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# Nanoemulsion as Pharmaceutical Carrier for Dermal Drug Delivery the Properties, Methods of Preparation and Promising Applications

*Sanjay Pandey(Review Scholar), Ms.Monika Joshi(Assistant Professor)
*Goel Institute of Pharmacy and Sciences, Lucknow.*

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**ABSTRACT**
An advanced method of drug delivery system has been created to beat the significant downsides related to conventional drug delivery systems. This survey gives an inside and out check of a nanoemulsion innovation. Nanoemulsions are nanoscale emulsions that are utilized to increase the deliverance of active therapeutic ingredients. These are thermodynamically consistent isotropic systems in which two immiscible liquids are joined into a solitary stage utilizing an emulsifying specialist like surfactant and co-surfactant. This review attempts to bring together information on the numerous nanoemulsion formulations and analyzed techniques that have been developed. The influence technique and the Brute power strategy are two techniques for creating nanoemulsion. Entrapment efficiency, particle size, Polydispersity index, zeta potential, and characterization using differential scanning calorimetric, Fourier-transform infrared spectroscopy (FTIR), and transmission electron microscopy are just a few of the techniques used to characterize nanoemulsion. In vitro drug release, stability, shelf life, dispersibility, viscosity, surface tension, friccohesity, refractive index, % transmittance, pH,osmolarity, and thermodynamic stability, are all used to assess nanoemulsions.

**Keywords:** Nanoemulsions, Drug delivery, Emulgents, High-pressure homogenization, entrapment efficiency.

## I. INTRODUCTION:

Nanoemulsions are colloidal particulate systems with submicron size particles that function as medication carriers. Their diameter ranges from 10 to 1,000 nanometers. These carriers are solid spheres with an amorphous, lipophilic, negative-charged surface. To improve site-specificity, fascinating nanoparticles can be utilized. As a medication delivery method, they improve the medicine's therapeutic efficacy while reducing side effects and hazardous responses. Infections of the RES, enzyme substitute therapy in the liver, cancer treatment, and immunization are all examples of major applications. An emulsion is a biphasic system in which one phase is distributed in the additional phase as minute droplets with diameters varying from 0.1 to 100 nm. It's a thermodynamically uneven system that can only be stabilized via adding an emulsifying agent. The internal phase, also known as the discontinuous phase, is the dispersed phase, whereas the dispersion medium, also known as the continuous phase, is the outer phase. Intermediate or interphase is another name for the emulsifying agent. An emulsion is a fine O/W or W/O dispersion with droplet sizes ranging from 20 to 600 nanometers that are stabilized via an interfacial film of surfactant molecules. Because of their little size, NE is transparent. Three different types of nanoemulsions may be made:

(a) The oil is disseminated in a continuous aqueous phase in an oil in water nanoemulsion.
(b) W/O nanoemulsion with distributed water droplets in a continuous oil phase
(c) bi-continuous nanoemulsions.

Nanoemulsions, otherwise called submicron, ultrafine, and smaller than usual emulsions, are isotropic scatterings that included two immiscible liquids, similar to water and oil, offset through an interfacial layer involved a fitting surfactant and co-surfactant to make a solitary stage. Several surfactants with varied characteristics have been utilized in these nanoemulsions. Nonionic surfactants anionic surfactants, cationic surfactants, and zwitterions surfactants were the most extensively employed among them (quaternary ammonium halide). Nanoemulsions are now divided into three types: O/W (oil dispersed in water), W/O (water dispersed in oil), and bi-continuous (water scattered in both phases. The mechanism of the emulsions can be changed to achieve conversion between these three forms. Multiple emulsions are a form of

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nanoemulsion that has both O/W and W/O emulsions in the same system. Both hydrophilic and lipophilic surfactants are utilized simultaneously to stabilize these two emulsions. Nanoemulsions provide several benefits over conventional dosage forms, including:

**Advantages of nanoemulsion**

(a) It can be utilized to replace liposomes and vesicles. [1]
(b) It increases the drug's bioavailability.
(c) It is naturally non-toxic and non-irritant.
(d) Its physical stability has improved.
(e) Nanoemulsions have tiny droplets with a larger surface area, allowing for higher absorption.
(f) In cell culture technology, it improves the absorption of oil-soluble nutrients.
(g) It aids in the solubilization of lipophilic drugs.
(h) Aids in the hiding of unpleasant tastes.
(i) There is a reduction in the quantity of energy required.

Nanoemulsion components Oil, emulsifying agents, and aqueous phases are the key components of nanoemulsion. [2][3].

Due to the coalescence of the scattered globules, a crude temporary emulsion made of oil and water may divide into two different phases after standing. Emulgents or emulsifying specialists can assist these systems to stay stable. Surfactants like spans and tweens, hydrophilic colloids like acacia, and finely separated solids like bentonite and see gum are all examples of emulgents.

In addition to emulsifying qualities, an emulgent should be safe and companionable with the product in terms of taste, odor, and chemical stability.

(1) Surface tension should be reduced to less than 10 dynes/cm.

(2) To avoid coalescence, it should be promptly adsorbed around scattered phase globules to produce a full and cohesive film.

(3) It should help in the creation of sufficient zeta potential and viscosity in the system to provide optimal stability.

(4) It should be effective at low concentrations. Around the scattered globules, emulgents create monomolecular, multimolecular, or particulate films[4].

Aspects of Nanoemulsions Formulation and Preparation Methods:

The active medication, additive, and emulsifier are all included in the nanoemulsion formulation. Two ways for preparing nanoemulsions are available:

There are two types of emulsification: high-energy and low-energy emulsification. Ultrasonic emulsification, persuasive homogenization, micro fluidization, High-energy stirring, and membrane emulsification are all examples of high-energy emulsification methods.

**Phase Inversion Temperature:**

Emulsion inversion point and spontaneous emulsification are all low-energy emulsification methods [5]. It is feasible to create repeal nanoemulsion in a very viscous solution using a combination technique that comprises both high-energy and low-energy emulsification. The persuasive technique of nanoemulsion preparation does not use any external force; instead, fine dispersions are formed when phase transitions occur by altering either the temperature or the composition while maintaining the other parameter constant. Persuasion methods may be broadly classified as:

- Phase conversion from the near-optimal condition by single variable alteration, which entails changing one formulation variable, such as temperature or salinity, to a near-optimal value. For a system that uses a higher temperature for microemulsion, the hydrophilic-lipophilic deviation (HLD) for the ideal value is near to the center level.
- Phase conversion from the near-optimal condition by multiple variable changes, i.e. changing more than one formulation variable. Using a higher temperature and adding extra salt to a micro emulsion, for example. Catastrophic inversion.
- Catastrophic inversion is the inversion of a low interior phase emulsion into an exterior phase emulsion.
- Liquid crystal formation stabilized phase transition, which involves nanodroplets stabilization from a condition near HLD-0 by liquid crystal formation.[6]

**Brute force Method:**

The use of physical force to shatter the oil droplets into the nano range is part of this procedure. High-pressure homogenizers, high-speed mixers, small-pore membranes, and high-frequency ultrasonic devices have all been used in the creation of nanoemulsions. Nanoemulsion features such as tiny size, optical transparency, and high kinetic stability are influenced by processing factors such as emulsification duration, degree of mixing, energy input, and emulsifying route, as well as the composition of variables. At both the industrial and laboratory scales, high-pressure homogenization and micro fluidization procedures

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are used to achieve very tiny nanoemulsion sizes using high-pressure equipment. Other techniques for preparing nanoemulsions, such as ultrasonication and in situ emulsification, are also being used[7].

**Emulsification with Ultrasonic waves:**

When it comes to lowering droplet size, ultrasonic emulsification is quite effective. The energy for ultrasonic emulsification comes from sonotrodes known as sonicator probes. It includes a piezoelectric quartz crystal that expands and contracts in reaction to alternating electric energy. When the sonicator's tip makes contact with the liquid, it causes mechanical vibration and cavitation. As a result, ultrasound may be used directly to make emulsion; it is mostly utilized in labs to obtain emulsion droplet sizes as small as 0.2 millimeters.

**Homogenization:**

Homogenization at high-pressure Nanoemulsions preparation necessitates high-pressure homogenization.The resulting emulsion is then exposed to high turbulence and hydraulic shear, resulting in a fine-particle emulsion. This has been proven to be the most proficient approach for preparing nanoemulsions; however, the sole disadvantage is the high energy utilization and emulsion temperature rise during processing. It also needs longer runs of homogenization cycles to get lower particle sizes. [10]A combination is driven through an aperture at extremely high pressure, ranging from 500 to 5000 psi, in this method. The resulting emulsion is then exposed to high turbulence and hydraulic shear, resulting in a fine-particle emulsion. This has been proven to be the most efficient approach for preparing nanoemulsions; however, the sole disadvantage is the high energy consumption and emulsion temperature rise during processing. It also needs longer runs of homogenization cycles to get lower particle sizes. Yilmaz et al. used a high-pressure homogenization approach to create phytosphingosine O/W nanoemulsions and discovered that after 8 homogenization cycles, the droplet size was reduced and the nanoemulsion was stable for over 6 months [8, 9, 10].

**Microfludization:**

Microfludization is a proprietary mixing process that employs a micro fluidizer device. The medicinal product is formed during the interaction chamber under high pressure, resulting in an extremely tiny particle in the submicron range. To make a consistent nanoemulsion, the procedure is repeated multiple times until the required particle size is achieved.The temperature of phase inversion A greater temperature is used to shift the phase of a Microemulsion in this procedure.

There are three steps to it:

(a) A homogeneous organic solution containing oil and surfactant in a water-miscible solvent and a hydrophilic surfactant is prepared;

(b) The natural stage is infused into the fluid stage under incessant magnetic stirring, forming an o/w emulsion.

(c) The aqueous stage is aloof by vanishing under diminished pressure [11, 12].

The emodin-loaded nanoemulsion was created using an ultrasonic emulsification technique at a frequency of 25 kHz, and the emodin-loaded nanoemulsion's mean diameter was determined to be in the range of 10-30 nm [13].

**Spontaneous emulsification**

This technique concerns the formulation of nanoemulsion in 3 stages. The first stage involved creating an organic solution including oil and surfactant in a water-miscible solvent with a hydrophilic surfactant and afterward infusing this organic phase into the aqueous phase under magnetic stirring to create the O/W emulsion [14].

**Nanoemulsions evaluation parameters**

**Determination of encapsulation efficiency**

The entrapment efficiency (EE) and loading efficiency (LE) of the drug can be calculated by using the following equation, drug EE = drug content in the product obtained (mg)/total amount of drug added (mg)×100 and drug LE = drug content in the product obtained (mg)/total product weight (mg)×100. Drug content could also be determined using reverse-phase high-performance liquid chromatography (HPLC) techniques.

**Determination of particle size and Polydispersity index (PDI):**

The diffusion technique is used to determine the droplet size of NE using a light-scattering particle size analyzer counter, the LS 230. Correlation spectroscopy, which investigates the disparity in light scattering owing to Brownian motion, is also used to quantify it. Transmission electron microscopy may also be utilized to inspect the size of nanoemulsion droplets. The theory behind photon correlation spectroscopy is that particles with a smaller size travel faster than particles with a larger size. The laser beam is diffracted in solution by sub-micron particles. Rapid variations in laser scattering intensity occur

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around a mean worth at a constant angle due to particle diffusion, and this is dependent on particle size. A histogram of the line width distribution is generated by the estimated photoelectron time correlation function, which may be connected to particle size. To measure particle size, a weighed quantity of formulation is dispersed in double-distilled water to achieve a homogeneous dispersion, which must be utilized immediately for particle size and PDI measurements. The PDI can be anyplace somewhere in the range of 0 and 1, with 0 (zero) showing a monodisperse framework and 1 demonstrating a polydisperse molecule scattering [28].
Determined the particle size and PDI of risperidone nanoemulsions, reporting a mean particle size of 160 nm and mean size distribution of less than 0.15 [29].

**Determination of Zeta Potential:**

When particles are submerged in liquid, the zeta potential is used to determine their surface charge. The zeta potential is a physicochemical characteristic of a medication, polymer, or vehicle that is utilized to expect dispersion stability. It is measured with Malvern Zetasizer equipment. The zeta potential of nanoemulsion is determined by diluting it and calculating it based on the electrophoretic mobility of oil droplets. For nanoemulsion physical stability, a zeta potential of 30 mV is regarded to be adequate.

**(FTIR) Spectral Analysis:**

Drug excipient interaction, polymerization and cross linking, in the formulation may all be assessed using FTIR analysis. At low temperature a particle exists in the ground state and on retaining the brilliant energy, they get eager to higher energy states. IR spectroscopy depends on deciding this energy difference (ΔE) between the excited and ground states of the molecule.Samples can be arranged for FTIR using appropriate methods such as potassium bromide pellets or Nujol mulls, and then scanned in FTIR at a modest scanning speed of 4000-400 cm-1.[17]

**Morphological study of nanoemulsion**

The morphological study of nanoemulsion is carried out by using transmission electron microscopy (TEM). These incoming electrons convert into unscattered electrons, elastically scattered electrons, or elastically scattered electrons when they contact with the specimen. [18]

**Atomic Force Microscope (AFM)**

AFM is a relatively recent technology that is being used to investigate the surface morphology of nanoemulsion formulations these days. AFM is performed by diluting nanoemulsions in water and then dropping the diluted nanoemulsion onto a glass slide. The coated droplets are then dried in an oven before being scanned at 100 mV/s. Drais et al. used AFM to examine carvedilol nanoemulsion and discovered that the size ranged from 42 to 83 nm with satisfactory formulation stability. [19]

**In vitro drug release study:**

In vitro, drug release studies help to estimate the in vivo performance of drug formulation. A USP dissolving equipment is used to determine a drug's in vitro release rate. The medication corresponding to 10 mg was disseminated in nanoemulsion or dried nanoparticles, which were then put into dialysis membrane pouches and placed in a flask containing buffer. This experiment is conducted at 370.5°F at a stirring speed of 50 rpm. At regular intervals, the sample is removed and replaced with an equal volume of new dissolving media. The absorbance of the sample is then measured spectrophotometrically at a certain wavelength after the samples have been diluted appropriately. Using a calibration curve, the absorbance of the collected sample is utilized to calculate the percent drug release at various time intervals[18, 20].

**pH and osmolarity measurements**

The pH of a nanoemulsion is measured using a pH meter, and the osmolarity of the emulsion is determined with a micro osmometer using the freezing point technique. This is done by transferring 100ul of nanoemulsions into a micro tube and taking measurements. [21, 22].

**Determining the Viscosity:**

A Brookfield-type rotational viscometer is used to test the viscosity of nanoemulsions at various shear rates and temperatures. The low viscosity of systems shows that it is O/W type and high viscosity shows that it is water in the oil type system[23].

**Test for Dilution:**

This kind may be identified by diluting a nanoemulsion with either oil or water. The test is predicated on the idea that a nanoemulsion may have an additional continuous phase added to it without losing its stability. A w/o nanoemulsion

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may be diluted with oil, whereas an o/w nanoemulsion can be diluted with water[24].

**Composition of the Drug:**

Pre-weighed nanoemulsions is extracted by dissolving in a suitable solvent, and the extract is compared to a drug reference solution using a spectrophotometer or HPLC.

**Polydispersity:**

It denotes the droplet size consistency in a nanoemulsion. The lesser the homogeneity of nanoemulsion droplet size, the more noteworthy the polydispersity value. The proportion of standard deviation to mean drop size it's called. A spectrophotometer is used to measure it.
A w/o nanoemulsion may be diluted with oil, whereas an o/w nanoemulsion can be diluted with water.

**Conductance:**

Measurement a conductometer is used to test the conductivity of nanoemulsion. A pair of electrodes linked to light and an electric source is dipped in emulsion in this test. Water conducts current in an o/w emulsion, and the lamp is illuminated as a result of the current passing between the electrodes. When the emulsion is w/o, the lamp does not light because the oil in the exterior phase does not conduct current.

**Test with filter paper:**

This test is based on the fact that when an o/w nanoemulsion is put onto filter paper, it spreads out quickly. A w/o nanoemulsion, on the other hand, will travel slowly. For excessively viscous creams, this procedure should not be employed.

## II. CONCLUSION

In pharmaceutical systems, nanoemulsions are usually employed. Nanoemulsion formulation enjoys different benefits, including pharmacological, natural, and demonstrative agent delivery. The most well-known utilization of nanoemulsion is for concealing. The terrible taste of oily fluids Nanoemulsion can possibly likewise defend meds that are helpless against hydrolysis, as well as oxidation Nanoemulsions, are being utilized in different applications. Photo shows multiple anticancer medications being delivered in a specific manner. therapeutic agents or sensitizers Nanoemulsion can be used in a variety of ways. ensure that the medication has a long-lasting effect All in all, The formulation of nanoemulsions might be regarded effective. safe and has a higher bioavailability It is anticipated that In the future, more research and development will be carried out. In terms of nanoemulsion, the future seems bright.

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