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Review on Nano-Emulsion

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ABSTRACT

This article provides a brief overview of the preparation process and evaluation of nano-emulsions as drug carriers for enhancing therapeutic agent delivery. For the preparation of nano-emulsion, several techniques such as microfluidization, high-pressure homogenization, low energy emulsification, and solvent evaporation method and parameters such as droplet size analysis, viscosity determination, drug content, refractive index, pH, zeta potential, transmission electron microscopy, thermal stability, release, and *in vitro* skin permeation study will be used. As a result, the focus of this review is on the advantages of nano-emulsion, various methods of preparation, characterization techniques, and the various applications of sub-micron size emulsion in various areas such as various routes of administration, chemotherapy, cosmetics, and so on.

Keywords: Homogenization; Composition; Preparation method; Characterization; Thermal stability

INTRODUCTION

Nano-emulsion, also known as submicron emulsions, ultrafine emulsions, and mini emulsions, are submicron-sized colloidal particulate systems considered as thermodynamically and kinetically stable isotropic dispersions, which consist of two immiscible liquids like water and oil, stabilized by an interfacial film consisting of a suitable surfactant and co-surfactant to form a single phase. A number of surfactants with diverse characteristics (ionic or non-ionic) had been used with such nano-emulsions [1-4].

LITERATURE REVIEW

- Oil-in-Water (O/W) emulsions with average droplet sizes ranging from 50 nm to 1000 nm are known as nano-emulsion. The average droplet size is usually between 100 nm and 500 nm, hence terms like sub-micron emulsion and mini-emulsion are used instead. The nano-emulsion is used to make polymer latex particles, nonporous polymeric solids, and other products. Furthermore, NEs with pharmaceutically approved excipients are employed in the production of medication formulations for oral administration.
- In comparison to regular emulsion or micro emulsion, nano-emulsion is a translucent system. It has been established that using nano-emulsion as a delivery mechanism can enhance the retention duration of a drug in the body, requiring a smaller amount of drug for therapeutic activity. Previous research has shown that nano-emulsion technology can improve the bioavailability of lipophilic drugs.
- Nano-emulsion have been used in a variety of fields, including drug delivery, where O/W nano-emulsion have been used to deliver hydrophobic drugs; the food industry, where flavored nano-emulsion with improved curcumin/carotene and absorbability have been developed; and the

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restorative industry, where nano-emulsion have been tested for skin hydration and application ease [5-8].

Advantages

- Increases the absorption rate.
- Supports the solubilization of lipophilic drugs.
- Provides aqueous dose forms for medicines that are water-insoluble.
- If the formulation contains biocompatible surfactants, it can be taken orally.
- The substance can be delivered *via* a variety of methods, including topical, oral, and intravenous.
- Nano emulsions are thermodynamically stable systems, and this stability allows the system to self-emulsify.
- It is non-irritating as well as non-toxic.
- It improves the uptake of oil-soluble nutrients in cell culture technology.
- They don't exhibit the issues with creaming, flocculation, coalescence, and sedimentation that occur naturally.
- When it comes to disguising the taste of something, this is a great tool [9-11].

Composition of Nano-emulsion

- **Oil phase**: The stability, formation, and properties of a nano-emulsion are determined by the physicochemical parameters of the oil phase. Viscosity, polarity, density, water-solubility, interfacial tension, refractive index, phase behaviour, and chemical stability are some of the bulk physicochemical properties of the oil phase. Non-polar components such as monoacylglycerol, triacylglycerols, free fatty acids, diacylglycerols, essential oils, flavoring oils, mineral oils, waxes, fat replacements, and others are commonly used in the oil phase.
- **Aqueous phase**: Water is commonly employed as the aqueous phase in nano-emulsion formulations. Proteins, carbohydrates, minerals, co-solvents, acids, and bases are examples of polar molecules. The ionic strength, pH, polarity rheology, density, refractive index, interfacial tension, and phase behaviour of the aqueous phase are all determined by the concentration and type of these components used, and this has a direct impact on the formation, physicochemical properties, and stability of the nano-emulsion formed.
- **Surfactant**: Surfactant must be able to minimize interfacial tension as close to zero as possible to facilitate the dispersion of all components. In the process of making a W/O nano-emulsion surfactants with HLB values of 3-6 are useful for the preparation of O/W nano-emulsions, whereas surfactants with higher HLB values of 8-18 are useful for the preparation of O/W nano-emulsions.
- **Co-surfactant**: High concentrations of single-chain surfactants are required to lower the interfacial tension between oil and water to a level that allows for the spontaneous creation of a nano-emulsion. Co-surfactant boosts the fluidity of the interface due to the presence of fluidizing groups such as unsaturated bonds, then demolishes the liquid crystalline or gel structure and changes the HLB value, resulting in the spontaneous creation of nano-emulsion.
- **Additives**: The ingredients used to make the nano-emulsions live longer [12-14].

Preparation Method of Nano-emulsion

- **High pressure homogenizer**: This approach entails applying high pressure to a solution that has an oil phase, an aqueous phase, and a surfactant or co-surfactant. The pressure is applied using a homogenizer, which is a piece of specialized equipment. Poor productivity, component deterioration due to difficult mass production, and the generation of a lot of heat are some of the issues that come with homogenizers. Only Oil in Water (O/W) liquid nano-emulsions with less than 20% oil phase may be made using this method, and cream nano-emulsions with a mean droplet diameter less than 200 nm cannot be made using this method. It is, nevertheless, the most extensively utilized approach.
- **Spontaneous emulsification**: When a solution containing a tiny concentration of oil in a water-miscible solvent is poured into water without the presence of surfactant, spontaneous emulsification has been described. The diameter of the oil droplets is determined by the proportion of surplus oil to water soluble solvent. As an alternative to ultrasonic and high-shear procedures, this method can be utilized. It has some drawbacks, such as the limited amount of oil that can be distributed and the requirement that the solvent be soluble in water in all amounts. Solvent removal is a difficult task.
- **Ultra-sonication**: This is the best method for making a nano-emulsion. The droplet size of a typical emulsion or micro emulsion is lowered *via* the sonication technique. However, one downside of this process is that it is not suitable for large batches; only tiny batches of nano-emulsions may be made using this method. Sneh priya et al., developed an efficient screening method for selecting excipients for the production of the best nano-emulsion formulation. The model drug was quetiapine fumarate. The ultra-sonication method is used to prepare nano-emulsions using a probe syndicator. It is possible to create desirable qualities by adjusting the levels of oil, surfactants, and secondary surfactants.
- **Phase inversion**: Chemical energy is obtained through phase transitions that occur during the emulsification method, resulting in fine dispersion. Changes in composition at constant temperature or temperature changes at constant composition provide appropriate phase transitions. The Phase Inversion Temperature (PIT) method was developed on the basis of changes in the solubility of polyoxyethylene type surfactants as a function of temperature. The dehydration of the polymer chain causes this surfactant to become lipophilic as the temperature rises. The surfactant monolayer has a large positive spontaneous curvature at low temperatures, generating oil swelling micellar solution phase.

- **Solvent displacement**: At room temperature, nano-emulsions can be made by flowing organic phase comprising oil dissolved in a solvent such as acetone or ethanol into an aqueous phase containing surfactants. To make small droplets, a high solvent to oil ratio is required. The solvent must be removed with more effort using this procedure.
- **Micro-fluidization**: Using a high pressure positive displacement pump, a rapidly flowing stream of premixed emulsion (reduce the droplet size by 10 m) is passed through stainless steel micro channels (100) to create strong dimensional flow (500 psi-20,000 psi). This produces incredibly small droplets in the sub-micron range. The premixed emulsion is continuously circulated through the microfludizer until the desired droplet size is obtained.

Characterizations of Nano-emulsion

- **Droplet size**: The droplet size distribution of nano-emulsion vesicles can be determined in this situation using either light scattering or electron microscopy. However, this method is thought to be the best at predicting the stability of nano-emulsions.
- **Zeta potential**: When particles are submerged in liquid, the zeta potential is used to determine their surface charge. The zeta potential is a physicochemical property of a medication, polymer, or vehicle that is used to predict dispersion stability. Its value is determined by the presence of electrolytes and their adsorption. The Malvern Zetasizer equipment is used to measure it. Nano-emulsion is diluted to determine zeta potential, which is calculated based on the electrophoretic mobility of oil droplets. A zeta potential of 30 mV is thought to be sufficient for ensuring nano-emulsion physical stability. Using the Malvern Zetasizer.
- **Viscosity measurement**: The viscosity of formulations was examined to identify their rheological qualities. This was accomplished using a Brookfield Rheometer viscometer (DV-+version 10) at 30°C with a CPE 61 spindle spinning at 100 rpm. The average was taken into account once the results were taken in triplicate.
- **Drug content**: The pre-weighed nano-emulsion is extracted by dissolving it in a suitable solvent, and the extract is compared to a drug standard solution using a spectrophotometer or HPLC.
- **pH**: A pH meter was used to check each nano-emulsion composition. The pH meter was calibrated using pH 4 and pH 7 standard buffer solutions before use in formulations. PH was measured using a pH meter electrode immersed in 10% nano-emulsion.
- **Refractive index**: RI is an optical feature that can be used to explain the nano-emulsions isotropic nature and, more importantly, the chemical interaction between the medicine and the excipients. The refractive indices of formulations generated by each approach did not differ significantly (p 40.05). The refractive index of all nano-emulsion formulations was closer to 1.42, the refractive index of water. The homogenous nano-emulsion structure is shown by a same refractive index value. We can deduce from these findings that the improved nano-emulsion formulations were not only stress stable, but also isotropic.
- **Phase behavior study**: The purpose of this research is to characterize and optimize constituents (surfactant, oil phase, and aqueous phase). In general, in order to determine the phase of nano-emulsion and dispersibility, a research is required in the case of nano-emulsion formulations created by phase inversion temperature method and self-emulsification method. The experiment is carried out by placing various nano-emulsion ingredients in glass ampules and thoroughly homogenizing them at a specific temperature for a period of time until equilibrium is reached. Polarized light can reveal the anisotropic phase.

DISCUSSION

Applications

- **Nano-emulsion in cosmetics**: Because of the enormous surface area of the droplets, nano-emulsion in cosmetic formulations allows active chemicals to penetrate the skin quickly. Nano-emulsion has been observed to penetrate easily through tough skin on occasion. This characteristic of nano-emulsion reduces the need for a particular penetration enhancer, which is responsible for formulation incompatibility.
- **Use as anti-microbial agent**: Antimicrobial Nano-Emulsions (NEs) are oil-in-water droplets with diameters ranging from 200 nanometers to 600 nanometers. Surfactants and alcohol stabilize them, which are made up of oil and water. The NE is effective against bacteria (e.g., *E. coli, Salmonella, S. aureus*), enveloped viruses (e.g., HIV, Herpes simplex), fungi (e.g., candida, dermatophytes), and spores (e.g., candida, dermatophytes) (e.g. anthrax). Thermodynamically, the NE particles are compelled to combine with lipid-containing organisms.
- **Nano-emulsion in cell culture technology**: *In vitro* experiments and the production of biological substances such as antibodies and recombinant proteins are both done with cell cultures. The culture media can be added with a number of specified compounds or blood serum to optimize cell growth. It has been difficult to supplement the media with oil-soluble molecules that are available to the cells in the past, and only modest amounts of these lipophilic compounds have been absorbed. The delivery of oil-soluble compounds to mammalian cell cultures using NEs is a novel approach. The delivery mechanism is based on a NE with phospholipids to stabilize it. These NEs are clear and can be sterilised by passing them through 0.1 mm filters. The cells readily absorb the NE droplets.
- **Topical delivery**: Topical medication delivery has various advantages over other approaches, the most prominent of which is the avoidance of hepatic first pass metabolism of the drug and its associated adverse consequences. The drug's target ability and direct distribution to the afflicted

area of the skin or eyes comes next. The nano-emulsion can attain a level of antibacterial activity on the skin that was previously only possible with systemic antibiotics. The nano-emulsion shows broad range action against bacteria and fungus.

- **Ocular delivery**: Drugs are mostly applied topically in the treatment of eye disorders. O/W nano-emulsions have been studied for ocular delivery, as well as for dissolving poorly soluble medicines, increasing absorption, and achieving a longer release profile.
- **Nano-emulsion in vaccine delivery**: The use of NEs as vaccine carriers is currently being researched. The current affective and well-organized approach involves administering an inactivated organism to a mucosal surface in order for the body to trigger an immune response. Vaccines that are administered into the nasal mucosa as needed have been shown to elicit genital mucosa immunity in studies. Proteins were delivered to the mucosal surface using NEs to act as an adjuvant and control antigen-presenting cell uptake. Physical adsorption, encapsulation, encapsulation with coating, encapsulation with targeting, chemical linkage, and conjugation with a targeting mechanism are all ways to capture the antigen in the nano-carrier.
- **Nano-emulsion in cancer therapy**: Recent natural product research has grown in order to improve present treatment in patients with multidrug resistance. Many medications, including vincristine, taxon, vinblastine, and camptothecin, have been developed as a result of these scientific studies, which largely focused on natural plants. Many studies on the anticancer properties of essential oils have been published. Essential oils are now being studied in the treatment of leukemia, glioblastoma, breast, melanoma, lung cancer, and different cancers of the mouth, cervix, bone, colon, liver, ovary, pancreas, kidney, prostate, and uterine. Hundreds of essential oils obtained from more than twenty plant families have been examined for more than twenty types of malignancies in the last decade. Pine nut oil nano-emulsions were employed to encapsulate Paclitaxel (PTX), the apoptotic signalling molecule C-(6)-Ceramide (CER), and mixtures of the two.
- **Pulmonary drug delivery**: Because of noninvasively administration by inhalation aerosols, avoidance of first-pass metabolism, direct transport to the site of action for the treatment of respiratory disorders, and the availability of a large surface area for local drug delivery, the lung is an appealing target for drug delivery. In pulmonary drug delivery, nano-carrier technologies provide homogeneous drug dose distribution in the nose, increased drug solubility, enhanced patient compliance, and reduced side effect incidence.
- **Percutaneous route**: Skin permeation is low in many drugs, resulting in poor efficacy. Organic solvents, which are common chemical skin penetration enhancers, are often linked to skin irritation, toxicity, and sensitization. A solvent-free topical carrier based on drug trapping in submicron-sized o/w emulsion droplets is more effective in terms of percutaneous absorption and may be free of side effects. NSAIDs, diazepam, tocopherol anti-fungal medicines (econazole or miconazole nitrate), and EMLA (Eutectic Mixtures of Local Anesthetic) are examples of medications that have proven to be effective through this method.
- **Nano-emulsion in food industry**: Nano-emulsions can be used in the food industry to create smart foods with ingredients that are often difficult to incorporate due to poor water dissolvability; one example is carotene, a pigment that gives foods their colour. Carrots, for example, provide numerous health benefits. Examined the size and stability of carotene nano-emulsions in relation to temperature, pH, and surfactant type lactoglobulin, a biocompatible emulsifier, was used to settle nano-emulsions with carotene. The bio accessibility of these nano-emulsions was further demonstrated by replicating the oral, gastric, and small digestive system settings. Various methods (such as high-pressure homogenization, etc.) have been used to create-carotene nano-emulsions. Emulsifiers, micro-fluidization, and evaporative maturation).
- **Nano-emulsion polymerization**: Recently, nano-emulsion polymerization has been utilized to combine the properties of many polymers or materials in a single particle. The specific synthesis of complex particles that cannot be obtained using traditional polymerization methods is an intriguing application of nano-emulsion polymerization. Nano-emulsion polymerization in the presence of iron oxide particles produces magnetic polymeric nano-spheres. Nano-emulsion polymerization can also be used to make core-shell SiO_2/polystyrene nanocomposite particles and particles with various morphologies.

CONCLUSION

Nano-emulsions can be used as colloidal carriers for a variety of lipophilic drugs, diagnostic agents, and other substances. It is a good carrier for Nano-emulsions for drug administration *via* various transdermal routes. Further research and development for clinical application of nano-emulsion will be carried out in the near future.

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