REVIEW ARTICLE

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Review article: Nanoemulsion Formulation for Enhancing the Aqueous Solubility and Systemic Bioavailability of Poorly Soluble Drugs

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Abstract

Nanoemulsions are systems for delivering drugs of poor water-solubility with extensive first-pass metabolism and improving their bioavailability. Different techniques develop nanoemulsions. Low-energy methods are more effective and do not require expensive equipment, so they should be used instead of high-energy methods. However, high-energy procedures are better for food-substance emulsions as they require a lower surfactant concentration than low-energy approaches. Particularly for low-energy processes, the formulation of nanoemulsions involves overlapping techniques.

Keywords: drug delivery systems, nanoemulsion, high-energy approach, and low-energy method.

1. Introduction

Nanoemulsions are systems for providing and enhancing the systemic bioavailability of pharmaceutical ingredients with limited water-soluble and bioactive dietary supplements. Most active pharmaceutical compounds have limited solubility and bioavailability because they are hydrophobic (Karthik, P., et al., 2017). In conventional dosage forms, the bioactive dietary ingredients likewise have modest bioavailabilities. Such ingredients have reduced ambiguous absorption patterns, oral bioavailability, dosage fluctuations, and a higher likelihood of food influence. Consequently, these medications and bioactive food ingredients demonstrate low therapeutic efficacy (Chatterjee, B., et al., 2016).

The delivery of drugs orally is a frequent, well-liked, not invasive, not painful, and simple system for drug delivery that frequently leads to increased patient compliance. The most widely used and advantageous oral dosage forms are solids. Solid pharmaceutical dosage forms don't need to be sterile during manufacture, may be made using a very straightforward and affordable procedure, have a high degree of stability and safety, and are easy to administer by oneself (Tapeinos, C., et al., 2017). Drug dissolution is commonly recognized as the crucial step of the oral absorption of solid dosage forms. The most critical element affecting the efficacy and development is water solubility. Yet, many newly created active compounds fall into Classes II and IV of the Biopharmaceutical Classification System (BSC), having poor water

solubility. As a result, many techniques have been created to change how these poorly water-soluble ingredients dissolve to achieve enhanced absorption performance (Göke, K., et al., 2018).

Numerous approaches have been investigated to improve the oral bioavailability of medicines with limited water solubility. This category includes liquid-solid pellets, inclusion complexes, nanocrystals, co-crystals, micro- and nanoparticles, salt production, solid dispersions, salt solutions, and co-amorphous systems. (Čerpnjak, K., et al., 2015; Göke, K., et al., 2018; De Espíndola, B., et al., 2019; Bazzo, G. C., et al., 2020; and Pinto, J. M. O., et al., 2020). One of the techniques developed is lipid-based drug delivery systems (LBDDS).

LBDDS covers a variety of formulations, ranging from simple lipid solutions to sophisticated SEDDS. Drug absorption and bioavailability are affected by the choice of lipid excipients and how efficiently pharmaceuticals dissolve in formulations and during fat digestion in the gastrointestinal system (Larsen, A. T., et al., 2012; Williams, H. D., et al., 2012). Lipid dispersion influences the kinetics of lipid digestion, solubility, and drug absorption in the digestive fluids (Mu, H., Holm, R., & Müllertz, A., 2013).

LBDDS examples include:

Self-emulsifying drug delivery systems (SEDDS)

Self-micro emulsifying drug delivery systems (SMEDDS).

Nanoemulsion

Nanoemulsion is lipid-based, which has the advantage of being an innovative colloidal delivery system that encloses, safeguards, and distributes lipophilic bioactive molecules (McClements, D. J., 2012). Nanoemulsion droplets have a diameter between 10 and 200 nm and are covered in emulsifier molecules for protection (Gibaud, S., & Attivi, D., 2012; Čerpnjak, K., et al., 2013; and Rehman, F. U., et al., 2017). Nanoemulsion technologies can be used for transmucosal and transdermal drug administration. As a result, these techniques can significantly raise bioavailability (Rehman, F. U., et al., 2017).

1. Nanoemulsion components:

Oils or lipids, hydrophilic co-solvents, surfactants, and water compensate the nanoemulsion systems. Triglycerides, mineral oils, vegetable oils, free fatty acids, etc., may all be included in the oil phase. (Qadir, J., et al., 2017; Gonçalves, A., et al., 2018). The selection of oil is based on its efficacy in solubilizing the drug. (Komaiko, J. S., & McClements, D. J., 2016; Singh, Y., et al., 2017). Co-surfactants or co-solvents are used alongside surfactants to achieve the ultra-low negative interfacial tension required to develop nanoemulsions (Khan, A. W., et al., 2015; Singh, Y., et al., 2017).

2. Methods of Nanoemulsion formulation:

There are numerous and overlapped methods used to develop nanoemulsion systems. These are divided into groups based on their energy demands, phase inversion characteristics, and self-emulsification, such as:

- **High energy methods:**

Ultrasonication
Homogenization using high-pressure
Microfluidization

- **Low energy methods:**
  - ✓ Phase inversion emulsification method

  Phase inversion composition (PIC)
  Phase inversion temperature (PIT)
  Emulsion inversion point (EIP)
  - ✓ The self-nano emulsification method

In this review, we discussed, in brief, the self-nano emulsification method as well as the ultrasonication technique.

2.1 Ultrasonication technique

In terms of use and cleanup, it is superior to other high-energy technologies (Mahdi Jafari, S., et al., 2006; Leong, T. S. H., et al., 2009). In this technique, the macroemulsion splits into a nanoemulsion under the influence of ultrasonic waves. We can modify the ultrasonic energy input and time to achieve the proper nanoemulsion stability and particle size (Akbas, E., et al., 2018). Nanoscale droplets are developed due to the extensive turbulence resulting from the collapse of microbubbles. When ultrasonic waves irradiate an oil and water mixture, cavitation forces are created. This extra energy leads to the creation of nanoscale emulsion droplets at the interfaces. Without the use of surfactants, nanoemulsions can be created using ultrasonication. The production of medicinal and food ingredient nanoemulsions has made considerable use of ultrasonication. Compared to previous high-energy methods, nanoemulsion has superior stability and smaller droplet size (Ghosh, V., et al., 2013; Salvia-Trujillo, L., et al., 2014).

2.2 Self-nano emulsification method

The preparation of nanoemulsions is accomplished without altering the nature of the surfactant. Turbulence and nanoscale emulsion droplets are

developed as the surfactant molecules and/or co-solvent rapidly move from the dispersed to the continuous phase. This is also known as a spontaneous emulsion (Solè, I., et al., 2012; Solans, C., et al., 2016). The self-emulsification phenomenon is the basis for SNEDDS, which contains reduced lipids with hydrophilic co-surfactants.

SNEDDS consist of a co-surfactant, a surfactant, and a drug in an isotropic blend (Alshamsan, A., et al., 2018). O/W nanoemulsion with thin, optically transparent characters is developed by this mixture when it is diluted by *in-vivo* aqueous fluids (Khan, A. W., et al., 2015). The two most frequently used mechanisms of nanoemulsion formation from SNEDDS are the transition from an organic phase into an aqueous phase of a hydrophilic co-solvent or co-surfactant and the development of nanoemulsion free energy at transiently negative or low interfacial tensions (Patel, G., et al., 2016). So they are the most often used as a delivery method for hydrophobic drugs with poor bioavailability.

3. Stability of nanoemulsion system

Turbidity or phase of the nanoemulsion may result from causes of instability during storage (Karthik, P., et al., 2017). Nevertheless, nanoemulsions are stable because the kinetics of their disintegration occurs gradually (Rehman, F. U., et al., 2017). In nano-sized emulsion systems, the attraction forces between the droplets are often relatively small, which leads to flocculation and coalescence (Qian, C., & McClements, D. J., 2011; Kumar, M., et al., 2019).

4. Characterization of nanoemulsions

It utilizes analytical methods that identify the nano-sized droplets' excellent transparency, changeable viscosity, and high stability, such as dynamic light scattering (DLS), zeta potential, small angle neutron scattering (SANS), viscosity, and atomic force microscopy (AFM) (Kheawfu, K., et al., 2018). DLS is considered a practical approach for the particle size determination of a nanoemulsion. The nanoemulsion system's viscosity helps evaluate its stability via changes in water, surfactant, and co-surfactant amounts that affect the system's viscosity. AFM is a technique that can be used to determine the droplet shape of a nanoemulsion system. A series of stability experiments, including centrifugation assays, thawing-freeze cycles, cooling-heating tests, and ambient settings, are used to examine the stability of nanoemulsion systems. Thus, one can predict the average lifespan of the prepared system.

5. Optimization of nanoemulsion system

The influence of many variables on the characteristics of nanoemulsions has led some researchers to suggest that factors like composition and preparation methods can be used as optimization tools to manage droplet size. To identify the values of the variables impacting nanoemulsion formation, the experimental design has been evaluated. (Villalobos-Castillejos, F., et al., 2018). Using variables impacting nanoemulsions' characteristics through experimental optimization is recommended (Sole, I., et al., 2006; Gutiérrez, J. M., et al., 2008; and Safaya, M., & Rotliwala, Y. C., 2020). A dispersibility test was performed to investigate the homogeneity of the systems (Akhtar, J., et al., 2016). Thermodynamic stability testing of nanoemulsion formulations is used to investigate the stable nanoemulsions and exclude the unstable or metastable nanoemulsions (Nasr, A., et al., 2016; Rai, V. K., et al., 2018). Zeta potential controls the strength of the electrostatic attraction between adjacent globules in a dispersion, which dictates the stability of the colloidal dispersion (Mohammadi-Jam, S., et al., 2022). Transmission Electron Microscopy (TEM) investigation of the structure and morphology of the generated nanoemulsion to confirm the uniformly dispersed globules without any drug precipitation or coalescence revealed that they produced physically stable nanoemulsions that have a uniform, dispersed and spherical shape and are pretty small in size (Hussein, H. A. A., & Maraie, N. K., 2022).

6. Applications of nanoemulsion drug delivery system:

Nanoemulsions are efficient at emulsifying active lipophilic substances and have a variety of uses due to their tiny particle sizes, which is a promising benefit over traditional emulsions. As a result, these systems seem optically transparent and exhibit improved stability (de Oca-Ávalos, J. M. M., et al., 2017). Food ingredients that have been nano-encapsulated as a nanoemulsion system also boost the bioactive compound stability (Singh, Y., et al., 2017). Additionally, nanoemulsion food component systems improve the diffusion of bioactive compounds into the intradermal layers, which is essential in developing herbal cosmetics (Karthik, P., et al., 2017). They can also be used extensively for antibiotics, cancer treatments, disinfectants, and antiseptics (Karthik, P., et al.,

2017). The nanoemulsion system has shown the capacity for efficient distribution of lipophilic substances through different administration routes (de Oca-Ávalos, J. M. M., et al., 2017; Feng, J., et al., 2018). Nanoemulsion systems' features, such as their transparency, low viscosity, and nano-sized droplets, make them useful for cosmetic applications. Antibiotics, anticancer agents, disinfectants, and antiseptics can all be delivered using nanoemulsion systems due to their versatile physio-chemical features, which also increase the bioactivity of the components encapsulated (Karthik, P., et al., 2017).

Conclusion:

Due to their hydrophobic nature and high first-pass metabolism, drugs and food ingredients have limited bioavailability. Nanoemulsion drug delivery devices can effectively solve this problem. High-energy technologies like ultrasonication are better suited for delivering nanoemulsions containing bioactive food components since they require less surfactant. Nonetheless, SNEDDS are the methods most frequently used in studies to deliver hydrophobic drugs with low bioavailability.

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