresh medium. The drug content in the samples was measured using UV analysis at the specific Lambda max of the drug ingredient, and the percentage of controlled release events was calculated [51].

Transmission Electron Microscopy (TEM)
Transmission Electron Microscopy (TEM) was utilized for the morphological and structural analysis of the nano-emulsion system, providing detailed images of the particles' shapes and structures.

Phase Behavior Study
The nano-emulsion system was evaluated using a pseudo-ternary phase diagram to define the phase behavior and the region of nano-emulsion formation [52].

Application of nano-emulsion
Parenteral Delivery
Nano-emulsions are used for intravenous administration, requiring droplet sizes smaller than 1 micrometer. Parenteral (or injectable) nano-emulsions are used for delivering nutrients such as fats, carbohydrates, and vitamins [53].

Oral Delivery
Nano-emulsion systems offer multiple advantages over traditional formulations for oral delivery, including enhanced absorption, increased therapeutic efficacy, and reduced drug toxicity.

Topical Delivery
Topical delivery of medications offers several advantages over other methods, such as minimizing hepatic first-pass metabolism and reducing potential adverse effects. This approach involves applying the medication directly to the affected skin or eye area, providing localized treatment.

Ocular Delivery
Nano-emulsions are used for the topical administration of drugs to treat eye disorders. This method improves the dissolution of poorly soluble drugs, enhances absorption, and achieves a prolonged release profile [54].

In Cosmetic Industry
Nano-emulsions are highly desirable in the cosmetic industry due to their low viscosity, translucency, and droplet sizes under 200 nm. These characteristics provide a high surface area, facilitating the transfer of active substances to the skin. Nano-emulsion technology is used to develop oil-in-water mini-emulsions that reduce transepidermal water loss, improve skin safety, and enhance drug penetration.

Nano-emulsions in Cancer Treatment
In chemotherapy, nano-emulsions can serve as carriers to prolong drug release following muscular injections and impact surrounding tissues (W/O systems). This non-irritating approach enhances the transdermal delivery of anti-cancer drugs by improving their lymphatic penetration through the skin.

Nano-emulsions in Gene Delivery
Nano-emulsion systems are used as potential platforms for genetic manipulation, offering stronger retention of the emulsion/DNA pair compared to traditional encapsulated transmitters. Studies have shown that this stable emulsion

process results in more effective gene delivery than microcapsules [55].

Nano-emulsions in Nose to Brain Drug Delivery System

The noninvasive nasal drug delivery system is a more efficient method than parenteral and oral routes for delivering medications, particularly those targeting the brain. The nasal mucosa has evolved as a viable pathway for drug administration due to its favorable characteristics. This method addresses the challenges associated with aqueous drugs and large molecular weight compounds.

An effective approach to bypass the barriers that prevent rapid drug entry into the brain is essential. Nasal drug delivery is non-invasive, painless, and efficient. The nasal mucosa is one of the most effective sites for drug administration due to its low catalase activity and high concentration of permeable sites. The mucous membrane's microvascular nature ensures a hermetic separation from the blood-brain barrier, facilitating drug delivery directly to the brain [56].

Nano-emulsions targeting the nasal mucosal olfactory region, which connects the nostrils to the brain, can treat various neurological conditions such as Alzheimer's disease, migraines, epilepsy, schizophrenia, Parkinson's disease, and meningitis. This method leverages the direct pathway between the nasal cavity and the brain to enhance drug delivery efficiency [57].

Conclusion

The nano-emulsion drug delivery system has found extensive application in the pharmaceutical field due to its numerous advantages for delivering drugs and biochemicals. It is suitable for multiple routes of administration and holds potential for various applications. This technological innovation addresses the challenges associated with poorly water-soluble drugs, providing a solution for delivering aqueous-insoluble drugs effectively. Nano-emulsions are currently used for the selective delivery of a wide range of drugs, including anti-cancer medications and photosensitizers. Overall, nano-emulsion formulations have proven to be efficient, secure, and patient-compliant options for pharmaceutical distribution. As research and development continue, further advancements in nano-emulsion technology are anticipated, promising even greater efficacy and broader applications in the future.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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