Nanoemulsion: A Comprehensive Review of Formation, Properties, and Applications

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Abstract: This comprehensive review provides an overview of nanoemulsions, focusing on their formation, properties, and applications. Nanoemulsions have gained attention for their unique properties and applications in various industries. The review discusses different techniques for producing nanoemulsions and explores the influence of formulation factors on their physicochemical properties. The effect of droplet size on stability and sensory attributes is examined. Interfacial properties and challenges in formulation and scale-up are also discussed. The review highlights the potential impact of nanoemulsions in drug delivery, food, and agriculture. Overall, nanoemulsions hold great promise for diverse applications. The conclusion section summarizes the key findings and contributions of Nanoemulsion research, highlighting the importance of understanding the physicochemical properties and formulation factors for achieving desirable Nanoemulsion characteristics. The article also emphasizes the potential impact of nanoemulsions in various industries and their role in revolutionizing drug delivery systems, enhancing food product formulations, and improving the effectiveness of agrochemicals.

Keywords: *Nanoemulsion, formation, properties, techniques, physicochemical, interfacial properties, formulation factors, droplet size, stability, applications*

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Introduction

Nanoemulsions, as a novel aspect of nanotechnology and have gained significant attention in recent years due to their extensive applications in numerous fields such as food science, cosmetics, pharmaceuticals, and drug delivery systems.

They are part of a class of dispersed systems, which consist of two immiscible liquids: one of the liquids is dispersed as droplets within the other liquid, with the droplet sizes typically in the range of 20–200 nm[1].

The formation and stability of Nanoemulsions are governed by a delicate balance of forces, including the interfacial tension between the two liquids, the kinetic energy input during emulsification, and the thermodynamic factors that drive phase separation[2]. Various methods can be used to prepare Nanoemulsions, including high-energy emulsification methods such as ultrasonication or high-pressure homogenization, and low-energy methods such as phase inversion temperature or spontaneous emulsification[3].

Nanoemulsions have several advantages over conventional emulsions, including higher stability against droplet aggregation and gravitational separation, greater solubilization capacity for hydrophobic compounds, and potential for controlled release of encapsulated substances[4]. However, despite these advantages, the practical application of Nanoemulsions is often limited by challenges related to their production, stability, and safety[5].

In the following sections, we will delve deeper into the principles of Nanoemulsion formation, discuss the various methods of preparation, and explore their applications and challenges in different fields.

Methods of Preparation

Nanoemulsions can be prepared using a variety of methods, which can be broadly classified into high-energy and low-energy methods. High-energy methods, such as ultra-sonication or high-pressure homogenization, involve the use of mechanical devices to disperse one phase into another, overcoming the interfacial tension between the two phases [6]. On the other hand, low-energy methods, such as phase inversion temperature or spontaneous emulsification, rely on the physicochemical properties of the system and the manipulation of the system's conditions to promote emulsification [6].

The choice of method depends on several factors, including the nature of the materials used, the desired droplet size and distribution, and the intended application of the Nanoemulsion. For instance, in the food industry, low-energy methods are often preferred due to their simplicity, cost-effectiveness, and the fact that no expensive equipment is required[6]. However, these methods may not be suitable for all types of materials or applications.

Recent studies have also explored the use of novel techniques for the preparation of Nanoemulsions. For example, a solvent-diffusion method in an aqueous system has been used to prepare lipid Nanoemulsions for the antitumor delivery of doxorubicin[7]. Another study reported the use of an ultrasonication technique to develop a Nanoemulsion of celery seed oil, which showed potential anticancer and antibacterial activity [8].

Despite the advances in Nanoemulsion preparation methods, challenges remain. These include the need for careful control of the preparation conditions to achieve the desired Nanoemulsion properties, as well as issues related to the stability and safety of the resulting Nanoemulsions [9].

Applications of Nanoemulsions

Nanoemulsions have found extensive applications in various fields such as pharmaceuticals, cosmeceuticals, and food science due to their unique properties. In the pharmaceutical and cosmeceutical fields, Nanoemulsions are often used as delivery systems for bioactive substances or drugs. Their small droplet size and high kinetic stability make them ideal for enhancing the performance and sensory experience of products[10]. For instance, lipid Nanoemulsions have been used for the antitumor delivery of doxorubicin [11].

In the food industry, Nanoemulsions are being increasingly used for the functional modification of proteins and the fabrication of nano-sized emulsion droplets [12]. They can also be used to encapsulate and deliver plant-based preservatives, improving food quality and safety [13]. For example, a Nanoemulsion of celery seed oil, which showed potential anticancer and antibacterial activity, was developed using an ultrasonication technique [11].

Furthermore, Nanoemulsions have been used in the agricultural sector for the development of nanopesticides. A study reported the formulation of Tebuconazole (TBZ) Nanoemulsions using a low-energy method, which could be beneficial for sustainable agriculture [14].

Despite the wide range of applications, the use of Nanoemulsions is not without challenges. These include the need for careful control of the preparation conditions, issues related to the stability and safety of the resulting Nanoemulsions, and the diffusion of active ingredients into the target area [14].

Review of Literature on Different Techniques of Nanoemulsion Preparation

The preparation of Nanoemulsions involves a variety of techniques, which can be broadly classified into high-energy and low-energy methods[15]. High-energy methods, such as ultrasonication or high-pressure homogenization, involve the use of mechanical devices to disperse one phase into another, overcoming the interfacial tension between the two phases[15]. On the other hand, low-energy methods, such as phase inversion temperature or spontaneous emulsification, rely on the physicochemical properties of the system and the manipulation of the system's conditions to promote emulsification[16].

The choice of method depends on several factors, including the nature of the materials used, the desired droplet size and distribution, and the intended application of the Nanoemulsion. For instance, in the food industry, low-energy methods are often preferred due to their simplicity, cost-effectiveness, and the fact that no expensive equipment is required [17]. However, these methods may not be suitable for all types of materials or applications.

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The preparation of Nanoemulsions involves a variety of techniques, each with its own advantages and challenges. The choice of method depends on several factors, including the nature of the materials used, the desired droplet size and distribution, and the intended application of the Nanoemulsion[20].

High-energy methods, such as ultrasonication or high-pressure homogenization, involve the use of mechanical devices to disperse one phase into another, overcoming the interfacial tension between the two phases [20]. These methods are often used in the pharmaceutical industry due to their ability to produce Nanoemulsions with small droplet sizes and narrow size distributions[21].

Low-energy methods, such as phase inversion temperature or spontaneous emulsification, rely on the physicochemical properties of the system and the manipulation of the system's conditions to promote emulsification[20]. These methods are often preferred in the food industry due to their simplicity, cost-effectiveness, and the fact that no expensive equipment is required[22].

Recent studies have also explored the use of novel techniques for the preparation of Nanoemulsions. For example, a solvent-diffusion method in an aqueous system has been used to prepare lipid Nanoemulsions for the antitumor delivery of doxorubicin[23]. Another study reported the use of an ultrasonication technique to develop a Nanoemulsion of celery seed oil, which showed potential anticancer and antibacterial activity[24].

Despite the advances in Nanoemulsion preparation methods, challenges remain. These include the need for careful control of the preparation conditions to achieve the desired Nanoemulsion properties, as well as issues related to the stability and safety of the resulting Nanoemulsions[25].

Formation and Stability of Nanoemulsion

The formation and stability of Nanoemulsions are critical aspects that determine their effectiveness and potential applications. The formation of Nanoemulsions involves the dispersion of one phase into another, facilitated by the use of surfactants[26]. The stability of Nanoemulsions, on the other hand, is influenced by factors such as the nature of the dispersed phase, the type of surfactant used, and the environmental conditions[26].

Research has shown that the type of ripening inhibitor used can significantly impact the formation, stability, and activity of Nanoemulsions. For instance, a study on the formation of thyme oil Nanoemulsions found that the antimicrobial activity of the Nanoemulsions decreased with increasing ripening inhibitor concentration[26]. This was attributed to a reduction in the amount of hydrophobic antimicrobial constituents transferred to the separated hydrophobic domain[26].

In another study, an epigallocatechin-3-gallate (EGCG) Nanoemulsion was prepared to improve the stability and reduce the side effects of EGCG for the treatment of human lung cancer cells[27]. The Nanoemulsion exhibited significant anticancer effects, which were attributed to the activation of AMP-activated protein kinase signaling pathways[27].

The stability of Nanoemulsions can also be enhanced by the addition of nano-additives. For example, a water-in-diesel Nanoemulsion was prepared by blending different percentages of water along with nano-Al additive[28]. The Nanoemulsion was found to be thermodynamically stable, with the surfactant Triton X-100 proving to be the most efficient in stabilizing the suspensions[28].

Furthermore, the incorporation of positively charged cosurfactants, such as phytosphingosine, into Nanoemulsions has been shown to enhance their stability and effectiveness in transdermal delivery systems[29]. This is because positively charged Nanoemulsions provide more effective penetration of the skin[29].

Methods for Producing Nanoemulsions

The production of Nanoemulsions involves a variety of methods, each with its own advantages and challenges. These methods can be broadly classified into high-energy methods, low-energy methods, and phase inversion methods[30].

High-Energy Methods

High-energy methods involve the use of mechanical devices to disperse one phase into another, overcoming the interfacial tension between the two phases[31]. These methods include high-pressure homogenization, microfluidization, and ultrasonication. High-energy methods are often used in the pharmaceutical industry due to their ability to produce Nanoemulsions with small droplet sizes and narrow size distributions [31].

Low-Energy Methods

Low-energy methods rely on the physicochemical properties of the system and the manipulation of the system's conditions to promote emulsification[32]. These methods include spontaneous emulsification, phase inversion composition, and phase inversion temperature. Low-energy methods are often preferred in the food industry due to their simplicity, cost-effectiveness, and the fact that no expensive equipment is required[32].

Phase Inversion Methods

Phase inversion methods involve the transition of an oil-in-water emulsion to a water-in-oil emulsion or vice versa[33]. This transition can be induced by changes in the composition or temperature of the system. Phase inversion methods are advantageous in that they can produce Nanoemulsions with a wide range of droplet sizes and can be used to encapsulate a variety of substances[33].

Physicochemical Properties of Nanoemulsion

The physicochemical properties of Nanoemulsions are crucial in determining their stability, efficacy, and potential applications. These properties include particle size, surface charge, viscosity, and phase behavior[34].

Particle Size

The size of the droplets in a Nanoemulsion is a critical factor that influences its stability and bioavailability[35]. Smaller droplet sizes can enhance the stability of the Nanoemulsion by reducing the likelihood of droplet aggregation and sedimentation. Furthermore, smaller droplets provide a larger surface area for interaction with biological membranes, thereby improving the bioavailability of encapsulated substances[35].

Surface Charge

The surface charge of Nanoemulsion droplets, often measured as zeta potential, plays a significant role in the stability of the system [35]. A high absolute zeta potential value indicates strong electrostatic repulsion between droplets, which can prevent droplet aggregation and coalescence, thereby enhancing the stability of the Nanoemulsion [35].

Viscosity

The viscosity of a Nanoemulsion is influenced by factors such as the concentration and type of surfactant, the oil-to-water ratio, and the droplet size [36]. Higher viscosity can improve the stability of the Nanoemulsion by reducing the movement of droplets, thereby preventing droplet aggregation and coalescence [36].

Phase Behavior

The phase behavior of a Nanoemulsion, which refers to the arrangement of the oil and water phases, can affect its stability and the release of encapsulated substance [37]. The phase behavior can be manipulated by adjusting the composition of the Nanoemulsion, such as the oil-to-water ratio and the type and concentration of surfactant [37].

Droplet Size and Its Effect on Stability, Transparency, and Sensory Attributes

The droplet size in Nanoemulsions plays a significant role in their stability, transparency, and sensory attributes[38].

Stability

The stability of a Nanoemulsion is largely influenced by the size of its droplets. Smaller droplets can enhance the stability of the Nanoemulsion by reducing the likelihood of droplet aggregation and sedimentation [39]. This is because smaller droplets have a larger surface area to volume ratio, which increases the effectiveness of the surfactant in stabilizing the droplets against aggregation [39].

Transparency

The transparency of a Nanoemulsion is also affected by the droplet size. Nanoemulsions with smaller droplets are typically more transparent than those with larger droplets[40]. This is because smaller droplets scatter less light, resulting in a more transparent appearance [40]. This property is particularly important for cosmetic and dermatological applications, where a transparent or translucent appearance is often desirable [40].

Sensory Attributes

The sensory attributes of a Nanoemulsion, such as its texture and feel on the skin, can be influenced by the droplet size. Nanoemulsions with smaller droplets often have a more pleasant texture and feel on the skin compared to those with larger droplets [41]. This is because smaller droplets can create a smoother and more homogeneous texture, which can enhance the sensory experience of the user [41].

Interfacial Properties of Nanoemulsion Systems

The interfacial properties of Nanoemulsion systems, including interfacial tension, interfacial composition, and charge, are critical determinants of their behavior and functionality[42].

Interfacial Tension

Interfacial tension is a measure of the force required to increase the surface area of a liquid by a unit amount. In Nanoemulsions, a lower interfacial tension can facilitate the formation of smaller droplets, which can enhance the stability of the Nanoemulsion [43]. Various surfactants can be used to reduce the interfacial tension in Nanoemulsions, thereby improving their stability and performance [44].

Interfacial Composition

The composition of the interface in a Nanoemulsion, which is typically formed by surfactants, can significantly influence its properties. The type and concentration of surfactants used can affect the size and stability of the droplets, as well as the interfacial tension [45]. Moreover, the presence of other components, such as proteins or polymers, at the interface can also influence the properties of the Nanoemulsion [46].

Charge

The charge of the droplets in a Nanoemulsion, which is typically conferred by the surfactants, can play a crucial role in its stability. For instance, droplets with the same charge can repel each other, thereby reducing the likelihood of aggregation and enhancing the stability of the Nanoemulsion [47]. The charge of the droplets can also influence the interaction of the Nanoemulsion with other substances, such as biological tissues, which can be important in applications such as drug delivery [48].

Influence of Formulation Factors on Physicochemical Properties

The formulation factors, including the type of surfactant, cosurfactant, and oil phase, significantly influence the physicochemical properties of Nanoemulsions[49].

Surfactant Type

The type of surfactant used in the formulation of Nanoemulsions plays a crucial role in determining their stability and droplet size. Surfactants reduce the interfacial tension between the oil and water phases, facilitating the formation of smaller droplets. The choice of surfactant can also affect the charge of the droplets, which can influence the stability of the Nanoemulsion[50].

Cosurfactants

Cosurfactants are often used in conjunction with surfactants to enhance the stability of Nanoemulsions. They can help to reduce the interfacial tension further and increase the fluidity of the interfacial film, leading to the formation of smaller and more stable droplets [51].

Oil Phase

The choice of oil phase in the formulation of Nanoemulsions can significantly impact their properties. The polarity of the oil phase can affect the size and stability of the droplets. Moreover, the solubility of the active ingredient in the oil phase can influence the drug loading capacity of the Nanoemulsion[52].

Recent Advancements and Emerging Trends in Nanoemulsion Research

The field of Nanoemulsion research has seen significant advancements and emerging trends in recent years. These advancements have been driven by the need to improve the efficiency and effectiveness of Nanoemulsions in various applications, including drug delivery, food and beverage, cosmetics, and other industries[53].

Epigenetic Drug Discovery

In the field of drug discovery, Nanoemulsions have been used to enhance the delivery of epigenetic drugs. These drugs have shown significant potential in treating various types of cancer. The use of Nanoemulsions has helped to improve the bioavailability of these drugs, thereby enhancing their therapeutic effectiveness [54].

Carotenoids Research

In the field of food and nutraceuticals, Nanoemulsions have been used to enhance the bioavailability of carotenoids. These natural compounds have shown significant health benefits, including antioxidant activity. The use of Nanoemulsions has helped to improve the stability and absorption of these compounds, thereby enhancing their health benefits [55].

Migraine Treatment

In the field of neurology, Nanoemulsions have been used to enhance the delivery of drugs for the treatment of migraines. These drugs have shown significant potential in reducing the severity and frequency of migraine attacks. The use of Nanoemulsions has helped to improve the bioavailability of these drugs, thereby enhancing their therapeutic effectiveness [56].

Plant Hormone Analysis

In the field of plant science, Nanoemulsions have been used to enhance the analysis of plant hormones. These hormones play a crucial role in the growth and development of plants. The use of Nanoemulsions has helped to improve the accuracy and efficiency of plant hormone analysis, thereby enhancing our understanding of plant growth and development [57].

Challenges in the Formulation and Scale-Up of Nanoemulsions:

Formulating Nanoemulsions and scaling up their production presents several challenges. These challenges are primarily related to the complexity of the formulation process, the stability of the Nanoemulsions, and the cost and feasibility of large-scale production[58].

Formulation Challenges

Formulating Nanoemulsions involves the careful selection and combination of various components, including the oil phase, surfactant, and cosurfactant. The choice of these components can significantly impact the properties and performance of the Nanoemulsion. Furthermore, the formulation process requires precise control over various parameters, such as temperature and mixing speed, to ensure the formation of stable Nanoemulsions[59].

Stability Challenges

Nanoemulsions are thermodynamically unstable systems, which mean they tend to separate into their constituent phases over time. This instability can lead to changes in the properties of the Nanoemulsion, such as droplet size and distribution, which can affect its performance. Various strategies, such as the use of stabilizers and the optimization of formulation parameters, are used to enhance the stability of Nanoemulsions [60].

Scale-Up Challenges

Scaling up the production of Nanoemulsions from the laboratory to industrial scale presents several challenges. These include the need for high-energy input, the difficulty in maintaining consistent quality and performance across different batches, and the high cost of production. Furthermore, the scale-up process must comply with various regulatory requirements, which can add to the complexity and cost [61].

Future Directions

Despite these challenges, significant progress has been made in recent years in the development and scale-up of Nanoemulsions. Future research in this field is likely to focus on further improving the stability and performance of Nanoemulsions, developing more cost-effective and energy-efficient production methods, and addressing the regulatory challenges associated with scale-up [62].

Conclusion

Summary of the Key Findings and Contributions of Nanoemulsion Research

Nanoemulsion research has made significant strides in recent years, contributing to a deeper understanding of the formulation, properties, and applications of Nanoemulsions[63]. The development of various high-energy and low-energy methods for producing Nanoemulsions has been a key achievement in this field [64]. Furthermore, research has shed light on the crucial role of droplet size, interfacial properties, and formulation factors in determining the physicochemical properties and performance of Nanoemulsions [65].

Importance of Nanoemulsions in Various Industries and Their Potential Impact

Nanoemulsions have emerged as a vital tool in various industries, including pharmaceuticals, cosmetics, food, and agriculture, due to their unique properties such as high surface area, stability, and ability to encapsulate both hydrophilic and hydrophobic substances [66]. They have the potential to revolutionize drug delivery systems, enhance the bioavailability of nutrients in food products, and improve the efficacy of agrochemicals [67]. However, the successful translation of Nanoemulsion research into industrial applications requires overcoming several challenges, including those related to formulation, stability, and scale-up [68].

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