IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Nano Emulsion: A Versatile Mode For Transdermal Delivery Of Drugs

Guide: Dr. S. C. Atram

Associate professor, Department of pharmaceutics, vidyabharati college of pharmacy, Amravati -444602

Mukteshwari S. Giri, Jayashree Diwate, Diksha Ghorpade

ABSTRACT:

Medications on the market today shown a significant amount of first-pass metabolism and a limited oral bioavailability, which can be solved by creating transdermal drug delivery systems. By utilizing chemical enhancers and different solvents, it improves the drug's ability to penetrate the skin. Chemical enhancers should only be used sparingly for long-term applications since they can irritate the skin where they are applied. Therefore, it would be advantageous to use a topical vehicle rather than chemical enhancers when creating a transdermal medication delivery system. The improvement of drug transdermal absorption through the use of microemulsion or Nano emulsion technology has proven to be one of the most effective methods.

Keywords: Nano emulsion, Gel, Transdermal delivery.

INTRODUCTION:

This work aims to propose Nano emulsion as a novel formulation capable of addressing challenging pharmaceutical challenges such toxicity, first-pass metabolic impact, drug solubility, and bioavailability. With the use of nanotechnology in pharmaceutical formulations, there has been an improvement in the potential and delivery of drugs using Nano emulsions. Its potential as a special nanocarrier that mobilizes and encourages transdermal therapeutic delivery is being reviewed. Drug penetration through the skin is improved via transdermal drug delivery systems, which can be accomplished by using various solvents and chemical enhancers. Chemical enhancers should only be used sparingly for long-term applications since they can irritate the skin where they are applied. One of the most effective ways to increase the transdermal absorption of drugs into the skin is through the use of microemulsion or Nano emulsion technology. The current article provides a

brief overview of many antihypertensive medications that have been developed as transdermal gel, Nano emulsion, or microemulsion-based formulations, as well as their methods in detail to increase bioavailability and increase patient compliance. The stability and clarity of Nano emulsion, which is a type of multiphase colloidal dispersion, are typically used to describe it. The droplet size can be reduced to as little as a nanometer by applying strong shear, which is typically produced via microfluidic or ultrasonic methods. Numerous researches have been carried out to correlate the varied transdermal medication releases from various delivery modes. Numerous formulations, including solid lipid nanoparticles, Nano emulsions, and polymeric nanosuspensions, have been demonstrated in studies to be efficient transdermal delivery systems for a variety of drugs. [1,2] Due to its exceptional and significant advantages over conventional and oral administrations, scientific researchers have identified transdermal therapeutic delivery as a different option for drug administration. However, this research has been hampered by the "skin barricade," which poses a significant obstacle. It requires a unique formulation that can address and get over the challenges that come with it. Nanotechnology is one of the technological areas that is rapidly increasing. Transdermal drug administration through the skin is also discussed because the majority of innovative medication candidates, particularly those found through phytopharmaceuticals, have less systemic circulation. [2,3]

Nano emulsions: A novel drug delivery for transdermal treatment

Nano emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm molecules having a droplet size of less than 100 nm [3,4] as shown in (Fig 1).

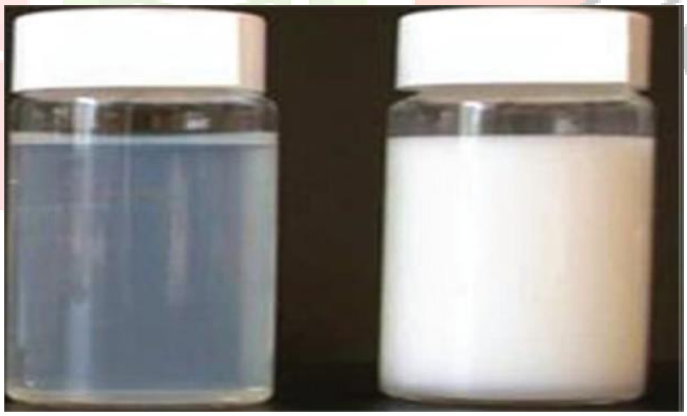

fig 1: picture of Nano emulsion (left) of size 35 nm and micro emulsion (right) of size 1µm. [4]

Nano emulsion formulations exhibit excellent transdermal and dermal distribution properties both in vitro and in vivo, according to a number of studies [5,6,7,8]. Nano emulsions have boosted the transdermal penetration of many medications over conventional topical formulations including emulsions and gels [3,4]. Since Nano emulsions are highly stabilized systems, the composition of the Nano emulsion is crucial to their formation and stabilization. Although the excipients of Nano emulsions themselves function as permeation enhancers, the formation and stabilization of Nano emulsion is the topic to be discussed. Therefore, employing non-irritating,

pharmaceutically acceptable components, the current work describes the potential of Nano emulsion systems in transdermal delivery of flurbiprofen. The correct oil, surfactant, and cosurfactants must be chosen. An explanation of the theory and This topic discusses the principle that underlies the development of the Nano emulsion. [9]

Transdermal Nano Emulsion Physical Characteristics:

According to McClements, NEs are a clear (translucent) liquid with a droplet size of less than 100 nm in a kinetically stable liquid colloidal dispersion system. [10] But he added that more recent research had identified a number of maximum limitations for NE particle size, including 200 and 500 nm. NEs have long-term physical stability that provides them unique properties and brings them closer to thermodynamic stability since they do not coalesce or flocculate [11]. A surfactant and a co-surfactant stabilize the aqueous and oil phases that make up NEs in a certain ratio [12]. The resistance to gravity of NE over conventional emulsion is one of its benefits.

Droplet sizes in the nanoscale range, separation, increased stability, and capacity to encapsulate additional medicines [13]. NEs have a much higher dispersibility than MEs because of the smaller droplet size that prevents flocculation and allows dispersion without separation [14]. NEs can be used to transport hydrophilic or lipophilic medications in water-in-oil (w/o) or oil-in-water (o/w) formulations, respectively [15].

o/w (oil-in-water) NE The bulk of products currently offered by pharmaceutical companies are lipophilic and only marginally soluble in water [16]. Recently, researchers' attention has turned to lipid nanotechnology-based systems such solid dispersions, solid lipid nanoparticles, liposomes, MEs, and NEs. These systems are also the most advanced commercial techniques and have enhanced drug solubilization, bioavailability, and carrying capacities. NE is a leading trend in transdermal drug delivery systems because it increases the bioavailability of poorly soluble medications and improves drug skin penetration when compared to alternative transdermal dose forms [16,17].

Oil-in-Water (without) NE

Less frequently than o/w NEs are type w/o NEs used for transdermal dispersion of hydrophilic substances. Even though its partitioning in the oil phase is unavoidable based on its oil-water partition coefficient, the drug resides in the water phase rather than the oil phase in the absence of NEs. The selection of surfactants in these preparations is based on an adequate hydrophile-lipophile balance (HLB) value because the medications used in this category are water-soluble [18]. The tension between the water phase and the oil phase is lowered as a result. This results in a stable formula.

Components of Transdermal Nano Emulsion:

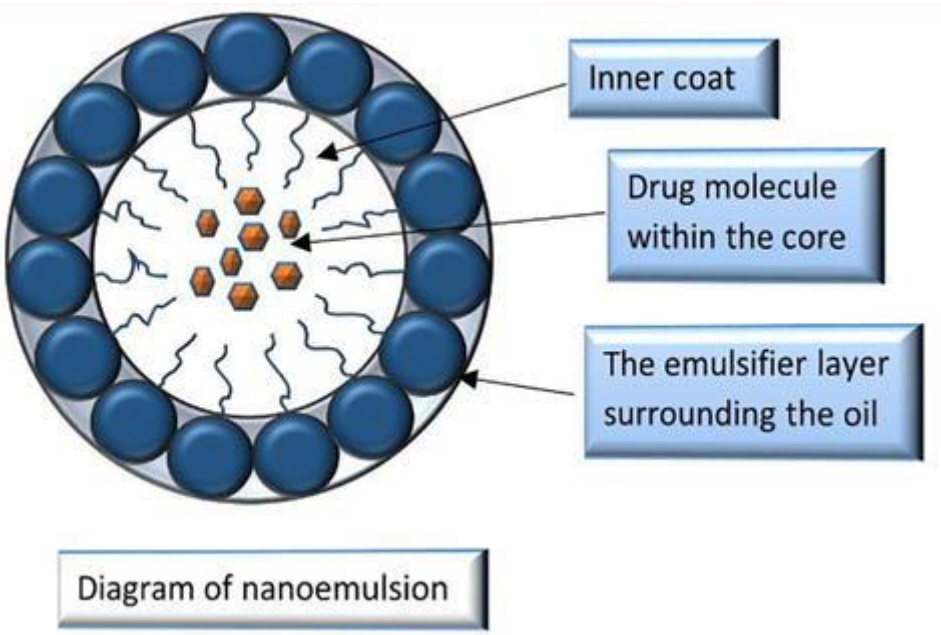

Fig 2: Diagrammatic representation of Nano emulsion [48]

1.Oil Phase

The typical oil phase employed in the composition of NEs is oleic acid (OA). OA has the intrinsic ability to improve penetration through this limiting and protective barrier because it causes the SC to absorb more water, expand, and degrade parts of its structural components [19]. Caproyl 90 [20] and isopropyl myristate are two more oils with permeability-improving qualities that have been mentioned in the literature.

2.Surfactants

Surfactants' ability to increase penetration through the skin is assumed to be due to their capability to reversibly bind to keratin filaments, which in turn disrupts corneocytes and alters the SC's diffusion coefficient [21,22,23]. These surfactants have the ability to fluidize SC lipids, which enhances drug absorption. These surfactants have the ability to fluidize SC lipids, which enhances drug absorption [24,25,26]. Their rate of growing penetration could be impacted by one of two distinct processes. The surfactant penetrates the SC and fluidizes, solubilizes, and extracts the lipid components starting with the intercellular regions [29]. A stronger interaction between keratin and lipids is exerted, for instance, by anionic surfactants, which enhances the ability of target molecules to permeate skin [27,28]. Furthermore, it's been proposed that sodium lauryl sulphate (SLS) alkyl chains have a role in the hydrophobic interaction with skin structures, exposing the surfactant's end sulphate group and creating extra bonding sites in the membrane, boosting skin moisture [30,31].

3. Co-Surfactants

A co-surfactant encourages the fluidity of the liquid-liquid interface by reducing interfacial tension by lowering its bending stress. The amount of alcohol needed to reach this minimum increase as the alcohol's alkyl chain gets shorter [32]. Medium-chain alcohols like n-butanol, n-hexanol, and n-pentanol are used to create NEs that have low interfacial tension between the water phase and the surfactant. The ability is constrained by longer alcohol chains [33]. The size and location of NEs can be significantly influenced by the presence of the surfactant and co-surfactant in the system [34], which can also change the stiffness and flexibility of the surfactant film and adopt different curvatures that are required to produce NEs over a wide range of compositions [35,36].

ADVANTAGES OF TRANSDERMAL NANOEMULSION:

1. It may be used in place of liposomes and vehicles.
2.It also makes the medication more bioavailable.
3. It is neither toxic nor irritant by nature.
4. As a result, physical stability has increased.
5. The surface area of the tiny droplets in Nano emulsions is high, which boosts absorption.
6. There are numerous ways to make it, including foams, creams, liquids, and sprays.
7. Capable of masking flavor.
8. Scaling up is easy and economical. [37]

DISADVANTAGES OF TRANSDERMAL NANOEMULSION:

1. Being limited in one's capacity to dissolve high malting material
2. The requirement for a high co- and surfactant concentration to stabilize the nanodroplets.
3. Pharmaceutical items must not contain any hazardous surfactants.
4. expensive process [37]

METHODS OF PREPARATION OF NANOEMULSION:

High Pressure Homogenization

This technique produces Nano emulsions with very minute particle sizes using a high-pressure homogenizer or piston homogenizer (up to 1 nm). The forces that combine in this process to produce Nano emulsions with exceedingly small droplet sizes include hydraulic shear, intense turbulence, and cavitation. A second round of high-pressure homogenization can be applied to the completed product to create a Nano emulsion with the desired droplet size and polydispersity index [38].

Micro fluidization

The unique mixing method known as micro fluidization employs a device known as a microfluidizer. The product is forced into the interaction chamber, which is made up of multiple microscopic channels known as "micro channels," using a high-pressure positive displacement pump (between 500 and 20,000 psi). Submicron-sized, incredibly small particles are produced as a result of the product flowing through the microchannels and onto the impingement area [39].

Phase Inversion Temperature Technique

Because of their small droplet sizes, Nano emulsions resist sedimentation and creaming, with Ostwald ripening acting as the main mechanism of breakdown [40]. Catastrophic inversion, which can also be brought on by modifying the surfactant's HLB number while maintaining a constant temperature using surfactant mixtures, and transitional inversion, which is brought on by changing variables that influence the system's HLB, such as temperature and/or electrolyte concentration.

Solvent Displacement Method

The organic solvent is taken out of the Nano emulsion using a suitable technique, such as vacuum evaporation. It has also been shown that spontaneous Nano emulsification occurs when an aqueous phase is mixed with a solution of organic solvents that contains a small quantity of oil. Solvent displacement methods allow for the production of Nano emulsions at room temperature with little stirring. As a result, pharmaceutical sciences researchers are using this technique to make Nano emulsions primarily for parenteral use [41].

Formulation of Nano emulsions:

1.Excipient Solubility Screening

It is feasible to evaluate the drug's solubility in various oils, surfactants, and cosurfactants by dissolving an excess amount of the medication in minor amounts of the chosen oils, surfactants, and cosurfactants and mixing them using a mixer. Allowing a mixture of oils to equilibrate at room temperature in an isothermal shaker can also reveal the solubility of the mixture [42].

2.Construction of Pseudo ternary Phase Diagram

Pseudo ternary phase diagrams are produced using the water titration method at room temperature in order to ascertain the permissible range of component concentrations for Nano emulsions [43]. On a pseudo ternary phase diagram, the aqueous phase is represented by one axis, the oil phase by the second, and the physical state of the Nano emulsions is represented by the third axis, which is a mixture of surfactant and cosurfactant at a specific weight ratio [44].

3. Nano emulsion Stability

A dosage form's chemical and physical integrity is referred to as its stability.

1. Screening for Excipient Solubility

   By dissolving a large amount of the medication in small amounts of the chosen oils, surfactants, and cosurfactants and mixing them using a mixer, it is possible to assess the drug's solubility in various oils, surfactants, and cosurfactants. The medication concentration in Nano emulsion formulations is assessed using HPLC stability-indicating methods while they are maintained at specified temperatures [45]. How much of the drug in the Nano emulsion formulation has been destroyed, and how much is still there? at every time interval.

Skin anatomy: The entire body's surface is covered by the complex organ known as the skin. It serves as a physical barrier between the body and the outside environment, preventing illnesses and bacteria from entering, reducing water and electrolyte loss, and limiting chemical penetration. Controlling body temperature and immune system activity need the skin. Autonomic nerves can sense messages thanks to their sensory receptors, which include touch, vibration, pressure, warmth, discomfort, and itching [46]. In cases of severe trauma, the dermis and epidermis separate, and a buildup of serous fluid results in blistering [47]. The stratum lucidum, stratum granulosum, stratum spinosum, and stratum Basale are examples of epidermis strata.

Dermis: The supple and elastic dermis' connective tissue-containing matrix is Collagen and tissue fibers are used to make elastic fibers. The elastic skin fibers in stretch marks and obesity break as a result of excessive straining. [48] The ability of collagen fibers to bind to water is what gives the skin its tension; but, as we get older, we lose this capacity, which results in wrinkles. The most important cells in the dermis are fibroblasts, macrophages, and mast cells. The areola and varying amounts of adipose tissue are located at the base of the innermost layer (fat). The dermis is composed of a variety of structures. [49,50]

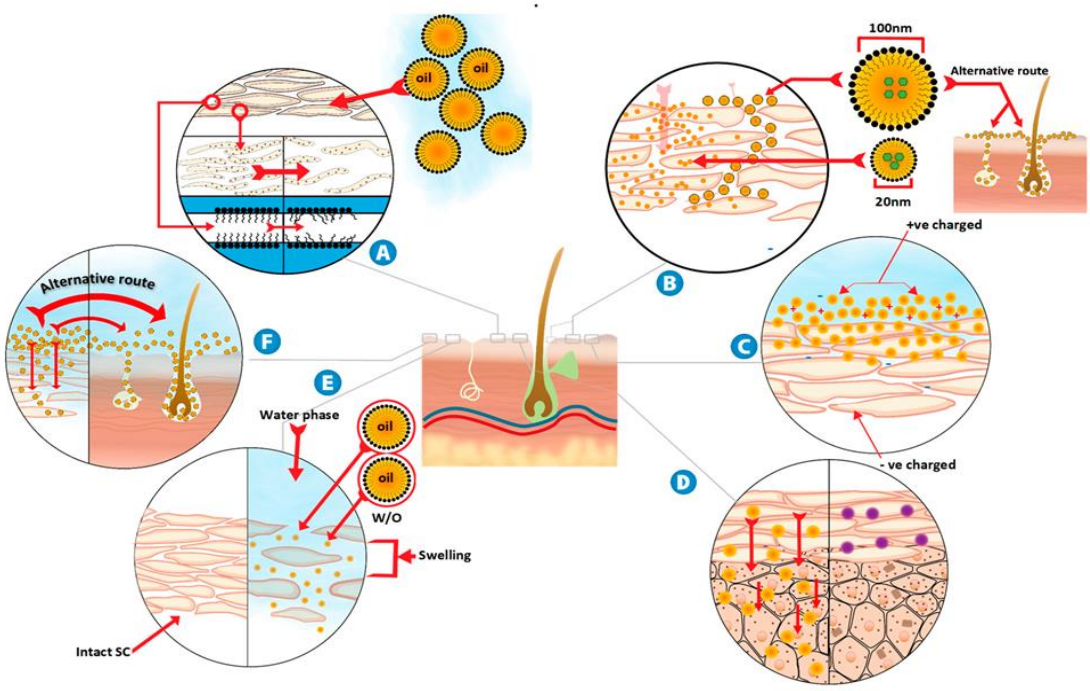

Fig 3: Transdermal enhancement of hydrophilic drugs from Nano emulsion [83]

GEL

Gels are categorized as semi-rigid systems where the movement of the dispersion medium is constrained by an interlacing three-dimensional network of dispersed phase particles or solvated macromolecules. The words "gel" and "jelly" have their roots in the Latin word's "gel" meaning "frost" and "glare," which mean "freeze" or "congeal," respectively. The term "gel" is derived from "gelatin." This genesis demonstrates the essential idea of the conversion of a liquid into a solid-like substance that does not flow but retains some liquid properties while being elastic. [51].

Fig4: Image of Gel [59]

In a perfect world, the gelling agent would be secure, inert, and incapable of interacting with other formulation elements. There must be no skin adhesion of the topical gel. When in the bottle or during topical application, the gelling agent should provide an acceptable solid-like quality that can quickly break when subjected to shear forces produced by tightening the tube and shaking it. They exhibit the characteristics of the solid-mechanical state [52].

Properties of gel: [53,54.55,56,57]

- The eye gel must be non-sticky and sanitary.
- The apparent viscosity or gel strength increases as the effective viscosity does. density of the crosslinks in the gel. However, a change in either the efficiency could result from a rise in temperature. Perceived viscosity is influenced by the molecular interactions between the solvent and polymer.
- When in storage, the gelling agent should generate a reasonable solid-like consistency that is easily broken when subjected to shear forces created by squeezing the tube, shaking the bottle, or applying topically.
- They demonstrate solid-state mechanical properties.
- When exposed to shear forces caused by squeezing the tube, shaking the bottle, or applying pressure to the topical gel at the time of topical administration or in the bottle, the gelling ingredient shall create a detectable solid-like character at the time of storage that is shortly shattered. [58,59]

Nano emulsion Evaluation:

Nano emulsions may become opaque over time due to an increase in droplet size. The elastic modulus and other phenomena related to the deformation of the droplets are frequently larger for Nano emulsions than for ordinary emulsions because the surface area to volume ratio of Nano emulsions is significantly higher than that of traditional emulsions. Nano emulsions require a larger concentration of surfactant to stabilize them than microscale emulsions, but less than lyotropic microemulsion phases in general because droplet surfaces in Nano emulsions have a great surface to volume ratio. Several Nano emulsion characterization parameters are covered in the following sections [60,61,62].

1. Nano emulsion morphology

Analyzing the morphology of Nano emulsions can be done using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). SEM [63] allows for the three-dimensional visualization of the globules. At various magnifications and an adequate accelerating voltage, usually 20 kV, the samples are examined. The surface morphology of the dispersion phase in the formulation can be effectively examined using SEM [64].

2.Zeta Potential, Polydispersity, and Nano emulsion Droplet Size

Dynamic light scattering, also known as photon correlation spectroscopy (PCS), is used to analyses the fluctuations in the intensity of scattering by droplets or particles due to Brownian motion [65,66]. Using a particle size analyzer, PCS may measure the zeta potential, polydispersity, and Nano emulsion droplet size. The polydispersity index [67] indicates the caliber or uniformity of the dispersion.

DN% denotes that the volume percentage of particles with sizes up to DN% equals N% (N = 10%, 50%, or 90%). (D90% D10%)/D50% is the span. The tighter the particle size distribution, the lower the span value. [67]

3. Viscosity Assessment

This is accomplished with a viscometer. The amount of surfactant, water, and oil in an emulsion determines how viscous it is. While adding more water decreases viscosity, reducing the amount of surfactant and cosurfactant lowers the interfacial tension between water and oil, increasing viscosity. For medicine release to be effective and stable, viscosity is essential. Monitoring of viscosity change is a method for assessing the stability of liquid and semi-solid preparations, including formulations for Nano emulsions. [67,68]

4. Studies on in vitro skin permeation

Once the skin of the ear or abdomen has been sliced, the underlying cartilage and lipids have been totally removed. Skin that has been cut to the proper size covers the diffusion cell that has previously been filled with receptor solution. The equipment is then turned on after the vesicular preparation samples have been placed on the skin's dorsal surface. At intervals of up to 24 hours, samples are removed from the receptor media and replaced with identical volumes of the medium. After that, drug penetration in the refilled samples is assessed by HPLC [69,70] or UV spectroscopy. A semi-permeable membrane like regenerated cellulose may be used in place of skin for in vitro release studies [71]. The equation: establishes the medication's flow J. across a membrane or skin.

$$J = D = dc/dx \quad (2)$$

The diffusion coefficient, D, relies on the size, shape, and flexibility of the diffusing molecule as well as the membrane resistance, where c is the concentration of the diffusing species and D is the coefficient [72]. The spatial coordinate is x.

5. Surface Properties and Thermodynamic Stability

Although a Nano emulsion and a Micro emulsion are both transparent and low viscosity systems, there is a significant difference between the two. A Nano emulsion is just slenderly more thermodynamically stable than a microemulsion [73]. Nano emulsions are more stable than microemulsions against sedimentation or creaming because of their small droplet size [74]. The two systems are quite unlike since self-assembly rather than mechanical shear is used to form microemulsion phases.

6. Thermodynamic Stability Studies:

Stability studies were conducted in order to address the issue with thermodynamic stability, and the results are as follows:

Heating Cooling Cycle:

A 48-hour heating and cooling cycle was carried out in a refrigerator with temperatures ranging from 4 to 45 degrees Celsius. A centrifuge test was performed on the formulations that remained stable at these temperatures.

Centrifugation:

The chosen formulations underwent a centrifugation examination for 30 minutes at 3500 rpm. For the freeze-thaw stress test, formulations without any phase separation were used.

Cycle of Freeze and Thaw

Three freeze-thaw cycles involving the storage of the formulation for at least 48 hours at each temperature were performed between 21°C and +25°C.Those formulations, which passed these thermodynamic stress tests, were selected for further study.

7. Refractive Index:

An Abbe-type refractometer was used to calculate the refractive index of drug-loaded formulations and placebo formulations (Macro Scientific Works, Delhi, India)

8. pH:

Using a digital pH meter that has been previously standardized, the apparent pH of the formulation was tested.

9. SEM: Scanning Electron Microscopy

Using scanning electron microscopy, the morphology and structure of the Nano emulsion were investigated. It was employed to make the shape and size of the Nano emulsion droplets apparent. A drop of the Nano emulsion was immediately applied to the grid of holes in the holey film for the observation [102].

Characterization tests performed for transdermal Nano emulsion:

1.Visual inspection

1.Naked eye visual inspection equipment Importance: To ascertain whether the NE was successfully formed. Rapid turbidity that can be seen visually is followed by the formation of clear, translucent NE. [103]

2.Viscosity

Rotational viscometer, equipment

Meaning: Low viscosity NE releases more quickly and penetrates the skin more quickly than high viscosity NE; typically, o/w NE have lower viscosities than w/o NE.

calculation of the torque required to rotate the paddle in the NE [104,105,106]

3.Morphology-

Transmission electron microscopy equipment (TEM)

Electron microscope for scanning (SEM)

Importance: To confirm that the droplets produced have adequate uniformity in their size and shape to be in the nanometer range. The NE sample is applied to the copper or carbon after being negatively stained with a

1% solution of phosphotungstic acid. Depending on the TEM or SEM model being utilized, coated grid. A quantitative measurement can be made along with the consistency and quality of the NE drops using the proper software and magnification and an accelerating voltage of typically 20 kV. [107,108,109]

4. Polydispersity index for particle size (PDI)

ZP spectroscopy, or zeta potential photon correlation (PCS)

Dynamic light scattering equipment (DLS)

NE homogeneity and dispersion, as well as the range and breadth of droplet size, are to be measured quantitatively. The more stable the NE is against onward ripping and other destabilizing forces, the lower the PDI value (0.2) and the greater the ZP. Size and size distribution are calculated using the data gathered from the dynamic light scattering of the droplets in the NE. The potential charge difference between the particles and the continuous phase, or ZP, is measured. [110,111,112]

5. A conductivity meter

for electro-conductivity equipment

Although there isn't a direct correlation between electrical conductivity and NE instability, this represents an early change in NE droplet size. The meter calculates the electrical conductance or current in the NE sample. The probe-equipped meter is inserted into the sample for measurement. Two electrodes inside the probe are subjected to a voltage applied by the meter. The overall electrical resistance of the sample's distributed particles results in a drop-in voltage that the meter measures. [113,114]

6. Index of Refraction

Tools: A refractometer

Strong evidence of homogeneity and the development of an isotropic NE. Comparing the refractive index (RI) of the NE with water (RI = 1.333), it can be seen that the NE is more uniform and transparent the closer its value is to that of water. [115,116]

7. Franz diffusion cell equipment

for in vitro skin permeation

To evaluate membrane retention or transcutaneous penetration.

Following the insertion of a variety of membranes, including artificial and animal model skin-excision membranes, a sample of NE is put into the donor compartment. A 7.4 pH phosphate buffer saline is used to replicate the blood stream in the Franz diffusion cell's receiver compartment. Then, it is heated to 37 °C while being agitated at 100 rpm. One milliliter of a sample is drawn manually or automatically, filtered, and then examined. utilizing HPLC or UV spectroscopy. Once the amount of medication released each hour has been established, the steady state flux (Jss) is computed using the equation Jss = P. CD, where CD is the donor chamber concentration and P is the permeability coefficient. [117]

8. Intact live animals

used for in vivo dermato-pharmacokinetic and pharmacodynamic research HPLC

Establishing a plasma drug concentration-time profile or evaluating a pharmacological drug impact are important. Applying NE to an animal's shaved skin. To determine how much of the medicine entered circulation, blood samples are taken at regular intervals, centrifuged, and the plasma is then examined using HPLC. Additionally, the pharmacological action of the medicine influences how the pharmacodynamics qualities of the NE are evaluated.[118,119,120]

9. Skin irritation

Equipment: Animals in motion (rats or rabbits)

Relevance: To ascertain whether or not NE caused inflammation.

The hairless skin of the experimental animals was uniformly dispersed with the formulation over a predetermined region over the groups of healthy animals. The application sites were evaluated using a visual scoring system, and the trial was typically run for 7 days. For 48 hours, the test locations were monitored to see if any erythema or edema developed following application. The Draize method was used to score skin irritation. [121,122]

Application of Nano emulsion:

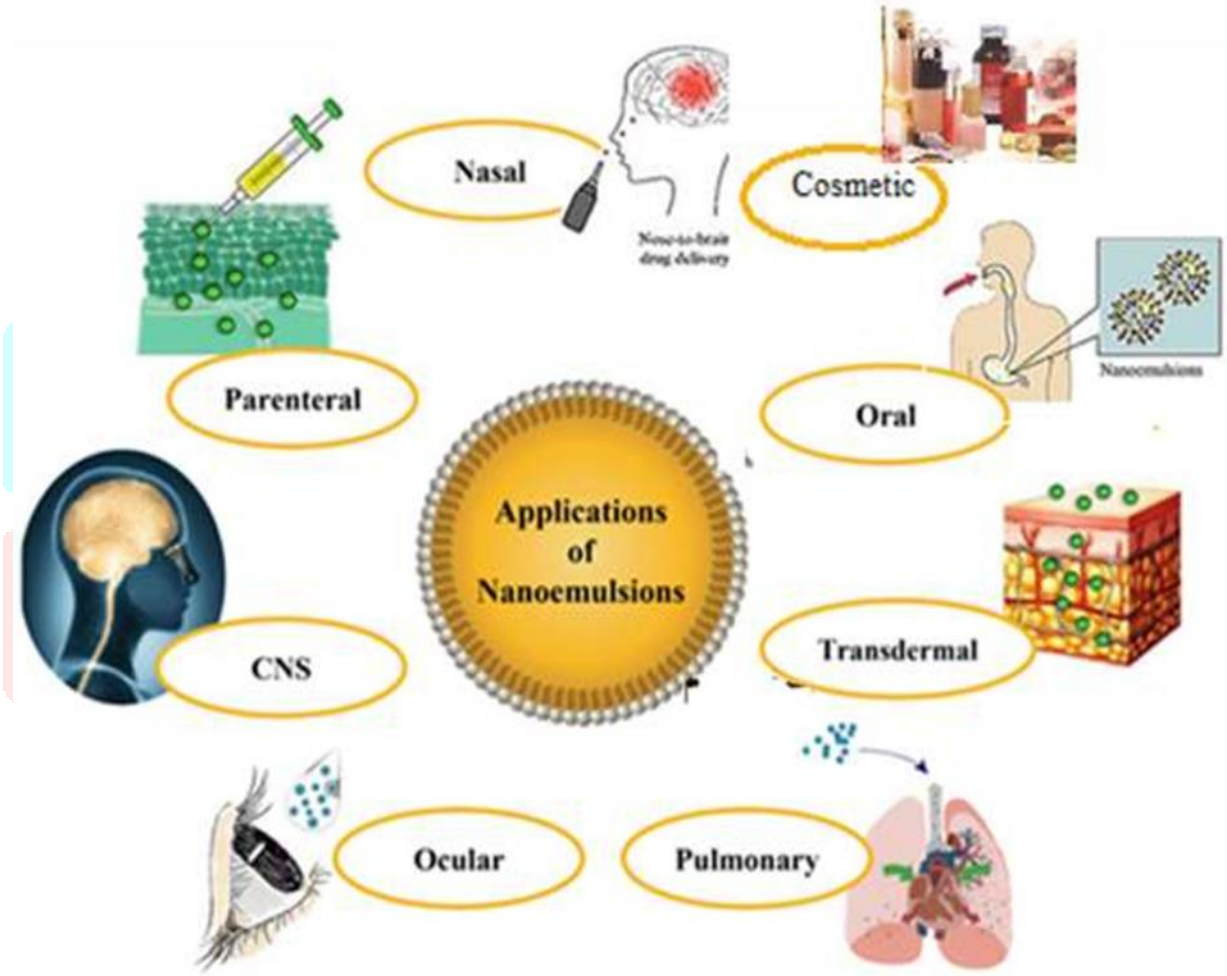

Fig 5: Application of Nano emulsion [84]

1. Target- or site-specific drug delivery methods can be utilized topically, parenterally, intranasally, or intravenously using Nano emulsion [75].

2. It is important to increase the water solubility of drugs that aren't particularly water soluble [76].

3. It is a state-of-the-art technique for avoiding the problem of first pass metabolism or presystolic metabolism and can provide a 100% bioavailability by flowing directly into systemic circulation [77].

4. Diabetes, Asthma, Hypersensitivity Reactions, Skin Infections, and Cancer (Brain, Lung, Breast, Ovarian, and Blood Cancer) are among the illnesses that can be treated using the Nano emulsion System [78, 79].

5. In the cosmetics business, the NE system also serves as an antibacterial NE system [80].

6. It's essential for preventing enzymatic and of biological and enzymatic drug degradation. [81]

7. It is also beneficial for biotechnology. [82]

List of drugs having its transdermal gel formulation

Drug name	**Formulation type**	**Authors name**
Amitriptyline	1. Transdermal gel 2. Topical gel	Dr. MA Scott et.al [85] D. F Thompson et.al [86]
Amlodipine besylate	Nanostructured lipid based nanogel	Kamble Meghana. S [87]
Atenolol	Ophthalmic gel	MA Hassan [88]
Benazepril HCL	1. Transdermal gel 2. Niosomal gel	Ameerah A. Radhi [89]
Budesonide	Oral gel	M. Bonnet [90]
Buspirone HCL	1. Nano vascular gel 2. Transferosomal gel	Dina M. Abdelnabi et.al [91] R. N. Shamma [92]
Chlorpheniramine Maleate	Nasal gel	Iman I. Soliman et.al [93]
Celecoxib	Topical gel	P. Karade [94]
Diltiazem	Transdermal gel	V. Sai Kishore [95]
Enalapril Maleate	Nanoproniosomal gel	M. Sabareesh et.al [96]
Famotidine	Insitu gel	D. Jorapur et.al [97]
Sildenafil citrate	1.Transdermal gel 2. Microemulsion loaded hydrogel	Mr. Hiren [98] A. Atipairin et.al [99]
Glibenclamide	Transdermal gel	Nosheen Anwar et.al [100]
Testosterone	Topical gel	Arver. S. et.al [101]

Conclusion:

Nano emulsion show a wide compatibility range with many drugs, the low toxicity of many of NE components makes this a very promising concept for future work in transdermal delivery system. Avoids the first pass hepatic metabolism, drug delivery can be easily eliminated in case of toxicity, dosing frequency get reduced which increases the patient compliance. Nano emulsion as a unique formulation that can address problematic pharmaceutical issues such toxicity, first-pass metabolic impact, drug solubility, and bioavailability. Reviewing its potential as a unique nanocarrier that mobilizes and encourages transdermal therapeutic delivery with the use of nanotechnology in pharmaceutical formulations, there has been an improvement in drug potential and delivery utilizing Nano emulsions. Special attention has been paid to the prospect of this drug travelling through the skin and its consideration as a multiple delivery technique. The Nano emulsion's extremely tiny droplets promote better medication absorption and targeting.

References:

1.Patel JK, Jani RK. Enhancing Effect of Natural Oils as Permeation Enhancer for Transdermal Delivery of Diltiazem Hydrochloride Through Wistar Rat Skin. skin. 2016; 6:15.

2. Oyelaja-Akinsipo OB, Dare EO, Oladoyinbo FO, Katare DP, Sanni LO, alayande so. nanoemulsion: a promising and novel nanotherapeutic vehicle for transdermal drug delivery application. journal of chemical society of nigeria. 2021 sep 6;46(4).

3. Shafiq S, Faiyaz S, Sushma T, Ahmad FJ, Khar RK, Ali M: Design and development of oral oil in water ramipril nanoemulsion formulation: in vitro and in vivo evaluation. J Biomed Nanotech, 2007; 3:28-44.

4. Shafiq S, Faiyaz S, Sushma T, Ahmad FJ, Khar RK, Ali M :Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm, 2007; 66:227-243.

5. Kemken J, Ziegler A, Muller BW: Influence of supersaturation on the pharmacodynamic effect of bupranolol after dermal administration using microemulsions as vehicle. Pharm Res 1992; 9:554-558.

6. Kreilgaard M: Dermal pharmacokinetics of microemulsion formulations determined by in-vitro microdialysis. Pharm Res 2001; 18:367-373.

7. Osborne DW, Ward AJ, and Neil KJ: Microemulsions as topical delivery vehicles: in-vitro transdermal studies of a model hydrophilic drug .J Pharm Pharmacol 1991; 43:450-454.

8. Dreher F, Walde P, Walter P, Wehrli E: Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. J Control Rel 1997; 45:131-140.

9. Kriwet K, Muller-Goymann CC: Diclofenac release from phospholipids drug systems and permeation through excised human stratum corneum. Int J Pharm 1995; 125:231-242.

10. McClements, D.J. Nanoemulsions versus microemulsions: Terminology, differences, and similarities.

11. Bouchemal, K.; Briançon, S.; Perrier, E.; Fessi, H. Nano-emulsion formulation using spontaneous emulsification: Solvent, oil and surfactant optimisation. Int. J. Pharm. 2004, 280, 241–251.

12. Suyal, J.; Ganesh, B. An introductory review article on nanoemulsion. J. Pharm. Pharm. Sci. 2017, 2, 35–40.

13. Montes de Oca-Ávalos, J.M.; Candal, R.J.; Herrera, M.L. Nanoemulsions: Stability and physical properties. Curr. Opin. Food Sci. 2017, 16, 1–6.

14. Sharma, N.; Bansal, M.; Visht, S.; Sharma, P.; Kulkarni, G. Nanoemulsion: A new concept of delivery system.Chron. Young Sci. 2010, 1, 2–6.

15.Barakat, N.; Fouad, E.; Elmedany, A. Formulation Design of Indomethacin-Loaded Nanoemulsion For Transdermal Delivery. Pharm. Anal. Acta 2011, 2, 1–8.

16. Shrestha, H.; Bala, R.; Arora, S. Lipid-Based Drug Delivery Systems. J. Pharm. 2014, 2014, 801820.

17. Kawakami, K.; Yoshikawa, T.; Moroto,Y.; Kanaoka, E.; Takahashi, K.; Nishihara, Y.; Masuda, K. Microemulsion formulation for enhanced absorption of poorly soluble drugs: I. Prescription design. J. Control. Release 2002.

18. Shakeel, F.; Ramadan, W. Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions. Colloids Surf. B Biointerfaces 2010, 75, 356–362.

19. Kogan, A.; Garti, N. Microemulsions as transdermal drug delivery vehicles. Adv. Colloid Interface Sci. 2006, 123, 369–385.

20. Mostafa, D.M.; Kassem, A.A.; Asfour, M.H.; Al Okbi, S.Y.; Mohamed, D.A.; Hamed, T.E.S. Transdermal cumin essential oil nanoemulsions with potent antioxidant and hepatoprotective activities: In-vitro and in-vivo evaluation. J. Mol. Liq. 2015, 212, 6–15.

21. Benson, H. Transdermal Drug Delivery: Penetration Enhancement Techniques. Curr. Drug Deliv. 2005, 2, 23–33.

22. Gupta, A.; Eral, H.B.; Hatton, T.A.; Doyle, P.S. Nanoemulsions: Formation, properties and applications. Soft Matter 2016, 12, 2826–2841.

23. Hosmer, J.; Reed, R.; Bentley, M.V.L.B.; Nornoo, A.; Lopes, L.B. Microemulsions Containing Medium-Chain Glycerides as Transdermal Delivery Systems for Hydrophilic and Hydrophobic Drugs. AAPS PharmSciTech

24. Mei, Z.; Chen, H.;Weng, T.; Yang, Y.; Yang, X. Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. Eur. J. Pharm. Biopharm. 2003, 56, 189–196.

25. Pandey, A. Role of Surfactants as Penetration Enhancer in Transdermal Drug Delivery System. J. Mol. Pharm. Org. Process Res. 2014, 2, 2–7.

26. Kitagawa, S.; Kasamaki, M.; Ikarashi, A. Effects of n-alkyltrimethylammonium on skin permeation of benzoic acid through excised guinea pig dorsal skin. Chem. Pharm. Bull. 2000, 48, 1698–1701.

27. Scheuplein, R.; Ross, L. Effects of surfactants and solvents on the permeability of epidermis. J. Soc. Cosmet. Chem. 1970, 21, 853–873.

28. Kouchak, M.; Handali, S. Effects of Various Penetration Enhancers on Penetration of Aminophylline Through Shed Snake Skin. Jundishapur J. Nat. Pharm. Prod. 2014, 9, 24–29.

29. Scott, R.; Guy, R.H.; Hadgraft, J. Prediction of Percutaneous Penetration: Methods, Measurements, Modelling. Scott, R.C., Richard, H., Guy, J.H., Eds.; IBC Technical Services: London, UK, 1990; ISBN 1852711175.

30. Breuer, M.M. The interaction between surfactants and keratinous tissues. J. Soc. Cosmet Chem. 1979, 30,41–64.

31. Froebe, C.L.; Simion, F.A.; Rhein, L.D.; Cagan, R.H.; Kligman, A. Stratum corneum lipid removal by surfactants: Relation to in vivo irritation. Dermatologica 1990, 181, 277–283

32. Gradzielski, M. Effect of the Cosurfactant Structure on the Bending Elasticity in Nonionic Oil-in-Water Microemulsions. Langmuir 1998, 14, 6037–6044.

33. Zana, R. Surfactant solutions: New methods of Investigation. In Surfuctant Solutions: New Methods of Investigation; Marcel Dekker Inc.: New York, NY, USA, 1979; pp. 2–51, ISBN 0824776232.

34. Yadav, S.A.; Singh, D.; Poddar, S. Influence of components of nanoemulsion system for transdermal drug delivery of nimodipine. Asian J. Pharm. Clin. Res. 2012, 5, 209–214.

35. Shafiq, S.; Shakeel, F.; Talegaonkar, S.; Ahmad, F.J.; Khar, R.K.; Ali, M. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur. J. Pharm. Biopharm. 2007.

36. Tenjarla, S. Microemulsions: An overview and pharmaceutical applications. Crit. Rev. Ther. Drug Carrier Syst. 1999, 16, 461–521.

37.Raj kumar Mishra and G.C .Soni ,Rekha Mishra,a novel drug delivery tool , int journal of pharmaceutical sciences review and research (2014).

38.Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015 Apr;5(2):123-7.

39. P. Shah, D. Bhalodia and P. Shelat, “Nanoemulsion: A Pharmaceutical Review,” Systematic Reviews in Phar- macy, Vol. 1, No. 1, 2010, pp. 2

40.C. Solans, P. Izquierdo, J. Nolla, N. Azemar and M. J. Garcia-Celma, “Nano-Emulsions,” Current Opinion in Colloid a4-32.

41. T. Tadros, P. Izquierdo, J. Esquena and C. Solans, “For-mation and Stability of Nanoemulsions,” Advances in Colloids and Interface Science, Vol. 108-109, 2004, pp. 303-318.

42.F. Shakeel, S. Baboota, A. Ahuja, J. Ali, M. Aqil and S.Copyright © 2011 SciRes. JBNB Current State of Nanoemulsions in Drug Delivery Copyright © 2011 SciRes. JBNB 639 Shafiq, “Nanoemulsions as Vehicles for Transdermal De-livery of Aceclofenac,” AAPS PharmSciTech, Vol. 8, No. 4, 2007, pp. 191-199. doi:10.1208/pt0804104

43.K. G. Pradip, J. Rita, M. U. Majithya and S. R. Rayassa, “Design and Development of Microemulsion Drug De-livery System of Acyclovir for Improvement of Oral Bioavailability,” AAPS PharmSciTech, Vol. 7, No. 3, 2006, pp. 1-6.

44.A. G. Floyd, “Top Ten Considerations in the Develop-ment of Parenteral Emulsions,” Pharmaceutical Science and Technology Today, Vol. 2, No. 4, 1999, pp. 134-143. doi:10.1016/S1461-5347(99)00141-8

45.F. Shakeel, S. Baboota, A. Ahuja, J. Ali, M. S Faisal and S. Shafiq, “Stability Evaluation of Celecoxib NanoemulSion Containing Tween 80,” Thailand Journal of Pharmaceutical Science, Vol. 32, 2008, pp. 4-9.

46.F. Shakeel, S. Baboota, A. Ahuja, J. Ali and S. Shafiq, “Skin Permeation Mechanism of Aceclofenac Using Novel Nanoemulsion Formulation,” Pharmazie, Vol. 63, No. 8, 2008, pp. 580-584.

47.S. Baboota, F. Shakeel, A. Ahuja, J. Ali and S. Shafiq, “Design Development and Evaluation of Novel Nanoemulsions Formulations for Transdermal Potential of Celecoxib,” Acta Pharmaceutica, Vol. 8, 2007, pp. 316- 332.

48. HimanshiTanwar, Ruchika sachdeva. Transdermal drug delivery system: A Review International journal of pharmaceutical science and research. 2016; 7(6): 2274-2290.

49. Vijay Kumar Singh, Praveen Kumar Singh, Purnendu Kumar Sharma, Peeyush Kumar Srivastava, Ashutosh Mishra. Formulation and evaluation of topical gel of Acelofenac containing piperine Indo American journal of pharmaceutical research. 2013; 3(7): 5266-5280.

50. Loveleen Preet Kaur, Tarun Kumar Guleri. Topical gel: A Recent Approach for novel drug delivery Asian Journal of Biomedical and pharmaceutical science. 2013; 3(17): 1-5.

51. Loyd VA., et al. "Ansel's pharmaceutical dosage forms, and drug delivery systems. 9th ed. Philadelphia: Lippincott Williams & Will-DNS; (2011).

52. Ofner CM., et al. "Encyclopedia of Pharmaceutical Technology". Informa Healthcare (2007): 1875-1890.
53. Cooper and Gunn. "Disperse systems. In Carter SJ, editor. Tutorial Pharmacy". CBS Publishers and Distributors (2000): 68-72.

54. Martin Sinko PJ and Singh Y. "Martin's Physical Pharmacy and Pharmaceutical Sciences". 6th ed. Philadelphia: Lippincott Williams &Willdns (2006): 430.

55. http://en.wikipedia.org [Internet]. Gel [updated 2014 December 13]. Available from:http://en.wikipedia.org/wiki/Gel.

56. Carter SJ. Disperse system. In: Cooper and Gunn's Tutorial Pharmacy. 6th ed. New Delhi: CBS Publishers and Distributors; 2000, 68-72.

57. Zatz JL and Kushla GP. Gels. In: Lieberman HA, Rieger MM and Banker GS. Pharmaceutical dosage form: Disperse system, 2nd ed. New York: Marcel Dekker; 2005, 399-421.

58. Niyaz BB., et al. "Formulation and evaluation of Gel containing Fluconazole-Antifungal agent". International Journal of Drug Development and Research 3.4 (2011): 109-128.

59. Global Transdermal Gel Market Booming Worldwide to Show Significant Growth by 2026| Boehringer Ingelheim International GmbH, Mylan N.V., Norvartis AG, GlaxoSmithKline plc., Novel Pharmaceutical Labs

60 H. S. Ruth, D. Attwood, G. Ktistis and C. Taylor, "Phase Studies and Particle Size Analysis of Oil-in-Water Phos-pholipid Microemulsions," International Journal of Pharmaceutics, Vol. 116, No. 2, 1995, pp. 253-261. doi:10.1016/0378-5173(94)00316-W

61 X. Li, N. Anton, T. M. C. Ta, M. Zhao, N. Messaddeq and T. F. Vandamme, "Microencapsulation of Nano-emulsions: Novel Trojan Particles for Bioactive Lipid Molecule Delivery," International Journal of Nanomedi-cine, Vol. 2011, No. 6, 2011, pp. 1313-1325.

62.T. G. Mason, S. M. Graves, J. N. Wilking and M. Y. Lin, "Extreme Emulsification: Formation and Structure of Nanoemulsions," Journal of Physics and Condensed Matter, Vol. 9, No. 1, 2006, pp. 193-199.

63. J. B. Kayes, "Disperse Systems," In: M. E. Aulton, Ed., Pharmaceutics the Science of Dosage Form Design, 1st Edition, Churchill Livingstone, Edinburgh, 1999, pp. 81-118, 571.

64. M. J. Barea, M. J. Jekins, M. H. Gaber, et al., "Evaluation of Liposomes Coated with a pH Responsive Polymer," International Journal of Pharmaceutics, Vol. 402, No. 1, 2010, pp. 89-94.

65. N. A, Samah, N. Williams and C. M. Heard, "Nanogel Particulates Located within Diffusion Cell Receptor Phases Following Topical Application Demonstrates Up-take into and Migration Across Skin," International Journal of Pharmaceutics, Vol. 401, No. 1-2, 2010, pp. 72-78. doi:10.1016/j.ijpharm.2010.08.011

66.H. S. Ruth, D. Attwood, G. Ktistis and C. Taylor, "Phase Studies and Particle Size Analysis of Oil-in-Water Phos-pholipid Microemulsions," International Journal of Pharmaceutics, Vol. 116, No. 2, 1995, pp. 253-261. doi:10.1016/0378-5173(94)00316-W

67.X. Li, N. Anton, T. M. C. Ta, M. Zhao, N. Messaddeq and T. F. Vandamme, "Microencapsulation of Nano-emulsions: Novel Trojan Particles for Bioactive Lipid Molecule Delivery," International Journal of Nanomedi-cine, Vol. 2011, No. 6, 2011, pp. 1313-1325.

68.Y. Agrawal, K. C. Petkar and K. K. Sawant, "Develop-ment, Evaluation and Clinical Studies of Acitretin Loaded Nanostructured Lipid Carriers for Topical Treatment of Psoriasis," International Journal of Pharmaceutics, Vol. 401, No. 1-2, 2010, pp. 93-102. doi:10.1016/j.ijpharm.2010.09.007

69. E. Touitou, N. Dayan, L. Bergelson, et al., "Ethosomes— Novel Vesicular Carriers for Enhanced Delivery: Charac-terization and Skin Penetration Properties," Journal of Controlled Release, Vol. 65, No. 3, 2000, pp. 403-418. doi:10.1016/S0168-3659(99)00222-9

70.E. R. Bendas and M. I. Tadros, "Enhanced Transdermal Delivery of Salbutamol Sulfate via Ethosomes," AAPS PharmSciTech, Vol. 8, No. 4, 2007, pp. 214-220.

71.S. Jain, A. K. Tiwary, B. Sapra, et al., "Formulation and Evaluation of Ethosomes for Transdermal Delivery of Lamivudine," AAPS PharmSciTech, Vol. 8, No. 4, 2007, pp. 249-257. doi:10.1208/pt0804111

72.V. Dave, D. Kumar, S. Lewis, et al., "Ethosome for En-hanced Transdermal Drug Delivery of Aceclofenac," In-ternational Journal of Drug Delivery, Vol. 2, 2010, pp. 81-92. doi:10.5138/ijdd.2010.0975.0215.02016

73. S. Shafiq, S. Faiyaz, T. Sushma, F. J. Ahmad, R. K. Khar and M. Ali, "Development and Bioavailability Assess-ment of Ramipril Nanoemulsion Formulation," European Journal of Pharmaceutics and Biopharmaceutics, Vol. 66, No. 2, 2007, pp. 227-243. doi:10.1016/j.ejpb.2006.10.014

74. S. Amselem and D. Friedman, "Submicron Emulsions as Drug Carriers for Topical Administration," In: S. Benita, Ed., Submicron Emulsions in Drug Targeting and Deliv-ery, The Netherlands, Harwood Academic Publishers, Amsterdam, 1998, pp. 153-173.

75. Abolmaali S.S, Tamaddon A.M., Farvadi F.S., Daneshamuz S., Moghimi H., Pharmaceutical Nanoemulsions and Their Potential Topical andTransdermal Applications. IJPS. 2011; 7(3):139-150.

76.Sapra K., Sapra A., Singh S.K, Kakkar S. Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs. Indo Global Journal of Pharmaceutical Sciences.2012; 2(3): 313-332.

77. Qian C., Decker E.A., Xiao H and McClements D.J. Nanoemulsion delivery systems: Influence of carrier oil on b-carotene Bioaccessibility. Food Chemistry. 2012; 135:1440-1447.

78. Kumar M., Misra A., Babbar A.K., Mishra A.K., Mishra P., Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of Risperidone. International Journal of Pharmaceutics.

79. Ragelle H., Seguin J., Brossard D., Scherman D., Arnaud P., Guy G. Chabot, et al., Nanoemulsion formulation of fisetin improves bioavailability and antitumour activity in mice. International Journal of Pharmaceutics. 2012; 427:452-459.

80. Hamouda T., Myc A., Donovan B., Shih A. Y., Reuter J. D., Baker J. R. A novel surfactant nanoemulsion with a unique non-irritant topical antimicrobial activity against bacteria, enveloped viruses and fungi. Microbiol. Res. 2001; 156:1-7. (antimicrobial)

81.Mishra N., Srivastava S. New Strategy for Solubilization of poorly soluble drug-SEDDS. Der Pharmacia Lettre. 2009; 1(2):60-67.

82.Nanoemulsion: A Review on Mechanisms for the Transdermal Delivery of Hydrophobic and Hydrophilic Drugs by Dalia S. Shaker 1ORCID,Rania A. H. Ishak 2ORCID,Amira Ghoneim 1,* andMuaeid A. Elhuon [skin fig]

83. Reza KH. Nanoemulsion as a novel transdermal drug delivery system. International journal of pharmaceutical sciences and research. 2011 Aug 1;2(8):1938.

84.Rana Abu-Huwaij,Sarah F. Al-Assaf,Rania Hamed Recent exploration of nanoemulsions for drugs and cosmeceuticals delivery First published: 28 December 2021

85. Scott MA, Letrent KJ, Hager KL, Burch JL. Use of transdermal amitriptyline gel in a patient with chronic pain and depression. Pharmacotherapy. 1999 Feb;19(2):236-9. doi: 10.1592/phco.19.3.236.30922. PMID: 10030776.

86.Thompson DF, Brooks KG. Systematic review of topical amitriptyline for the treatment of neuropathic pain. J Clin Pharm Ther. 2015 Oct;40(5):496-503. doi: 10.1111/jcpt.12297. Epub 2015 Jun 7. PMID: 26059975.

87.Kamble, Meghana S.; Dange, Sandeep M.; Bhalerao, Kishor K.; Bhosale, Ashok V.; Nanjwade, Basavaraj K.; Shinde, Saurabh A.; Chaudhari, Pravin D. Journal of Bionanoscience, Volume 9, Number 1, February 2015, pp. 22-27(6)

88.Hassan MA. A long acting ophthalmic gel formulations of atenolol. Drug Dev Ind Pharm. 2007 Nov;33(11):1192-8. doi: 10.1080/03639040701377433. PMID: 18058315.

89. Ameerah a. Radhi Assistant Lecturer, Department of Pharmaceutics, College of Pharmacy, University of Al-Mustansiryah, Baghdad, Iraq Jun 2018

90.Mathilde Bonnet*, Marine Dermu, Clara Roessle, Marc Bellaiche, Tarik Abarou,Véronique Vasseur, Samira Benakouche and Thomas StormeFormulation of a 3-months Stability Oral ViscousBudesonide Gel and Development of an IndicatingStability HPLC Method.

91.Abdelnabi DM, Abdallah MH, Elghamry HA. Buspirone Hydrochloride Loaded In Situ Nanovesicular Gel as an Anxiolytic Nasal Drug Delivery System: In Vitro and Animal Studies. AAPS PharmSciTech. 2019 Mar 4;20(3):134. doi: 10.1208/s12249-018-1211-0. PMID: 30830481.

92.Shamma RN, Elsayed I. Transfersomal lyophilized gel of buspirone HCl: formulation, evaluation and statistical optimization. J Liposome Res. 2013 Sep;23(3):244-54. doi: 10.3109/08982104.2013.801489. Epub 2013 May 28. PMID: 23713516

93. Iman I. Soliman, Nadia A. Soliman & Ebtsam M. Abdou (2010) Formulation and stability study of chlorpheniramine maleate nasal gel, Pharmaceutical Development and Technology, 15:5, 484-491, DOI: 10.3109/1083745090328654

94.Karade P. formulation and evaluation of celecoxib gel. jddt [Internet]. 14May2012 [cited 2Dec.2022];2(3). Available fromhttps://jddtonline.info/index.php/jddt/article/view/148

95.Formulation and evaluation of transdermal gels of diltiazem hydrochloride July 2008 T.E. Gopala Krishna Murthy, V Sai Kishore Bapatla College of Pharmacy

96.Sabareesh, m., j. P. Yanadaiah, and k. B. C. Sekhar. “a novel vesicular approach for transdermal administration of enalapril maleate loaded nanoproniosomal gel: formulation, ex vivo evaluation and in vivo antihypertensive study”. International Journal of Applied Pharmaceutics, vol. 12, no. 5, Sept. 2020, pp. 190-02, doi:10.22159/ijap.2020v12i5.38463.

97.Devika Jorapur, Nagesh C, Suma N, Chandrasekhara S, Sunil L Attimarad, Savitha Kengeri. Ion Sensitive Floating in Situ Gel for Controlled Delivery of Famotidine and Domperidon Maleate for the Treatment of Gastro Oesophageal Reflux Disease. Research J. Pharm. and Tech 2018; 11(5):1984-1989. doi: 10.5958/0974-360X.2018.00369.4

98.Hiren Patel, M. Panchal, S. Shah ,K.R.Vadalia "Formulation and Evaluation of Transdermal Gel of Sildenafil Citrate" Int. J. of Pharm. Res. & All. Sci.2012; Volume 1, Issue 3,103-118

99.Atipairin A, Chunhachaichana C, Nakpheng T, Changsan N, Srichana T, Sawatdee S. Development of a Sildenafil Citrate Microemulsion-Loaded Hydrogel as a Potential System for Drug Delivery to the Penis and Its Cellular Metabolic Mechanism. Pharmaceutics. 2020 Nov 4;12(11):1055. doi: 10.3390/pharmaceutics12111055. PMID: 33158184; PMCID: PMC7694282.

100.Formulation and evaluation of glibenclamide gel for transdermal drug delivery nosheen anwar syed umer jan, rehman gul

101.Arver S, Stief C, de la Rosette J, Jones TH, Neijber A, Carrara D. A new 2% testosterone gel formulation: a comparison with currently available topical preparations. Andrology. 2018 May;6(3):396-407. doi: 10.1111/andr.12487. Epub 2018 Mar 30. PMID: 29600542.

102. Haritha P, Basha S.P, Rao K and Chakravarthi P. A brief introduction to methods of preparation, applications and characterization of nanoemulsion drug delivery systems. Indian Journal of Research in Pharmacy and Biotechnology. 1(1); 2015: 25-28.

103. Sharma N, Mishra S ,Sharma S and Deshpande R. Preparation and Optimization of Nanoemulsions for targeting Drug Delivery. Int J of Pharma Professional Res 5(4); 2013:37-48.

104. Halnor, V.; Pande, V.; Borawake, D.; Nagare, H. Nanoemulsion: A Novel Platform for Drug Delivery System. J. Mater. Sci. Nanotechnol. 2018, 6, 104–115.

105. Chiesa, M.; Garg, J.; Kang, Y.T.; Chen, G. Thermal conductivity and viscosity of water-in-oil nanoemulsions. Colloids Surf. A Physicochem. Eng. Asp. 2008, 326, 67–72.

106. Nakabayashi, K.; Amemiya, F.; Fuchigami, T.; MacHida, K.; Takeda, S.; Tamamitsu, K.; Atobe, M. Highly clear and transparent nanoemulsion preparation under surfactant-free conditions using tandem acoustic emulsification. Chem. Commun. 2011, 47, 5765–5767.

107.Kwon, S.S.; Kong, B.J.; Cho, W.G.; Park, S.N. Formation of stable hydrocarbon oil-in-water nanoemulsions by phase inversion composition method at elevated temperature. Korean J. Chem. Eng. 2015, 32, 540–546.

108. Mason, T.G.; Graves, S.M.; Wilking, J.N.; Lin, M.Y. Extreme emulsification: Formation and structure of nanoemulsions. Condens. Matter Phys. 2006, 9, 193–199.

109. Samah, N.A.; Williams, N.; Heard, C.M. Nanogel particulates located within diffusion cell receptor phases following topical application demonstrates uptake into and migration across skin. Int. J. Pharm. 2010, 401, 72–78. [Google Scholar] [CrossRef] [PubMed]

110.Preetz, C.; Hauser, A.; Hause, G.; Kramer, A.; Mäder, K. Application of atomic force microscopy and ultrasonic resonator technology on nanoscale: Distinction of nanoemulsions from nanocapsules. Eur. J. Pharm. Sci. 2010, 39, 141–151.

111. Li, X.; Anton, N.; Ta, T.M.C.; Zhao, M.; Messaddeq, N.; Vandamme, T.F. Microencapsulation of nanoemulsions: Novel Trojan particles for bioactive lipid molecule delivery. Int. J. Nanomed. 2011, 6, 1313–1325.

112. Khurana, S.; Jain, N.K.; Bedi, P.M.S. Nanoemulsion based gel for transdermal delivery of meloxicam: Physico-chemical, mechanistic investigation. Life Sci. 2013, 92, 383–392.

113. Saint Ruth, H.; Attwood, D.; Ktistis, G.; Taylor, C.J. Phase studies and particle size analysis of oil-in-water phospholipid microemulsions. Int. J. Pharm. 1995, 116, 253–261.

114. Bernardi, D.S.; Pereira, T.A.; Maciel, N.R.; Bortoloto, J.; Viera, G.S.; Oliveira, G.C.; Rocha-Filho, P.A. Formation and stability of oil-in-water nanoemulsions containing rice bran oil: In vitro and in vivo assessments. J. Nanobiotechnol. 2011, 9, 44.

115.Ali, H.H.; Hussein, A.A. Oral nanoemulsions of candesartan cilexetil: Formulation, characterization and in vitro drug release studies. AAPS Open 2017, 3, 4.

116. Kotta, S.; Khan, A.W.; Ansari, S.H.; Sharma, R.K.; Ali, J. Formulation of nanoemulsion: A comparison between phase inversion composition method and high-pressure homogenization method. Drug Deliv. 2015, 22, 455–466.

117. Gurpreet, K.; Singh, S.K. Review of Nanoemulsion Formulation and Characterization Techniques. Indian J. Pharm. Sci. 2018, 80, 781–789.

118. Elsheikh, M.A.; Elnaggar, Y.S.R.; Gohar, E.Y.; Abdallah, O.Y. Nanoemulsion liquid preconcentrates for raloxifene hydrochloride: Optimization and in vivo appraisal. Int. J. Nanomed. 2012, 7, 3787–3802.

119. Debnath, S.; Satayanarayana Kumar, G.V. Nanoemulsion-a method to improve the solubility of lipophilic drugs. Pharmanest 2011, 2, 72–83.

120. Ganta, S.; Sharma, P.; Paxton, J.W.; Baguley, B.C.; Garg, S. Pharmacokinetics and pharmacodynamics of chlorambucil delivered in long-circulating nanoemulsion. J. Drug Target 2010, 18, 125–133.

121.Yang, M.; Gu, Y.; Yang, D.; Tang, X.; Liu, J. Development of triptolide-nanoemulsion gels for percutaneous administration: Physicochemical, transport, pharmacokinetic and pharmacodynamic characteristics. J. Nanobiotechnol. 2017, 15, 88.

122. Shahtalebi, M.A.; Sadat-Hosseini, A.; Safaeian, L. Preparation and evaluation of clove oil in emu oil self-emulsion for hair conditioning and hair loss prevention. J. HerbMed Pharmacol. 2016, 5, 72–77.