



Review Article

A Review on Preparation and Evaluation of Nanoemulsions

Dasari Prasad ^{1,*}, G P Mohanta ², M Sudhakar ³

¹ Research Scholar, Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar – 608 002, Tamilnadu, India.

² Professor, Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar – 608 002, Tamilnadu, India.

³ Principal & Professor, Mallareddy College Of Pharmacy, department of Pharmaceutics, Osmania University, Hyderabad ,500100, Telangana, India

ARTICLE INFO

A B S T R A C T

Received: 13 Feb 2019
Accepted: 26 Feb 2019

An advanced mode of drug delivery system has been developed to overcome the major drawbacks associated with conventional drug delivery systems. This review gives a detailed idea about a nanoemulsion system. Nanoemulsions are nano-sized emulsions, which are manufactured for improving the delivery of active Pharmaceutical ingredients. These are the thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, i.e., surfactant and co-surfactant. The droplet size of nanoemulsion falls typically in the range 20-200 nm. The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase. In this review, the attention is focused to give a basic idea about its formulation, method of preparation, characterization techniques, evaluation parameters, and various applications of nanoemulsion.

Key Words: Nanoemulsion, surfactant, co-surfactant.

Corresponding author *
Dasari Prasad
Research Scholar
Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar, 608002, Tamilnadu, India
E-mail: Prasad.mrcp@gmail.com

1. INTRODUCTION

Nanoemulsions are emulsions with droplet size on the order of 100 nm. A typical nanoemulsion contains oil, water and an emulsifier. The addition of an emulsifier is critical for the creation of small sized droplets as it decreases the interfacial tension i.e., the surface energy per unit area, between the oil and water phases of the emulsion. The emulsifier also plays a role in stabilizing nanoemulsions through repulsive electrostatic interactions and steric hindrance.¹ Their size

varies from 10 to 1,000 nm. These carriers are solid spheres and their surface is amorphous and lipophilic with a negative charge. The term ‘nanoemulsion’ also refers to a mini emulsion which is fine oil/water or water/oil dispersion stabilized by an interfacial film of surfactant molecule having droplet size range 20–600 nm. Because of small size, nanoemulsions are transparent. The dispersed phase is also known as internal phase or discontinuous phase while outer phase is called the dispersion medium, external phase or continuous phase. The emulsifying agent is also known as intermediate or interphase.² Preparation of nanoemulsions are broadly classified into two primary categories: high-energy and low-energy methods.³ High energy methods such as high pressure homogenization (HPH) and ultrasonication⁴ consume significant energy (B108 –1010 W kg1) to make small droplets. On the other hand, low energy methods exploit specific system properties to make small droplets without consuming significant energy (B103 W kg1). Phase inversion temperature (PIT)⁵ and emulsion inversion point (EIP)⁶⁻⁸ are two examples of low energy approaches for the formation of nanoemulsions. Recently, a few novel technologies such as bubble bursting at oil/water interface⁹ and evaporative ripening have also been developed for making nanoemulsions¹⁰. The term nanoemulsion refers to thermodynamically stable or isotropically clear dispersion of two immiscible liquids a nanoemulsion is a thermodynamically or kinetically stable liquid dispersion of an oil phase and water phase in combination with a surfactant. Three types of Nanoemulsions are most likely to be formed are

- Oil in water nanoemulsions: wherein oil droplets are dispersed in continuous aqueous phase.
- Water in oil nanoemulsions: wherein water droplets are dispersed in continuous oil phase.
- Bi-continuous nanoemulsions: wherein micro domains of oil and water are interdispersed within the system.

In all the three types of nanoemulsions, the interphase is stabilized by an appropriate amount of surfactant and/or co-surfactants.¹¹

Nanoemulsion is a translucent system. It has been demonstrated that with the help of nanoemulsion as delivery system, drug retention time in the body can be increased, so low amount of drug is required for the therapeutic action.¹²

Advantages of nanoemulsion^{13, 14}

- It may be used as substitute for liposomes and vesicles.
- It improves the bioavailability of drug.
- It is non-toxic and non-irritant in nature.
- It has improved physical stability.
- Nanoemulsions have small-sized droplets having greater surface area providing greater absorption.
- It can be formulated in variety of formulations such as foams, creams, liquids, and sprays.
- It provides better uptake of oil-soluble supplements in cell culture technology.

- It helps to solubilize lipophilic drug.
- Helpful in taste masking.
- Less amount of energy is required.

Disadvantages of nanoemulsions:

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Limited solubilizing capacity for high-melting substances.
- The surfactant must be nontoxic for using pharmaceutical applications.

Nanoemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon nanoemulsion delivery to patients.

Table 1: Components of Nano emulsions

Component	examples
Oils	Corn oil, coconut oil, evening prime rose oil, castor oil, mineral oil, olive oil, linseed oil, peanut oil.
Emulgent	Natural lecithins from plants or animals, phospholipids, castor oil derivatives.
Surfactant	Polysorbates, sterylamine, polysorbate 20, polysorbate 80, castor oil, polyoxy 60, sorbitan monooleate, PEG300, caprylic glyceride
Co-surfactant	Ethanol, glycerine, PEG300, PEG400, polyene glycol, poloxamer.
Tonicity modifiers	Glycerol, sorbitol, xylitol
Anti oxidants	Ascorbic acid, tocopherol
Additives	Lower alcohol(ethanol), propylene glycol, 1,3-butylene glycol, sugars such as glucose, sucrose, fructose, and maltose

2. FORMULATION ASPECTS AND METHOD OF PREPARATION OF NANOEMULSION

Formulation of nanoemulsion includes active drug, additive and emulsifier. The methods for the preparation of nanoemulsion include two methods: (a) high-energy emulsification and (b) low-energy emulsification. The high-energy emulsification method includes high-energy stirring, ultrasonic emulsification, high-pressure homogenization, micro fluidization, and membrane emulsification.¹⁶

The low-energy emulsification method includes phase inversion temperature, emulsion inversion point, and spontaneous emulsification. Using a combined method, which includes the high-energy and low-energy emulsification, it is possible to prepare reverse nanoemulsion in a highly viscous system.¹⁷

High energy methods:¹⁸⁻²⁰

1. High-Pressure Homogenization: The preparation of nanoemulsions requires high- pressure homogenization. This technique makes use of high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1nm). The dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing their

mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion. The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids. This technique has great efficiency, the only disadvantage being high energy consumption and increase in temperature of emulsion during processing.

2. Micro fluidization: Micro-fluidization is a mixing technique, which makes use of a device called micro-fluidizer. This device uses a high-pressure

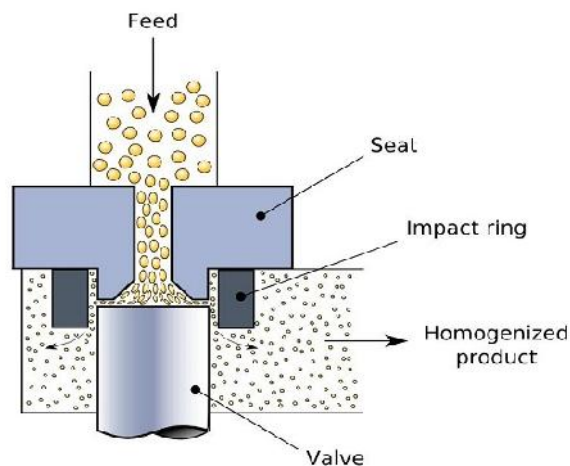


Fig 1: High pressure homogenization

Positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called „micro-channels“. The product flows through the micro channels on to an impingement area resulting in very fine particles of sub-micron range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. 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. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion.¹⁸

3. Ultrasonic emulsification: Ultrasonic emulsification is very efficient in reducing droplet size. In ultrasonic emulsification, the energy is provided through sonotrodes called as sonicator probe. It contains piezoelectric quartz crystal which can expand and contract in response to alternating electric voltage. As the tip of sonicator contacts the liquid, it produces mechanical vibration and cavitation occurs. Cavitation is the formation and collapse of vapour cavities in liquid. Thus, ultrasound can be directly used to produce emulsion; it is mainly used in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained.

4. Spontaneous emulsification: It involves three steps: (a) preparation of homogeneous organic solution consisting of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant, (b) the organic phase is injected in aqueous phase under continuous magnetic stirring, o/w emulsion is formed, and (c) the aqueous phase is removed by evaporation under reduced pressure. It involves three steps: (a) preparation of homogeneous organic solution consisting of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant, (b) the organic phase is injected in aqueous phase under continuous magnetic stirring, o/w emulsion is formed, and (c) the aqueous phase is removed by evaporation under reduced pressure.

Low energy methods:^{21,22}

1. Persuasion method/phase inversion technique: Nanoemulsion preparation by persuasion method doesn't require any external force, but instead it involves formation of fine dispersions when phase transitions occur by changing either the temperature or composition while keeping the alternate parameter constant. Persuasion method can be broadly categorized as, (i) phase transition from near-optimum state via change in single variable, which includes altering one variable of formulation such as temperature or salinity close to optimal value. Hydrophilic-lipophilic deviation (HLD) for optimal value is close to centre level for a system, for example, employing higher temperature to microemulsion. (ii) Phase transition from near optimal state via change in multiple variables, meaning altering more than one variable of formulation. For example, employing higher temperature and including an additional salt in a microemulsion. (iii) Catastrophic inversion, an inversion of low internal phase emulsion so that the internal phase converts to external phase. (iv)Phase transition stabilized by liquid crystal formation, which includes nanodroplets stabilization from a state close to HLD-0 by liquid crystal formation.

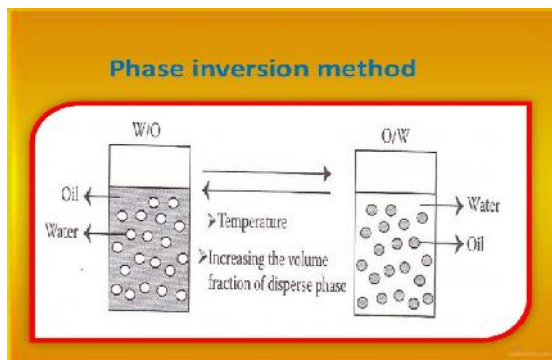


Fig 2: Phase Inversion Method

2. Solvent evaporation technique/Hydrogel method: In this technique, drug solution is prepared and emulsified into another liquid (non-solvent for drug) and then solvent is evaporated, which led to drug precipitation. High speed stirrer can be employed for regulating the crystal growth and particle aggregation. Hydrogel method is very similar the solvent evaporation method. The only difference from the

solvent evaporation method is that the drug solution in this case is miscible with the drug anti-solvent.

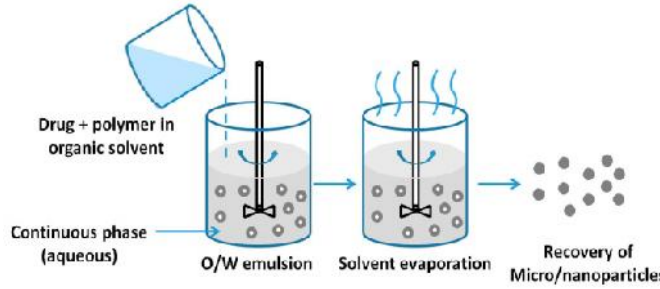


Fig 3: Solvent evaporation technique

3. CHARACTERIZATION OF NANOEMULSIONS

A stable nanoemulsion is characterized by the absence of the internal phase, absence of creaming, absence of deterioration by microorganisms, and maintenance of elegance in respect of appearance, colour, odour and consistency. Hence the instability of emulsion can be classified as follows:

Flocculation and creaming

Flocculation consists of the joining together of globules to form large clumps or floccules, which rise or settle in the emulsion more rapidly than the individual globules. The rising up or settling down of dispersed globules to give a concentrated layer is known as creaming. Thus flocculation leads to creaming.

Creaming or Sedimentation of Emulsions This is the result of gravity, when the density of the droplets and the medium are not equal. When the density of the disperse phase is lower than that of the medium, creaming occurs, whereas if the density of the disperse phase is higher than that of the medium, sedimentation occurs.²³

Creaming or Sedimentation Rates

1) Very dilute emulsions ($\phi < 0.01$). In this case, the rate could be calculated using Stokes' law that balances the hydrodynamic force with gravity force

$$\text{Hydrodynamic force} = 6 \pi \eta_0 R v_0$$

$$\text{Gravity force} = \frac{4}{3} \pi R^3 \Delta \rho g$$

$$v_0 = \frac{2 \Delta \rho g R^2}{9 \eta_0}$$

v_0 is the Stokes' velocity and η_0 is the viscosity of the medium.

For an O/W emulsion with $\phi = 0.2$ in water ($\eta_0 \sim 10^{-3}$ Pa·s), the rate of creaming or sedimentation is $\sim 4.4 \times 10^{-5}$ ms⁻¹ for 10 μ m droplets and $\sim 4.4 \times 10^{-5}$ ms⁻¹ for 10 μ m droplets. This means that in a 0.1m container creaming or sedimentation of

the 10 μ m droplets is complete in ~ 0.6 h and for the 1 μ m droplets this takes ~ 60 h.

2) Moderately concentrated emulsions ($0.2 < \phi < 0.1$). In this case, one has to take into account the hydrodynamic interaction between the droplets, which reduces the Stokes velocity to a value v given by the following expression²⁴

$$v = v_0(1 - k \phi)$$

Where, k is a constant that accounts for hydrodynamic interaction. k is of the order of 6.5, which means that the rate of creaming or sedimentation is reduced by about 65%.

3) Concentrated emulsions ($\phi > 0.2$). The rate of creaming or sedimentation becomes a complex function of ϕ . This also shows the change of relative viscosity η_r with ϕ .

Flocculation is the result of van der Waals attraction that is universal for all disperse systems. The vander Waals attraction G_A was described before. G_A is inversely proportional to the droplet–droplet distance of separation h and it depends on the effective Hamaker constant A of the emulsion system. One way to overcome the Vander Waals attraction is by electrostatic stabilization using ionic surfactants, which results in the formation of electrical double layers that introduce a repulsive energy that overcomes the attractive energy. Emulsions stabilized by electrostatic repulsion become flocculated at intermediate electrolyte concentrations (see below). The second and most effective method of overcoming flocculation is by ‘steric stabilization’ using nonionic surfactants or polymers. Stability may be maintained in electrolyte solutions (as high as 1 mol dm⁻³ depending on the nature of the electrolyte) and up to high temperatures (in excess of 50 C) provided that the stabilizing chains (e.g., PEO) are still in better than $\phi < 0.5$ conditions ($\phi < 0.5$).

Flocculation of Electrostatically Stabilized Emulsions²⁵

As discussed before, the condition for kinetic stability is $G_{\max} > 25 kT$. When $G_{\max} < 5 kT$, flocculation occurs. Two types of flocculation kinetics may be distinguished: fast flocculation with no energy barrier and slow flocculation when an energy barrier exists. The fast flocculation kinetics was treated by Smoluchowski, who considered the process to be represented by second-order kinetics and the process is simply diffusion controlled. The number of particles n at any time t may be related to the final number (at $t = 0$) n_0 by the following expression

$$n = \frac{n_0}{1 + kn_0 t} \quad (1)$$

where k is the rate constant for fast flocculation that is related to the diffusion coefficient of the particles D , that is

$$k = 8 \pi D R$$

D is given by the Stokes–Einstein equation

$$D = \frac{kT}{6\pi\eta R} \quad (2)$$

Combining Eqs. (1) and (2)

$$k = \frac{4kT}{3\eta} = 5.5 \times 10^{-18} \text{ m}^3\text{s}^{-1} \text{ for water at } 25 \text{ C}$$

The half life $t_{1/2}$ ($n = (1/2)no$) can be calculated at various no or volume fraction

The slow flocculation kinetics was treated by Fuchs²⁶ who related the rate constant k to the Smoluchowski rate by the stability constant W

$$W = \frac{k_0}{k}$$

W is related to G_{max} by the following expression²⁷

$$W = \frac{1}{2} \text{Exp}(G_{max}/kT)$$

Cracking

Cracking of an emulsion refers to separation of the dispersed phase as a layer. Whereas a creamed emulsion may be reconstituted by shaking or agitation, a cracked emulsion cannot be corrected. Cracking represents permanent instability. Cracking of the emulsion may be due to: (1) addition of an emulgent of opposite nature, (2) decomposition or precipitation of emulgent, (3) addition of a common solvent in which both oily and aqueous phases are miscible, (4) extremes of temperature, (5) microorganisms, (6) creaming.

Ostwald Ripening²⁸

The driving force for Ostwald ripening is the difference in solubility between the small and large droplets (the smaller droplets have higher Laplace pressure and higher solubility than the larger ones).

The difference in chemical potential between different sized droplets was given by Lord Kelvin.

$$S(r) = S(\infty) \exp\left(\frac{2\gamma V_m}{rRT}\right)$$

Where, $S(r)$ is the solubility surrounding a particle of radius r , $S(\infty)$ is the bulk solubility, V_m is the molar volume of the dispersed phase, R is the gas constant, and T is the absolute temperature. The quantity $(2\gamma V_m/RT)$ is termed the characteristic length. It has an order of ~ 1 nm or less, indicating that the difference in solubility of a 1 μm droplet is on the order of 0.1% or less. Theoretically, Ostwald ripening should lead to condensation of all droplets into a single drop.

Emulsion Coalescence²⁹

When two emulsion droplets come in close contact in a flock or creamed layer or during Brownian diffusion, thinning and disruption of the liquid film may occur resulting in eventual rupture. On close approach of the droplets, film thickness fluctuations may occur – alternatively, the liquid surfaces undergo some fluctuations forming surface waves, as illustrated in The surface waves may grow in amplitude and

the apices may join as a result of the strong van der Waals attraction (at the apex, the film thickness is the smallest). The same applies if the film thins to a small value (critical thickness for Coalescence).

Phase inversion³⁰

It is the change in the type of emulsion from o/w to w/o and vice versa. It is the physical process. Phase inversion may be brought about by varying the phase volume ratio, addition of electrolytes, and temperature changes.

Evaluation of nanoemulsion:

Drug content:

The drug content of drug nanoemulsion formulation was measured using UV visible spectroscopic method. The 2 $\mu\text{g/ml}$ of aliquot was prepared using nanoemulsion formulation using diluting solvent. The samples were measured as 278.2 nm using UV VIS spectroscopic method. Results were taken in triplicate and the average was taken into consideration.³¹

Viscosity:

The viscosity was measured to determine rheological properties of formulations.

Brookfield Rheometer viscometer at 30°C with a CPE 61 spindle at 30 rpm was used to serve this purpose. Results were taken in triplicate and the average was taken in to consideration.³²

pH :

Another important parameter of nanoemulsion is pH. The excipients used in the formulation decide the pH of the final preparation and hence the route of administration. The change in the pH may affect the zeta potential of the formulation which in turn can affect the stability of preparation. The pH of the formulations was measured using digital pH meter. Results were taken in triplicate and the average was taken in to consideration.³³

Dilution test:

If the continuous phase is added in nanoemulsion, it will not crack or separate into phases. Maximum amount of water and oil were added to o/w and w/o formulations respectively and then inspected visually for clarity and phase separation. Here 50 and 100times aqueous dilution of the formulation were visually checked for phase separation and clarity. Results were taken in triplicate and the average was taken in to consideration.³⁴

Globule size and Zeta potential analysis:

Nanoemulsion formulation was diluted 50 times and 100 tomes with distilled water. The resultant samples were prepared by gentle agitation for 5 min using a magnetic stirrer. In addition, globule size distribution (PSD) and zeta potential of the final nanoemulsion were determined using dynamic light scattering technique by Malvern zetasizer (NANOZS). Results were taken in triplicate and the average was taken in to consideration.³⁵

Centrifugation:

This parameter was characterized to check the physical stability. The nanoemulsion system was centrifuged at 5000

rpm for 10 minutes to determine whether the system shows signs of creaming or phase separation. The system was observed visually for appearance.³⁶

Stability of Drug nanoemulsion:

Samples of Drug nanoemulsion formulations was sealed in ampoules and then placed in Stability chambers at different temperature conditions i.e., room temperature (25°C) and accelerated temperature (40±20°C) for 2 months. Duplicate samples were withdrawn at 0,1 and 2 months to evaluate their physical and chemical stabilities. The physical stability Was, evaluated by visual inspection for physical changes (such as phase separation and drug precipitation), and a globule size analyzer was used to determine the mean globule size and zeta potential after dilution with water. Chemical stability was expressed as the content of Drug determined by UV visible spectroscopic method at 257 nm.³⁷

In vitro drug release:

In vitro drug release for the nanoemulsion formulation should be done in order to measure and detect the formulation that releases the maximum amount drug release from the nanoemulsion formulation. This test was performed in 500 ml of Phosphate buffer pH7.4 using USP Dissolution apparatus Type II at 75 rpm and 37±0.5 °C. 2 ml of nanoemulsion formulation containing single dose 10mg of drug was placed in a dialysis bag (Himedia dialysis membrane150). Samples (5mL) were withdrawn at regular time intervals (0, 0.5, 1, 1.5, 2, 4, 6, 8 h) and an aliquot amount of phosphate buffer was replaced. The release of drug from nanoemulsion formulation was compared with the conventional tablet formulation (ZOCOR TM) and the suspension of pure drug. The samples were analyzed for the drug content using UV-Visible spectrophotometer at 416nm.³⁸

4. APPLICATIONS OF NANOEMULSIONS

Nanoemulsion never shows the creaming and sedimentation kind of problems due to its very small droplet size. These problems are very common with conventional emulsion and even microemulsion. Basically both problems are associated with the influence of gravitational force over the droplet of emulsion. But in case of nanoemulsion the droplet size is very small which minimized the working of gravitational force over the droplets and posses creaming and sedimentation of emulsion.

- Again small droplet size of nanoemulsion prevents the coalescence of droplets. In the coalescence process droplets come together and form a large droplet with increased size which is responsible for the instability of emulsion. But the small droplet size of nanoemulsion prevents the coalescence among them and prevents the deformation and then surface fluctuation.
- Dispersibility of nanoemulsion is very high as compared to microemulsion because small droplet size prevents the

flocculation of droplets and this process makes the system dispersed without separation.

- Nanoemulsion formulation provides a rapid penetration of active ingredients through skin due to the large surface area of droplets. Even sometimes it is found that nanoemulsion penetrate easily through rough skin. This property of nanoemulsion minimizes the additional utilization of special penetration enhancer which is responsible for incompatibility of formulation.
- Nanoemulsion formulation required low amount of surfactant compared to microemulsion. For example about 20- 25 % surfactant is required for the preparation of microemulsion but 5-10 % surfactant is sufficient in case of nanoemulsion. Again with the help of nanoemulsion surfactant utilization can be minimized.
- Nanoemulsion has a transparent and fluidity property which improves the formulation patient compliance and safe for administration due to the absence of any thickening agent and colloidal particles.

It is also reported that nanoemulsion may be used for the target delivery of active ingredient especially in cancer therapy.

- Nanoemulsion formulation may become the stable alternate for the liposomes and vesicle type of delivery systems.
- Nanoemulsion formulation can be administered by the various routes of body. There are various reported methods which support the administration of nanoemulsion formulation through paranteral³⁹⁻⁴², oral⁴³⁻⁴⁵, topical^{46, 47}, nasal⁴⁸ and ocular⁴⁹ route.
- These formulations may be used to increase the bioavailability of poor water soluble drug by developing oil in water type of nanoemulsion.

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Conflict of Interest: None

Source of Funding: Nil