Review Article

Nanoemulsion: A Novel Drug Delivery Tool

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ABSTRACT

Nanoemulsion (NE) is defined as an O/W or W/O emulsion producing a transparent product that has a droplet size from 20-200nm and does not have the tendency to coalesce. It is promising for transdermal delivery of drugs as an efficient route of drug administration. Several mechanisms have been proposed to explain the advantages of nanoemulsions for the transdermal delivery of drugs. In transdermal delivery, the goal of dosage design is to maximize the flux through the skin into systemic circulation. A useful strategy for improving percutaneous flux is to improve the concentration of drug or choose an appropriate vehicle for the transdermal delivery. The nanoemulsions system should be a promising vehicle due to powerful ability to deliver drug through skins. With these approaches, **t**he aim of this present study is to review the potential of nanoemulsion formulation for transdermal delivery of pure phytopharmaceuticals and poorly soluble drugs. Some nanoemulsions have however exhibited sufficiently high level of stability for them to be proposed as vehicle for drug delivery. Using the transdermal route eliminates the side effects, increases patient compliance, avoids first-pass metabolism, enhance bioavailability and maintains the plasma drug level for a longer period of time. Cosmetics formulations require this delivery system in order to show their effect more prominently.

Keywords: Transdernmal, poorly soluble drug, phytopharmaceuticals, nanoemulsion

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INTRODUCTION

An emulsion is a system in which one fluid is dispersed in another with which it immiscible. Macroscopic separation of the phases is prevented by the addition of a suitable surfactant. In the vast majority of emulsion research, one of the liquid phases is water.

The term "Nanoemulsion" [1] refers to a thermodynamically stable isotropic ally clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A Nan emulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, Nanoemulsions are transparent. The Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a co surfactant or co solvent is used in addition to the surfactant, the oil phase and the water phase.

Three types of Nan emulsions are most likely to be formed depending on the composition:

1. Oil in water Nan emulsions wherein oil droplets are dispersed in the continues aqueous phase

2. Water in oil Nan emulsions wherein water droplets are dispersed in the continuous oil phase;

3. Bi-continuous Nan emulsions wherein micro domains of oil and water are inter dispersed within the system.In all three types of Nan emulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

The key difference between emulsions and Nan emulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate.1 Another important difference concerns their appearance; emulsions are cloudy while Nan emulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while Nan emulsions do not. The latter point has obvious implications when considering the relative cost of commercial production of the two types of system.

Classification of Surfactants

- Non-ionic- Fatty alcohols, glycerol esters, fatty acid esters.
- Anionic- Contain carboxyl ate groups. Soaps, Suffocates, Divalent ions.
- Cationic- Amines and quaternary ammonium compounds. Cetyltrimethyl ammonium bromide. Incompatible with anionic. Zwitterionic- Higher pH, anionic surfactants.

ADVANTAGES OF NANOEMULSION OVER OTHER DOSAGE FORMS

- Increase the rate of absorption.
- Eliminates variability in absorption.
- Helps solubilise lipophilic drug.
- Provides aqueous dosage form for water insoluble drugs.
- Increases bioavailability.
- Various routes like tropical, oral and intravenous can be used to deliver the product.
- Rapid and efficient penetration of the drug moiety.
- Helpful in taste masking.
- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W Nan emulsion is not exposed to attack by water and air.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.
- Nan emulsions are thermodynamically stable system and the stability allows self-emulsification of the system

Whose properties are not dependent on the process followed?

- Nan emulsions can carry both lipophilic and hydrophilic drugs.
- Nan emulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

DISADVANTAGES OF NANOEMULSION BASED SYSTEMS

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Limited solubilising capacity for high-melting substances.
- The surfactant must be nontoxic for using pharmaceutical applications.
- Nanoemulsion stability is influenced by environmental parameters such as temperature. These parameters change upon Nanoemulsion delivery to patients.

COMPONENTS OF NANOEMULSION

Main three components of Nan emulsions are as follows:

1. Oil
2. Surfactant/Co-surfactant
3. Aqueous phase

Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy Nanoemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable Nanoemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the Nanoemulsions transparent liquids [2]. In principle, Nanoemulsions can be used to deliver drugs to the patients via several routes, but the topical application of Nanoemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. These factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum. Nanoemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions [3,4] and gels [5,6]. Mobility of drugs in Nanoemulsions is more facile

[4,6,7], as compared to the Nanoemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin [5] The superior transdermal flux from Nanoemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin [4,7,8]. Nanoemulsions may affect the permeability of drug in the skin. In this case, the components of Nanoemulsions serve as permeation enhancers. Several compounds used in Nanoemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum. For example, short chain alkanols are widely used as permeation enhancers [9-11]. It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum [12-14] Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood.[15] Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function [16] It is of interest to explore the effects of these components in the organized Nanoemulsion structures. The aim of the present study was to investigate the potential of several Nanoemulsion formulations in transdermal delivery of lipophilic drugs.

A unique attempt was made [17] to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether (Brij 52) and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in Nanoemulsion.

The surfactants used to stabilise such systems may be:

(i) Non-ionic
(ii) Zwitterionic
(iii) Cationic
(iv) Anionic surfactants

A combinations of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the Nanoemulsion region. Examples of non-ionics include polyoxyethylene surfactants such **as** Brij 35 (C12E35) or sugar esters such as sorbitanmonooleate (Span 80). Phospholipids are a notable example of zwitterionic surfactants and exhibit excellent biocompatibility. Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent.[18-21] Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl ammonium bromide (CTAB) (Rees et al., 1995), and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known (Olla et al., 1999). The most widely studied anionic surfactant is probably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o Nanoemulsions.[22]

Attempts have been made to rationalise surfactant behaviour in terms of the hydrophile¡Vlipophile balance (HLB) **23,** as well as the critical packing parameter (CPP)24,25. Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3¡V6) surfactants are favoured for the formation of w/o Nanoemulsions whereas surfactants with high HLBs (8¡V18) are preferred for the formation of o/w Nanoemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than **20,** often require the presence of a cosurfactant to reduce their effective HLB to a value within the range required for Nanoemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself.In most cases, single-chain surfactants alone are unable to reduce the oil /water interfacial tension sufficiently to enable a Nanoemulsion to form, a point

made in a number of pertinent Nanoemulsions reviews [26-30]. Medium chain length alcohols which are commonly added as cosurfactants, have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface thereby increasing the entropy of the system [27,28]. Medium chain length alcohols also increase the mobility of the hydrocarbon tail and also allow greater penetration of the oil into this region.

PREPARATION OF NANOEMULSION [29]

The drug is be dissolved in the lipophilic part of the Nanoemulsion i.e. oil and the water phases can be combined with surfactant and a cosurfactant is then added at slow rate with gradual stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then being allowed to equilibrate. Gel may be prepared by adding a gelling agent to the above Nanoemulsion. Carbomers (crosslinkedpolyacrylic acid polymer agent.

Drug delivery routes across human skin

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, *via* the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum (**Fig. 1**).

The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years [20-22] and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways. In vitro experiments tend to involve the use of hydrated skin or epidermal membranes so that appendages are closed by the swelling associated with hydration. Scheuplein and colleagues [23, 24] proposed that a follicular shunt route was responsible for the pre steady-state permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum.

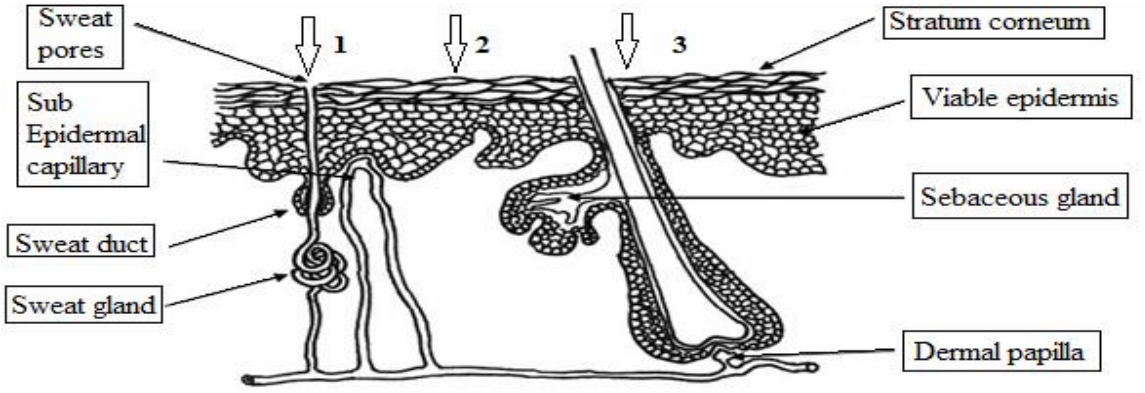

Figure 1: Simplified representation of skin showing routes of penetration: through the sweat ducts; . directly cross the stratum corneum; . via the hair follicles

Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness. Traditionally it was thought that hydrophilic chemicals diffuse within the aqueous regions near the outer surface of intracellular keratin filaments (intracellular or transcellular route) whilst lipophilic chemicals diffuse through the lipid matrix between the filaments (intercellular route) [24] (**Fig. 2**).

Factors to be considered during preparation of nanoemulsion

Three important conditions:

- Surfactants must be carefully chosen so that an ultra low interfacial tension (< 10-3 mN/m) can be attained at the oil / water interface which is a prime requirement to produce Nanoemulsions.

- Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the microdroplets to be produced by an ultra low interfacial tension.
- The interface must be flexible or fluid enough to promote the formation of Nanoemulsions.

Construction of Phase Diagram

Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. Formation of monophasic/biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring; the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the Nanoemulsion region of existence.

METHODS OF NANOEMULSION PREPRATION [30].

Phase Inversion Method

In this method, fine dispersion is obtained by chemical energy resulting of phase transitions occur through emulsification method. The adequate phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition, phase inversion temperature (PIT) method was introduced by Shinoda et al. based on principle of the changes of solubility of polyoxyethylene-type surfactant with temperature. This surfactant becomes lipophilic as increase in temperature because of dehydration of polymer chain. At low temperature, the surfactant monolayer has a great positive spontaneous curvature forming oil swollen micellar solution phase [33].

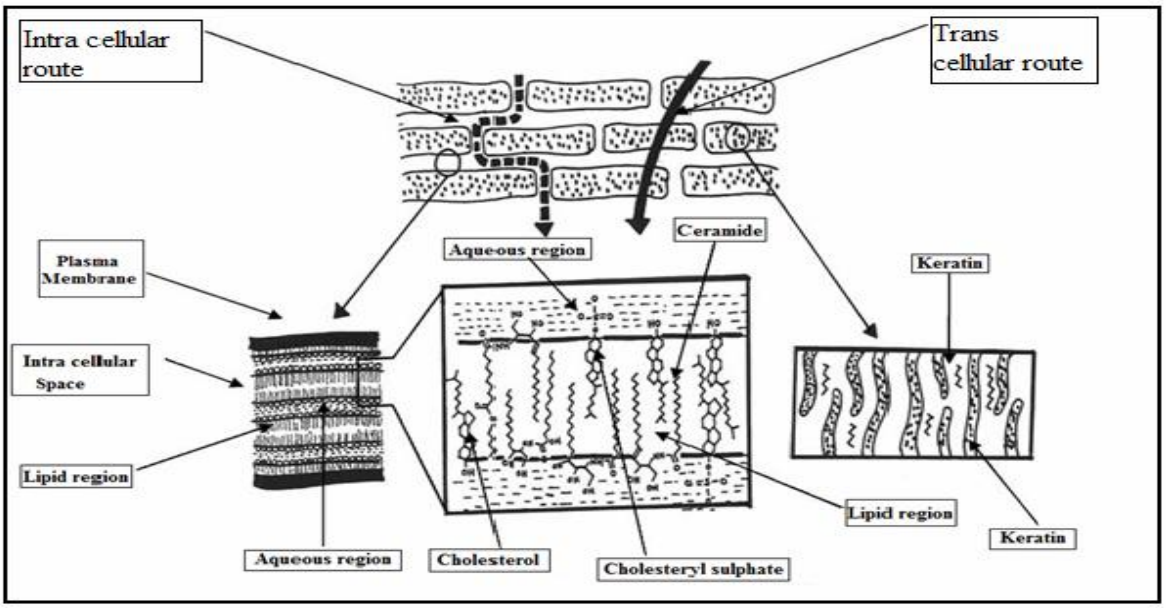

Figure 2: Diagrammatic representation of the stratum corneum and the intercellular and transcellular routes of penetration

Sonication Method

Sonication method is best way to prepare nanoemulsions. In sonication method the droplet size of conventional emulsion or microemulsions are reduced with the help of sonication mechanism. This method is not applicable for large batches, but only small batches of nanoemulsions can be prepared by this method [34].

Ultrasonic System

In ultrasonic emulsification, the energy input is provided through so called sonotrodes (sonicator probe) containing piezoelectric quartz crystals that can be expand & contract in response to

alternating electrical voltage. As the tip of sonicator probe contacts the liquid, it generates mechanical vibration and therefore cavitations occurs, which is the main phenomenon responsible for ultrasonically induced effects. Cavitation is the formation and collapse of vapour cavities in a flowing liquid. Such a vapour cavity forms when the local pressure is reduced to that of at the temperature of the flowing liquid because of local velocity changes. The collapse of these cavities causes powerful shock waves to radiate throughout the solution in proximity to the radiating face of the tip, thereby breaking the dispersed droplets. Within the ultrasound range, the power available varies inversely with the frequency and only powerful ultrasound (0-200kHz) is able to produce physical and chemical changes such as emulsification.

Ultrasound can be used directly to produce emulsion, but since breaking an interface requires a large amount of energy, it is better to prepare coarse emulsion before applying acoustic power. Due to small product throughput the ultrasound emulsification process mainly applied in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained.[35]

Microfluidizer

It is possible to produce emulsion at much higher pressures up to approximately 700 Mpa, in the nozzle of microfludizer that is the heart of this device (the interaction chamber) two jets of crude emulsion from two opposite channels collide with one another. The process stream is delivered by a pneumatically powered pump that is capable of pressurizing the in-house compressed air (150-650 Mpa) up to about 150 Mpa. Forcing the flow stream by high pressure through microchannels toward an impingement area creates a tremendous shearing action, which can provide an exceptionally fine emulsion.

Jet Disperser

Forcing the flow stream by high pressure through microchannels towards an impregnated area creates a tremendous shearing action, which can provide an exceptionally fine emulsion. In general, initial forces in turbulent flow along with cavitations are predominantly responsible for droplet disruption in microfludizer. Disruption in laminar elongation also possible, especially when emulsion has high viscosity.In the jet disperser two or more jets of crude emulsion each from opposing bores collide with one another but at a different design than microfludizer, the diameter of the bores in jet dispersers are typically 0.3-0.5mm. Finally an "orifice plate" is the simplest construction form for a homogenizing nozzle. The diameter of orifice bore is of same order of magnitude as the jet dispersers and inlet head diameter of orifice plate is typically 10-60nm, in jet dispersers & orifice plates, droplets are disrupted predominantly due to laminar elongation flow ahead of the bores.

CHARACTERIZATION OF NANOEMULSION

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the Nanoemulsion. The droplet size distribution of Nanoemulsion vesicles can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting Nanoemulsion stability.Dye Solubilization: A water soluble dye is solubilized within the aqueous phase of the W/O globule but is dispersible in the O/W globule. An oil soluble dye is solubilized within the oil phase of the O/W globule but is dispersible in the W/O globule.Dilutability Test: O/W Nanoemulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nanoemulsion. Conductance Measurement: O/W Nanoemulsion where the external phase is water, are highly conducting whereas W/O are not, since water is the internal or dispersal phase. To determine the nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful. A sharp increase in conductivity in certain W/O Nanoemulsion systems was observed at low volume fractions and such behaviour was interpreted as an indication of a ¡¥percolative behaviour¡¦ or exchange of ions between droplets before the formation of bicontinuous structures. Dielectric measurements are a powerful

means of probing both structural and dynamic features of Nanoemulsion systems.

Dynamic light-scattering measurements: The DLS measurements are taken at 90¢X in a dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm. The data processing is done in the built-in computer with the instrument.

Polydispersity: Studied using Abbe refractometer.

Phase analysis: To determine the type if Nanoemulsion that has formed the phase system (O/W or W/O) of the Nanoemulsions is determined by measuring the electrical conductivity using a conductometer.

Interfacial Tension: The formation and the properties of Nanoemulsion can be studied by measuring the interfacial tension. Ultra low values of interfacial tension are correlated with phase behaviour, particularly the existence of surfactant phase or middle-phase Nanoemulsions in equilibrium with aqueous and oil phases. Spinning-drop apparatus can be used to measure the ultra low interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.

Viscosity measurement: The viscosity of Nanoemulsions of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37 ¡Ó 0.2¢XC by a thermobath, and the samples for the measurement are to be immersed in it before testing.

In-vitro Drug Permeation Studies: Release studies can be performed using vertical passive diffusion cells (HTD 96, HT Dialysis, USA), with a cellulose membrane. The cellulose (molecular weight <12 000) membrane was first hydrated in the buffer solution at 20¢XC for 24 hours. The receptor solution will contain 0.20 mL of phosphate buffer pH 7.4 containing 1% SLS (Sodium lauryl sulphate) to, and it will be maintained at 37¢XC ¡Ó 0.5¢XC using a thermostatic shaker bath and stirr at 200 rpm throughout the experiment. The donor compartment will contain 0.2 ml of nanoemulsion sample.

The release can be modulated (or) altered based on pharmacokinetic needs by selecting appropriate Formulation excipient at right composition. For example the formulation scientist can tailor the formulation for Sustained or immediate release by choosing high solubilizing oil or low solubilizing oil respectively. Also by reducing the oil content with respect to the aqueous content will give slightly enhanced flux with high solubilizing oil. The flux can be further increased by using high amount of surfactant in the nanoemulsion system irrespective of the solubilizing nature of the oil, since drug will be soluble in the surfactant solution. Another way of increasing the flux would be selection of low solubilizing oil with high amount of aqueous content for highly lipophilic compound. The sustained release can be achieved either by means of using high amount of medium/high solubilizing oils. There are several biological factors should be considered like thickness of the diffusion membrane, unionized state of the molecule at the absorption site because their degree of ionization depends upon the pH of the biological fluid. Only the unionized fraction of the drug, if sufficiently lipid soluble can permeate the membrane passively until the concentration of unionized drug on either side of the membrane becomes equal until equilibrium is attained. Also the amount of fluid available at the site, were dilution can takes place after ingestion of nanoemulsion will determine the effective formation of micro droplets. The existence of bile salts and few surfactants in biological system will also help in the effective formation of micro droplets along with the peristaltic movement present in the stomach.

Determination of permeability coefficient and flux: Excised human cadaver skin from the abdomen can be obtained from dead who have undergone postmortem not more than 5 days ago in the hospital. The skin is stored at 4¢XC and the epidermis separated. The skin is first immersed in purified water at 60¢XC for 2 min and the epidermis then peeled off. Dried skin samples can be kept at 20¢XC for later use. Alternatively the full thickness dorsal skin of male hairless mice

may be used. The skin shall be excised, washed with normal saline and used. The passive permeability of lipophilic drug through the skin is investigated using Franz diffusion cells with known effective diffusional area. The hydrated skin samples are used. The receiver compartment may contain a complexing agent like cyclodextrin in the receiver phase, which shall increase the solubility and allows the maintenance of sink conditions in the experiments. Samples are withdrawn at regular interval and analyzed for amount of drug released.

APPLICATIONS OF NANOEMULSIONS

- Parenteral delivery
- Oral drug delivery
- Topical drug delivery
- Ocular and pulmonary delivery
- Nanoemulsions in biotechnology

Parenteral Delivery: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. Nanoemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle Nanoemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O Nanoemulsion can be used for parenteral delivery. The literature contains the details of the many Nanoemulsion systems, few of these can be used for the parenteral delivery because the toxicity of the surfactant and parenteral use. An alternative approach was taken by Von Corsewant and Thoren in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, polyethylene glycol (400) / polyethylene glycol (660) 12-hydroxystearate / ethanol, while maintaining a flexible surfactant film and spontaneous curvature near zero to obtain and almost balanced middle phase Nanoemulsion. The middle phase structure was preferred in this application, because it has been able to incorporate large volumes of oil and water with a minimal concentration of surfactant.

Oral Delivery: Nanoemulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency,and decreased drug toxicity. Therefore, Nanoemulsion have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-Nanoemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered parenterally, so require multiple dosing. A Nanoemulsion formulation of cyclosporine, named NeoralR has been introduced to replace SandimmuneR, a crude oil-in-water emulsion of cyclosporine formulation. NeoralR is formulated with a finer dispersion, giving it a more rapid and predictable absorption and less inter and intra patient variability.

Topical Delivery: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to affected area of the skin or eyes. Both O/W and W/O Nanoemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1. The Nanoemulsions were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and Plurol Oleique CC 497 as surfactant. Although enhanced delivery rates were observed in the case of the O/W Nanoemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin/IPP/water Nanoemulsion for the transdermal transport of indomethacin and diclofenac has also been reported. Fourier transform infra red (FTIR) spectroscopy

and differential scanning calorimetry (DSC) showed the IPP organogel had disrupted the lipid organisation in human stratum corneum after a 1 day incubation. The transdermal delivery of the hydrophilic drug diphenhydramine hydrochloride from a W/O Nanoemulsion into excised human skin have also been investigated. The formulation was based on combinations of Tween 80 and Span 20 with IPM. However two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection.

Ocular and Pulmonary Delivery: For the treatment of eye diseases, drugs are essentially delivered topically. O/W Nanoemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile. The Nanoemulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and IPM as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications. The formation of a water-in-HFA propellent Nanoemulsion stabilized by fluorocarbon non-ionic surfactant and intended for pulmonary delivery has been described.

Table 1: List of patented Nanmoemulsion Formulations 35

Patent Application Title	Patent App No.	Date
Topical compositions and methods of detection and treatment	20120039814	2012/02/16
Cancer vaccine compositions and methods of using the same	20110280911	2011/11/17
Methods of using nanoemulsion compositions having anti- inflammatory activity	20110200657	2011/08/18
Stable nanoemulsions for ultrasound-mediated of drug delivery and imaging	20110177005	2011/07/21
Method for the preparation of nanoparticles from nanoemulsion	20110135734	2011/06/09
Nanoemulsion formulations for direct delivery	20110045050	2011/02/24
Lyophilized nanoemulsion	20110015266	2011/01/20
Antimicrobial nanoemulsion compositions and methods	20110070306	2011/03/24
Nanoemulsion vaccines	20100316673	2010/12/16
Perfluorocarbon nanoemulsion containing quantum dot nanoparticles and method for preparing the same	20100233094	2010/09/16
Nanoemulsion of resveratrol-phospholipid complex and method for preparing the same and applications thereof	20100297199	2010/11/25
Compositions for treatment and prevention of acne, methods for making the compositions, and methods of use thereof	20100226983	2010/09/09
Stable mixed emulsions	20100069511	2010/03/18
Oil-in-water nanoemulsion, a cosmetic composition	20090208541	2009/08/20

Nanoemulsions in Biotechnology: Many enzymatic and biocatalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of pure apolar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous. Enzymes in low

water content display and Increased solubility in non-polar reactants. Possibility of shifting thermodynamic equilibria in favour of condensations.

Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures. Many enzymes, including lipases, esterases, dehydrogenases and oxidases often function in the cells in microenvironments that are hydrophobic in nature. In biological systems many enzymes operate at the interface between hydrophobic and hydrophilic domains and these usually interfaces are stabilized by polar lipids and other natural amphiphiles. Enzymatic catalysis in Nanoemulsions has been used for a variety of reactions, such as synthesis of esters, peptides and sugar acetals transesterification; various hydrolysis reactions and steroid transformation. The most widely used class of enzymes in microemulsion-based reactions is of lipases [31].

CONCLUSION [35]

Nanoemulsion formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents and able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Traditionally, Nanoemulsions have been used in clinics for more than four decades as total parenteral nutrition fluids. Nanoemulsions are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, photosensitizers, neutron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumor area. Moreover, targeting moiety has opened new avenues for targeted delivery of drugs, genes, photosensitizers, and other molecules to the tumor area. It is expected that further research and development work will be carried out in the near future for clinical realization of these targeted delivery vehicles.

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