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Review Article

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NANOEMULSIONS: AS MODIFIED DRUG DELIVERY TOOL

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ABSTRACT

The delivery of poorly water-soluble drugs has been the subject of much research, as approximately 40% of new chemical entities are hydrophobic in nature. One area in which published literature is lacking is the field of Nano emulsions. This review gives a conceptual idea about Nanoemulsion system. It provides reservoir vehicles for transdermal systems and controlled drug delivery systems or hydrolytically unstable drugs. The design and development of new drug delivery systems with the intention of enhancing the efficacy of existing drugs is an ongoing process in pharmaceutical research. It is necessary for a pharmaceutical solution to contain a therapeutic dose of the drug in a volume convenient for administration.

The main difference between emulsions and Nanoemulsions lies in the size and shape of the particles dispersed in the continuous phase: these are at least an order of magnitude smaller in the case of Nanoemulsions (10-200 nm) than those of conventional emulsions (1-20 μm). Also, whereas emulsions consist of roughly spherical droplets of one phase dispersed into the other, nanoemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures, making the usual “oil in water” and “water in oil” distinction sometimes irrelevant. Nanoemulsions are formed when and only when the interfacial tension at the oil/water interface is brought to a very low level and the interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions, and by the use of a “co-surfactant” which brings flexibility to the oil/water interface. These conditions lead to a thermodynamically optimised structure, which is stable as opposed to conventional emulsions and does not require high input of energy (i.e. through agitation) to be formed.

Keywords: Nanoemulsions, Drug delivery, Phase Diagram, Surfactant, Droplet Size.

INTRODUCTION

An emulsion is a system in which one fluid is dispersed in another with which it is 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*" refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A Nanoemulsion 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 cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase.

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

- Oil in water Nanoemulsions wherein oil droplets are dispersed in the continuos aqueous phase
- Water in oil Nanoemulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous Nanoemulsions wherein microdomains of oil and water are interdispersed within the system.

In all three types of Nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

The key difference between emulsions and Nanoemulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate.[1] Another important difference concerns their appearance; emulsions are cloudy while Nanoemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while Nanoemulsions 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

- Nonionic- Fatty alcohols, glycerol esters, fatty acid esters.

- Anionic- Contain carboxylate groups. Soaps, Sulfonates, Divalent ions.
- Cationic- Amines and quaternary ammonium compounds. Cetyl trimethyl ammonium bromide. Incompatible with anionics. Zwitterionic- Higher pH, anionics surfactants.

ADVANTAGES OF NANOEMULSION OVER OTHER DOSAGE FORMS

- Increase the rate of absorption.
- Eliminates variability in absorption.
- Helps solublize 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 Nanoemulsion is not exposed to attack by water and air.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.
- Nanoemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.
- Same Nanoemulsions can carry both lipophilic and hydrophilic drugs.
- The use of Nanoemulsion 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 solubilizing capacity for high-melting substances.
- The surfactant must be nontoxic for using pharmaceutical applications.
- Nanoemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon Nanoemulsion delivery to patients.

COMPONENTS OF NANOEMULSION

Main three components of Nanoemulsions are as follows:

1. Oil (Table **1**)
2. Surfactant/Co-surfactant (Table **2**)
3. Aqueous phase (Table **3**)

Table 1. List of oils used in nanoemulsions

Name	Chemical Name	Make
Captex 355	Glyceryl Tricaorylate/Caprate	Abitec
Captex 200	Propylene Dicaprylate/Dicaprate Glycol	Abitec
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)	Abitec
Witepsol	90:10 % w/w c12 Glyceride tri: diesters	Sasol pharmaceutical excipients
Myritol 318	c8/c10 triglycerides	Russia
Isopropyl myristate	Myristic acid isopropyl ester	Fluka

Table 2. List of Surfactant used in nanoemulsions

S.No	Solubilizing agents, surfactants, emulsifying agents adsorption enhancers
1	Capryol 90
2	Gelucire 44/14, 50/13
3	Cremophor RH 40
4	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
5	Labrafil M 1944 CS, M 2125 CS
6	Lauroglycol 90
7	PEG MW > 4000
8	Plurol Oleique CC 497
9	Poloxamer 124 and 188
10	Softigen 701, 767
11	Tagat TO
12	Tween 80

Table 3. List of Co-Surfactant used in nanoemulsions

S.No	Co Surfactant
1	TranscutolP
2	Glycerin,Ethylene glycol
3	Propylene glycol
4	Ethanol
5	Propanol

REVIEW

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.[9,10,11] 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.[12,13,14] 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 ($C_{12}E_{35}$) or a sugar esters such as sorbitan monooleate (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 microemulsions.[22]

Attempts have been made to rationalise surfactant behaviour in terms of the hydrophile–lipophile 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 (3–6) surfactants are favoured for the formation of w/o Nanoemulsions whereas surfactants with high HLBs (8–18) 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 microemulsion to form, a point made in a number of pertinent microemulsions 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

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 (crosslinked polyacrylic acid polymers) are the most widely used gelling agent.

Factors to be considered during preparation of nanoemulsion

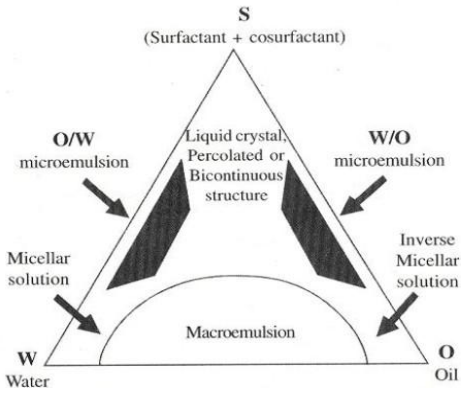
Three important conditions:

- 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.

Figure 1. Hypothetical Phase Regions of Microemulsion Systems[32]



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° 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 ± 0.2°C 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°C 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°C ± 0.5°C 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°C and the epidermis separated. The skin is first immersed in purified water at 60°C for 2 min and the epidermis then peeled off. Dried skin samples can be kept at 20°C 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 Neoral® has been introduced to replace Sandimmune®, a crude oil-in-water emulsion of cyclosporine formulation. Neoral® 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 (C_8 and C_{10} 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.

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 have –

- 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]

STABILITY STUDIES

The physical stability of the Nanoemulsion must be determined under different storage conditions (4, 25 and 40 °C) during 12 months. Fresh preparations as well as those that have been kept under various stress conditions for extended period of time are subjected to droplet size distribution analysis. Effect of surfactant and their concentration on size of droplet is also being studied.

CONCLUSION

To date Nanoemulsions have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. There is still however a considerable amount of fundamental work characterizing the physico-chemical behaviour of Nanoemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles. Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to emphasis on its characterization part including *in-vitro* evaluation. Besides this, research papers shows higher percentage of

surfactant (much higher than CMC level) used for the formation of Nanoemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared Nanoemulsion, which can be a broad research area in future.

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