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ADVANCED DEVELOPMENT OF NANO EMULTION IN DRUG DELIVERY SYSTEM

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1. ABSTRACT

Nanoemulsions are biphasic dosage form possessing the dispersion of two immiscible liquids one may be either oil in water (O/W) or either water in oil (W/O) droplets stabilized by amphiphilic surfactants. These are examples of the unstable heterogeneous biphasic dosage form system. These act as an important dosage form for water insoluble drugs. These are used to mask the taste and also act in the sustained release formulations. This review tries to focus on the current advanced methods including Micro emulsion, Multiple emulsion, and Nanoemulsion. In this modern era an advanced mode of drug delivery system has been introduced to overcome the major drawbacks associated with conventional drug delivery system. This review tries to focus on the new idea about the nanoemulsion system also the attention is focused on the basic idea about its formulation, method of preparation, characterization techniques, evaluation parameters, and various applications of nanoemulsion.

KEYWORDS: Nanoemulsion, Micro Emulsion, Multiple Emulsion, Parenteral, Oral, Drug Delivery, High- pressure homogenization.

2. INTRODUCTION

Nanoemulsion also called Sub-micron emulsion or the Mini-emulsion is oil-in-water [o/w] emulsions where the mean droplet diameter ranges between 10 to 1000nm. Nanoemulsion are a colloidal particulate system in the submicron size which ranges as a carrier of drug molecule. Their size varies from about 10 to 1000 nm. As a drug delivery system they lead to

increase the therapeutic efficacy and minimize adverse effect and toxic reactions.[1] Nanoemulsion can be divided into several dosage forms including liquid, creams, sprays, gels, aerosols, foams, and can be administered by equally different routes like topical, oral, intravenous, intranasal, pulmonary, and ocular.[2] The important application is that it helps in the treatment of reticuloendothelial system [RES]disorder, enzyme replacement therapy in the liver, also in the treatment of cancer, and acts as a vacinizer. Emulsion is a biphasic system in which one phase is initimately dispersed in the other phase by the fomation of minute droplets which in diameter ranges between 0.1 to 100µm. It is thermodynamically unstable system in nature it can be stabilized in the the presence of an emulsifying agent also called as emulgent or emulsifier. The dispersed phase is also known as internal phase or discontinuous phase while the outer phase is called as the external phase or continuous phase. The emulsifying agent used is also known as intermediate or inter phase.Nanoemulsion‟ also called as a miniemulsion is a oil/water or water/oil dispersion stabilized by an interfacial film of surfactant molecule having droplet size range 20-600nm. Due to their small size nanoemulsion are transparentin nature.

3. Types of nanoemulsion

3.1 Oil in Water nanoemulsion {O/W}: In this type of nanoemulsion oil is dispersed in the continuous aqueousphase.

3.2 Water in Oil nanoemulsion {W/O}: In this type of nanoemulsion water droplets are dispersed in continuous oil phase.

3.3 Bi-continious nanoemulsion: In this type of nanoemulsion both water and oil are act as continuous phases.The given below diagram illustrate the the Bi-Continious nanoemultions.

In all above three types of Nanoemulsions, the interface is stabilized by use of an appropriate combination of surfactants and also the 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. 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.[1]

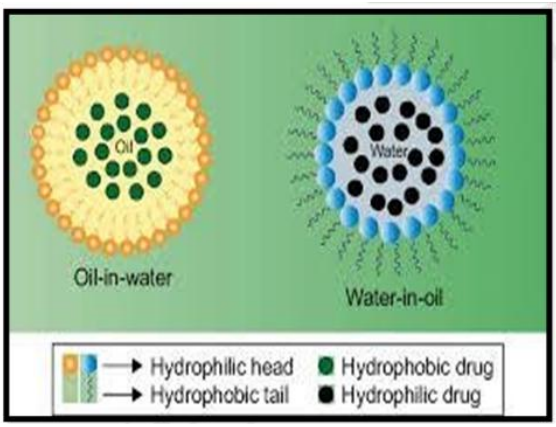

Figure No.1: O/W and W/O Nanoemulsion.

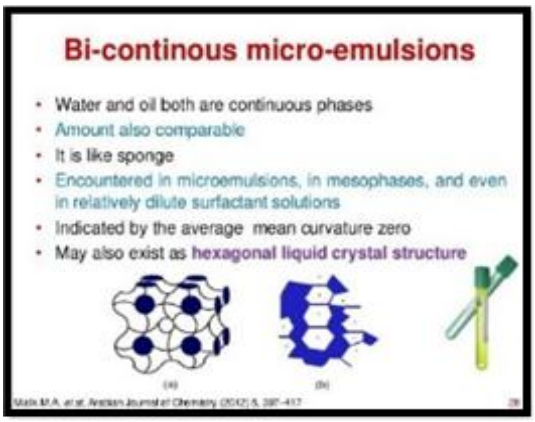

Figure No.2: Bi-continious nanoemulsion.

4. Advantages of nanoemulsion

i. It may be used as alternative for the liposomes andvesicles.
ii. It helps to enhance the bioavailability ofdrug.
iii. It is non-toxic and irritant by nature.
iv. It has improved to show high physical stability.
v. Nano emulsions have small-sized droplets having greater surface area which shows high absorption.[1]

5. Properties of nanoemulsion: Nanoemultion i.e, NE is biphasic mixture combined with oil and aqueous phase which is stabilized by the use of the surfactant molecules. The structure generated at the end as a result of orientation of surfactant molecules attributes NE with exceptional properties. Due to the unique properties of NE which are highly useful in drug delivery, these are one of the prime Nano-carriers in pharmaceutical field. NEs have number of sensible properties including optical clarity with simplest method of preparation, Nano sized droplets giving increased surface area and ultimately effective drug release. NEs are

formed using lower surfactant concentration which makes it prone to thermodynamic instability. However, external application of considerable energy reduces the size of macro emulsion into nanoscale making them more kinetically stable. Kinetic stability is one of the most important properties of NE which can result into formation of more stable formulation for pharmaceutical drug delivery. Gibbs free energy change in NE is positive which necessitates external energy application during NE manufacturing. NE, as described earlier, is mainly manufactured using low surfactant concentration making it necessary to apply external shear for generation of nano droplets as spontaneous formation is not possible at low surfactant concentrations. This point is accompanied with the benefit of less toxicity or no toxicity with NE as surfactant concentration is very low theoretically as compared to ME. Looking to the thermodynamic instability and practical approach, NE is prone to destabilization, temperature fluctuations and even to dilution due to limited amount of surfactant which cannot resist film formed on the large surface area for longer time. However, literature suggests that NE is very robust carrier against temperature changes and even on dilution. This point is always a matter of doubt about the exact molecular phenomena in influence of environmental stressful condition on stability of NE.[3]

6. Components of Nanoemulsion

6.1Oil/lipids-Nanoemulsions generally contain 5–20% oil/lipid droplets in case of O/W emulsions, though it may sometimes be significantly larger (upto70%). Lipids/oils to be used in nanoemulsions are generally propositioned on solubility of drug. Reesterified fractions derived from soybean oil sesame oil, cottonseed oil, safflower oil, coconut oil, rice bran oil [labeled as long chain triglycerides (LCT), medium-chain triglycerides (MCT) or short chain tri glycerides (SCT) depending on their chain lengths] are used either alone or in combination to formulate nanoemulsions. D-α-Tocopherol (vitamin E) family has been extensively used as a carrier in nanoemulsions. Oleic acid and ethyl oleate have also been used in oral, topical and parenteral nanoemulsions. Efforts have been put into finding suitable marine oils (salmon oil) for emulsification purpose. These marine oils are polyunsaturated i.e. possess more than one double bond in their structure with several therapeutic benefits and have proven to be a safer alternative for atherosclerotic patients who cannot tolerate regular LCT and MCT. Type of oil used in formulation of nano emulsion sometimes determines bioavailable fraction of active constituent. McClements and Xiao have investigated influence of formative components and droplet size on bioavailability of curcumin nanoemulsion. Bio-relevant testing revealed that maximum systemic availability was attained in nanoemulsions made

with LCT and MCT which were digested to an appreciably lesser extent than thosemadewith SCT.[1,2]

6.2 Andco-Surfactants-Surfactants are amphiphilic molecules which stabilize nanoemulsions by reducing interfacial tension, and prevent droplet aggregation. They tend to rapidly adsorb at oilwater interface and provide steric or electrostatic or dual electro-steric stabilization. A common surfactant employed in nanoemulsions is lecithin (phosphatidlcholine) derived from egg yolk or soybean. Surfactants like sodium deoxycholate (bile salt) and cremophor EL (Polyoxyl-35 castor oil) have been used in marketed parenteral products. Tween 20, 40, 60 and 80 (Polyoxyethlenesorbitanmonolaurate), Span 20, 40, 60 and 80 (Sorbitan monolaurate), Solutol HS-15 (polyoxyethylene- 660-hydroxystearate) are also regularly used.Other common surfactants include those belonging to poloxamer family, sodium dodecyl sulfate, amphiphilic proteins like casein, β-lactoglobulin, polysaccharides (e.g., gums, starch derivatives), and PEG containing block copolymers. Selection of asurfactant surfactant blend not only influences size and stability of nanoemulsion but sometimes also determines its toxicity, pharmacokinetics and pharmacodynamics. For instance desirable concentration of surfactant in parenteral nanoemulsions is pretty narrow.

EX: poloxamer 188 if used in a concentration N 0.5% has renal toxicity potential. Surfactants may also be used as decorative templates to attach ligand for active targeting of certain cancers. Sometimes, co-surfactants are used to complement surfactants, as they fit suitably in between structurally weaker areas, fortifying the interfacial film. Co-surfactants that are commonly used include propylene glycol, polyethylene glycol, ethanol, transcutol IP, glycerine, ethylene glycol andpropanol.

6.3 Antioxidants And Chemo Protectants: Preservatives employed in Nano emulsions should meet criteria like low toxicity, stability to heat and storage, physical and chemical compatibility, reasonable cost, ease of availability, acceptable odor, taste and color and should have a broad antimicrobial spectrum. Microorganisms thrive in both oil and water, and consequently selected preservative should attain effective concentration in both the phases. Use of preservatives in parenteral Nano emulsions is more or less avoided due to their toxic potential. Acid and acid derivatives viz. benzoic acid, sorbic acid, propionic acid, dehydrate acetic acid can be used as antifungal agents in formulation. Alcohols like cholorobutanol and phenoxy-2-ethanol are routinely used in ophthalmic. Phenolic and quaternary ammonium compounds serve as broad spectrum preservatives. Emulsified oil and

lipids are subject to autoxidation upon exposure to air; many drugs used in nanoemulsion are also highly susceptible to oxidative degradation. Upon oxidation, unsaturated oils give rise to rancidity. If oxidation is to be avoided it is advisable to employ synthetic lipids which lack the sensitive acyl group. This however is not always feasible, so an extra component namely an antioxidant is added. Antioxidants offer oxidative stability to formulation by acting either as: Reducing agents - e.g. ascorbic acid, sodium bisulfite, metabisulfite, thiourea and sodium formaldehyde or Blocking agents e.g. ascorbic acid esters, butyl hydroxytoluene and tocopherols or Synergists e.g. ascorbic acid, citranoic acid, phosphoric acid, citric acid and tartaricacid.Nanoemulsions are usually transparent which implies that entire spectrum of radiation including visible and UV rays can easily penetrate oil layers and catalyse photo degradation of drug molecule. Inclusion of chelating agents, pH stabilizers, UV protectants etc. is therefore sometimes required to counter environmental degradation.[2]

7. Technique used for Preparation of Nanoemultion: Formulation of Nanoemultion includes active drug, additive and emulsifier. The various methods for the preparation of Nanoemultion include two methods: (a) high-energy emulsification and (b) low-energy emulsification. The high-energy emulsification method includes high-energy stirring, ultrasonic emulsification, high-pressure homogenization, micro fluidization, and membrane emulsification. The low-energy emulsification method includes phase inversion temperature, emulsion inversion point, and spontaneous emulsification. Using a combined method, which includes the high-energy and low-energy emulsification, it is possible to prepare reverse Nanoemultion in a highly viscous system.[1]

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

7.2 High-Pressure Homogenization-The preparation of Nanoemultion requires high-pressure homogenization. This technique makes use of high pressure homogenizer/piston homogenizer to produce Nanoemultion of extremely low particle size (up to 1 nm).[1,2]

7.3 Micro Fluidization- Micro fluidization is a patented mixing technology, which makes use of a device called micro fluidizer. This device uses high pressure. which forces the drug product through the interaction chamber resulting in a very fine particle of submicron range. The process is repeated several times to obtain a desired particle size to produce uniform Nanoemultion.[1] It forces feed material through an interaction chamber consisting of microchannel under influence of a high-pressure displacement pump (500-50,000 psi), resulting in very fine droplets.[2]

7.4 Phase inversion temperature-This method involves change in phase by applying a higher temperature to a microemulsion.

7.5 Spontaneousemulsification: It involves three steps.

1. Preparation of homogeneous organic solution consisting of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.
2. The organic phase is injected in aqueous phase under continuous magnetic stirring, o/w emulsion is formed.
3. The aqueous phase is removed by evaporation under reduced pressure.[1]

7.6 Piston gap homogenizer: Piston gap homogenizers work on principle of colloid mills. A coarse emulsion is made to pass through a narrow gap (of dimension less than 10 μm) between a fixed stator and a rapidly moving rotor. Size reduction is caused by high shear, stress and grinding forces generated between rotor and stator. The upper ceiling of droplet size can be ascertained by fixing dissipation gap to required size, which implies that a yield will not be obtained unless and until emulsion is ground down to a size which is equal or lower to that of the gap between rotor and stator.[2,4]

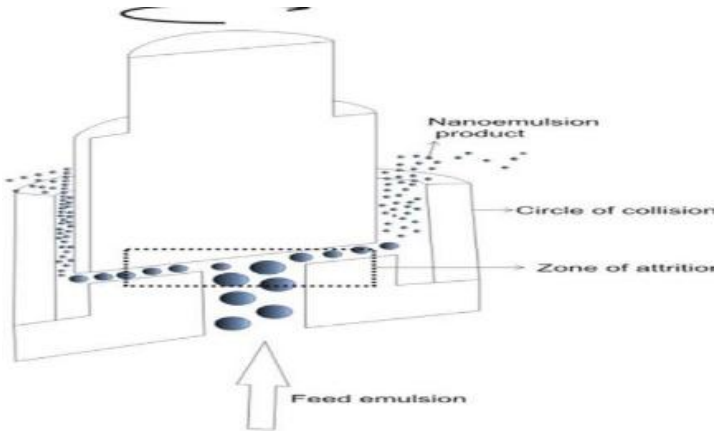

Figure No 3: Section of piston gap homogenizer.

7.7 Spontaneous emulsification-Spontaneous emulsification is akin to nanoprecipitation method utilized in manufacturing polymeric nanoparticles. However, instead of polymer, oil is used. The procedure involves preparation of two phases, one a hydrophilic surfactant containing aqueous phase and other an organic or oil phase such as mygliol containing a drug, an oil soluble surfactant such as Span and a partially water miscible organic solvent such as acetone or ethyl acetate. Organic phase is added drop wise to aqueous stirred phase (although the reverse i.e. adding water to oil is equally feasible in case of W/O emulsions) to form small nanoscale emulsion.[2]

8. Evaluation test for nanoemulsion

8.1 Screening of components-The most important criteria for the screening of components for nanoemulsion is the solubility of poorly soluble drug in oils, surfactants, and co-surfactants. Since the aim of this study to develop an oral formulation, therefore, solubility of drug in oils is more important as the ability of nanoemulsion to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase.

8.2 Dispersibilitytest- The efficiency of self-emulsification of oral nanoemulsion was assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37 *C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation.

The in vitro performance of the formulations was visually assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.[5]

8.3 Globule size analysis-The formulation (0.1 mL) was dispersed in 50 mL of water in volumetric flask and gently mixed by inverting the flask. Globule size of the Nanoemultion was determined by photon correlation spectroscopy that analyzes the fluctuations in light

scattering due to Brownian motion of the particles, using a Zetasizer 1000 HS (Malvern Instruments, UK). Light scattering was monitored at 25 ^{0}C at a 90^0 angle.

8.4 Viscocity- The viscosity of the formulations (0.5 g) was determined as such without dilution using Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA) using spindle # CPE40 at 25 ^{0}C. The software used for the calculation was Rheocalc V2.6.

8.5 Transmission electron microscopy- Morphology and structure of the Nanoemultion were studied using transmission electron microscopy (TEM) TOPCON 002B operating at 200 kV capable of points-point resolution. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of the Nanoemultion. In order to perform the TEM observations, the Nanoemultion drop of the diluted Nanoemultion was then directly deposited on the holey film grid and observed after drying.[1,5]

8.6 Dyesolubilization- 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.

8.7 Dilutabilitytest- O/W Nanoemulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nanoemulsion.

8.8 Conductancemeasurement- 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 behavior was interpreted as an indication of a percolative behaviour or exchange of ions between droplets before the for mation of bicontinuous structures. Dielectric measurements are a powerful means of probing both structural and dynamic features of Nanoemulsion systems.

8.9 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.

8.10 Polydispersity- The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 25 ^{0}C using a He-Ne laser.

8.11 Phaseanalysis- 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 conduct meter.[1] Properties of Nanoemultion 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.[1]

8.12 pH- The apparent pH of the formulation was measured by pH meter.

8.13 Refractive index- The refractive index, n, of a medium is defined as the ratio f the speed, c, of a wave such as light or sound in a reference medium to the phase speed, vp, of the wave in the medium. n=c/vp; It was determined using an Abbes type refractometer at 25±0.5°C.[1,6]

8.14 In-vitro skin permeation studies- In vitro skin permeation studies were performed by using Keshary Chien-diffusion cell. It was performed on abdominal skins and was obtained from male rats weighing 250±10 gm with a recirculating water bath and 12 diffusion cells. The skins were placed between the donor and the receiver chambers of vertical diffusion cells. The receiver chambers were filled with freshly water containing 20% ethanol. The receiver chambers were set at 37oC and the solution in the receiver chambers was stirred continuously at 300 rpm. The formulations were placed in the donor chamber. At 2, 4, 6, 8 h, 0.5 ml of the solution in the receiver chamber was removed for GC analysis and replaced immediately with an equal volume of fresh solution. Each sample was performed three times. The cumulative corrections were made to obtain the total amounts of drugs permeated at each time interval. The cumulative amounts of drug permeated through rat skins were plotted as a function of time. The permeation rates of drug at a steady-state through rat skins were calculated from the slope of linear portion of the cumulative amount permeated through the rat skin per unit area versus time plot.[2]

8.15 Percentagetransmittance- Percentage transmittance of nanoemulsion is measured by a UV-visible spectrophotometer.

8.16 Filter paper test- This test is based on the fact that an o/w nanoemulsion will spread out rapidly when dropped onto filter paper. In contrast, a w/o Nanoemultion will migrate only slowly. This method should not be used for highly viscous creams.[1]

8.17 Nuclear magnetic resonance (nmr)- NMR measurement were performed on a Bruker Avance 300MHz (7.05T) spectrophotometer.[7]

9. Stability Innanoemulsion

9.1 Dropletaggregation- Instability affecting nanoemulsion is usually mediated by droplet aggregation which causes growth of droplet size,implying that all special characteristics impaired due to nano scale are lost. Greater aggregation may ultimately results in phase separation which causes irreversible damage. Working with classical Newtonial mechanics an empirical approach towards energetics driving aggregation process has been drawn. Overall interaction between droplets can be described by a sum of total of van der waals, electrostatics, hydrophobic, and steric interactions occurring in between droplets, although there are be numerous other factors also which influence level ofinteraction.

Ie = Ivdw + Ih + Is.[2]

9.2 Coalescence- Another aspects which creates instability in nanoemulsaion are coalescence of droplets. Ostwld ripening and coalescence act simultaneously to accelerate destabilization of nanoemulsion. Coalescence is borne out of kinetic phenomenona such as creaming, sedimentation, and sometimes even random thermodynamics fluctuations which remove segregation, attachement and impingement as droplet can be re-dispersed by simple shaking but coalescence leads to irreversible emulsion damage, Rate of sedementaion in an emulsion is governed by Stokes law.

$Vs=2(Pc-Pd)r2g/9Nk$

Where, Vs is the terminal velocity of setting drop, Pc and Pd are individual densities of the continuous phase and dispersed phase respectively. G is acceleration due to gravity, r is radius of droplets whose Settiling Velocity Is Being Monitored And Nk Is Viscosity Of Continuous Phase.[2]

10. Nanoemultion In Drug Delivery system

10.1 Oral Delivery-The most convenient process, easiest, and effective way for the noninvasive administration of drugs is via the oral route, and so, drug delivery system based on this principle currently dominate the pharmaceutical market. Moreover increased patient compliance makes it the optimal means for achieving therapeutics targets. However, this route of delivery has its limitations with respect to the geriatric, pediatric, and possibly trauma epileptic patients where patient cooperation is a major constraint. In addition, certain drugs are inherently difficult to deliver through the oral route because of their non-conducive physiochemical properties. Oral delivery of poorly soluble drugs poses some serious problems with respect to drug solubility, stability, and absorption in the gastrointestinal tract (GIT). Peptide drugs are known to undergo hydrolysis and enzymatic degradation that limits their intestinal absorption and bioactivity. The limited ability of some drugs to permeate through the epithelium cell wall may also present additional drawbacks. Many approaches have been put forth to increase the overall bioavailability of drugs, including micronization/nanonization, solid dispersions, complexation with cyclodextrins, amorphization, and utilization of particulate delivery systems that are dispersible in aqueous environments. In the past decade, many research groups have reported significant oral bioavailability improvement of poorly soluble and hydrophobic drugs employing nanoemulsion technology. Substantial improvements in C_{max} and the area under the curve (AUC) have been documented by many researchers when poorly soluble drugs were delivered using nanoemulsions. Peyer‟s patches are the most important structural units of the gut-associated lymphoid tissue, which are specialized for endocytosis and transport into intraepithelial spaces. Nanoparticles are engulfed by the M-cells, after which they are rapidly internalized and “shuttled” to the lymphocytes. The lymphatic absorption of a drug has an advantage over the portal blood route, because it avoids presystemic metabolism by the liver. In brief, lymphatic targeting of nanoemulsions can permit oral delivery of labile drugs protected by the carrier, oral delivery of poorly soluble drugs for improved bioavailability, oral delivery of vaccine antigens to gutassociated lymphoid tissue, translocation of antineoplastic drugs for treatment of lymphomas, sustained/controlled drug release, reduction of drug-related mucosal irritation, and avoidance of the hepatic first-passeffect.In the GIT, lipids are effectively absorbed through various mechanisms. Thus, one of the feasible approaches to increase the absorption of drugs (especially protein drugs) is to load them inside lipids, such that there would be a significant increase in the level of absorption of drugs along with the lipids. The strategy is to use lipids as components of nanoemulsions to

load the drugs, ultimately leading to increased absorption of drugs in the GIT. Use of nanoemulsions as oral drug delivery systems has been shown to increase the effectiveness of the drug at the targetsite. In vitro transport studies (PAMPA and Caco-2models) have shown enhanced permeation of flavonoids and iridoids from Vitex agnus-castus extract-loaded nanoemulsions using triacetin as an oil phase and labrasol and cremophor EL as Surfactant and cosurfactant, respectively. In an interesting method to deliver nanoemulsion, developed self-nanoemulsifying tablets to improve the dissolution of simvastatin.

10.2 Parenteral Delivery- For drugs with low bioavailability and narrow therapeutic index, the parenteral route is considered to be one of the most common and effective routes. However, for drugs with poor aqueous solubility, parenteral administration represents a major challenge in the area of drug delivery. Diverse strategies are described in the literature for this purpose, including modification of vehicle pH, addition of cosolvents, or formation of inclusion complexes with cyclodextrins. However, adjuvant biocompatibility, induction of pain, and possible precipitation of the drugs during the administration are considered as limiting factors for many of these approaches. In this context, nanostructured systems have shown promise. Lipid emulsions have been successfully used over the past few decades in patients requiring parenteral nutrition. The biocompatibility of the raw materials used for their production (oils of natural or semisynthetic origin and phospholipids) makes these systems a promising alternative for the administration of several types of pharmaceutical and nutritional molecules. The composition, structural properties, and preparation conditions of parenteral nanoemulsions should be strictly controlled, aiming at the parenteral administration and the stability of the system. The stability of nanoemulsions used for parenteral delivery mainly depends upon their compositions, preparation techniques, and storage conditions. However, the capacity of nanoemulsions to dissolve large quantities of hydrophobic bioactive substances, along with their biocompatibility, and the ability to protect drugs from chemical and enzymatic degradation make them ideal vehicles for parenteral delivery.Selection of suitable emulsifiers capable of forming mono- or multilayers around the oil droplets so as nanoemulsion formation and improve nanoemulsion stability is essential for this type of delivery system. The phospholipids most commonly used in the preparation of parenteral delivery systems originate from natural sources, such as lecithin, or are semisynthetic materials, such as dioleoylphosphatidylethanolamine (DOPE) and distearoylphosphatidylcholine (DSPC). Lecithins may be of animal or plant origin and hence are biocompatible and biodegradable. An appreciable fraction of lecithin phospholipids have

charged polar head groups, such as phosphatidylserine, phosphatidylglycerol, and phosphatidic acid, which is of great importance to the long-term stability of the emulsions as they impart a relatively high-negative charge at the droplet surfaces that generates an electrostatic repulsion. Although naturally occurring surfactants are preferred to synthetic surfactants, having suitable emulsification results, adjuvant emulsifying agents have been employed to impart greater emulsion stability. Nonionic surfactants from the poloxamers and polyoxyethylene sorbitans (Tweens) group have been shown to give promising result when used in combination with phospholipids because they lead to the formation of compact mixed films, giving greater stability to the formulation. However, hemolytic reactions and changes in the droplet diameter of nanoemulsions stabilized by Tween 80 during autoclaving limit their use. Polyoxyethylated castor oil derivatives (Cremophor EL) have also received considerable attention for parenteral use, but the occurrence of hemolysis and toxicity has been described for some of these compounds. Most of the lipophilic drug candidates delivered as nanoemulsions, after parenteral administration, show a higher plasma concentration compared with the solution form. Moreover, an increase in the volume of distribution and reduction of the clearance leads to an increase in the half-life. Further, the frequency and dosage of injections can be reduced throughout the drug therapy period as these emulsions guarantee the release of drugs in a sustained and controlled mode over long periods of time. Additionally, the lower tendency for droplet aggregation or gravitational separation to occur offers advantages over conventional emulsions for this route of administration.

10.3 Transdermal and Topical Delivery- Systemic drug delivery via the skin is particularly convenient for certain clinical conditions. In particular, the advantage of steady-state controlled drug delivery with self-administration also being possible, which may not be the case with the parenteral route, renders the transdermal delivery systems very attractive. The drug input can be terminated at any time by the patient just by removing the transdermal patch. However, the fundamental disadvantage that currently limits the use of this mode of administration for many applications is the barrier imposed by the skin to effective penetration of the bioactives. Transdermally applied drugs may penetrate the skin through hair follicles, sweat ducts, or stratum corneum and then reach the systemic circulation. However, the stratum corneum restricts their absorption to a large extent and therefore limits their bioavailability. For improved drug pharmacokinetics and targeting, the primary skin barriers need to be overcome. The utilization of delivery systems containing nanosized

particles has been highly successful in overcoming this barrier. Nanoemulsion droplets are able to easily penetrate through the pores of the skin and reach the systemic circulation, thus getting channelized for effective delivery. There are various ways that the penetration of drugs through the skin can be enhanced by optimization of drug and vehicle properties, e.g., maximum penetration is usually observed when the drug is at its maximum thermodynamic activity like in the case of supersaturatedsolutions. There has been a plethora of different drug molecules delivered to or through the skin using nanoformulations, including betamethasone, clobetasol, corticosterone, flufenamic acid, flurbiprofen, tocopheryl acetate, tolterodine tartrate, and amlodipine.[3,7]

10.4 Intranasal Delivery- Intranasal drug delivery is another reliable route for the administration of certain types of drugs. Indeed, the nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic drugs and also appears to be a favorable way to overcome the obstacles for the direct entry of drugs to the target site. This system has been accepted in the Ayurvedic system of Indian medicine since ancient times, and more recently, it has often been preferred over oral administration of drugs because it leads to better systemic bioavailability, presumably by avoiding the gastrointestinal metabolism of the drug. The intranasal route is also painless, noninvasive, and tolerated favorably. There are several problems associated with targeting drugs. to the brain, especially hydrophilic ones and those of high-molecular weight. This is because of the impervious nature of the endothelium that divides the systemic circulation from the brain, i.e., the blood-brain barrier. The olfactory region of the nasal mucosa provides a direct connection between the nose and the brain. Nanoemulsions loaded with drugs have been exploited for the treatment/management of conditions such as hormone replacement therapy (estradiol), osteoporosis (raloxifene), schizophrenia (olanzapine), smoking cessation (nicotine), enuresis (desmopressin), endometriosis (nafarelin), and motion sickness (metoclopramide). The possibilities for central nervous system (CNS) delivery via nasal administration have been investigated for the delivery of polar drugs to treat chronic CNS conditions such as Parkinson‟s or Alzheimer‟s disease. The brain is considered to be one of the sanctuary sites for HIV, and hence, saquinavir has been targeted effectively to the brain as an intranasal nanoemulsion to treat this condition. Vaccines are also delivered as nanoemulsions through the intranasal route (discussed elsewhere in this chapter) and often have advantages over oral and parenteral routes. However, the major constraints on nasal drug delivery include a restricted capacity, difficulty in attaining dose accuracy, and reproducibility of delivery. The

delivery device, formulation, and administration technique often influence drug distribution in the nasal cavity that in turn affects permeability, residence time, and metabolism in the nasal cavity.

10.5 Ocular Delivery- Most of the ocular therapeutic have been administered to the eye as simple aqueous solutions as eye drops by instillation to the lower conjunctival sac. However, the major limitations of aqueous eye drops include their inability to deliver lipophilic and/or insoluble drugs, low ocular retention time, and limited resistance to the wash out effect of blinking and tear turnover. Further, the less than 20% of the applied topical dose that remains in the ocular cavity is challenged by enzyme binding and metabolism, ocular permeation barriers, phagocytic activity, partial distribution to adjacent tissues, and systemic circulation. Hence, elimination is very significant in topical ocular drug administration leading to 1% or less of the administered dose actually penetrating the ocular surface. Moreover, when targeting a remote target tissue like the retina, the fraction of the administered dose that reaches the site of action will be much less due to further anatomical barriers, aqueous humor turnover, intraocular metabolic activity, binding to intraocular pigmented tissues, and phagocytosis by cell line other than the targeted tissuecells.Consequently, there are major challenges in the pharmaceutical industry to the successful development to effective formulations for topical ocular administration of drugs that can encapsulate many different active ingredients, remain longer on the ocular surface, and provide sustained therapeutic concentrations, in addition to meeting the regulatory criteria for approval. Nanoemulsions could be employed to overcome some of these problems. Nanoemulsions are potent drug delivery vehicles for ophthalmic use due to their numerous advantages as sustained effect and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor. Compared to currently available approaches for administering eye drops, cationic nanoemulsions that have bioadhesive properties have been shown to be more efficient at delivering appropriate concentrations of bioactive molecules to the eye. The mechanism underlying the bioadhesiveness of these nanoemulsions is an electrostatic interaction that prolongs the residence time of the small oil droplets on the ocular surface. For instance, a commercial cationic nanoemulsion technology (Novasorb) uses positively charged droplets to create an electrostatic attraction with the –ve charged cells of the ocularsurface. Oil coreEmulsifier/surfactant Cations The corneal and conjunctival cells and the mucus layer of glycosyl amino glycans lining the ocular surface are negatively charged at a physiological pH, and upon application of a positively charged formulation to the eye, it is likely that an

electrostatic attraction will occur prolonging the residence time of the formulation on the ocular surface. In addition, the small size of the oil droplets may facilitate enhanced absorption.

10.6 Nanoemulsions for Vaccine Delivery- Most of the research on nanoemulsions for vaccine delivery concentrates on intranasal mucosal methods. As opposed to traditional vaccination routes, in the intranasal mucosal vaccination, the oil-based emulsion is administered into the nostrils. Intranasal vaccination is considered as the preferred immunization route due to the ease of administration and the lesser amount of antigen needed to induce an immune response. Though the exact mechanism of vaccine adjuvants is still to be explored, it is believed that improved antigen delivery and innate immune activation are possible mechanisms by which adjuvants enhance the immune response. Interestingly, nanoemulsion-based vaccine adjuvants act by enhancing antigen uptake by dendritic cells (DCs) and activating toll-like receptors (TLR) 2 and 4, which in turn enhance both humoral and cell- mediated Th1 and Th17 immune responses. Moreover, nanoemulsion-based mucosal adjuvants act without damaging the mucosal epithelium and have been demonstrated to be safe and well tolerated in early phase human clinical trials. The delivery of nucleic acid-based vaccines is discussed elsewhere in this chapter. Since, HIV can attack the mucosal immune system, developing mucosal immunity through the use of nanoemulsions has been considered as a useful strategy against HIV infection. Moreover, it is now demonstrated that genital mucosa immunity may be attained with vaccines that are administered into the nasal mucos. Nanoemulsions are now being used as adjuvants to transport attenuated organisms to a mucosal surface to produce the desired immune response. Nanoemulsion (with a 1:6 ratio of cationic-to-nonionic surfactants) adjuvanted inactivated influenza vaccine delivered intranasally was found to elicit a strong mucosal influenza-specific IgA response, offering an important advantage over immune responses driven by parenteral vaccination. Studies indicate that nanoemulsions appear to be an effective mucosal adjuvant for a recombinant Bacillus anthracis protective antigen anthrax vaccine. These developed vaccines were found to induce long-lasting, robust, and specific humoral and cellular responses and further appear to lack adverse effects and have the ability to stabilize the antigen.

10.7 Nanoemulsion for genedelivery- The concept of gene delivery is quite straightforward and involves the insertion of genes into somatic cells of patients for correction of an inborn genetic defect or creation of a new cellular functi. Since liposomes can easily bind to the cell

surface, they have been used as nonviral vectors for gene delivery. Unlike nonviral vectors, viral gene delivery systems have improved transfection capabilities. However, relative toxicities of these systems limit their applications. Some of the limitations of the use of viral vectors in gene therapy have stimulated research in nonviral strategies such as cationic nanoemulsions. The presence of cationic surfactants allows the complexation with negatively charged DNA via electrostatic interaction, resulting in DNA compaction and consequently nanocomplex formation. Stearylamine, a cationic lipid, is reported to be a suitable cationic surfactant for gene delivery. Stearylamine (a cationic lipid) containing cationic nanoemulsions with a droplet size smaller than 200 nm and a zeta potential higher than+30 mV was able to effectively complex the plasmid model PIRES2-EGFP, as confirmed by an agarose gel electrophoresis assay. Cationic nanoemulsion systems have been used to intranasally deliver TNFα siRNA to protect against neuroinflammation, as demonstrated using an LPS- induced model of neuroinflammation. These results indicate that intranasal delivery of cationic nanoemulsions encapsulating TNFα siRNA offered an efficient means of gene knockdown, and this approach has significant potential in the prevention of neuroinflammation. Self-amplifying messenger RNA (mRNA) of positive-strand RNA viruses has now evolved as effective nonviral vectors for in situ expression of vaccine antigens. For oral gene delivery, cell-penetrating peptides are found to amplify cellular uptake of plasmid DNA (pDNA)-loaded self- nanoemulsifying drug delivery systems (SNEDDS) by mucosal epithelialcells.Liposomes are also widely exploited for delivery of genes. However, the distinct advantage of nanoemulsions over liposomes is their greater physical stability. It has been shown that most liposomal preparations aggregate on interaction with DNA, which can cause embolism upon systemic administration, limiting their applications in gene delivery. This is likely to be less of a problem with nanoemulsion-based delivery systems.[7]

11. Recent Advances: A few advancements in emulsion system for improved stability, for sustained release and to increase efficiency of formulation are also available.

1. emulsion {Emulsion in gel}- Have emerged as one of the most interesting topical drug delivery system as it has dual release control system i.e. emulsion and gel. Also the stability of emulsion is increased when it is incorporated in gel. Itraconazole is an orally or topically active antifungal agent with abroad spectrum of activity. The objective of this project was to develop a Gellified emulsion for control delivery for Itraco nazole. In present work we

prepare emulsion and then incorporated in carbapol gel. The prepared formulation was evaluated on basis of pH, spreadability, Viscosity, drug content, in vitro release and Stability Studies. Microbial assay and Skin irritation studies on rabbit was performed. Studied revealed that the optimized batch shows 95.08% release in 48 hours and. The result of microbial assay compared with marketed product, the result shows 46.6% inhibition of optimized batch whereas marketed preparation shows only 32.3% in hibition.While result of skin irritation test shows no edema and erythema. Hence it can be concluded that emulsion system offer more effective and safe sustained release.

2. Pickeringemulsion- The solid particles in the colloidal size may be used as emulsion stabilizers. Such particles are known as Pickering emulsion. Pickering emulsions are recently employed in many areas like cosmetics, food, pharmaceuticals, oil recovery and waste water treatment.

3. Self-emulsifying drug delivery system- These are used to improve the bioavailability of hydrophobic drugs. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. SEDDS is ideally an isotropic mixture of oils and surfactants and sometimes co solvents. The multi-component delivery systems have optimized by evaluating their ability to self-emulsify when introduced to an aqueous medium under gentle agitation, and by determination of particle size of the resulting emulsion. Upon oral administration, these systems form fine (micro) emulsions in the gastrointestinal tract (GIT) with mild agitation provided by gastric mobility. Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. SEDDS are characterized by using various methods like Characterization of SEDDSs: Visual assessment. This may provide important information about the self-emulsifying and micro-emulsifying property of the mixture and about the resulting dispersion. Turbidity measurement is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. Droplet Size is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a

Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. Reduction of the droplet size to values below 50 µm leads to the formation of SMEDDSs, which are stable and clear o/w dispersions.[8]

12. Comparisons of various Nanoemultion.[8]

Criteria	Micro	Multiple	Non Aqueous	Liposome	Emulsion	Nano
	Emulsion	Emulsion	Emulsion	Emulsion	Polymerization	emulsion
Type	Both O/W or W/O	W/O/W or O/W/O	O/O type	O/W or W/O	O/W or W/O	O/W or W/O
Particle size	0.01 µm-10 µm	0.1- 100 µm	0.1- 100 µm	0.1- 100 µm	0.1- 100 µm	10-200 nm
Surfactant	All	Lipophilic & non Ionic	Oil soluble	HLB 4-7	Mostly W/O	ALL
Composition	Oil+water+surfactant	Oil+water	Oil+surfactant	Oil+water+ liphophilic	Oil+water+surfactant	Oil+ water
	+cosurfactant	+surfactant		material+ Surfactant	+polymer material	+Surfactant
Phase	Single Phase	Triple Phase	Single Phase	Double Phase	Double Phase	Single Phase
Purpose	Rapid action	Prolonged action & taste masking	Reservoir	Drug targeting	Manufacturing of polymer	rapid action
Marketed example	Sandimune	sorbitanmonooleate,	Silicone	Lubrizol liposome	TufCOR™	indomethacine,
	Neoral Novartis	Sorbitantrioleate	(Dimethicone, Cyclopentasiloxane)	Emulsion		indobene gel

13. Markated Formlations

DRUG	BRAND	INDICATION
Propofol	Diprivan	Anesthetic
Dexamethasone	Limethason	Steroid
Flurbiprofen axetil	Ropion	Non-steroidal analgesic
Vit. A,D,E & K	Vitalipid	Parenteral nutrition

14. CONCLUSION

NE formulations offer several advantages for the delivery of drugs, biological, or diagnostic agents. Traditionally, NEs have been used in clinics for more than four decades as total parenteral nutrition fluids. Several other products for drug delivery applications such as Diprivan, Liple and Ropion have also reached the marketplace. Although NEs 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. 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 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 infuture.

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