NANO EMULSION: A PROMISING APPROACH IN TRANSDERMAL DRUG DELIVERY

Susheela S[1], Srinivas Hebbar [1*], Akhilesh Dubey[1], Amitha Shetty[1]

[1] Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.

ABSTRACT:

Nano emulsion is one of the most successful strategies for transdermal drug delivery and offers many advantages, such as higher storage stability, lower preparation costs, good manufacturing feasibility, thermodynamic stability, lack of organic solvents and no need for intensive sonication. When compared to emulsions, nano emulsions do not show any stability problems such as creaming, flocculation, coalescence, and sedimentation and has better appearance and consistency because of nano size range. Drug to be delivered topically is incorporated into oil phase and then incorporated in water phase along with surfactant/co-surfactant. After primary emulsion is formed the particle size is reduced by low energy process or high energy methods. It was observed that nano emulsions are better than emulsions or micro emulsions because of better stability and appearance and also shows good permeation and retention ability. This review focuses on nano emulsions including its properties, mechanism of action and formulation considerations with characterization parameters to study the effectiveness in drug delivery.

Keywords: Nano emulsion, transdermal drug delivery, mechanism of action, formulation, characterization.

Corresponding author

Srinivas Hebbar

INTRODUCTION

Transdermal drug delivery is an important and effective field of drug delivery and known for improving therapeutic effectiveness, bioavailability and preventing any adverse effects. In recent

years, there has been upward interest to improve skin permeation rate of the drug with the applications of nano or microemulsions. Nano emulsion (NE) is one of the most successful strategies which offers many advantages, such as higher storage stability, lower preparation costs, good manufacturing feasibility, thermodynamic stability, and lack of organic solvents. NE is a thermodynamically stable transparent or translucent dispersion of oil and water stabilized by a surfactant interface film usually in combination with a droplet size co-surfactant less than 100 nm [1]. NE is also developed to avoid creaming, flocculation, coalescence and sedimentation and to be more stable than normal emulsions [2].

Advantages of nano emulsion:

NE has grown in popularity as a delivery vehicle for pharmaceuticals and even cosmetics. The following are the reasons for this [3, 4]:

1. It can be used to increase the bioavailability of poorly water-soluble drugs.
2. Owing to its small droplet size, NE never causes creaming or sedimentation because smaller droplet size reduces the effect of gravitational force on the droplets so it does not allow for creaming and sedimentation.
3. NE tiny droplet size prevents the coalescence that is responsible for the emulsion's instability as well as prevents deformation and subsequent surface fluctuation.
4. NE has a much higher dispersibility than emulsion due to the smaller droplet size which prevents flocculation, so that drug disperses uniformly without separation.
5. In NE formulations, active ingredients penetrate the skin quickly. This property of NE decreases the need for additional penetration enhancers.
6. In comparison to microemulsions, NE needs a small amount of surfactant. For example, microemulsions preparation necessitates about 20-25 percent surfactant, while NE only 5-10 percent of surfactant. As a result, surfactant use can be also reduced.
7. NE have a translucent, fluid property that improves patient compliance and safety.
8. Liposomes and vesicle-based delivery systems can be replaced by NE formulations as a safe alternative.

Limitations of nano emulsion:

Although the NE formulation has many advantages, the smaller droplet size is often the reason for its restricted use. Some limitations of NE are as follows [3, 4]:

1. The manufacture of NE formulations is an expensive process since it involves a specific type of instruments and process methods. For example, the arrangement of homogenizers is a costly process.
2. NE stability is unacceptably low, posing a significant problem when storing formulations for extended periods of time. Ostwald ripening is the most common cause of unacceptability. This is because small droplets with a high rate of curvature have more solubility than large droplets with a low radius of curvature.

MECHANISM OF PENETRATION OF NANO EMULSION

The penetration of NE through the epidermal layer of the skin involves 4 different ways. The various routes are the transcellular, the intercellular, appendageal route through hair follicle with associated sebaceous glands, and via sweat glands. The transcellular and intercellular routes constitute the trans epidermal pathway [5]. The combined flux of these two pathways, lipid and pore, determines the overall observed flux across the skin. It is widely accepted that the trans epidermal pathway is usually the predominant pathway of skin permeation and that under sink conditions, diffusion across the stratum corneum constitutes the rate-limiting step that determines the overall flux of the permeant [6]. The figure 1 represents the various route for penetration of NE through skin and table 1 illustrates the mechanism of penetration of hydrophilic and hydrophobic drugs.

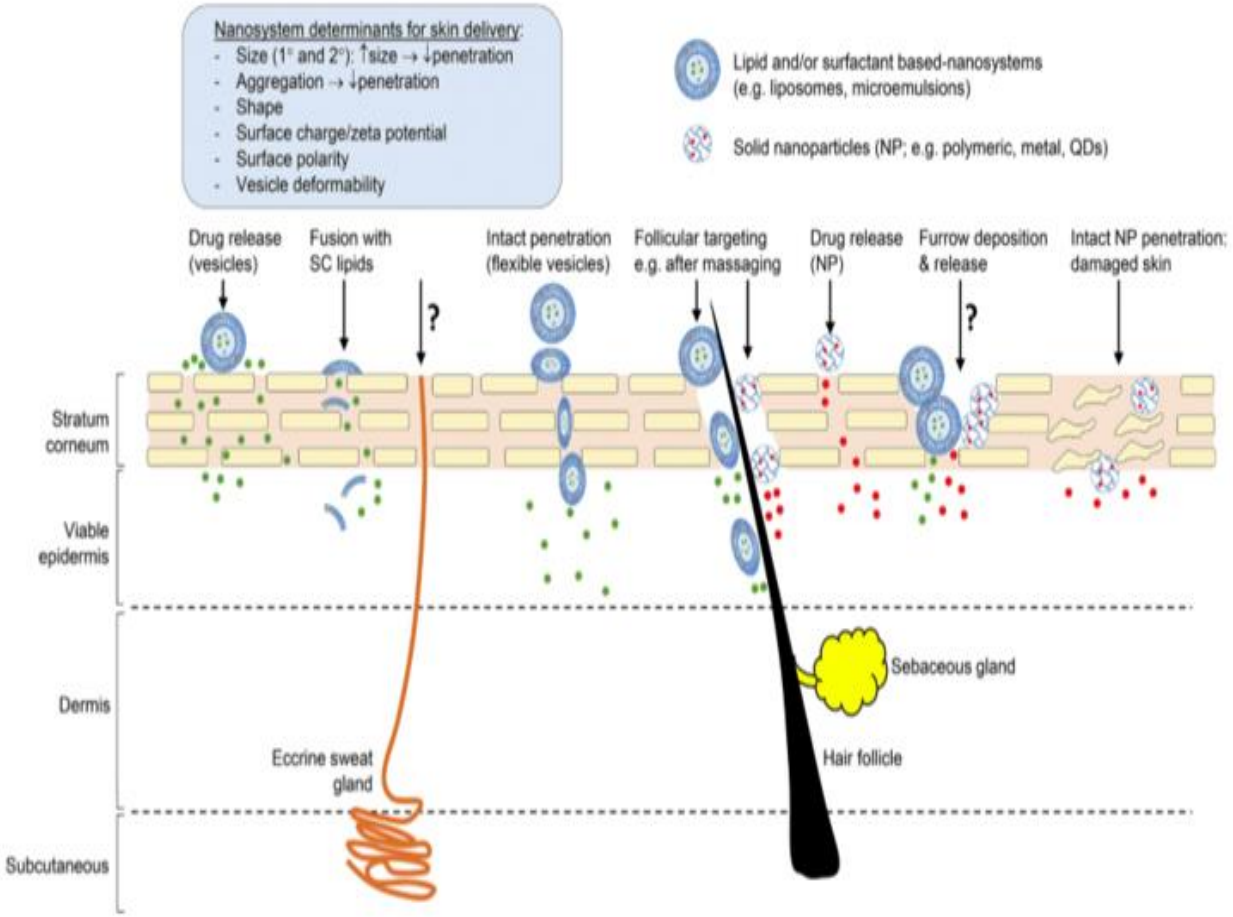

Figure 1: Schematic representation of various route for penetration of nano emulsion through skin

Table 1: Mechanism of penetration of hydrophilic and hydrophobic drugs through skin

Permeation of Hydrophilic drugs	Permeation of Hydrophobic drugs
Increasing thermodynamic activity of drugs	Stratum corneum lipid bilayer disruption
Modification of surface electrical charge of ionic drugs	Improvement of transdermal permeation through nano sizing oil droplets
Solubilization of sebum by NE components to facilitate follicular delivery	Binding to negatively charged skin
Transport of large water soluble molecules loaded in w/o NE via pore transport	Changing drug partition into skin layer
Transport of small water -soluble molecules loaded in o/w NE via follicular delivery	Dilation of intercellular channels of stratum corneum by hydrating skin

COMPONENTS OF NANO EMULSION

NE are commonly made up of: drug, oil/lipid, surfactant, co-surfactant, and aqueous phase [7] and excipients such as preservatives, buffers, stabilizers, antioxidants, polymers are added based on physicochemical properties of drug and oil [8].

Drug

The hydrophilic drugs will be dissolved in water phase and hydrophobic drugs will be dissolved in oil phase. The physicochemical and biological nature of the intended drug to be formulated determines the further selections of excipients.

Oil/Lipids

The oil phase is the most important excipient in a NE, because it plays major role in solubilizing hydrophilic drugs. 5- 20% part of o/w NE is made of oil/ lipid phase. The selection of oil is based on the balance between its drug solubility capacity and the emulsification tendency of the same to determine the bioavailability of active ingredients [8]. The selected oil should be primarily analysed for its compatibility with the particular route of administration. The short chain oils have low viscosity while the long chain oils form stable but larger particle NE. Hence the length of fatty acid is an important factor in determining the stability of NE [9]. The commonly used natural oils are sesame oil, cottonseed oil, coconut oil, rice bran oil, oleic acid, ethyl acetate etc.

Surfactants

Surfactants are the amphiphilic molecules; it stabilizes the NE and enhances the permeation through skin by retaining the globule size in nano range [10]. The permeation rate is enhanced by its ability to reversibly bind to keratin filaments and hence alters the diffusion coefficient. The stability of the NE is improved by reducing interfacial tension at oil-water interphase and

providing steric or electrostatic [11] or dual-steric stabilization [12] otherwise the individual globules might merge together and lead to phase separation [13]. The selection of surfactant or surfactant blend also influences the toxicity, pharmacokinetics and pharmacodynamics parameters [14]. The commonly used surfactants for transdermal formulations are tween 20, 40, 60, 80, Span 20, 40, 60 and 80 etc. Surfactants like sodium deoxycholate and cremophor EL (Polyoxyl-35 castor oil) have been used in marketed parenteral products [15, 16, and 17].

Co-surfactants

Co-surfactants are often used to supplement surfactants because it fit well in between structurally weaker areas, strengthening the interfacial film. Propylene glycol, polyethylene glycol, ethanol, transcutol IP, glycerine, ethylene glycol and propanol are all popular co-surfactants.

Preservatives, antioxidants and chemo protectants

The preservatives used in any NE should be of low toxicity, heat and storage stability, physical and chemical compatibility, fair cost, ease of availability, suitable odour, taste and colour and strong antimicrobial range. Since microorganisms live both in oil and water, the preservative chosen should achieve successful concentration in both phases. When exposed to sunlight, emulsified oil and lipids undergo autoxidation; many drugs used in NE are also highly susceptible to oxidative degradation. Unsaturated oils become rancid as they oxidize. If oxidation is to be avoided, synthetic lipids without the susceptible acyl group should be used. Since NE are always transparent, the entire spectrum of radiation, including visible and UV rays, can easily penetrate the oil layers and catalyse drug molecule photodegradation. To combat environmental degradation, chelating agents, pH stabilizers, UV protectants and other additives are often needed [18].

FORMULATION OF NANO EMULSION

The primary goal of the formulation is to achieve a droplet of size in the range of 100-600 nm and to provide a stable state. The preparation of NE necessitated a significant amount of energy and it can be provided by mechanical equipment or the chemical potential inherent in the product. Figure 2 illustrates the classification of various methods of formulation of NE.

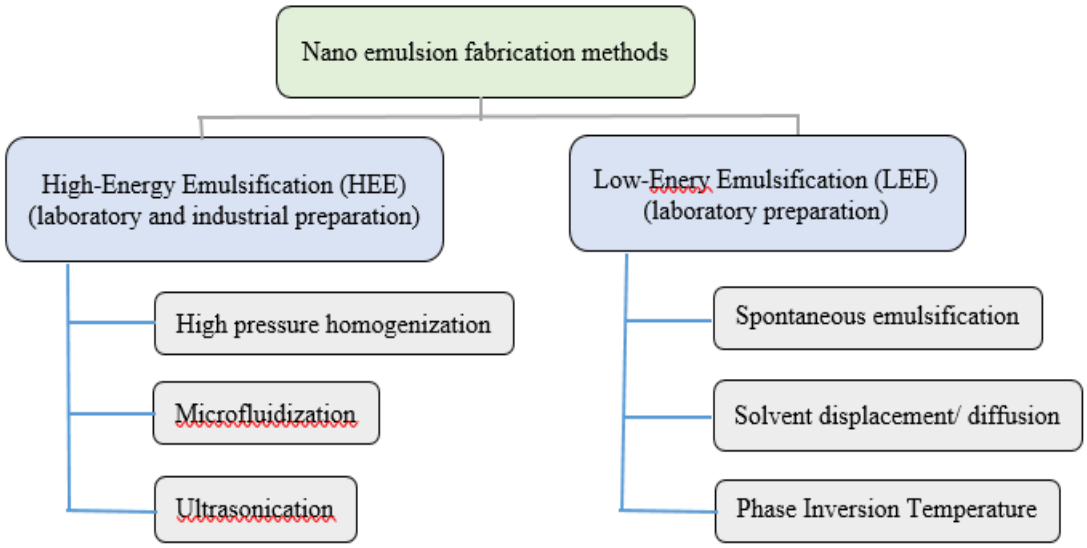

Figure 2: Classification of various methods of formulation of nano emulsion

High energy emulsification method:

Mechanical devices are used in high-energy methods to create powerful disruptive forces to reduce the droplet size. Ultra sonicators, microfluidizers, and high-pressure homogenizers, are industrially scalable, used to create disruptive forces. The fact that most of the oil can be subjected to nano emulsification adds to its versatility. Instrument expense and the generation of high operating temperatures are two major drawbacks, which may rule out thermolabile drugs in some cases.

High-pressure homogeniser:

This process is carried out by applying a high pressure over the oil-phase, aqueous phase, and surfactant or co-surfactant system. The pressure is exerted by an equipment known as

homogenizer. There are several issues with homogenizers, such as low productivity, component degradation due to difficult mass processing, and heat generation. Only oil in water (o/w) liquid NE of less than 20 % oil phase can be made with this technique, and high viscosity or hardness cream and it is not possible to prepare a cream-NE with a mean droplet size less than 200 nm.

Micro fluidisation:

A microfluidizer uses a combination of hydraulic shear, stress, attrition, impingement, heavy turbulence and cavitation to reduce size scale. A coarse emulsion is usually passed through a microfluidizer several times (sometimes up to 100 times) to achieve the desired size and dispersity.

Ultrasonication:

High-frequency sound waves are used in ultrasonication techniques (20 kHz and up). It can either be used to formulate a NE in real time or to shrink a pre-formed emulsion. A piezoelectric probe at the tip of a bench-top sonicator produces an extreme disparaging force. When ultrasonic waves are dipped into sample, then bubbles appear to expand until its break down. This mechanism generates shock waves that, in turn, produce a Jetstream of surrounding liquid, pressurizing and reducing the size of dispersed droplets. As compared to other high-energy processes, ultrasonication uses the least amount of energy.

Low energy emulsification method:

Low-energy emulsification methods were developed to formulate NE after the complete analysis of the oil, surfactants, co-surfactants, medicines, aqueous portion, hydrophilic-lipophilic balance of the oil surfactant mixture used, and operating temperature.

Spontaneous emulsification:

The process of making polymeric nanoparticles by nanoprecipitation is similar to spontaneous

emulsification by using oil instead of polymer. Two phases are involved, the first is a water-soluble surfactant containing phase, and the second is an organic phase containing an oil-soluble surfactant like span, and partially water-mixable organic solvent like ethyl acetate or acetone. To make nanoscale emulsion, the organic phase is applied dropwise to the aqueous stirred phase (although the opposite, i.e. adding water to oil is also possible in the case of w/o emulsions).

Phase inversion temperature method:

Phase inversion temperature method has advantage of changes in solubility of surfactant in aqueous and oil in response to temperature changes. It involves the regulated conversion of w/o to o/w emulsion or vice versa. The mixture of oil, water, and surfactant is heated to specific temperature, known as phase inversion temperature, and then rapidly cooled. The opening and reversal of the interfacial structure occurs when the temperature changes from low to high, resulting in phase inversion. After rapid quenching, the interfacial structure closes again, trapping oil or water. Thermosensitive drugs cannot be used in phase inversion temperature method due to the requirements for heat input [19].

EVALUATION PARAMETERS OF NANO EMULSION

NE are evaluated for various parameters such as:

1. Physico-chemical characterization of formulation involves macroscopic evaluation and microscopic evaluation, pH determination and electrical conductivity.
2. Thermo stability tests involves heating cooling cycle, centrifugation test, freeze thaw cycle, viscosity, transmission electron microscopy (TEM), droplet size, PDI and zeta potential and *in vitro* skin permeation studies.

Table 2 depicts in detail explanation of various evaluation parameters for NE.

Table 2: Various evaluation parameters for nano emulsion

Test	Instrument	Description	Significance
Physical- chemical characterization of formulation			
Macroscopic evaluation & microscopic evaluation	Microscope	Formulation observed with naked eyes & under microscope.	To determine the successful formation of the nano emulsion & morphology of globules
pH Value determination	pH meter	The pH meter dipped into the formulation.	pH of NE should be in the range 4- 6
Electrical conductivity	Conductivity electrode	The conductance electrode was dipped into the formulation at room temperature.	The electrical conductivity should be in the range 70- 75 µs/cm [20]
Thermo stability test			
Heating cooling cycle	Refrigerator	Formulation is kept in 4 ℃ & 45 ℃ in 3 cycles.	To determine the successful formation of the nano emulsion & morphology of globules & also to observe any instabilities or phase separation [21]
Centrifugation test	Centrifuge	3500 rpm for 30 minutes.	
Freeze thaw cycle	Refrigerator	Formulation kept in a temp range between -21 ℃ & +25 ℃.	
Viscosity	Rotational viscometer	The spindle rotation was adjusted to 100 rpm & shear rate to 100 s^{-1}.	Low viscosity nano emulsion has faster drug release & rapid penetration than high viscosity nano emulsion [22]
Transmission electron microscopy (TEM)		Negative staining of nano emulsion was done by using phosphotungstinic acid & then applied to the grid. An accelerating voltage of 20 kV was applied & the	To check the formulated nano emulsion has optimum size & shape in nano-range. It confirms if the droplets in formulation are uniformly distributed or not [23]

		quantitative measurement achieved.	
Droplet size, PDI & Zeta potential	Malvern zeta sizer		The lower PDI & the higher ZP, the greater resilience of nano emulsion against onward ripping & other destabilising properties. The diameter of the droplets should be in the range of 100 nm & the PDI should not exceed 0.5. Zeta potential around 20 mV is commonly associated with good physical stability [24]
In vitro skin permeation studies	Franz diffusion cell	Porcine ear skin was taken as the membrane. 32 ± 1 ℃.	To determine the amount of drug permeated & retained in a specified time period. [25]

MARKETED NANO EMULSION FORMULATIONS:

Table 3 gives the list of various NE formulations available in the market.

Table 3: The list of marketed available nano emulsion

Drug	Dispersed phase	Surfactant	Method	Purpose	Size (nm)
Turmeric oil	Turmeric oil	-	Spontaneous emulsification	Topical delivery against psoriasis	75-300
Lipophilic drugs	Soyabean oil	Soyabean lecithin, Tween 80, Poloxamer 407	Ultraturrax then HPH	Enhancing penetration	-
Tributyl phosphate	Soyabean oil	Triton *100	Spontaneous emulsification	Novel effective topical biocide	400-800
Ceramide	Sphingolipid	Lipoid	Ultraturrax followed by HPH	Alter skin permeability	210±18
Antisense oligonucleotide	MCT	Lipoid E-80 Poloxamer	HPH	Prevention of degradation up to 72h	95
Nimesulide	Caprylic/ capric triglyceride	Span 60	Spontaneous emulsification	Release of drug in viable layer of the skin	202-277
Tranexamic acid	Water	Tween 80	Spontaneous emulsification	Transfollicular transport	-

CONCLUSION

NE is one of the most promising techniques for transdermal delivery of drugs and presents many advantages like higher storage stability, lower preparation cost, and good production feasibility. The most effective, better and convenient NE are thermodynamically stable transparent or translucent dispersions of oil and water stabilized by an interfacial film of surfactant usually in combination with co-surfactant having the droplet size range of 20 – 100 nm. The smaller particle size range helps to permeate through the skin easily and retain in the skin and can provide a good activity with minimum drug dose. NE is made to prevent the occurrence of creaming, flocculation, coalescence, and sedimentation, as well as more stable than regular emulsions.

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CONFLICT OF INTEREST:

No conflict of interest.

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Authors:

First Author- Susheela S, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.

Second Author- Srinivas Hebbar, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.

Third author- Akhilesh Dubey, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.

Fourth author- Amitha Shetty, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.

Corresponding Author*
Srinivas Hebbar, Department of Pharmaceutics,
NGSM Institute of Pharmaceutical Sciences,
Nitte (Deemed to be University),
Paneer, Deralakatte, Mangaluru-575018,
Karnataka, India.