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# A COMPREHENSIVE REVIEW ON NANOEMULSION AS AN TOPICAL DELIVERY

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**ABSTRACT**

Submicron-sized emulsified systems called nanoemulsions are useful carriers for improving the delivery of medicinal substances. As one of the more advanced nano particle systems, they offer controlled or sustained release and facilitate targeted medication delivery. With the help of appropriate surfactants, two immiscible liquids-typically water and oil-combine into a single phase to form these thermodynamically stable and isotropic dispersions. Nanoemulsions, which typically have droplet sizes between 10 and 100 nm with a restricted size distribution, have enormous potential in the fields of biotechnology, medicines, diagnostics, and cosmetics. This review highlights the benefits and drawbacks of nanoemulsions, talks about how they are prepared and characterised, and covers their many uses, such as different routes of administration, chemotherapeutic delivery, and cosmetic formulations.

**Key words:** Skin, Topical drug delivery, Nanoemulgel, Nano emulsion.

## INTRODUCTION

The skin is the human body's biggest organ and plays a crucial part in different dynamic processes that assist maintain homeostasis. Our skin, which is composed of various cell types, serves as a powerful defence against environmental dangers like sun exposure, chemical contact, bacteria, and physical trauma.[1]

A formulation that is applied to the skin and other areas to treat skin disorders is known as a topical medication delivery system. Modern methods are being developed to increase the systemic influence of topical medication delivery, which is mostly employed for localised dermatological effects. Antiseptics, antifungal medications, anti-acne therapies, skin moisturisers, and protective agents are commonly employed in these systems.[2]

Oil-in-water (o/w) or water-in-oil (w/o) nanoemulsions are transformed into nanoemulgels by adding a gelling agent. Because they have better qualities than nanoemulsions, nanoemulgels in their gelled state are ideal for transdermal applications. The physiochemical properties of nanoparticles have a major impact on how they interact with biological systems.[3]

As a component of nanotechnology, nanoemulsion (NE) is a nanocarrier delivery technique for transdermal drug delivery, has attracted a lot of attention. Their particle sizes range from 100 to 500 nm, and they are optically transparent. It is made up of the aqueous phase, co-surfactant, oil and surface active agent. In any case, applying nanoemulsion to human skin is inappropriate due to its low viscosity. Transdermal application is made more convenient by using a gelling agent in conjunction with a nanoemulsion. The dosage form is known as nanoemulgel when gelling agent and nanoemulsion are used in conjunction.Most of the hydrophobic medicines cannot be integrated directly into the gel base because the solubility problem that develops after the drug release. Nanoemulgel help in the hydrophobic medicines merger into the oil phase and then oil droplets are disseminated in aqueous phase leading to oil in water (o/w) nanoemulsion then this nanoemulsion can be mixed into gelling agent to create appealing delivery method which is nanoemulgel. Also, patient compliance is boosted due to improved spreadability relative to ointments and creams and less stickiness.[4]

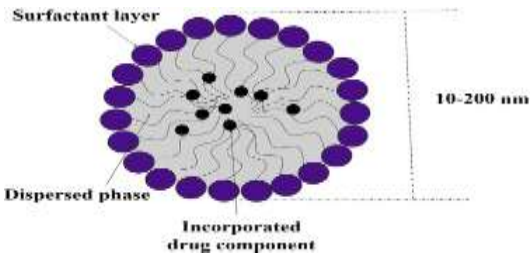



**Fig. 1: Diagram of nanoemulsion**.

**Types of nanoemulsions**

**Three types of Nanoemulsions** are most likely to be formed depending on the composition:

1. **Oil in water Nanoemulsions:** It contains oil droplets dispersed in the continuous aqueous phase.
2. **Water in oil Nanoemulsions:** It contains water droplets dispersed in the continuous oil phase.
3. **Bi-continuous Nanoemulsions**: It contains micro domains of oil and water are interdispersed within the system.

In all three types of Nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants. The key difference between emulsions and Nanoemulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate. Another important difference concerns their appearance; emulsions are cloudy while Nanoemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while Nanoemulsions.[5]

**Potent components for nanoemulsion formulation**

Nanoemulgel is a fusion of two separate systems, viz. the nanoemulsion and a gel system. Nanoemulsion acting as a vehicle for drug delivery can be either water-in-oil or oil-in-water type. In both cases, it consists of an oil phase, aqueous phase, surfactant and sometimes cosurfactant. Overview of commonly used major components of nanoemulgel formulation has been apprehended in this section.[6]


**Fig.2: components for nanoemulsion formulation**

**Oils:**

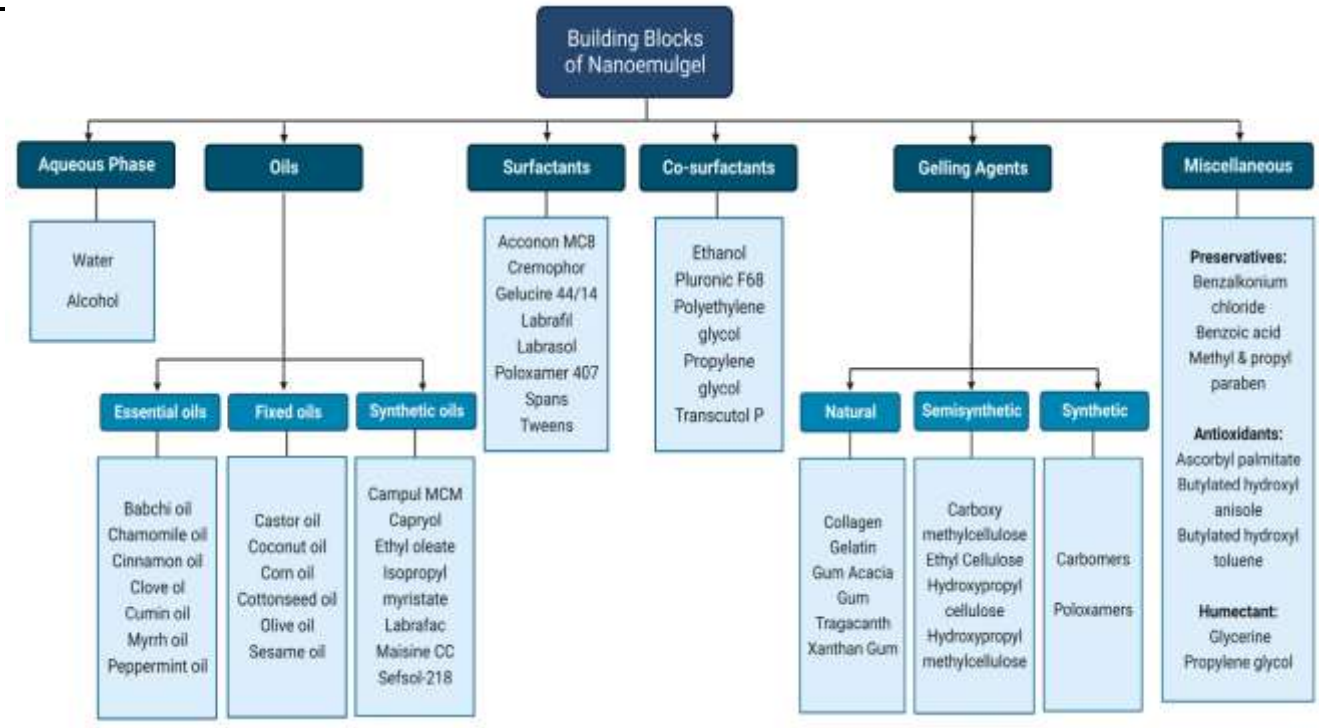
The oil selection used in Nanoemulsion formulation considers as an important factor since the drug will be incorporated as a droplet in the oily phase that dispersed in the aqueous phase. So, the oil which is selected should able to dissolve the substances used in dosage form to get a higher % of drug-loaded, also oil selected must be compatible with other Nanoemulsion component. The oil used in Nanoemulsion either natural, synthetic or semi-synthetic.[7]

**Surfactant:**

To facilitate the dispersion of all components surfactant must be able to reduce the interfacial tension nearest to zero. In preparation of w/o nanoemulsion Surfactants with HLB values 3-6 are useful where for the preparation of o/w nanoemulsion surfactants with higher HLB values 8-18 are useful. Surfactants which having the HLB value more than 20 are acts as cosurfactants for reduction of concentrations of the surfactants to an acceptable limit and micro emulsion formation.[8]

**Co-surfactants:**

Sometimes, co-surfactants are used to complement surfactants, as they fit suitably in between structurally weaker areas, fortifying the interfacial film.[9]




**Techniques of Preparation of Nanoemulsions:**

The most used methods for producing nanoemulsions are as follows:

- High-Pressure Homogenization
- Micro fluidization
- Ultrasonication
- Phase inversion method
- Spontaneous Emulsification
- Solvent Evaporation Technique
- Hydrogel Method

**High Pressure Homogenization:**

Nanoemulsions are prepared using high-pressure homogenization. This method employs a high-pressure homogenizer or piston homogenizer to create nanoemulsions with small particle sizes (down to 1 nm). The emulsification of two liquids (oil phase and water phase) is accomplished by pushing their combination through an inlet opening, under very high pressure (500 to 5000 psi) exposing the mixture to strong turbulence and hydraulic shear which leads to the formation of ultra-fine emulsion particles. The particles which are created exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids.[10]

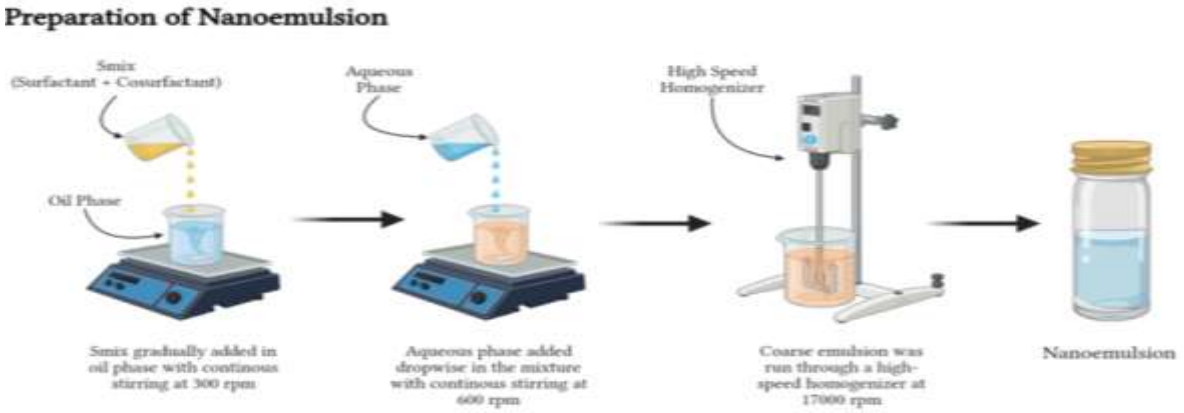



**Fig.3: High Pressure Homogenization**

**Micro fluidization:**

Micro-fluidization is a method of mixing that utilizes an instrument known as a micro-fluidizer. This tool employs a pressure positive displacement pump (ranging from 500 to 20000 psi) to push the product through the interaction chamber, which contains narrow passages termed micro channels. The product passes through these channels onto an impingement zone

producing extremely fine particles in the sub-micron size range. The two solutions i.e., aqueous phase and oily phase are combined and processed in an in turn to homogenizer to yield a coarse emulsion formed. The coarse emulsion is into a micro-fluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber micro-fluidizer repeatedly until desired particle size is obtained through it. The bulk emulsion is then get filtered through a filter under nitrogen to remove large droplets present in it and this results in a uniform nanoemulsion.

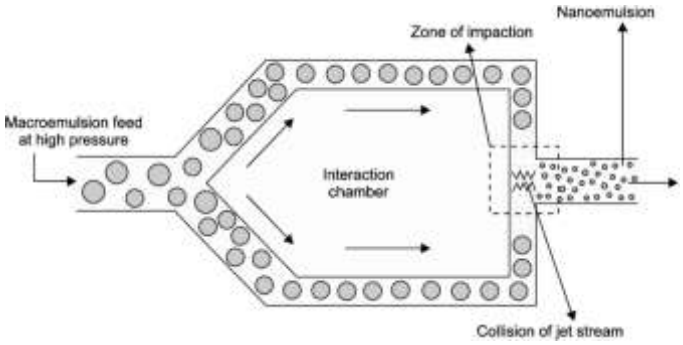



**Fig.4: Micro fluidization**

**Ultrasonication:**

Numerous research studies document the preparation of nanoemulsions focusing on employing frequencies to minimize droplet size. The optimal method involves the use of a sonotrode with amplitude operating at system pressures above ambient levels. It is established that raising the pressure elevates the cavitation threshold, in an ultrasonic environment resulting in fewer bubbles. However higher external pressure also boosts the collapse pressure of cavitation bubbles. This means that the collapse of the bubbles when cavitation occurs becomes stronger and more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a low frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to optimum level


**Fig. 5: Ultrasonication**

**Phase Inversion Method:**

The phase inversion technique involves obtaining dispersion through chemical energy generated by phase transitions triggered via the emulsification process. This phase transition occurs by altering the emulsions composition while maintaining a temperature. The initial study on phase inversion temperature showed that raising the temperature causes modifications in polyoxyethylene surfactants due to degradation of the polymer chain, with heat. This approach is applied to create o/w nanoemulsions. The main advantage of this system is that it is based on the phase transition that takes place during the emulsification process. In this technique, varying the composition of constituents changes the hydrophilic-lipophilic behaviour of emulsifier.

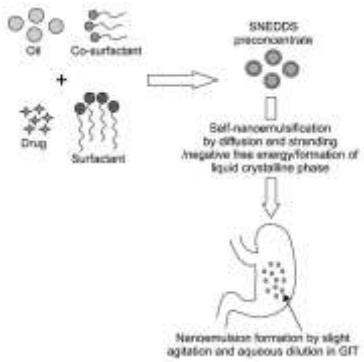



**Fig.6: Phase inversion emulsification techniques**

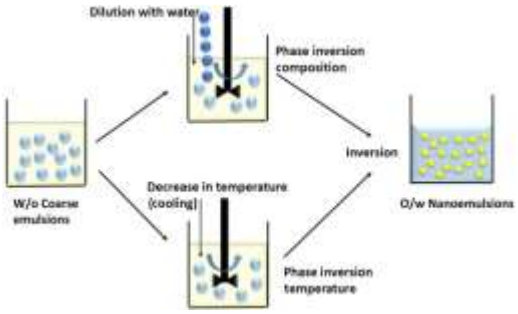



**Fig.7: Low energy methods for phase inversion**

**Spontaneous Emulsification Method:**

In this technique, spontaneous emulsions are formed on mixing water and oil together with an emulsifier by gentle stirring at a particular temperature. The mixing of phases by gentle magnetic stirring causes the emulsifier to enter the aqueous phase leading to increase of oil-water interfacial area resulting in oil droplet formation. Spontaneous emulsification involves three main steps and they are as follows:

• Preparation of homogeneous organic solution composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.

• The organic phase was injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.

• The water-miscible solvent was removed by evaporation under reduced pressure.

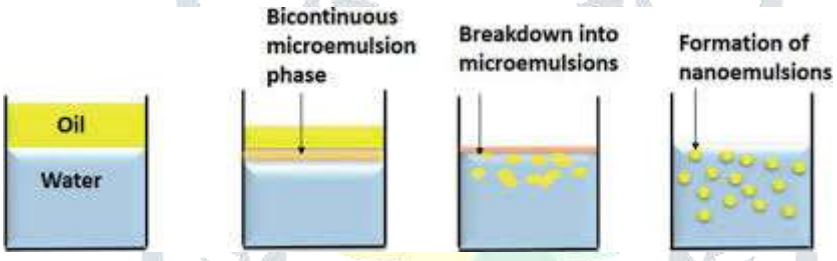



**Fig.8: Spontaneous Emulsification Method**

**Solvent Evaporation Technique**:

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

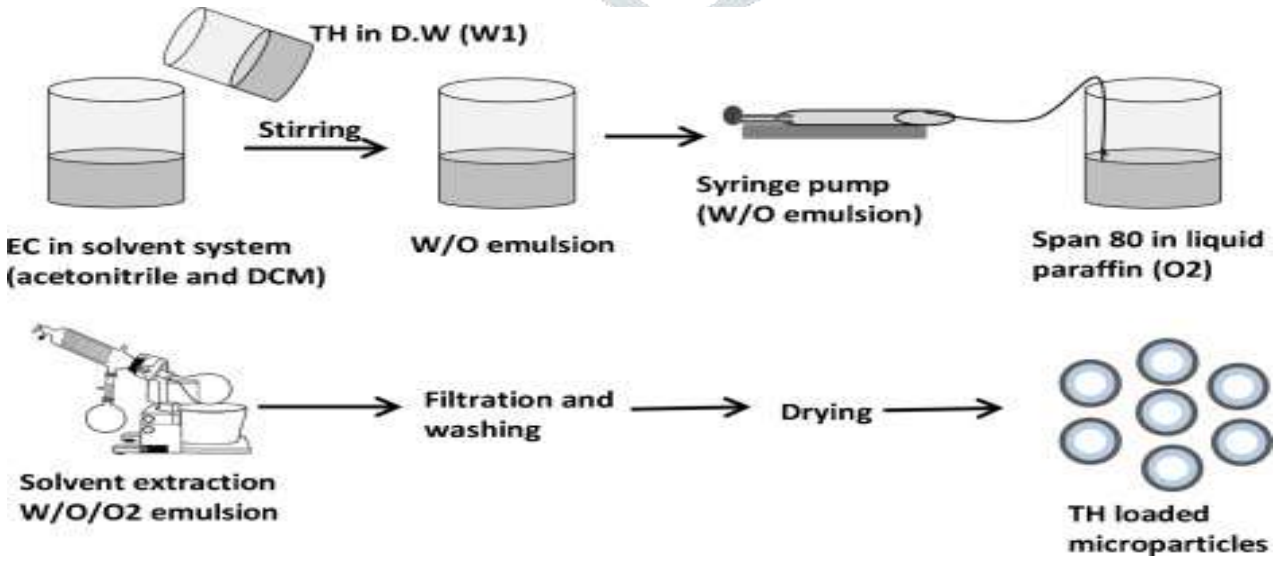



**Fig.9: Solvent Evaporation Technique**

**Hydrogel Method:**

It is similar to the solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening. Other method used for Nanoemulsion preparation is the phase inversion temperature technique.

**Advantages of Nanoemulsions:**[11]

- Eliminates variability in absorption.
- Increases the rate of absorption.
- Helps in solubilizing lipophilic drug.
- Provides aqueous dosage form for water insoluble drugs.
- Increases bioavailability.
- Various routes like topical, oral and intravenous can be used to deliver the product.
- Rapid and efficient penetration of the drug molecule.
- Helps in taste masking.

**Disadvantages of Nanoemulsion:**[12]

- Large concentration of surfactants / cosurfactants is required for stabilization.
- Nanoemulsion stability is affected by environmental factors like temperature and pH.
- Instability can be caused due to Oswald ripening effect.
- The stability of nanoemulsions is quite unacceptable and produces a big problem during the storage of formulation for the longer time.

**Characterization of nanoemulsions:**

**1. Dye Solubilisation:**

A water-soluble dye is solubilized within the aqueous phase of the w/o globule but is dispersible in the o/w globule. An oil soluble dye is solubilized within the oil phase of the o/w globule but is dispersible in the w/o globule.[13]

**2. Droplet Size Analysis:**

Droplet size analysis of nanoemulsion is measured by a diffusion method using a lights catering, particle size analyser counter. It is also measured by correlation spectroscopy that analyses the fluctuation in scattering of light due to Brownian motion. Droplet size analysis of nanoemulsion can also be performed by transmission electron microscopy (TEM).[13]

**3. Viscosity and Rheology:**

Viscosity is very essential parameter since it influences the flow properties and spreadability of the nanoemulsion. When compared to conventional emulsions, nanoemulsion often has a higher viscosity, which facilitates its application. Generally, in oral and injectable formulations, lower viscosity is frequently preferable; nevertheless, for prolonged release in topical applications, a higher viscosity may be desirable. Viscosity is determined utilizing instruments such as rheometers and viscometers, which can reveal information about the flow properties of the nanoemulsion in different conditions. Concerning with rheology, it is the study of material flow and deformation behaviour. It includes characteristics such as viscosity, elasticity and plasticity in nanoemulsion. The rheological behaviour of nanoemulsion affects how it is handled and applied.[14]

**4. Phase inversion:**

Phase inversion is the conversion of an o/w emulsion to a w/o emulsion and vice versa. It is the result of a physical process. Variations in the phase volume ratio, the addition of electrolytes, and temperature variations can all cause phase inversion.[15]

**5. Spreadability:**

A pre-marked glass slide was covered with a second glass slide after a 0.5 g gel sample was put in a circle on the first glass slide with a diameter of 1 cm. A weight of 2 g was let to rest on the top glass slide for one minute. The gel's dispersion led to an increase in diameter. In order to determine spreadability, the following formula was used:

$S = M.L / T$

Where S stands for spreadability, M for the weight fastened to the higher slide, L for spread, and T for time.[16]

**6. In vitro Diffusion studies:**

The diffusion studies of the prepared nanoemulsions are performed by using Franz diffusion cell with the aid of cellophane membrane. Nanoemulsion sample (5ml) is taken in cellophane membrane and the diffusion studies are carried out at 37 ± 1 °C using 250 ml of (25%) methanolic phosphate buffer (pH 7.4) as the dissolution medium. 5 ml of each sample was

withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample is replaced with equal volume of fresh dissolution medium in order to maintain sink condition. Samples are analysed by UV- spectrophotometer at 271 nm for drug content.[17]

**7. Bio-Adhesive Property:**

Bio-adhesive strength is used to determine the force required to detach the drug carrier system from a biological surface. This property is important for a topical dosage form if prolonged contact is required. This test is usually performed using rat or pig skin, the latter is preferred because of its resemblance to human skin. There are various techniques to measure this property but none of them is approved by FDA. The texture analyser is one such technique, where the upper mobile probe and stationary lower base plate will be covered with skin. The dosage form is placed on the skin of the base plate. The upper probe is lowered to contact the lower base plate and the contact is maintained for at least a minute. The upper probe is lifted slowly until the separation of skin sheets. The force required to separate the two skin sheets will be measured by the instrument and represented as the area under the force-distance curve.[18]

**CONCLUSION**

Nanoemulsion are a promising and versatile platform for the development of advanced drug delivery systems, offering improved performance, reduced side effects and targeted delivery. However, challenges such as scaling up production, ensuring regulatory approval and long term stability need to be addressed for their widespread adoption in clinical settings.

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