Development and Application of the Nanoemulsions in Drug Delivery Systems

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Abstract. Nanoparticle drug delivery systems (NDDS) have emerged as a promising alternative to traditional drug delivery methods, offering significant improvements in drug bioavailability, targeting, and reduced toxicity. Among these, nanoemulsions (NE) have shown considerable potential across various therapeutic applications, addressing the limitations of conventional drug delivery systems. This review explores the preparation methods, characterization techniques, and advantages of nanoemulsions in drug delivery. Key preparation methods, including ultrasonic emulsification, high-pressure homogenization, and spontaneous emulsification, are discussed in terms of their advantages and challenges. The review also examines critical characterization parameters, such as droplet size, viscosity, stability, and polydispersity, which influence the effectiveness of nanoemulsions in therapeutic applications. central nanoemulsions in nasal-cerebral delivery for central nervous system tumors, intravenous delivery for gout treatment, and topical applications for urticaria are highlighted, demonstrating their ability to enhance drug efficacy, targeting, and patient outcomes. Despite the promising benefits, nanoemulsions face challenges in large-scale production, stability, and regulatory approval. Future research must address these issues to optimize nanoemulsion preparation and application for broader clinical use.

Keywords: Nano emulsion, drug delivery, nanoparticle drug delivery systems.

1. Introduction

The use of drugs is traditionally regarded as a crucial element in treatment processes. Currently, drug delivery systems are categorized into five main types: topical, intravenous, ocular, nasal, and oral delivery. However, despite fulfilling their therapeutic purposes, traditional drug delivery systems exhibit several significant drawbacks. These issues often impact treatment outcomes or negatively affect patient experiences. Key challenges include uncontrollable adverse effects due to drug toxicity, increased treatment costs driven by low bioavailability, and reduced efficacy arising from the low precision of drug targeting [1]. Addressing these limitations is critical for improving therapeutic outcomes.

In response to these challenges, NDDS has emerged as a promising solution. NDDS utilizes particles ranging from 1 to 1000 nm in size, formulated from various drugs and medicinal materials. This system represents a significant advancement over traditional drug delivery methods. The main forms of nanoscale drugs include nanoparticles (NP), nanospheres (NS), nanocapsules (NC), nanoliposomes (NL), and nanoemulsions (NE). Owing to their unique nanoscale properties, NDDS offers several benefits over conventional systems, such as reducing toxicity and adverse reactions, improving drug bioavailability to lower treatment costs, and providing better targeting. Additionally, NDDS enhances the stability, solubility, and polarity of drug particles, leading to more effective therapeutic interventions [2].

This review focuses on the application of NE in drug delivery systems, particularly their advantages across various delivery methods. Nanoemulsions have demonstrated notable efficacy in targeted delivery and immunotherapy when used as vaccine adjuvants [3]. In nasal-cerebral drug delivery systems, NE reduces drug toxicity and enhances the ability to bypass the blood-brain barrier [4]. In gene therapy, nanoemulsions facilitate efficient gene transfection, while in oral and topical delivery systems, they extend drug residence time, improve skin permeability [5], support sustained drug release [6], and enhance intestinal absorption [7]. Nanoemulsions have also shown potential in anti-cancer treatments [8] (Figure 1).

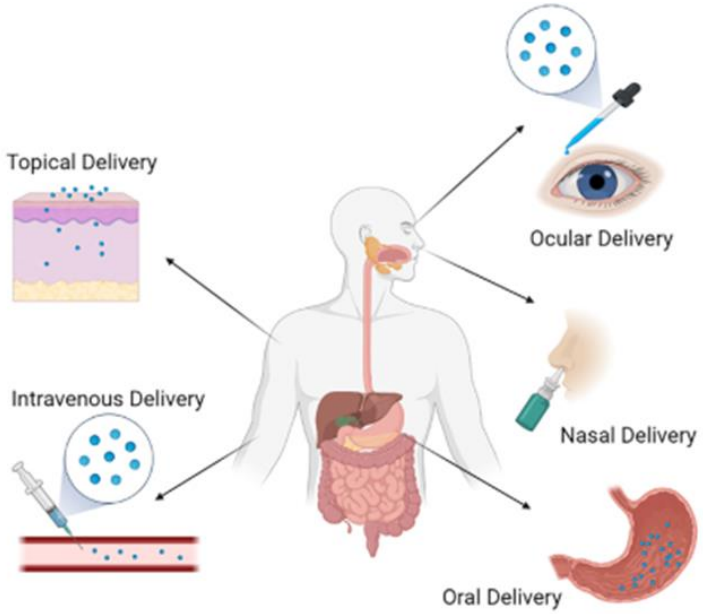

Fig. 1 Different routes of administration for nanoemulsion drug delivery [8]

This review explores several key aspects of nanoemulsions in drug delivery, beginning with their preparation methods and characterization techniques. It then addresses the specific advantages of NE in improving drug delivery. Furthermore, the application of NE in treating various diseases—including central nervous system tumors, cancer, gout, and allergic reactions—is discussed. Finally, the review examines the challenges and future prospects of nanoemulsions in drug delivery systems.

2. Preparation and Characterization of Nanoemulsions

2.1. Preparation Method of Nanoemulsion

The preparation of nanoemulsions can be divided into two main stages. The first stage involves the formation of a coarse emulsion, typically achieved through physical stirring and mixing. The second and more critical stage focuses on reducing the droplet size of the coarse emulsion to the nanoscale, resulting in the formation of a fine emulsion, or nanoemulsion [3]. The specific methods employed in this process, along with their respective advantages and limitations, are discussed below.

The ultrasonic emulsification method utilizes cavitation phenomena caused by mechanical vibrations to reduce droplet size. Cavitation refers to the repeated formation and collapse of cavities within the liquid. Ultrasonic emulsification is commonly used in laboratory settings and can produce nanoemulsions with droplet sizes as small as 0.2 micrometers [9]. While it is a fast and efficient method for droplet size reduction, its large-scale application is limited due to the significant energy input required, leading to increased costs.

In the high-pressure homogenization method, droplets are reduced in size under high-pressure conditions, allowing the formation of nanoemulsions with particle sizes as small as 1 nanometer. However, similar to ultrasonic emulsification, this method requires substantial energy input to maintain the process [9].

Micro/nanofluidic flow focusing method employs a specialized microfluidic device to reduce droplet size by subjecting the droplets to high-pressure interactions. The process is repeated several times to achieve the desired droplet size. While this method offers controllability and moderate flow rates, it has limitations in reducing droplet size and is typically suitable for water-in-oil (W/O) emulsions [2].

Phase inversion temperature (PIT) method relies on the application of high temperatures to alter surface tension, leading to the formation of nanoscale droplets. It is a low-flow, controllable process but also requires significant energy input and is primarily suitable for nonionic surfactant applications [2].

The spontaneous emulsification approach, the organic phase is gradually added to the aqueous phase while continuously stirring. The aqueous phase typically contains water-soluble solvents and hydrophilic surfactants, whereas the organic phase includes oils and lipophilic surfactants. Following this, the aqueous phase is removed via vacuum evaporation [9]. An example of this process can be seen in the preparation of curcumin-coated nanoemulsions. The components, including 95% curcumin, 58.6% MCT C8, 41.4% MCT C10, Tween-80, whey protein concentrate, pepsin, and pancreatic enzymes, are mixed in precise proportions. A coarse emulsion is formed through continuous stirring with a magnetic mixer, followed by ultrasonic emulsification to obtain the desired nanoemulsion [10] (Figure 2).

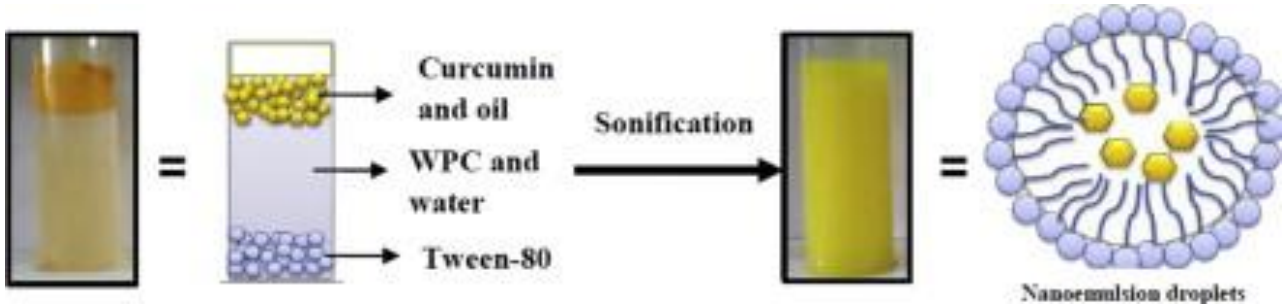

Fig. 2 Different routes of administration for nanoemulsion drug delivery [10]

There are three key factors to consider in the preparation of nanoemulsions. First, the selection of an appropriate surfactant is crucial for achieving low interfacial tension, a fundamental requirement in nanoemulsion production. Second, the concentration of the surfactant must be sufficient to stabilize the microdroplets and facilitate nanoemulsion formation. Finally, the surfactant must possess adequate flexibility or fluidity to promote nanoemulsion formation effectively.

2.2. Characterization

The characterization of nanoemulsions involves several critical parameters and test methods that help evaluate their performance, stability, and suitability for various applications. One key parameter is droplet size, which can be measured using two primary techniques: spectroscopy, which utilizes light scattering caused by Brownian motion, and Transmission Electron Microscopy (TEM), which provides high-resolution images for direct droplet size measurement. These methods are essential in determining the nanoscale properties of the emulsion.

Another important factor is viscosity, which is influenced by temperature variations. Viscosity is typically measured using a Brookfield-type rotary viscometer at different shear rates to assess the fluidity of the nanoemulsion system. Understanding viscosity is crucial for predicting the behavior of nanoemulsions under various operational conditions.

Stability is a key consideration in nanoemulsion systems, often evaluated through dilution tests. For oil-in-water (O/W) nanoemulsions, dilution with water helps assess stability, while water-in-oil (W/O) systems are tested by dilution with oil. These tests determine the emulsion's resistance to phase separation and destabilization over time, which is critical for ensuring the longevity and reliability of the formulation.

The polydispersity index (PDI) is used to measure the uniformity of droplet size within the emulsion. Lower PDI values indicate more uniform droplets, and this parameter is commonly assessed using a spectrophotometer. A uniform droplet size distribution is vital for achieving consistent performance in nanoemulsion applications.

Additional characterization methods include measuring the pH, refractive index, and zeta potential of the nanoemulsion. Zeta potential provides insights into the surface charge of droplets, which influences their stability, while the refractive index helps in evaluating optical properties. These parameters, along with techniques for distinguishing between O/W and W/O nanoemulsions, provide a comprehensive understanding of the system's characteristics and potential for specific uses.

3. Application and Advantages of Nanoemulsion Drug Delivery System in Various Therapeutic Area

Nanoemulsion systems have found wide applications across various therapeutic areas, demonstrating significant advantages in different drug delivery systems. These advantages can be better understood through specific examples, highlighting their role in improving drug efficacy, targeting, and minimizing side effects [11].

3.1. Nasal-Cerebral Drug Delivery System (Lomustine for Central Nervous System Tumors)

In traditional chemotherapy for central nervous system (CNS) tumors, lomustine is widely used due to its ability to kill and inhibit cancer cell growth. However, lomustine lacks selectivity, affecting both cancerous and healthy cells, which leads to unwanted side effects. Moreover, since lomustine is typically administered orally, its lipophilic nature results in extensive first-pass metabolism in the liver, with a metabolic half-life of around 94 minutes. This not only reduces the bioavailability of the drug but also increases the liver's metabolic burden, requiring higher dosages that elevate toxicity and adverse effects. The application of a nanoemulsion system offers a solution by replacing oral administration with nasal-cerebral delivery, bypassing liver metabolism. This method improves drug targeting to the brain and increases permeability, potentially enhancing the treatment's effectiveness and reducing systemic toxicity [4].

3.2. Intravenous Delivery Systems (Colchicine for Gout)

Colchicine remains the primary drug for treating gout. Traditionally, it is administered orally, but dosage control is challenging due to individual patient differences. To ensure prolonged drug action, higher doses are often administered, leading to intensified side effects. Low doses of colchicine can cause gastrointestinal disturbances, while higher doses may lead to severe conditions like anemia, bone marrow suppression, and even liver and kidney damage. Using a nanoemulsion system for intravenous administration via joint injection addresses these issues. Research using titration methods and radiolabeling showed that nanoemulsion-based joint injections not only avoid the gastrointestinal side effects of oral administration but also prolong the drug's residence time in the joint, thereby improving its anti-gout efficacy [6] (Figure 3).

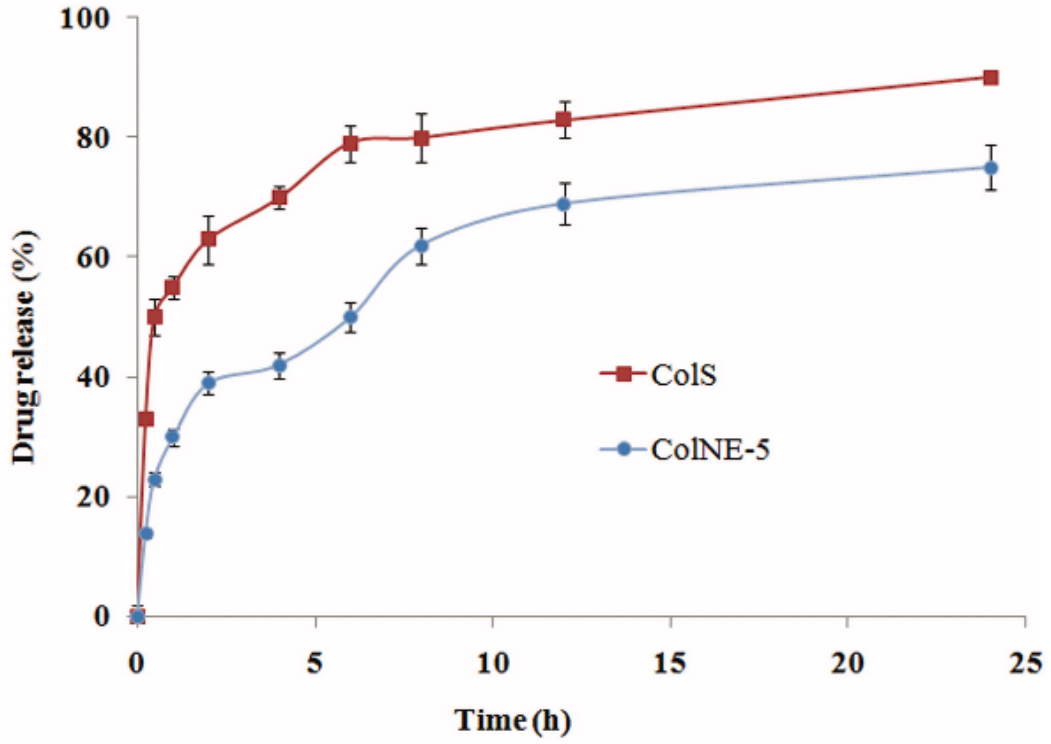

Fig. 3 Comparative in vitro release profiles of ColNE-5 and ColS [6].

3.3. Topical Drug Delivery System (Cetirizine for Urticaria)

In the case of topical drug delivery, a study on cetirizine for treating urticaria demonstrated that nanoemulsion formulations significantly enhanced drug absorption through the skin. Experimental results from mice showed that the skin permeation rate of nanoemulsion-based cetirizine was higher compared to standard cetirizine solutions, improving the bioavailability and efficacy of the drug for treating urticaria [5] (Figure 4). This highlights the potential of nanoemulsions to enhance the effectiveness of topical treatments through better drug absorption.

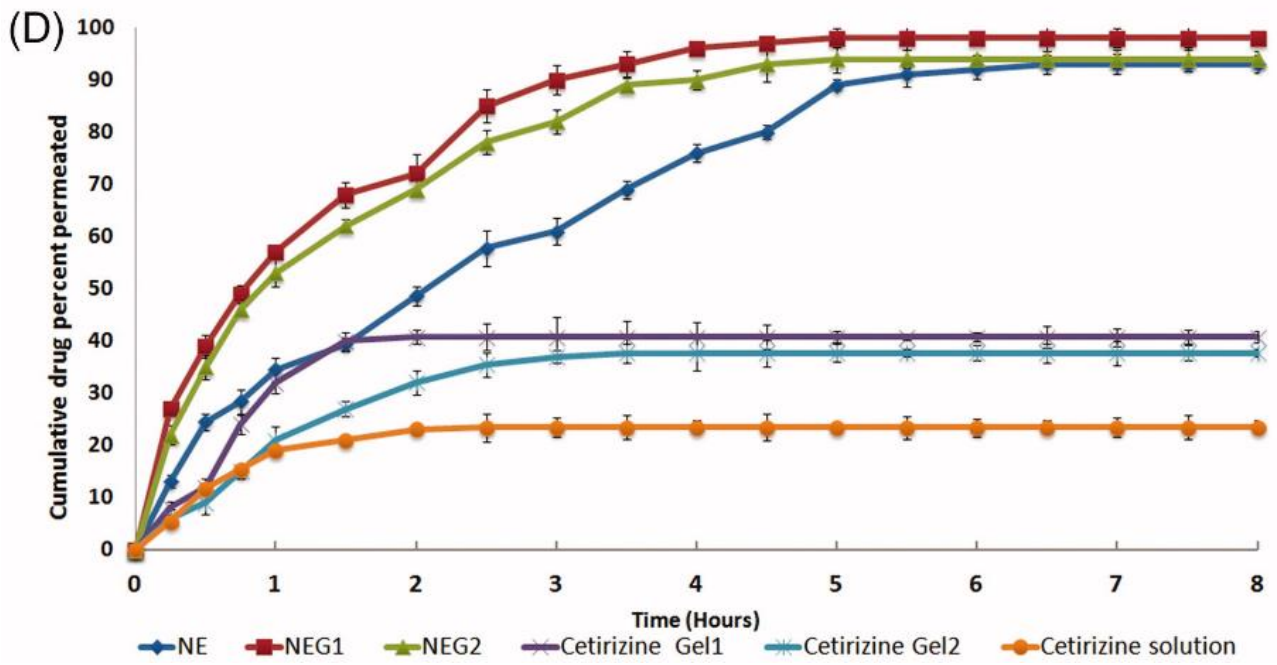

Fig. 4 Cumulative percent of cetirizine permeated through rat skin [5]

These examples underscore the multifaceted benefits of nanoemulsion drug delivery systems in enhancing drug targeting, improving bioavailability, and minimizing side effects across different routes of administration [12].

4. Challenges and Perspectives

4.1. Challenges

While nanoemulsion systems have shown significant promise in addressing clinical challenges in drug delivery, there remain certain limitations in their preparation through traditional methods. One major issue is that the particle size of nanoemulsion droplets produced using conventional techniques tends to be too large for newer applications. As droplet size decreases, the energy required for production increases, and the stability of the nanoemulsion correspondingly decreases. This poses a considerable challenge for scaling up production and achieving large-scale clinical applications. Although various successful preparations of nanoemulsions have been demonstrated in research, challenges persist, such as enhancing the stability of these emulsions, improving the control of their internal structure, and advancing characterization techniques [7]. Additionally, regulatory hurdles, production costs, and safety concerns are critical factors that must be addressed before nanoemulsion-based drug delivery systems can be widely adopted in the medical market.

For instance, the phase inversion temperature method, often used in nanoemulsion preparation, presents a notable disadvantage. Despite efforts to lower the reaction temperature, nanoemulsions produced through this method can be highly unstable over extended periods. Furthermore, the high solubility of the components involved can hinder the broad application of such emulsions [13].

Moreover, while certain emulsification methods can reduce polydispersity and improve stability, not all these methods are applicable to a wide range of potential components, further complicating the development and application of nanoemulsions in drug delivery systems [14]. These limitations highlight the need for continued research and innovation to overcome the existing barriers and fully realize the potential of nanoemulsions in clinical practice.

4.2. Perspectives

To effectively control the morphology and structure of various nanoemulsions, it is essential to establish robust theoretical frameworks, models, and guidelines that facilitate the study of their formation and stabilization mechanisms [7]. Developing the fundamental principles of multiphase nanodroplet synthesis and refining interfacial thermodynamic models will enable the prediction of the most favorable energy configurations for nanodroplets, especially during processes such as phagocytosis [7].

Research should prioritize the investigation of key factors such as transport, stability, rheology, and optical properties, all while ensuring that the desired chemical composition and functional integrity of the nanoemulsions are preserved [2]. Furthermore, controlling the polydispersity of droplets in diverse compositions and emulsification conditions holds significant potential for optimizing nanoemulsion applications [2].

Another critical area of study involves understanding the interactions between nanoemulsions and other colloidal dispersions or surfaces under a broad range of conditions. Such research would provide valuable insights into the behavior and stability of nanoemulsions in complex environments, thereby enhancing their functionality and effectiveness in practical applications [15].

5. Conclusion

This review highlights the application of nanoemulsion systems in drug delivery, focusing on three key aspects: preparation methods, characterization techniques, and their advantages in drug delivery systems. Nanoemulsions have become an area of extensive research due to their potential to improve drug bioavailability, reduce toxicity, enhance sustained-release effects, and improve drug targeting. Several preparation methods are used to synthesize nanoemulsions, including ultrasonic emulsification, high-pressure homogenization, micro/nanofluidic flow focusing, phase inversion temperature, and spontaneous emulsification. Each method has distinct advantages and limitations, tailored to different applications.

The characterization of nanoemulsions, such as droplet size analysis, viscosity, stability, and polydispersity, provides insights into their composition, chemical properties, and overall stability. These parameters are essential for ensuring the effectiveness and reliability of nanoemulsions in various applications.

Nanoemulsions present significant improvements over traditional drug delivery systems. They enhance drug efficacy by improving bioavailability, reducing adverse effects, and minimizing metabolic burdens on patients. Additionally, nanoemulsions improve drug absorption in target organs, including the skin and intestines, and increase the precision of drug targeting. However, despite these promising advantages, the clinical application of nanoemulsions requires further research and validation. Current challenges, such as high preparation costs, product stability, and the scalability of production methods, need to be addressed before large-scale clinical use can be realized. Future research should focus on optimizing the preparation and application of nanoemulsions to ensure their practicality and efficacy in clinical settings.

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