WORLD JOURNAL OF PHARMACEUTICAL RESEARCH

SJIF Impact Factor 8.084

Volume 12, Issue 11, 458-475. Review Article ISSN 2277– 7105

A REVIEW OF TECHNIQUES FOR FORMULATING NANOEMULSION DRUG DELIVERY SYSTEMS

Ragini Dwivedi* and Dhananjay Rai

Institute of pharmacy Harish Chandra P.G. College, Bawan Beegha, Azamgarh Road Varanasi.

Article Received on 07 May 2023,

Revised on 28 May 2023,
Accepted on 18 June 2023

DOI: 10.20959/wjpr202311-28778

***Corresponding Author**
Ragini Dwivedi
Institute of pharmacy Harish Chandra P.G. College, Bawan Beegha, Azamgarh Road Varanasi.

ABSTRACT

Nanoemulsion drug delivery systems have gained significant attention in recent years due to their potential for improving drug solubility, bioavailability, and targeting efficiency. This review provides a comprehensive overview of various techniques employed for the formulation of nanoemulsion drug delivery systems. It covers the principles, advantages, and challenges associated with each technique, along with recent advancements in the field. Understanding the formulation techniques for nanoemulsion drug delivery systems can aid in the development of effective and efficient drug delivery strategies. Nanoemulsion drug delivery systems have emerged as a promising approach for enhancing the therapeutic efficacy of poorly soluble drugs. These systems consist of nanosized droplets of oil dispersed in an aqueous medium stabilized by surfactants or co-surfactants. The small droplet size and large interfacial area of nanoemulsions contribute to their improved drug solubility, stability, and absorption. This review explores the various techniques used to formulate nanoemulsion drug delivery systems.

KEYWORDS: Nanoemulsion, drug delivery, high energy method, low energy method, phase inversion methods.

INTRODUCTION

Emulsions are biphasic liquid systems in which the internal or dispersed phase of one liquid is scattered as tiny droplets through the external or continuous phase of the other liquid. They have enormous promise for the manufacturing of food, drugs, and cosmetics since they may be used to combine polar and non-polar molecules, alter the texture, flavour, and aroma of goods, and enhance the effectiveness of medical treatments (Grumezescu et al., 2016; Ohshima et al., 2014; Sakamoto et al., 2017). Emulsions can easily be tailored to any number of formulations to satisfy the unique requirements of a product or a process, such as dispersing oil in water or water in oil. Emulsions offer immense promise in a variety of industries. Emulsions are thermodynamically unstable systems, and unless surface active molecules, also known as emulsifiers, are introduced to the mixture to stabilise the droplets, they will quickly separate into two different phases. Nanoemulsions are emulsions that are only a few tens to many hundreds of nanometers in size. Surfactants act as a barrier to emulsion coalescence, which is caused by the system's desire to reach a state of minimal Gibbs free energy, by lowering the surface tension at the interface between the two immiscible phases. Nanoemulsions are emulsions that are only a few tens to many hundreds of nanometers in size (Kabalnov et al., 1998).

Since they can easily solubilize hydrophobic pharmaceuticals, lessen severe side effects, and be easily transformed into next-generation smart nanomaterials, nanoemulsions have a great deal of potential as powerful nanomedicines (Sutradhar et al., 2013).

Nanoemulsions Emulsion varieties Emulsions are made up of two phases, one of which is spread through the other and is called a hydrophobic phase in their most basic form (Fig. 1). These emulsions are therefore known as oil-in-water (O/W) emulsions, where small oil droplets are scattered through water, or alternatively, water-in-oil (W/O) emulsions, where small water droplets are dispersed through oil. However, by enclosing an emulsion within an emulsion known as a double emulsion and creating water-in-oil-in-water (W/O/W) or oil-in-water-in-oil (O/W/O) emulsions, more complexity can be added to these straightforward systems. In the past, creating double emulsions required creating an initial interior emulsion, which was then encircled by creating a second emulsion on top of the initial emulsion.

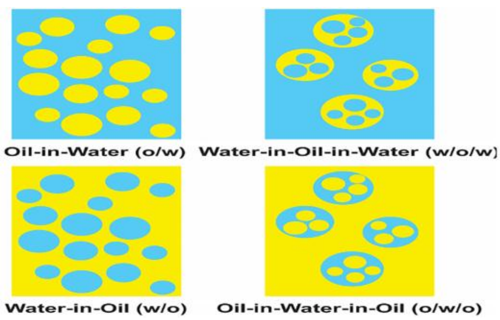

Fig. 1: Emulsion forms are divided into continuous and scattered phases. Hydrophobic medications that are put into the oil core can be delivered using oil-in-water emulsions.

Double emulsions of water-in-oil-in-water are appropriate for dispersing hydrophilic and hydrophobic actives into the water and oil phases, respectively.

Due to the diffusion between each phase, double emulsions are more difficult to form and stabilise because they must preserve the integrity of the first emulsion when creating the second one, require both a lipophilic and a hydrophilic surfactant to stabilise each oil-water interface, and are more susceptible to coalescence and degradation (Leister et al., 2020). Pickering first described Pickering emulsions in 1907 as O/W or W/O emulsions stabilised by very minute particles at the oil-water interface that act as a steric barrier to coalescence rather than small molecules that change the interfacial tension (Pickering et al., 1907).

Nanoemulsions are kinetically stable but thermodynamically unstable. In other words, nanoemulsion phase separation happens with enough time. For use in a variety of pharmacological, culinary, and cosmetic applications, nanoemulsions have been produced. They must be toxic-free and biocompatible for all of these purposes. As a result, choosing the right oil and surfactants is crucial. It is preferable to use biocompatible oils and surfactants, such as vegetable or pharmaceutical grade oils. The stabilisation of nanoemulsions has also frequently utilised proteins and lipids as surfactants.

Component of nanoemulsion

Oils, lipids, surfactants, water-soluble co-solvents, and surfactants are all components of nanoemulsion systems. Vegetable oils, mineral oils, free fatty acids, and other triglycerides, as well as tri-, di-, or mono-acylglycerols, may all be included in the oil phase for creating nanoemulsions. (Gonçalves et al., 2018). Drug solubility is typically taken into account when choosing an oil. Typically, oil phases with high drug loading are employed to create nanoemulsions (Qadir et al., 2016).

In the nanoemulsion systems for drug delivery and food ingredients, common surfactants include spans (sorbitan fatty acid esters), tweens (polyoxyethylene (POE) derivatives of sorbitan fatty acid ester), CremophorR EL (polyoxyl-35 castor oil), lauroyl macrogolglycerides (GelucireR 44/14), polysaccharides (gum and starch derivatives), phospholipid (Komaiko et al., 2016; Singh et al., 2017). The generation of nanoemulsions requires extremely low negative interfacial tension. Co-surfactants or co-solvents are employed in conjunction with a surfactant for this purpose. In the creation of nanoemulsion systems, co-surfactants or co-solvents such as polyethylene glycol, propylene glycol, ethanol, transcutol-P (diethylene glycol monoethyl ether), ethylene glycol, glycerin, and propanol are frequently utilised (Khan et al., 2012; Singh et al., 2017).

Advantages and Challenges

In comparison to alternative drug delivery methods and conventional emulsions, nanoemulsions have a number of advantages. Active chemicals are more stable and bioavailable thanks to the small droplet size and broad interfacial area, which makes them suited for a variety of uses in the pharmaceutical, cosmetic, and food industries. Nanoemulsions are attractive for formulations that call for transparent, fluid products due to their transparency and low viscosity. The distribution of a variety of therapeutic agents is made possible by the fact that nanoemulsions can encapsulate both hydrophilic and hydrophobic medicines. But there are additional difficulties with the creation of nanoemulsions. Due to the droplets' tendency to consolidate and create larger droplets over time, creating a stable and homogenous nanoemulsion can be difficult. It is essential for stabilising the nanoemulsion and avoiding phase separation to choose the proper co-surfactants and surfactants, as well as the concentration at which they should be used. Additionally, it might be challenging to scale up nanoemulsion production since process variables need to be constantly monitored to maintain the proper droplet size and stability.

Techniques for Nanoemulsion Formulation (Ragelle et al., 2012)

2.1. High-Energy Methods

2.1.1 High-pressure homogenization (HPH)

2.1.2 Microfluidization (MF)

2.1.3 Ultrasonication (US)

2.1.4. High-Pressure Microfluidization

2.1.5. Membrane Emulsification

2.1. High-Energy Methods

For the creation of nanoemulsions, high-energy techniques are frequently used. These methods entail the use of outside energy to split up bigger droplets into smaller ones, creating stable nanoemulsions as a result. Here are a few of the most popular high-energy techniques for creating nanoemulsions:

2.1.1. High-Pressure Homogenization

High-pressure homogenization is one of the most widely used methods for nanoemulsion formulation. In this technique, the emulsion is passed through a high-pressure homogenizer, which applies intense shear forces and pressure to the emulsion. This process leads to the disruption of larger droplets into smaller ones, resulting in the formation of nanoemulsions. The homogenization process can be performed either in a single pass or multiple passes, depending on the desired droplet size. High-pressure homogenization can achieve high encapsulation efficiency and produce stable nanoemulsions with a narrow droplet size distribution.

2.1.2. Microfluidization

Microfluidization is another high-energy method used for nanoemulsion formulation. In this technique, the emulsion is forced through a small channel or microfluidizer at high velocities. The emulsion passes through high shear zones, resulting in the breakup of larger droplets into smaller ones. Microfluidization offers precise control over the droplet size distribution and can produce nanoemulsions with a narrow size range. This method is particularly suitable for heat-sensitive materials as the process can be carried out at lower temperatures compared to other high-energy methods.

2.1.3. Ultrasonication

Ultrasonication involves the use of high-frequency ultrasound waves to create nanoemulsions. The emulsion is subjected to ultrasonic waves, which generate cavitation bubbles in the liquid. The rapid expansion and collapse of these bubbles create intense shear forces, leading to the disruption of larger droplets into smaller ones. Ultrasonication is a relatively simple and cost-effective method for nanoemulsion formation. However, it may require longer processing times and can generate heat, which may be a concern for temperature-sensitive formulations.

2.1.4. High-Pressure Microfluidization

High-pressure microfluidization combines the principles of high-pressure homogenization and microfluidization. In this technique, the emulsion is passed through a narrow gap at high pressure, resulting in intense shear forces. The combination of pressure and shear forces leads to the formation of smaller droplets and enhances the stability of the nanoemulsion. High-pressure microfluidization offers advantages such as precise control over droplet size and distribution, improved uniformity, and increased encapsulation efficiency.

2.1.5. Membrane Emulsification

Membrane emulsification is a technique that utilizes a porous membrane to create nanoemulsions. The emulsion is forced through the membrane, which acts as a barrier, leading to the formation of small droplets on the other side of the membrane. The pore size of the membrane determines the droplet size of the resulting nanoemulsion. Membrane emulsification offers the advantage of producing monodisperse nanoemulsions with a narrow droplet size distribution. It also allows for continuous processing and can be easily scaled up for industrial production.

These high-energy methods provide efficient means to produce nanoemulsions with small droplet sizes and improved stability. The choice of technique depends on factors such as the desired.

Several factors influence the formation of nanoemulsions. These include

Surfactant Selection: The choice of surfactant and its concentration significantly affects the interfacial tension between the immiscible phases, leading to the formation of smaller droplets and improved stability.

Co-surfactant: The addition of co-surfactants, such as short-chain alcohols or glycols, can enhance the stability of nanoemulsions by reducing interfacial tension and promoting the formation of a structured interfacial film.

Oil-to-Water Ratio: The ratio of the oil phase to the water phase plays a crucial role in determining the droplet size and stability of the nanoemulsion. Higher oil-to-water ratios typically result in smaller droplets.

Mixing Method: The method used to apply mechanical energy, such as high-pressure homogenization or microfluidization, affects the droplet size distribution and the uniformity of the nanoemulsion.

Temperature: Temperature influences the interfacial tension and viscosity of the formulation, which can affect the droplet size and stability of the nanoemulsion (**Qian et al., 2011)**

2.2. Low-Energy Methods

2.2.1. Phase Inversion Temperature (PIT) Method

2.2.1.1 Principle and Mechanism of Nanoemulsion Formation: Nanoemulsions are thermodynamically stable systems consisting of oil droplets dispersed in an aqueous medium, typically with droplet sizes in the nanometer range. The formation of nanoemulsions involves overcoming the inherent immiscibility between oil and water phases by utilizing various methods. The principle behind nanoemulsion formation lies in reducing the interfacial tension between the oil and water phases, thereby allowing the formation of small and uniform droplets. This is achieved through the use of emulsifiers or surfactants that stabilize the droplets by forming a protective interfacial film (**Sokolov et al., 2014)**.

The mechanism of nanoemulsion formation using low-energy methods, such as the Phase Inversion Temperature (PIT) method, involves the following steps

1. **Selection of components:** An oil phase, aqueous phase, and suitable surfactants or emulsifiers are chosen based on their compatibility and desired properties.
2. **Emulsifier selection:** Surfactants or emulsifiers are selected based on their ability to reduce interfacial tension and stabilize the droplets. They form a monolayer or bilayer at the oil-water interface, preventing droplet coalescence.
3. **Emulsification process:** The oil phase and aqueous phase are mixed together with the emulsifier under controlled conditions, such as temperature and shear. The energy input is kept low to avoid excessive droplet size reduction or phase separation.
4. **Phase inversion:** In the PIT method, the temperature is gradually increased, causing a change in the emulsion system from oil-in-water (O/W) to water-in-oil (W/O) or vice versa. This phase inversion leads to the formation of nanoemulsion droplets.
5. **Cooling and stabilization:** The emulsion is then cooled to room temperature or below, ensuring the stabilization of the nanoemulsion droplets through the continued presence of the surfactant or emulsifier (**Karthik et al., 2017)**.

Karthik P, Ezhilarasi PN, Anandharamakrishnan C. Challenges associated in stability of food grade nanoemulsions. Crit Rev Food Sci Nutr. 2017. 57:1435-1450.

Advantages and Challenges of Nanoemulsion Formation

Advantages: a. Enhanced stability: Nanoemulsions exhibit improved physical and chemical stability compared to conventional emulsions, thanks to their small droplet size and the presence of surfactants.

b. Increased bioavailability: Nanoemulsions enhance the solubility and bioavailability of poorly water-soluble drugs or bioactive compounds, promoting their efficient absorption and therapeutic effects.

c. Targeted delivery: Nanoemulsions can be designed to encapsulate active ingredients and target specific sites within the body, enabling controlled and localized delivery.

d. Versatile applications: Nanoemulsions find applications in various fields, including pharmaceuticals, cosmetics, food, and agriculture, due to their ability to encapsulate and deliver different types of compounds.

Challenges

a. Formulation complexity: Developing a stable nanoemulsion formulation requires careful selection of components, optimization of processing parameters, and understanding the interactions between the emulsion components.

b. Manufacturing scalability: Scaling up the production of nanoemulsions while maintaining their desired properties (**Solans et al., 2006).**

2.2.2. Phase Inversion Composition (PIC) Method

Nanoemulsions are colloidal dispersions consisting of nanoscale droplets of one immiscible liquid dispersed within another immiscible liquid, stabilized by a surfactant or a combination of surfactants. They have gained significant attention due to their unique properties and a wide range of applications in various fields, including pharmaceuticals, cosmetics, food, and agriculture. The formation of nanoemulsions can be achieved through different methods, and one of the commonly employed techniques is the Phase Inversion Composition (PIC) method. This note explores the principle and mechanism of nanoemulsion formation, discusses the advantages and challenges associated with nanoemulsions, and highlights the factors influencing the PIC method.

1. Principle and Mechanism of Nanoemulsion Formation: The principle behind nanoemulsion formation involves the reduction of interfacial tension between immiscible liquids, resulting in the formation of small droplets with a high surface area. This is achieved by the addition of surfactants that lower the interfacial tension between the two immiscible phases. The surfactants align themselves at the oil-water interface, forming a monolayer that stabilizes the droplets and prevents their coalescence (**Solè et al., 2010)**.

The mechanism of nanoemulsion formation can be described in several steps

Step 1: Pre-mixing and thermodynamic instability: The oil phase and water phase, along with appropriate surfactants, are mixed to create a pre-mixture. This pre-mixture is thermodynamically unstable due to the presence of excess energy at the oil-water interface.

Step 2: Phase inversion: By manipulating the composition of the pre-mixture, such as adjusting the surfactant concentration, temperature, or the ratio of oil and water, phase inversion can be induced. Phase inversion is the transition of the system from an oil-in-water (O/W) to a water-in-oil (W/O) emulsion or vice versa.

Step 3: Droplet formation and stabilization: During phase inversion, small droplets are formed due to the reduction of interfacial tension. These droplets are stabilized by surfactant molecules that adsorb onto the oil-water interface, forming a protective layer around the droplets. The surfactant layer prevents droplet coalescence and ensures the long-term stability of the nanoemulsion.

2. Advantages and Challenges of Nanoemulsions

Advantages: Enhanced stability: Nanoemulsions possess excellent physical stability due to the small droplet size and the presence of surfactants, which prevent coalescence and sedimentation.

b) Increased bioavailability: The small droplet size in nanoemulsions enhances drug or nutrient absorption, leading to improved bioavailability.

c) Versatile formulation: Nanoemulsions can accommodate both hydrophobic and hydrophilic compounds, making them versatile for the delivery of various active ingredients.

d) Optimal functionality: Nanoemulsions can improve the solubility, encapsulation, controlled release, and targeted delivery of active compounds.

Challenges

a) Manufacturing complexity: The production of nanoemulsions often requires specialized equipment and processes, which can be more complex and expensive compared to conventional emulsions.

b) Formulation optimization: Achieving the desired droplet size, stability, and drug-loading efficiency requires extensive optimization of formulation parameters, such as surfactant concentration, oil-to-water ratio, and processing conditions.

c) Long-term stability: While nanoemulsions exhibit improved stability compared to conventional emulsions, long-term stability can still be a challenge, especially in the presence of environmental factors, such as temperature fluctuations (Kumar et al., 2019).

2.2.3. Spontaneous Emulsification

Spontaneous emulsification, also known as self-emulsification or phase inversion emulsification, is a method used in the development of nanoemulsions. It involves the rapid formation of emulsions without the need for external energy input, such as high shear or homogenization. This technique relies on the spontaneous creation of small droplets through the spontaneous phase inversion of a pre-emulsion system.

The principle behind spontaneous emulsification lies in the selection of appropriate surfactants and co-surfactants, which are capable of reducing the interfacial tension between oil and water phases. The surfactants chosen should have low molecular weight and possess high emulsification power. Additionally, the surfactant and co-surfactant system should exhibit a high degree of affinity for both the oil and water phases, allowing them to form a stable interface (Solans et al., 2016).

The mechanism of spontaneous emulsification involves the following steps

1. **Pre-emulsion formation:** A mixture of oil, water, surfactants, and co-surfactants is prepared. The oil phase is typically a hydrophobic substance, while the water phase is hydrophilic.
2. **Phase inversion:** Upon gentle agitation or self-mixing, the pre-emulsion system undergoes a phase inversion, resulting in the spontaneous formation of small oil droplets dispersed in the water phase. This occurs due to the emulsifying agents adsorbing at the interface of the oil and water phases, reducing the interfacial tension.
3. **Emulsion stabilization:** The formed droplets are stabilized by the surfactant and co-surfactant system, preventing their coalescence and ensuring long-term stability (Solans et al., 2016).

Advantages and Challenges of Spontaneous Emulsification

Advantages

1. **Energy efficiency:** Spontaneous emulsification does not require the use of high shear or homogenization, which reduces the energy consumption during the emulsification process.

2. **Simplicity:** The technique is relatively simple and easy to implement, requiring minimal equipment and expertise.
3. **Rapid emulsion formation:** Spontaneous emulsification allows for the rapid formation of emulsions, enabling a faster and more efficient manufacturing process.
4. **Nanoemulsion production:** This method is particularly effective in producing nanoemulsions, which have smaller droplet sizes and enhanced stability compared to conventional emulsions.
5. **Improved bioavailability:** Nanoemulsions produced through spontaneous emulsification have increased surface area, leading to improved bioavailability of encapsulated substances, such as drugs or nutrients.

3. Factors Influencing Nanoemulsion Formation

3.1 Composition of the Oil Phase

3.2 Surfactant and Co-surfactant Selection

3.3 Mixing Parameters (speed, time, temperature)

3.4 pH and Ionic Strength

3.5 Presence of Co-solvents

3.6 Characterization Techniques

When creating emulsions or microemulsions, it's crucial to take into account the composition of the oil phase, the choice of the surfactant and co-surfactant, the mixing parameters, the pH and ionic strength, the presence of co-solvents, and the characterization technique. These elements are essential in establishing the stability, physical characteristics, and functionality of the finished product. Let's examine each of these features in greater detail:

1. Composition of the Oil Phase: The oil phase in emulsions or microemulsions typically consists of oils, lipids, or hydrophobic substances. The choice of oil phase depends on various factors such as the desired viscosity, compatibility with other ingredients, stability, and functionality. Common examples include mineral oils, vegetable oils, silicone oils, and hydrocarbon-based oils. The oil phase may also include active ingredients, antioxidants, or preservatives depending on the desired functionality of the formulation.

2. Surfactant and Co-surfactant Selection: Surfactants are essential components in emulsion formulations as they help stabilize the interface between the oil and water phases. They have hydrophilic (water-loving) and hydrophobic (oil-loving) regions, enabling them to reduce interfacial tension and promote emulsification. The selection of surfactants depends on factors like desired HLB (hydrophilic-lipophilic balance), compatibility with the oil phase, stability, and ability to form a stable emulsion. Co-surfactants are often used in combination with surfactants to enhance emulsion stability and reduce interfacial tension further.

3. Mixing Parameters (Speed, Time, Temperature): Mixing parameters are crucial for achieving a stable emulsion or microemulsion. The mixing speed, time, and temperature can affect the droplet size, distribution, and the overall stability of the formulation. High shear mixing methods such as homogenization, sonication, or high-pressure homogenization are often employed to break down large droplets and promote uniform mixing. The duration of mixing and the temperature should be optimized to ensure proper emulsification without causing degradation of sensitive ingredients.

4. pH and Ionic Strength: The pH and ionic strength of the formulation can significantly influence the stability and performance of emulsions or microemulsions. The choice of pH is important as it can impact the charge and solubility of the emulsion components. Additionally, the ionic strength, determined by the concentration of electrolytes, affects the electrical double layer around the droplets, which in turn influences their stability. It is essential to optimize the pH and ionic strength to ensure long-term stability and prevent phase separation.

5. Presence of Co-solvents: Co-solvents are sometimes used in emulsion formulations to improve solubility, enhance the stability of active ingredients, or modify the rheological properties of the system. Co-solvents can be water-miscible or oil-miscible compounds that aid in the solubilization of hydrophobic or hydrophilic ingredients, respectively. Care should be taken to select co-solvents that are compatible with other formulation components and do not negatively impact the stability or performance of the emulsion.

6. Characterization Technique: Characterizing the emulsion or microemulsion is crucial to assess its stability, droplet size distribution, and other physical properties. Various techniques are available for characterization, including microscopy (such as optical microscopy, electron microscopy), droplet size analysis (such as dynamic light scattering or laser diffraction), rheology analysis, zeta potential measurement, and stability studies (such as centrifugation or freeze-thaw cycling). The choice of characterization technique depends on the specific properties of interest and the stage of formulation development (Wooster et al., 2008).

3.6.1 Droplet Size Analysis (Dynamic Light Scattering, Nanoparticle Tracking Analysis)

Droplet size analysis is a critical aspect of characterizing and understanding colloidal systems, emulsions, and nanoparticle suspensions. Two commonly used techniques for droplet size analysis are Dynamic Light Scattering (DLS) and Nanoparticle Tracking Analysis (NTA). These methods provide valuable information about the size distribution, stability, and behavior of droplets or nanoparticles in a liquid medium. In this note, we will explore the principles, applications, and advantages of DLS and NTA for droplet size analysis.

3. 6.1.1 Dynamic Light Scattering (DLS)

Dynamic Light Scattering, also known as Photon Correlation Spectroscopy, is a non-invasive technique used to measure the size distribution of particles in a suspension. DLS analyzes the fluctuations in the intensity of scattered light caused by Brownian motion of the droplets or nanoparticles. The underlying principle is based on the fact that smaller particles will exhibit faster and more intense fluctuations compared to larger particles. By analyzing the autocorrelation function of the scattered light, DLS provides information about the size distribution and polydispersity of the droplets or nanoparticles. Some others parameters are used for the evaluation of nanoemulsion such as

1. Zeta Potential Measurement
2. Stability Studies (Centrifugation, Freeze-Thaw Cycling)
3. Rheological Analysis
4. Transmission Electron Microscopy (TEM)
5. In-Vitro Drug Release Studies

4. Applications of Nanoemulsion Drug Delivery Systems

A lot of interest has been paid to nanoemulsion drug delivery systems lately because of their distinctive characteristics and exciting potential in the pharmaceutical industry. Oil, water, surfactants, and co-surfactants are the basic building blocks of nanoemulsions, which are stable, thermodynamically stable, and optically clear systems. Nanoemulsions are perfect for effective drug administration because their usual droplet size varies from 20 to 200 nanometers. This note examines the numerous uses of nanoemulsion medication delivery devices in several fields (Jaiswal et al., 2015).

Oral Drug Delivery

Nanoemulsions have revolutionized oral drug delivery by enhancing the solubility and bioavailability of poorly soluble drugs. The small droplet size of nanoemulsions increases the surface area available for drug absorption, leading to improved drug dissolution and absorption in the gastrointestinal tract. They have been successfully utilized in delivering lipophilic and hydrophilic drugs, making them a versatile option for oral drug administration.

Topical Drug Delivery

Nanoemulsion-based topical formulations offer several advantages, such as enhanced skin permeation, prolonged drug release, and improved stability of active ingredients. They are widely used in dermatology for delivering drugs, such as anti-inflammatory agents, antibiotics, and antifungals. Nanoemulsions enable efficient penetration through the skin's barrier, leading to targeted drug delivery to the site of action.

Transdermal Drug Delivery

Nanoemulsion systems have emerged as promising carriers for transdermal drug delivery. They facilitate the delivery of drugs through the skin layers, overcoming the limitations of conventional formulations. Nanoemulsions can encapsulate hydrophobic and hydrophilic drugs, enabling controlled release and improved penetration across the skin. They offer advantages like sustained drug release, reduced side effects, and enhanced patient compliance.

Ophthalmic Drug Delivery

Nanoemulsions have demonstrated significant potential in ophthalmic drug delivery due to their ability to improve drug solubility and prolong drug release within the ocular tissues. They can enhance the corneal penetration of drugs, allowing for efficient treatment of various ocular diseases. Nanoemulsion-based eye drops or ointments offer improved bioavailability, reduced drug wastage, and increased patient comfort.

Cancer Therapy

Nanoemulsions have shown promise in delivering anticancer drugs to tumor sites with improved efficacy and reduced systemic toxicity. These systems can encapsulate hydrophobic drugs, such as paclitaxel and docetaxel, improving their solubility and targeting specific cancer cells. Nanoemulsion-based drug delivery systems can also be functionalized with ligands for active targeting, enhancing selective drug delivery to tumor tissues.

Vaccine Delivery

Nanoemulsion-based vaccine formulations have gained attention in recent years. They offer improved stability, prolonged antigen release, and enhanced immune response. Nanoemulsions can encapsulate antigens and adjuvants, facilitating their efficient uptake by antigen-presenting cells. This approach shows promise in developing novel vaccine delivery systems for infectious diseases and immunotherapies.

Nanoemulsion drug delivery systems have emerged as versatile carriers with diverse applications in the pharmaceutical field. From enhancing oral drug delivery to improving transdermal penetration and enabling targeted cancer therapy, nanoemulsions offer unique advantages over conventional drug delivery systems. With ongoing research and development, nanoemulsion-based formulations hold great potential for advancing drug delivery and improving patient outcomes in various therapeutic areas (**Sutradhar et al., 2013).**

CONCLUSION

Drugs and food ingredients that are hydrophobic and have a high first pass metabolism suffer from limited bioavailability, which is efficiently addressed by nanoemulsion drug delivery devices. Based on the energy needed, the type of phase inversion, and self-emulsification, methods for nanoemulsion drug delivery system formulation may be readily categorised rigidly. High energy techniques are more adaptable in terms of composition choice and have better control over the dispersion of particle sizes in nanoemulsion drug delivery systems. Researchers have employed high energy techniques to enhance medication delivery and bioactive dietary ingredients. High energy methods are more expensive than low energy methods since the former require less energy and are more effective. High energy methods need sophisticated devices to provide it. Due to their minimal surfactant requirements, high energy techniques are better suited for delivering nanoemulsions containing bioactive food ingredients. SNEDDS are the most widely employed techniques by researchers for delivering hydrophobic medicines with low bioavailability. The promise of phase inversion emulsification techniques for efficient drug loading and distribution, however, still has to be explored. Systems for delivering drugs using nanoemulsions have a number of benefits over traditional drug delivery methods. Optimising medication delivery effectiveness necessitates a thorough understanding of formulation methods and variables affecting nanoemulsion production. To fully realise the promise of nanoemulsions in the field of medicine delivery, additional research and development are necessary.

REFERENCES

1. Grumezescu, A. Emulsions (1st ed.). Cambridge, MA: Academic Press, 2016.
2. Ohshima, H., & Makino, K. Colloid and interface science in pharmaceuticalresearch and development. Kidlington, Oxford: Elsevier, 2014.
3. Sakamoto, K., Lochhead, R. Y., Maibach, H. I., & Yamashita, Y. Cosmeticscience and technology: Theoretical principles and applications (1st ed.).Cambridge, MA: Elsevier, 2017.
4. Kabalnov, A. S., Pertzov, A. V., & Shchukin, E. D. Ostwald ripening intwo-component disperse phase systems: Application to emulsion stability. Colloids and Surfaces, 1987; 24: 19–32.
5. Sutradhar, K. B., & Amin, M. L. Nanoemulsions: Increasing possibilities indrug delivery. European Journal of Nanomedicine, 2013; 5: 97–110.
6. Leister, N., & Karbstein, P. H. Evaluating the stability of doubleemulsions—A review of the measurement techniques for the systematicinvestigation of instability mechanisms. Colloids and Interfaces, 2020; 4.
7. Uniform double emulsions generated using microfluidic devices havereceived renewed research interest for applications in food scienceand as microreactors or templates for particle synthesis (Ran et al., 2017; Zhao et al., 2011; Zhao et al., 2013).
8. Ran, R., Sun, Q., Baby, T., Wibowo, D., Middelberg, A. P. J., & Zhao, C.-X. Multiphase microfluidic synthesis of micro- and nanostructures forpharmaceutical applications. Chemical Engineering Science, 2017; 169: 78–96.
9. Zhao, C. X. Multiphase flow microfluidics for the production of single ormultiple emulsions for drug delivery. Advanced Drug Delivery Reviews, 2013; 65: 1420–1446.
10. Zhao, C.-X., & Middelberg, A. P. J. Two-phase microfluidic flows. ChemicalEngineering Science, 2011; 66: 1394–1411.
11. Pickering, S. U. CXCVI Emulsions. Journal of the Chemical Society, Transactions, 1907; 91: 2001–2021.
12. Gonçalves A, Nikmaram N, Roohinejad S, Estevinho BN, Rocha F, Greiner R, et al. Production, properties, and applications of solid self-emulsifying delivery systems (S-SEDS) in the food and pharmaceutical industries. Colloids Surf A Physicochem Eng Aspects, 2018; 538: 108-126.

13. Qadir A, Faiyazuddin MD, Talib Hussain MD, Alshammari TM, Shakeel F. Critical steps and energetics involved in a successful development of a stable nanoemulsion. J Mol Liq., 2016; 214: 7-18.
14. Komaiko JS, McClements DJ. Formation of food-grade nanoemulsions using low-energy preparation methods: a review of available methods. Compr Rev Food Sci Food Saf., 2016; 15: 331-352.
15. Singh KK, Vingkar SK. Formulation, antimalarial activity and biodistribution of oral lipid nanoemulsion of primaquine. Int J Pharm., 2008; 347: 136-143.
16. Khan AW, Kotta S, Ansari SH, Sharma RK, Ali J. Potentials and challenges in self-nanoemulsifying drug delivery systems. Expert Opin Drug Deliv, 2012; 9: 1305-1317.
17. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, et al. Nanoemulsion: concepts, development and applications in drug delivery. J Control Release, 2017; 252: 28-49.
18. Ragelle H, Crauste-Manciet S, Seguin J, Brossard D, Scherman D, Arnaud P, et al. Nanoemulsion formulation of fisetin improves bioavailability and antitumour activity in mice. Int J Pharm., 2012; 427: 452-459.
19. Qian C, McClements DJ. Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: factors affecting particle size. Food Hydrocoll, 2011; 25: 1000-1008.
20. Sokolov YV. Nanoemulsion formation by low-energy methods: a review. Vìsn farm, 2014; 3: 16-19.
21. Solans C, Morales D, Homs M. Spontaneous emulsification. Curr Opin Colloid Interface Sci., 2016; 22: 88-93.
22. Solè I, Pey CM, Maestro Al, González C, Porras M, Solans C, et al. Nano-emulsions prepared by the phase inversion composition method: preparation variables and scale up. J Colloid Interface Sci., 2010; 344: 417-423.
23. Kumar M, Bishnoi RS, Shukla AK, Jain CP. Techniques for Formulation of Nanoemulsion Drug Delivery System: A Review. Prev. Nutr. Food Sci., 2019; 24(3): 225-234.
24. Solans C, Morales D, Homs M. Spontaneous emulsification. Curr Opin Colloid Interface Sci., 2016; 22: 88-93.
25. Wooster TJ, Golding M, Sanguansri P. Impact of oil type on nanoemulsion formation and Ostwald ripening stability. Langmuir, 2008; 24: 12758-12765.

26. Kumar M, Bishnoi RS, Shukla AK, Jain CP. Development and optimization of drug-loaded nanoemusion system by phase inversion temperature (PIT) method using Box-Behnken design. Drug Development and Industrial Pharmacy, 2021; 47(6): 977-989.
27. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. Biotech, 2015; 5(2): 123–127.
28. Sutradhar KBS, Amin ML. Nanoemulsions: increasing possibilities in drug delivery. Eur. J. Nanomed, 2013; 5(2): 97–110.