NANOEMULSIONS: DELIVERY SYSTEM FOR DRUGS

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ABSTRACT
In recent years, the nanoscale emulsion has gained undivided attention from research groups worldwide for delivery encapsulation, and protection of different sensitive bioactive ingredient. Nanoemulsions are different from emulsions as they have different shapes or sizes of particles dispersed in the continuous phases. They have improved functional, properties when compared to conventional emulsions. Nanoemulsions are small-sized emulsion that can be obtained as a colloidal dispersion of two immiscible liquids which is stabilized by surfactant molecules. The droplet size of nanoemulsion varies from 20 to 500 nm. The formulation of nanoemulsion depends upon the diameter and surface properties of the droplets. They are manufactured to enhance the delivery of different pharmaceuticals ingredients. Biological amphiles-based nanoemulsion are studied by various research groups as they have potential applications in pharmaceuticals, cosmetics and the food industries. They can be fabricated easily for the delivery of different drug components with different properties. Due to this, they are now developing rapidly as a system for the delivery of bioactive substances or drugs in beauty products or dermatological formulations. The appearance of the product remains unaffected during the addition of the oil phase due to the very small size of nanoemulsion. To address the issue of incorporation of the different lipophilic bioactive agents into food gel nanoemulsion are proposed to be loaded with lipophilic bioactive compounds into hydrogels. These hydrogels which have been loaded with nanoemulsions can be used for various functional food or pharmaceuticals formulation that is to be used for topical application.

Keywords: Emulsion; oil phase; nanoscale; formulation; pharmaceutical

INTRODUCTION
Nanoemulsions are fine oil-in-water dispersions, having a very small diameter (varies from 20 to 500 nm). They are usually spherical in shape and act as vectors that have shown great promise in the field of cosmetics, diagnostics, drug therapies, and biotechnologies. They are defined as heterogeneous liquid carrier systems which are stabilized by the addition of surfactants that are adsorbed at the interface and lower the interfacial tension. It is an ideal drug delivery system as it maximizes therapeutic effect while lowering toxicity. With the advancement in the field of science, they have evolved from simple mixtures or drugs to a highly advanced system called the novel drug delivery systems [1, 2]. They are non-toxic and non-irritant to human and animal cells which makes them ideal therapeutic agents. They can also be fabricated easily for the delivery of different drug components with different properties. Due to this, they are now developing rapidly as a system for the delivery of bioactive substances or drugs in beauty products or dermatological formulations.
Nanoemulsions are different from emulsions as they have different shapes or sizes of particles dispersed in the continuous phase. They have improved functional, properties when compared to the conventional emulsion. The formulation of nanoemulsion depends upon the diameter and surface properties of the droplets. They are manufactured for the purpose of enhancing the delivery of different pharmaceuticals’ ingredients. Biological amphiles-based nanoemulsions are studied by various research groups as they have potential applications in pharmaceuticals, cosmetics, and the food industry [1-4].

Nanoemulsions mean those emulsions with droplet size i.e. 100 nm and these nanoemulsions are generally made up of oil, water and emulsifier. The major objective of emulsions is to create small sized droplets and decreases the surface energy per unit area which is mainly seen in oil and water phases of the emulsion. In other words, these nanoemulsions are used as surfactant and it may directly or indirectly affect the components of proteins and lipids. In literature, various studies were conducted related to nanoemulsions using several methods concerning their synthesis and characterization. In addition, these nanoemulsions are mainly classified into two categories [2-5] i.e.

- High energy (i.e. $\sim 10^8$–$10^{10}$ W/kg is required using high pressure homogenization and ultrasonication to create small sized droplets), where we require a device to produce intense forces to generate smaller formulation. In this method, high shear stirring, ultrasonication and high-pressure homogenization are also used in this technique. The amount of energy is inversely proportional to Nano size emulsion during the high-energy method to magnify nanoemulsion. These strong forces were furnished through an ultrasonic processor which may be able to split the droplets in order to create and produce nanoemulsion.
- Low energy (i.e. less consuming significant energy) is required to make small droplets e.g. emulsion inversion point, phase inversion temperature etc.). The low energy method means the existence of components in a solution which is dependent on the behavior of surfactants during the process of emulsification process.

In addition, novel technologies are also developed i.e. evaporative ripening and bubble bursting using oil/water interface.

**Stability**- Several studies were conducted related to the stability studies of nanoemulsions and understanding their mechanism (destabilization and stability control). One of the examples related to stability studies for determining its drug stability (used in the form of nanoemulsion) and measuring various environmental factors i.e. light, temperature, humidity etc. In addition, storage conditions are also one of the major criteria for assessing its stability (i.e. stored at room temperature or 4 °C or at low temperature -20 °C to 4 °C. In contrast, storing this formulation for 24 months in both states (i.e. dispersed and freeze-dried) and stored in glass bottles and tightly sealed as per the Harmonization guidelines (International conference). Various studies were conducted related to stability studies [6-9] as shown below-

Accelerated stability- Studies were conducted related to determining the shell life of nanoemulsion. For assessing shell life using formulations were stored for 3 months at different temperatures (30°, 40° and 50 °C). Within the time frame (3 months), samples were introverted at different time intervals (0, 28, 60 and 90 day) and analyzed these samples through HPLC and measured $\lambda_{\text{max}}$ for...
evaluating the concentration of drug content. Those samples were withdrawn at 0 day marked as control. For estimating the order of reaction, the reaction constant rate is measured before and after the reaction and evaluated its degradation using a slope of the equation at a particular temperature (slope = −K/2.303, where K represents its logarithm values using variable temperatures against the absolute temperature (Arrhenius plot [10]).

Thermodynamic stability, studies were conducted and performed [11] in 3 major steps i.e.

- a. Heating-cooling cycle- observing the effect using different temperatures for measuring the stability of nanoemulsion. Exposed to these nanoemulsions (i.e. six cycles between 4°C to 40°C) derived formulations are stored at each temperature (> 48 h). Select only those formulations which are stable at different temperatures and then selected for centrifugation studies.

- b. Centrifugation studies- These formulated nanoemulsions were centrifuged (5000 rpm; 30 min) and observed for phase separation. Those formulations do not show any instability so these are directly subjected to freeze-thaw cycle.

- c. Freeze-thaw cycle- these nanoemulsion derived formulations when treated (with different temperature i.e. –21°C and +25°C) with three freeze-thaw cycles. If these formulations once again not showed any signs of instability, it means clear this test i.e. good stability. Thereafter, these formulations were evaluated for dispersibility studies about evaluate its self-emulsification efficiency.

- d. Dispersibility studies for determining the self-emulsification efficiency of nanoemulsion using standard i.e. USP XXII dissolution apparatus. In this method, nanoemulsion derived formulation (2.1 ml) is incorporated into distilled water (500 ml) and kept at 37 °C. In this technique, we prefer to use i.e. stainless steel dissolution paddle which mainly rotates (50 rpm) for providing gentle agitation. For assessing the nanoemulsion formulations in vitro which is measured and evaluated through a grading system based on grade as mentioned below-
  - a. A (clear or bluish colour) forms rapidly.
  - b. B (bluish white) forms immediately but these slightly less clear emulsions.
  - c. C (formation of milky emulsion).
  - d. D (greyish white emulsions were formed) having a slightly oily appearance.
  - e. E (poor emulsification) with large oil globules.

One of the parameters i.e. Viscosity, which is used for assessing the physicochemical characterization (using instruments like stormer, hoeppler falling ball, Ostwald, Brookfield) of nanoemulsion. Out of these, Brookfield viscometer is more preferred and reliable and determined its viscosities whether nanoemulsion is in the form of oil in water (having low viscosity) or water in oil (showed high viscosity). In addition, survismeter is widely used and applied for measuring dipole moment, particle size, surface tension, viscosity etc. [5-8]

Refractive index (determined through Abbes type refractometer and compared with a refractive index of water), is another important criterion of nanoemulsion where light disseminates through the medium and measures its nanoemulsion transparency [8-10]. If nanoemulsion has transparent nature
it means the refractive index of nanoemulsion is almost similar to or equal to the refractive index of water. In addition, percent transmittance is estimated at a particular wavelength (using distilled water as blank) in the case of nanoemulsion through UV spectrophotometer. If nanoemulsion is transparent, it means percent transmittance is greater than 99 percent. Similarly, pH meter and microosmometer are applied in the case of nanoemulsion for measuring its pH value and osmolarity (based on freezing point method) of emulsion. Similarly, the principle of dilution test in case of nanoemulsion means the existence of continuous will be added in a larger amount without causing any issue or problem in terms of its stability.

In the literature, various types of oils were reported that showed fluorescence using UV light. If we observed water in oil nanoemulsion under the microscope using fluorescence light, the whole field will fluoresce and if it is oil in water emulsion, fluorescence will have appeared in the form of spots.

APPLICATIONS- Nanoemulsions have a huge potential tool for drug delivery regarding its Quality assurance and quality control. These features showed their own importance i.e.

- **NANO EMULSION BASED PESTICIDE FORMULATION**- Decline in the crop yield because of pests and disease so researchers still working on the expansion of safe, green and ecofriendly pesticide formulations. The main issue or misadventure which is generally overlooked by any agriculture industry is the usage of lineal agro chemicals that allow broad-spectrum effects on the environment. Pesticide nanoemulsion formulations are those formulations in which prepared chemicals are incorporated into the nano emulsion system for preventing the crops from any disease which is harmful to the agriculture yielding. Based on their targeted organisms these types of pesticides are classified [3-5]. The common pesticide formulation uses active chemicals to kill fungi and weeds and insects such as snail and slug etc. To obtain the maximum efficiency of pesticide distribution, the nano emulsion act as a vector that carries and distributes the bio active compounds i.e. agro chemicals to the target or desired pest in the plants. Their irresistible physicochemical properties i.e. nanosize provide enough surface area to release and uptake active ingredients more efficiently. In nanoemulsion, active ingredients were incorporated in the formulation which mainly contributes and provides better kinetic stability, low surface tension and a good soak. The nano emulsion can also form a coated layer for pesticides, which provide greater protection against photodegradation [11-14].

- **NANO EMULSION FOR SYNTHESIS OF BIOMEDICAL NANO CARRIERS**- According to the chemical nature, nanocarriers formed in nano emulsions are classified as polymeric, inorganic or hybrid. The use of nano particles and nano capsules as carriers of effectual material for diagnosis (example- biosensing or bio imaging), therapeutics (example – drug delivery) has evolved a lot in the last 20 years and has become very useful and productive in research area. Nanoparticles and nanocapsules are used in a wide range, which is synthesized by the nanoemulsions. Sometimes, emulsions and nanoemulsions are used directly as a drug carrier with active regulations contained in the unplaced droplets [2-5]. Nano emulsions are a very versatile system for encapsulating components that dissolves in the unplaced phase. Direct systems are convenient for encapsulating the hydrophobic component whereas inverse system allows an easy way to encapsulate the hydrophilic component. The preparation used in the synthesis of biomedical carriers is divided into those involving polymerization in nano
emulsions, and also those particles that formulations take place without polymerization. Finally, another potential to form inorganic or hybrid nano carriers is given by sol-gel process that takes place in nanoemulsions [10-12].

- **NANOEMULSIONS AS A NEW CONCEPT IN THE DRUG DELIVERY SYSTEM**

The drug delivery market is dominated by the oral route, which is the most convenient and cost-effective non-invasive drug route. Due to greater patient compliance and the utilization of this method for individualized therapy, it has been recognized as the best way to achieve therapeutic goals. However, there are a number of drawbacks to this technique, including geriatric, pediatric, and potentially deranged, where maintaining patient compliance is difficult. Drugs having a low aqueous solubility have a lot of trouble staying stable in the gastrointestinal tract. Peptide medication absorption is limited in the intestine due to hydrolysis and enzymatic breakdown. Micronization, solid dispersion, and other techniques have been used to increase their bioavailability.

To prepare oral nanosuspensions for these poorly soluble drugs, Niwa et al (2011) developed wet milling techniques. It was based on breaking down the drugs into tiny particles using stirring, oscillating, and turbulent motions to better incorporate them into nanosuspensions for delivery. When compared to traditional delivery, smaller particles can penetrate GIT membranes much better. However, extensive formulation optimization is required from an industrial standpoint. By improving oral bioavailability and brain disposition, nanoemulsions made from polyunsaturated fatty acids and Saquinvir show promise for HIV-AIDS therapy [10-16].

- When compared to an administered control water solution, nanoemulsions containing PTX (paclitaxel), an antineoplastic medication with antitumor activity, pine nut oil as the lipophilic phase and egg lecithin as the emulsifier showed increased bioavailability as measured in the systemic circulation. It showed promising targeting effects by getting adsorbed in the liver, kidneys, and lungs. When PTX-2 hydroxypropyl beta-cyclodextrin and polyanhydride nanoparticles were combined, a beneficial effect on the drug's intestinal permeability was discovered. As a result, it has been demonstrated to be an effective and non-invasive protein delivery mechanism. Nanoemulsions enhanced the absorption rate of ramiprilat from ramipril (i.e. 2.94 times) when compared with conventional types of capsules. Similarly, these capsules (5.4 times) enhanced their absorption rate when compared to drug suspensions [10-16].

- Ophthalmic delivery- Due to nasolacrimal secretion and drainage in the eyes, doctors recommended using traditional eye drops as ophthalmic drug delivery has low bioavailability and biological effects. The nasolacrimal duct carries a considerable portion of the delivered medicine to the gastrointestinal system via tear drainage. Sometimes, these medicines are absorbed and showed negative effects. Several efforts were taken to solve this problem; the medicine must be in contact with the eyes for a longer amount of time and show no side effects. Other medicines, such as ointment or aqueous gels, induce eyesight blurring [10-14].

- Parenteral delivery- Low-solubility drugs had long been thought to be unsuitable for
parenteral administration; however, nanoemulsification techniques have allowed them to be created as parenteral dosage forms. Usage of these biodegradable surfactants may ensure and provide effective and strong immunopharmacological action without interfering with the body's normal biological functions. Carbamazepine is a commonly used anticonvulsant based medicine is poorly soluble and synthesized as a nanoemulsion using a spontaneous emulsification process.

In the future, we predict that nanoemulsions will become as ubiquitous as many polymer solutions and solid particulate dispersions are today.

REFERENCES