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Nanoemulsion an Overview

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ABSTRACT:
To tackle the major limitation associated with current drug delivery system, an enhanced form of drug delivery system has been created. This review provide an in-depth look at an emulsion technology.nanoemulsion are emulsion that are nanoscale in size and are used to improve the delivery of active medical substances .these are thermodynamically stable isotropic systems in which an emulsifying agent such as surfactant and co-surfactant is used to combine two immiscible liquid into single phase .Nano emulsion droplet are nanometer in size , the size and shape of particles dispersed are fundamental difference between emulsion and Nano emulsion .this review focuses on providing a Nano emulsion formulation, preparation process, characterization technique, assessment criteria and numerous application.

Keywords: Nano emulsion, drug delivery, medical substances, characterization.

I. INTRODUCTION

Nanotechnology is the advancement of technology on a nanometer scale ranging from 0.1to 100 nanometer. "NANO PHARMACEUTICALS" are pharmaceuticals developed using nanotechnology and include a variety of nanoparticles .Nano emulsion, Nano suspension, nanosphere,nanotube, nanoshell,nanocapsule,lipide nanoparticle are currently being used or are in the process of being created.nanoemulsion are form of dispersed particulate used in pharmaceutical and biomedical aids and vehicles with significant potential for future diagnostics drug therapies and biotechnologies'.

Nano emulsion is a colloidal particulate system with a size of less than one micron that acts as a drug carrier.an emulsion is a biphasic system in which one phase is dispersed in the other phase as a tiny droplets with diameter ranging from 0.1 to 100 um .it is thermodynamically unstable system that can be stabilized by presence of emulsifying agent the internal or discontinuous phase is known as the dispersed phase and the dispersion medium is also known as outer phase.

Nano emulsion is often referred as miniemulsion. There are three type of Nano emulsions (A) oil in water Nano emulsion in which oil is dispersed in continuous phase (B) water in oil Nano emulsion in which water droplets are dispersed in a continuous oil phase (C) bi continuous Nano emulsion. The majority of drugs are hydrophobic in nature which contributes to poor solubility and bioavailability issues. Nano emulsion drug delivery systems are enhancing the bioavailability of hydrophobic drug and bioactive food components in the blood.

Nano emulsion drug delivery systems are lipid based formulation system that increases hydrophobic drug and bioactive food components solubility and bioavailability. Food bioactive compounds such as flavonoids, non-flavonoids and carotenoids have been successfully encapsulated in Nano emulsion formulation. Since Nano emulsion system can deliver drug through Trans mucosal and transdermal routes they can significantly improves bioavailability. The high interfacial area and stability of these Nano emulsion system protect compounds from adverse environmental condition and increases their stability.

ADVANTAGES OF NANOEMULSION

- It may be used as ancillary for liposomes and vesicles.
- It increases the bioavailability of drug.
- It is nontoxic and nonirritant in nature.
- It has enhanced physical stability
- Nano emulsion has small sized droplets having superior surface area providing greater absorption.
- It can be framed in variety of formulation such as foam, cream, liquid, and sprays.
- It delivers better uptake of oil soluble supplement in cell culture technology.
- It helps solubilize lipophilic drug
- Nano emulsion has free energy that make them effective transport system
- Nano emulsion do not show problem of inherent creaming, flocculation, coalescence and sedimentation.

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- Nano emulsion are formulated with surfactant ,which are approved by human consumption and they can be taken by enteric route
- Nano emulsion do not damage healthy human and animals cell hence are suitable for human and veterinary therapeutic purpose
- The very small droplet size causes a large reduction in the gravity force and the Brownian motion may be sufficient for overcoming gravity. This means that no creaming or sedimentation occurs on storage.
- The small droplet size also prevents any flocculation of the droplets. Weak flocculation is prevented and this enables the system to remain dispersed with no separation.
- The small droplets also prevent their coalescence, since these droplets are elastic, surface fluctuations are prevented.
- Nanoemulsions are suitable for efficient delivery of active ingredients through the skin. The large surface area of the emulsion system allows rapid penetration of actives.
- The transparent nature of the system, their fluidity (at reasonable oil concentrations) as well as the absence of any thickeners may give them a pleasant aesthetic character and skin feel.
- The small size of the droplets allows them to deposit uniformly on substrates. Wetting, spreading and penetration may be also enhanced as a result of the low surface tension of the whole system and the low interfacial tension of the o/w droplets.
- Nanoemulsions can be applied for delivery of fragrants, which may be incorporated in many personal care products. This could also be applied in perfumes, which are desirable to be formulated alcohol free.
- Nano emulsions may be applied as a substitute for liposomes and vesicles (which are much less stable) and it is possible in some cases to build lamellar liquid cryscrystalline phases around the nanoemulsion droplets.

DISADVANTAGES OF NANOEMULSION

- Preparation of Nano emulsions requires in many cases special application techniques, such as the use of high pressure homogenizers as well as ultrasonics. Such equipment (such as the Microfluidiser) became available only in recent years.
- There is a perception in the personal care and cosmetic industry that nanoemulsions are expensive to produce. Expensive equipment are required as well as the use of high concentrations of emulsifiers.
- Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and cosurfactants.
- Lack of demonstration of the benefits that can be obtained from using Nano emulsions when compared with the classical macro emulsion systems.
- Lack of understanding of the interfacial chemistry that is involved in production of nanoemulsions.

Nano emulsion are colloidal particulate system of submicron size particles that serves as a drug carrier an emulsion is a biphasic method in which one phase is distributed in the other phase as a minute droplets with diameter varying from 0.1 to 100 micrometers.

TYPES OF NANO EMULSION

Depending on constituents and relative distribution of the internal dispersed phase/phases and the more ubiquitous continuous phase, Nano emulsions are termed as biphasic (O/W or W/O) or multiple Nano emulsions (W/O/W). Phase volume ratio (Φ) measures comparative volumes of internal and external phase comprising a Nano emulsion and determines its droplet number and overall stability. Normally, phase present in greater volume becomes the external phase. To predict type of Nano emulsion formed under given conditions, interaction of various components making up the Nano emulsion must be estimated. Nano emulsion are made up of tiny droplets of one immiscible substances dispersed in another. Oils and water are the two most widely used immiscible liquids in commercial applications. Oil in water is made up of small oil droplets dispersed in an aqueous medium, while water in oil is made up of small water droplets in an oily medium. The use of o/w Nano emulsion .droplets in an Nano emulsion are coated with hydrophilic emulsifier, while droplets in an w/o Nano emulsion are coated with lipophilic emulsifier.nanoemulsion are often used as templets to shape other structure.

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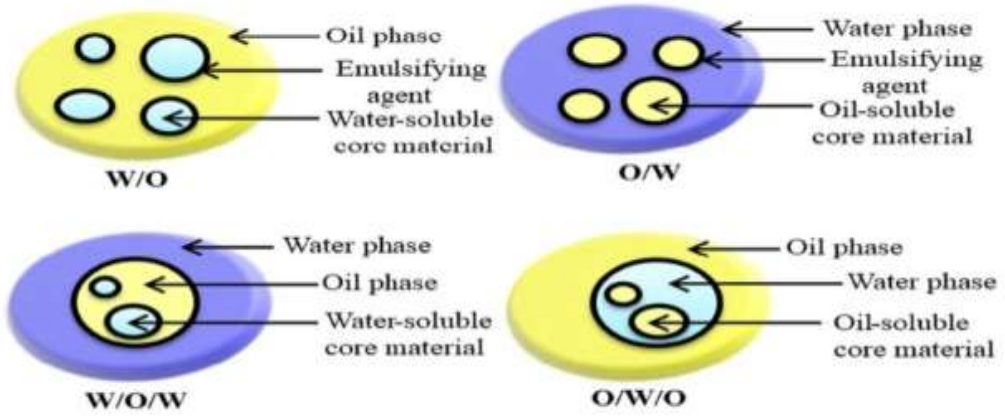

Fig1.1; Types of nanoemulsion

COMPONENTS OF NANOEMULSION

The selection of and ingredients is the critical role for the effective formulation of Nano emulsions. These ingredients primarily include oil phase, water phase, and emulsifier, texture modifiers, weighting agents and ripening inhibitors.

- OIL PHASE

The oil phase also known as the hydrophobic phase is mostly made up of substances such as oil, fat and soluble vitamins. Nutraceuticals preservatives the majority of the oil is made up of triglycerides. A blend of essentials oils scented oils the oil phase is differ from the aqueous phase in term of viscosity, polarity, refractive index melting point and interfacial stress all of which have an effect on stability of the system.
e.g:Coconut,caster,corn,cottonseed,eveningprimrose,fishoil,jojoba,lard,linseed,mineral,olive,peanut,perflurochemicals,pinenut,squalene.

- AQUEOUS PHASE

Water serves as a vehicle in the aqueous phase but is also serves as buffer salt, cosolvent.the physicochemical and physiological properties of aqueous phase vary from those of the oil phase.

- EMULSIFIER

Emulsifier also known as surfactant is a substances that decrease the interfacial stress between the oil and water phase by absorbing on the interface and causing droplet disruption as well as inhibiting aggregation.e.g:Natural lecithin, poloxamers, plysorbates, polyglycolized glycerides, stearlyamine, oleylamine

- TEXTURE MODIFIER

Rheological properties are altered by using texture modifier.it acts as a gelling or thickening agent, preventing molecule droplet movement and retarding gravitational separation.e.g Xanthan gum, plant proteins, alginate, carrageeman, pectin

- WEIGHTNING AGENT

Weighting agent is primarily used in o/w emulsion to minimize the risk of separation. Brominated vegetable oils, sucrose acetate iso butyrate, ester gum,

- RIPENING INHIBITORS

Ripening inhibitors are widely used in o/w emulsion to prevent droplet growth through the Ostwald droplet mechanisme.gCorn, palm, rape seed, sunflower oil,

METHODS OF PREPARATION OF NANOEMULSION

Emulsification is the process of dispersing one liquid in second immiscible liquid by electrostatic, hydrophobic, or hydrogen bonding interaction between the bioactive compounds and encapsulated material. There are two types of emulsification method high energy method and low energy method, high energy method also known as mechanical method.

A) LOW –ENERGY METHOD

For the production of Nano emulsion system these methods require little energy .low

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energy emulsification methods are more energy efficient because they use the systems internal chemical energy and require only gentle stirring to produce Nano emulsion phase inversion emulsification and self-emulsification are two low energy emulsification methods.

1) PHASE INVERSION EMULSIFICATION METHOD

A) CATASTROPHIC PHASE INVERSION TECHNIQUE FOR NANO EMULSIFICATION

This emulsification process also known as phase inversion composition this method involves titration of one immiscible liquid into other immiscible liquids using either surfactant or solid particles to stabilize droplets. Water and oil are two immiscible liquids that can be titrated into a stirred surfactant oil mixture causing the device to invert from water in oil emulsion to an oil in water nanoemulsion.this procedure is carried out under low energy flow condition so it is considered as a low energy method. The change in the phase behavior of the system when the surfactant oil water ratio is changed is one of the most important factors regulating this procedure. The appearance of bi continuous intermediate phase or lamellar structure that is broken down by dilution with water during the emulsification process, giving rise to extremely fine droplet, frequently precedes phase inversion .various pharmaceutical and nutraceuticals ingredients have been successfully encapsulated in Nano emulsion using this method

A) EMULSION INVERSION POINT METHOD (EIP)

In the EIP method due to CPI mechanism changing the fractioned volume of the dispersed phase rather than surfactant properties.as water is applied to oil surfactant mixture ,the device begins to behave like a w/o Nano emulsion water droplet combine with each other and the phase inversion point is reached when growing volume of water are applied above a critical water content with constant stirring this result in formation of bi continuous or lamellar structure .via an intermediate bi continuous micro emulsion ,further dilution with water induced phase inversion from w/o to an o/w device.. The size of the Nano emulsion droplets produced is determined by the process variables like water addition rate and stirring speed.

B) TRANSITIONAL NANOEMULSIFICATION METHOD

Transitional phase inversion occur as a result of change in the surfactants spontaneous curvature or affinity as a result of changes in parameter such as temperature and composition.CPI on other hand occur when dispersed phase is continuously added before the dispersed phase drops accumulates and form bi-continuous /lamellar structural phases.

a) PHASE INVERSION TEMPERATURE (PIT)

surfactant spontaneous curvature is inversed in the PIT method by changing tempearature.nonionic surfactant such as polyethoxylated surfactant have their POE groups dehydrated which cause the surfactant to become more lipophilic and cause change in curvature as a result phase inversion occur and resulting in formation of nanoemulsion.oil, water and nonionic surfactants are combined at room temperature to create oil-in-water emulsion in this process. Then as temperature rise the surfactant POE groups dehydrate, making the surfactant more lipophilic and causing it to have a stronger affinity for oily process.at hydrophile-lipophile balance temperature the nonionic surfactant has zero curvature and has similar affinity to the aqueous and oily phases causing phase inversion from the initial o/w emulsion to water in oil Nano emulsion through an intermediate liquid crystalline or bi-continues structure.at hydrophobic lipophilic balance temperature the non-ionic surfactant has zero curvature and show similar affinity to the aqueous and oil phase. For efficient phase inversion rapid cooling or heating of HLB is needed.

b) PHASE INVERSION COMPOSITION. (PIC)

the phase inversion composition or PIC process is similar to the phase inversion temperature method but instead of adjusting the system temperature phase inversion is accomplished by changing the system composition.PIC involves adding one of the ingredient such as water to mixture and then adding oil surfactant to the water surfactant mixture .nonionic surfactant of POE type are commonly used in PIC process to create Nano emulsion but other forms may also be used. Surfactant POE chain hydration occurs as water is steadily applied to the oil process and amount of water fraction is increases. A bi continuous or lamellar structure is formed during this transition. When more water is required. Traditional phase inversion is also responsible for Nano size emulsion droplet when other composition such as salt addition and pH changes are modified.

2) THE SELF NANOEMULSIFICATION METHOD/SPONTANEOUS EMULSIFICATION.

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Nano emulsion formulation is accomplished using the self-emulsification process without altering the surfactants spontaneous curvature. Surfactant and /or cosolvent molecules diffuse quickly from the dispersed to the continuous phases, causing turbulence and the formation of Nano-sized emulsion droplets. The spontaneous emulsification method is another name for self-emulsification method.SNEDDS are based on the self-emulsification phenomenon and have a lower lipid content as well as more hydrophilic surfactants.an isotropic mixture of an oil, surfactant, co-surfactant, and drug is known as SNEDDS.when this mixture is mixed with aqueous fluid in vivo, it form a fine and optically transparent o/w nanoemulsion,which is assisted by gentle agitation . Diffusion of the hydrophilic solvent or co-surfactant from the organic phase into the aqueous phase and formation of Nano emulsion negative free energy at transient negative or ultra-low interfacial tension are the two most commonly reported mechanism of

A) **HIGH ENERGY METHOD/MECHANICAL METHOD**

Nano emulsions are frequently crated using high frequency technologies. High mechanical energy is employed to create strong disruptive forces that break apart big droplets into Nano sized droplet ,resulting in a high kinetic energy Nano emulsion .mechanical devices such as ultrasonicator,microfluidizers,ahd high pressure homogenizer are used to create disruptive forces. High energy approaches can also be used to modify the emulsion stability, rheology and color

1) ROTAR-STATOR EMULSIFICATION

The rotar starter mixer head consist of a rotar mounted on a motor shaft and a perforated status and is widely used for emulsion formation in various fields of process industry such as food,pharmaceutical,cosmetic it also consider as standard method for emulsion with intermediate to high viscosity dispersed phase value fraction the reduction in main drop diameter from passing through the rotar stator region is relatively slow, and the each fluid element must generally make a significant number of passages. The hydrodynamic intensity and the resulting immersion drop size depends on rotar speed, which is often described in term of rotar tip speed ,which generally ranges from 30 to 10 m/s in industrial application. The drop diameter is specifically designed to produce the small droplet size needed for Nano emulsion the rotar stator mixer can be used in batch mode by mounting it in a closed tank in continuous mode by enclosing it within an arrow centrifugal pump like casing for in line operation or in semi continuous mode by recirculating the immersion across as in line device. The colloidal mill is a subtype of rotar stator emulsification in which the immigration is questioned through a rotar with an incline ,stator blocks drops entering the rotar stator clearance are elongated and breakup is caused by stresses.

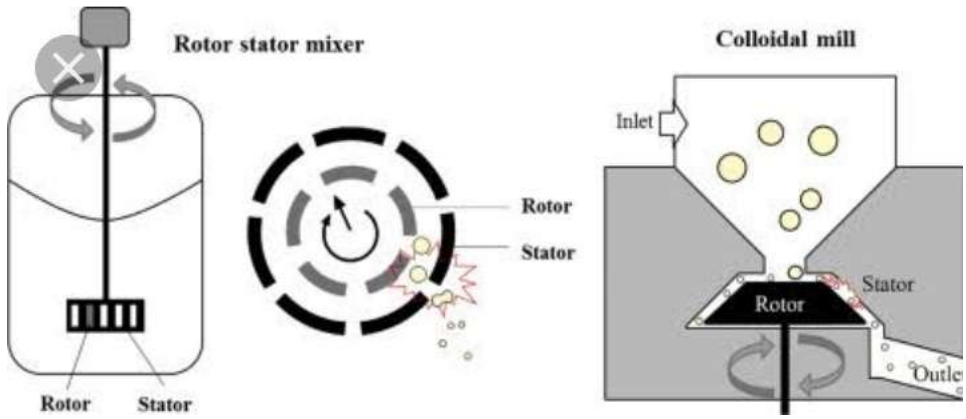

Fig 1.3: rotar stator emulsification devices rotar stator mixer and colloidal mill.

2) HIGH PRESSURE VALVE HOMOGINIZATION

High pressure valve homogenizer is one of the most widely used methods in industrial Nano emulsion formulation.it is used to reduce drop size to coarse preemulsion into narrow drop distribution with smaller drop sizes. For Nano emulsion creation the high pressure valve for homogenizer consist of pump for forcing the promotion through a valve forming narrow gap under high pressure usually between 50 and 200 Mpa.it accelerates the velocities in order of magnitude 10meter per second giving rise to an elongation flow in the valve entrance. The high local velocity also reduces

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the local pressure below vapour point, forming cavitation bubbles.as the bubble travel further downstream in the valve they experience higher local pressure and burst, sending out powerful shockwaves. Drop breakdown has been detected in visualization experiment in the turbulent jet form downstream of the gap. From small laboratory to big production scale, high pressure homogenizers are available in wide range of scale and loving for continuous production.

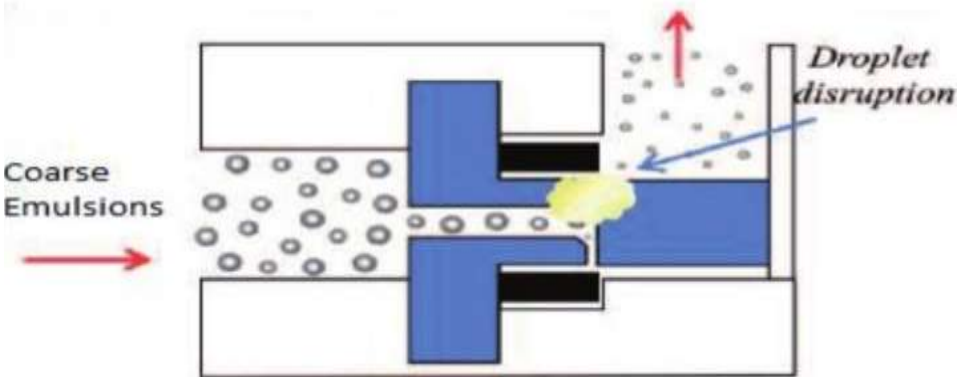

Fig1.4: high pressure homogenizers

3) MICROFLUIDIZATION

A micro fluidizer concomitantly uses hydraulic shear, impact, attrition, impingement, intense turbulence and cavitation, to effect size reduction. Simplified working of microfluidizer. It forces feed material through an interaction chamber consisting of microchannels under influence of a highpressure displacement pump (500–50,000 psi), resulting in very fine droplets.The micro fluidizer is similar to a homogeneous high pressure valve in that it has a purpose for coarse preemulsion into a narrow flow channel often referred as the reaction chamber. The liquid is accelerated as it enters the annular narrow channel but instead of allow using the fluid from a turbulent jet emerging into a stationary outlet chamber at the channel exist, it is angled such that it can flow into the reaction chamber. High pressure valve are available in broad range of scale from batches of 10 ml up to continuous production in 10000l/h.

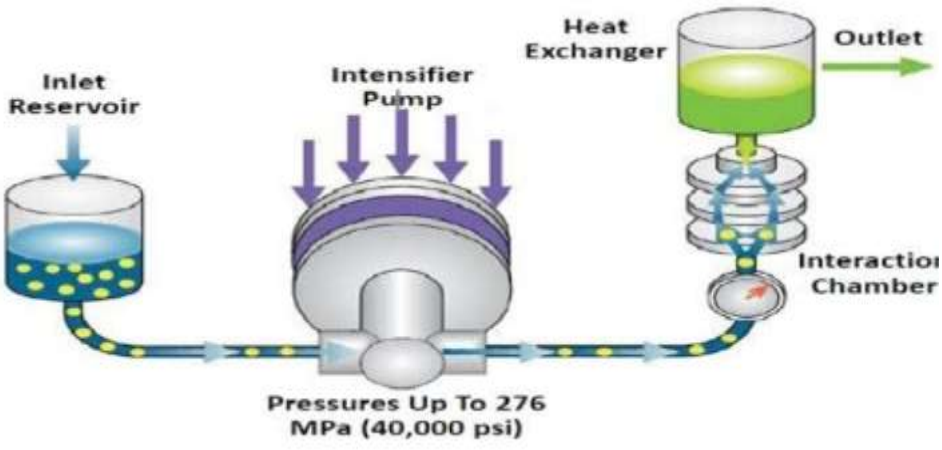

Fig 1.2; micro fluidizer

4) ULTRASONOCATION

Ultra-sonication is a technique that uses high frequency sound waves to generate a Nano emulsion in situ or to shrink the size of pre formed emulsion. When a piezoelectric probe is dipped in a sample it generates an intense disruptive force at its tip which causes cavitation bubble to build until they implode. This implosion causes shock wave which causes shock waves which cause a jet stream of surrounding liquid to pressurize dispersed droplets causing them to shrink in size. Droplet size reduces as sonication time and input power probes

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in and ultrasonicators are available in according to research operational parameter. Probes in ultrasonicators come in a variety of sizes which affect their functionality. Narrower probes are usually proffered for working on small batch size and relative probe placement in sampke.it should not touch any solid surface because it will change the pattern of wave reflection and pressure distribution.in comparison to other high energy method, a coarse emulsion is prepared by adding a homogeneous oil phase to an aqueous phase under mechanical stirring. The emulsion then is subjected to an ultra-sonication at different amplitude for short time cycle until desired properties are obtained for Nano emulsion. Ultra-sonication requires the least amount of energy.

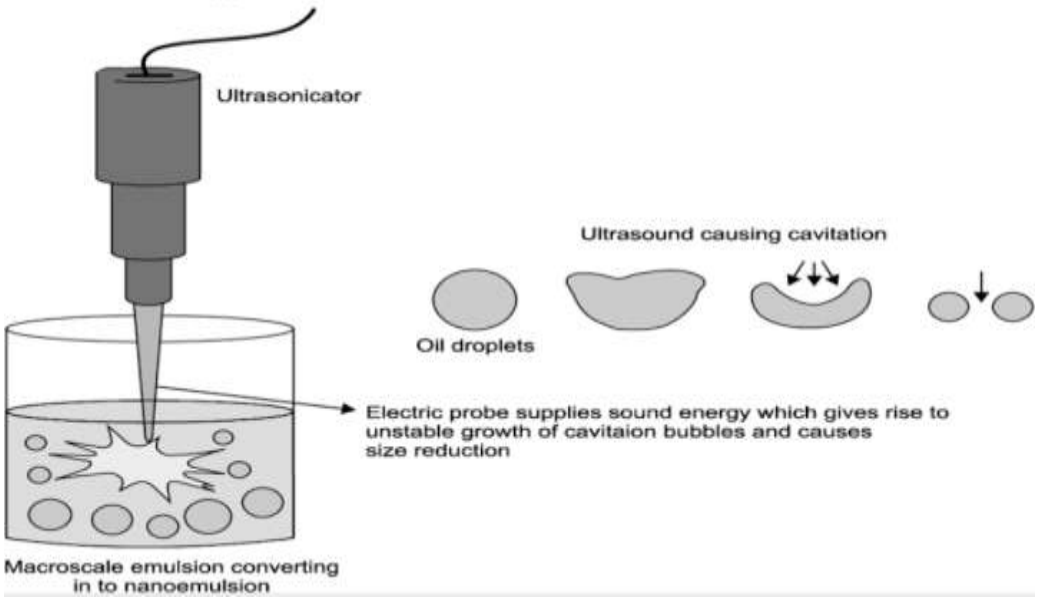

Fig 1.6: ultrasonicator

PROPERTIES OF NANOEMULSION

A) PHYSICOCHEMICAL PROPERTIES OF NANOEMULSION

1) STABILITY

The term stability refers to a Nano emulsion capacity to withstand changes in its physical and chemical properties thought time and emulsion .Nano emulsion are thermodynamically unstable because the separated oil and water phase have lower free energy than the emulsified once as a result, they always tend to break down given enough time with the Rate of change depending on the height of any kinetic energy barrier in system. There are several pathways by which Nano emulsion are break down, including flocculation, coalescence and Ostwald ripening and phase inversion. Many commercial application require that a Nano emulsion based product remain physically and chemically stable when exposed to specific environmental condition during manufacturing,storage,transportation,and use on the Nano emulsion may have to break down under a different set of environmental conditions. Physical and chemical changes in environmental properties can lead to change in formulation

2**) APPERANCE**

The overall appearance of Nano emulsion is determined by its optical qualities, which dependent on its interaction with light waves. The look of Nano emulsion based product is usually the first sensory impression that a consumer has and so play a key role in consumer approval appearance of an emulsion when the droplet are equally spread over a Nano emulsion it appear homogenous ,but it is heterogeneous .because of the high light scattering by the oil droplet ,traditional emulsion (200nm<d<200um)tend to have a opaque(d<50) or cloudy(50nm<d<200nm) look when substantial droplet aggregation,creaming,or oiling off occues.the degree of light scattering relies on the number size and refractive index of droplet in an emulsion the color of Nano emulsion depends on the presence of any chromophore that selectively absorb light in the visible region of electromagnetic spectrum.

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3) **RHEOLOGY**

Rheology is the science that studied the deformation and flow of matter and is an important factor in manufacture and functional performance of many materials. Understanding the rheology of an Nano emulsion is important for several reason .1) the efficiency of the droplet distribution inside the homogenizer is determined by the viscosity of the separate oil and water phase and the rheology of nanoemulsion.2)the shelf life of a Nano emulsion based product is determined by the rheology of an individual phases.as the viscosity of the aqueous phase increase the creaming rate of o /w Nano emulsion decreses.3) the way a Nano emulsion flows through a pipe that is directed inside a vessel, and passage via a heat exchanger for packing into a product container affect the design and operation of many essential industrial process.4) the sensory attributes of Nano emulsion based products are the influenced by the rheology which includes perceived creaminess, thickness and ability to flow.as a result, a manufacturer must carefully design and consistently produce Nano emulsion products with the rheological attributes desired for specific application.

4) **RELEASE CHARACTERISTICS**

A potentially important commercial application of Nano emulsion is to encapsulate hydrophobic or hydrophilic or a bioactive agent such as pharmaceuticals, vitamins, nutraceutical's, color's and preservatives .it is thus critical to understand the retention and release characteristics of bioactive components from Nano emulsion based delivery systems.

STABILITY OF NANOEMULSION

Stability studies are carried out to determine the drug substance's stability in the presence of various environmental conditions such as temperature, humidity, and light. Nanoemulsion stability tests are carried out after storing the formulation for 24 months in a dispersed and freeze-dried state, as per the standards of the International Conference on Harmonization. The following storage conditions were used: ambient (252°/605% RH), refrigerated (53°), and freeze (–205°). The required amount of nanoemulsion is kept in glass vials that are hermetically sealed. Samples are taken at predetermined intervals and analyzed for particle size, loading, and EE, as well as in vitro drug reactivity.

1) SHELF LIFE DETERMINATION

Accelerated stability studies are used to determine the shelf life of a nanoemulsion. The formulations are kept for approximately three months at three different temperatures and humidity levels (30°, 40°, and 500.5°). After a certain amount of time has passed (0, 30, 60, or 90 days), samples are extracted and analyzed using HPLC at max to determine the remaining drug content. As controls, samples taken at zero time are taken. This determines the sequence of the reaction, and then the reaction rate constant (K) for deterioration is computed from the slope of the lines using the equation below at each raised temperature slope = K/2.303 the logarithm values of K are displayed against the reciprocal of absolute temperature at different high temperatures using slope. The plot value of K at 25° is determined from this, and the value is then used to calculate shelf life using the following Eqn:

$$t0.9=0.1052/K25$$

t0.9=0.1052/K25 t0.9=0.1052/K25

Where t0.9 denotes the time necessary for a medicine to degrade by 10% and is referred to as shelf life. Found that clobetasol propionate-loaded Nano emulsions have a shelf life of roughly 2.18 years at room temperature (25°) and concluded that Nano emulsions can improve clobetasol propionate stability.

2) THERMODYNAMIC STABILITY STUDIES

Thermodynamic stability studies are usually carried out in three steps. Firstly heating-cooling cycle, which is performed for observing any effect on the stability of nanoemulsion by varying temperature conditions. Nanoemulsion is exposed to six cycles between 4° (refrigeration temperature) and 40° by storing the formulation at each temperature for not less than 48 h. The formulations which are stable at these temperatures are further chosen for centrifugation studies. Secondly, centrifugation studies in which the formulated Nano emulsions are centrifuged at 5000 rpm for 30 min and observed for phase separation or creaming or cracking. Thermodynamic stability tests are typically performed in three steps. The first is a heating-cooling cycle, which is used to see if temperature changes have any effect on nanoemulsion stability. Nanoemulsion is subjected to six temperature cycles ranging from 4° (freezer temperature) to 40° by storing the formulation at each temperature for at least 48 hours. For centrifugation experiments, the formulations that are stable at these temperatures are chosen. Second, a centrifugation investigation in which the formed Nano emulsions are centrifuged for 30 minutes at 5000 rpm and phase separation, creaming, and

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cracking are observed . Those that showed no signs of instability were put through a freeze-thaw cycle. Finally, the freeze-thaw cycle, which involves exposing nanoemulsion formulations to three freeze-thaw cycles at temperatures ranging from –21° to +25°. Formulations that pass this test and show no evidence of instability are considered to be stable. These formulations are then put through dispersability tests to see how effective they are at self-emulsification. Conducted thermodynamic investigations on glipizide nanoemulsion by subjecting it to three stability cycles and found that the nanoemulsion had good physical stability with no signs of phase separation, creaming, or cracking.

INSTABILITY OF NANOEMULSION

Nano emulsion are thermodynamically unfavorable system that has tendency to breakdown over time due to a range of physicochemical process like flocculation ,Ostwald ripening, and phase separation .the peace at which the process happens in an Nano emulsion is typically different that of traditional emulsion due to change in droplet size.

1) GRAVITATIONAL SEPERATION

In a Nano emulsion a droplet has a different density than the surrounding liquid so gravitational force act on it .if the droplet has lower density than the surrounding liquid it tends to move forward but if it has a higher density it tends ti move downward most liquid oils have lower densities than liquid water so oil tends to move upward and water tends to move downward having said that under some condition the oil droplet in oil by water emulsion may sediment. The oil droplet in oil by water Nano emulsion segment under specific circumferences1) the oil phase crystallize2) if they are quoted by a thick dense interfacial densities. The creaming velocity of an isolated rigid homogenous spherical particles is an ideal liquid defined by stoke law

$$\text{Vstokes}' = 2\text{gr}(\rho 2 - \rho 1)/9\text{n}1$$

Here Vstoke is the creaming velocity is the particle radius, g is the accerlation due to gravity is the shear viscosity

In case of Nano emulsion stoke law; the creaming velocity determines whether the droplet moves upward or downwards .Brownian motion is critical for small droplet since the surrounding fluid may not be perfect. The small size of the droplet has an effect on its creaming stability by changing the effective density of droplet in Nano emulsion .the volume occupied by the shell layer may be a significant fraction of the total volume of droplet

2) Droplet aggregation

The droplet in a Nano emulsion continuously colloid with each other as they move around due to Brownian motion ,gravity or mechanical agitation after it collision depending on strength and range of various attractive and repulsive force acting between them the droplet may move apart or stick together the two most common type of droplets aggregation and flocculation and coagulation in flocculation a number of droplet come together to form an aggregate each of which is return in its own integrates where as in coagulation droplet are merge together to form single layer droplet .the major kind of colloidal interaction operating between the droplet in an Nano emulsion are van deer Walls ,electrostatic,steric,hydrophobic, deplection and bridging .the Vander walls ,hydrobhobic,deplection and bridging interaction are usually attractive whereas the steric and electrostatic interaction are usually repulsive . In general the strength of both attractive and repulsive colloidal interaction tends to increase when increasing the droplet size.

Separated-when the attraction is relatively weak and there is large repulsive energy barrier

Weakly flocculated-when the attraction is moderately strong but there is large repulsive energy barrier Strongly flocculated-when the attraction is very strong the repulsive energy barrier is small and short range repulsion is very strong Coalcense-when the attraction is strong the repulsive energy barrier is small and there is no short range repulsion.

3) Ostwald ripening

In Nano emulsion Ostwald ripening is formed by oil molecules diffusing from a tiny droplet to a larger droplet through the surrounding liquids, causing the bigger droplets to grow at the expense of smaller once .the driving force of thermodynamics the fact that the water solubility of molecules scattered within spherical drop increases as the droplet radious shrinks droplet radious can be estimated using the equation

$$\mathbf{S(r) = S(\infty)\ exp\left(\frac{2\gamma Vm}{RTr}\right) = S(\infty) exp\left(\frac{\alpha}{r}\right)}$$

Here S (∞) is the water solubility of oil molecules for a planner oil water system, S (r) is the oil solubility of oil molecules when they are present within a spherical droplet of radious .the water solubility of the oil phase is usually the main

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determining the stability of nanoemulsion.nanoemulsion formulated from oil phase that are composed of primary of long chain triglycerides tends to be stable to internal ripening because of very low water solubility.

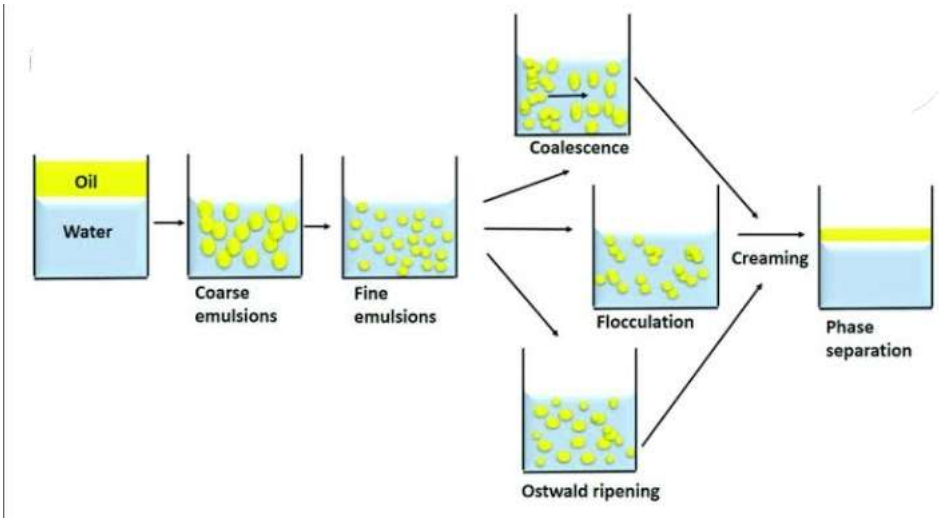

Fig1.7: instabilities of Nano emulsion.

CHARACTRIZATION OF NANOEMULSION

EVALUATION PARAMETER OF NANOEMULSION

1) DROPLETE SIZE ANALYSIS

The size of nanoemulsion droplet is determined using a diffusion method and a light scattering particle size analyzer counter.correlation spectroscopy ,which investigate the flocculation in light scattering owing to Brownian motion ,it also used to measure it.transmission electron microscopy can also be used to be examine the size of nanoemulsion droplet is determined using a diffusion method and a light scattering particle size analyzer counter .correlation spectroscopy which investigates the fluctuation in light scattering owing to Brownian motion is also used to examine the size of nanoemulsion droplets.

2) VISCOSITY DETERMINATION

At different shear rate and temperature the viscosity of nanoemulsion is determined using a Brookfield type rotary viscometer.

3) DILUTION TEST

This type can be identified by diluting a nanoemulsion with either oil or eater the test is predicted on the idea that a nanoemulsion can have more continuous phase added to it without loading stability. An o/w nanoemulsion can be diluted with water.

3) DRUG CONTENT

Preweighed nanoemulsion is extracted by dissolving in a suitable solvent and the extract is compared to a drug reference solution using a spectrophotometer or HPLC.

4) POLYDISPERSITY

It denotes the droplet size consistency in a nanoemulsion. The lesser the homogeneity of nanoemulsion droplet size, the higher the polydispersity value .the ratio of standard deviation to mean droplet size is what it's called a spectrophotometer is used to measure it.

5) DYE TEST

When a water soluble dye test is applied to an o/w nanoemulsion the colour is uniformly taken up by the nanoemulsion .in contrast if the emulsion is w/o type and the dye is water soluble the emulsion only takes up the color in the dispersion phase, resulting in an emulsion that is not uniformly coloured.a microscopic study of the emulsion can disclose this right away

6) REFRACTIVE INDEX

Refractive index of nanoemuslon is measured by Abbes refractometer

7) ZETA POTENTIAL

The zeta PALS equipment is used to measure zeta potential.it s used to determine the charge on a droplets surface in a nanoemulsion.

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8) FLOURANCE TEST

When exposed to ultraviolet light many oils glow .the entire field fluorescence's when a w/o nanoemulsion is subjected to fluorence is patchy use an o/w nanoemulsion

9) CONDUCTANCE MEASUREMENT

A conductometer is used to test the conductivity of nanoemulsion .a pair of electrodes linked to a lamp and an electric source are dipped in emulsion in this test. water conductance current in o/w emulsion ,and the lamp is illuminated as a result of current passing between the electrodes .when the emulsion is w/o the lamp does not light because the oil in the exterior phase does not conduct current

10) FILTER PAPER TEST

This test is based on the fact that when an o/w nanoemulsion is dropped onto filter paper, it spreads out quickly. A w/o nanoemulsion, on the other hand will travel slowly .for excessively viscous creams this procedures should not be employed.

APPLICATION OF NANOEMULSION

1) NANOEMULSION FOR PARENTERAL USE

- Parenteral Nano emulsions have varying applications. They are used to deliver drugs with lower bioavailability and/or narrow therapeutic indices. Chlorambucil, a lipophilic anticancer agent has been administered parenterally as a Nano emulsion (fabricated using ultra sonication and high pressure homogenization method) for treatment of ovarian and breast carcinoma.
- Tagne et al. have developed a water soluble nanoemulsion of tamoxifen to increase its effectiveness in breast cancer. TOCOSOL™ a vitamin E nanoemulsion containing paclitaxel was formulated using high pressure homogenization for treatment of various cancers like ovarian cancer, breast cancer etc.
- O/W parenteral lipid Nano emulsion of diclofenac has been investigated for treatment of arthritic conditions. Nanoemulsion containing diclofenac with mean droplet size of 200 nm was prepared by high pressure homogenization and ultrasonication. It was observed in vivo that diclofenac Nano emulsion provided sustained drug release allowing substantial dose reduction. Nano emulsions can be converted into stealth/long circulating Nano emulsions by coating or attaching a hydrophilic moiety such as PEG on to their surface which prevents identification.
- Kansal et al. developed a layer by layer polyelectrolyte coated nanoemulsion bearing doxorubicin for intervention in visceral leishmaniasis (caused by a parasite which resides in MPS). They utilized phosphatidyl serine as a targeting ligand. It was found that phosphatidyl serine coated nanoemulsion was taken up massively by macrophages allowing selective payload delivery in deep (normally inaccessible) residence site of parasite

2). NANOEMULSION FOR ORAL DRUG DELIVERY SYSTEM

Nano emulsions are ideal vehicles for oral delivery of lipophilic drugs like antibiotics, hormones, steroids, cytotoxic, diuretics, antifungals etc. Nano emulsions with their ability to coat drugs provide a platform for protecting them against hydrolytic enzymes or harsh pH and other environmental conditions. Nano emulsions trapped in structured organogel have been developed to increase oral bioavailability of curcumin. Candesartan cilexetil (CC), an antihypertensive, exhibits incomplete intestinal absorption due to its low aqueous solubility which ultimately reduces its oral bioavailability.

- Gao et al. have used Tween 80 and Solutol® HS-15 to develop an orally administered nanoemulsion of Candesartan cilexetil to placate this issue. Developed nanoemulsion increased peak plasma concentration of candesartan cilexetil 27 folds, whereas overall bioavailability increased 10 times in comparison to plain drug suspension. Clathrin-mediated endocytosis of nanoemulsion followed by lymphatic entry was proposed as the contributive mechanism responsible for bioavailability increment.
- Nano emulsions have also been developed using phase-inversion method for oral delivery of protein drugs like bovine serum albumin (BSA). It was found that bioactivity, specificity and conformational structure of encapsulated BSA was highly conserved in the system
- Xiaoyang Li have encapsulated insulin in a Labrafac® CC, phospholipid, Span™ 80 and Cremorphor® EL nanoemulsion by homogenization and coated it with chitosan alginate for oral delivery.

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- Polyelectrolyte coating on nanoemulsion template provided a robust interphase capable of withstanding rigors of gastric environment. Conformity of insulin in coated nanoemulsion was established using circular dichroism. In vivo testing revealed that upon oral administration, insulin loaded nanoemulsion produced significantly greater and longer hypoglycemic effect than subcutaneously administered plain insulin solution.

3) NANOEMULSION FOR TOPICAL USE

- It is a challenge to enhance permeation of several drugs intended for topical application. These are limited by poor dispersibility in topical vehicles like gels, creams, patches or possess skin irritant action.
- Nano emulsions have been explored for topical uptake of such drugs. They provide a combination of penetration enhancement (by altering lipid bilayers) and concentration gradient by acting as tiny reservoirs of drugs. For instance, a nanoemulsion (made of soybean lecithin, tween and poloxamer) containing menthol, methyl salicylate and camphor was prepared by high energy method and incorporated in a hydrogel. The resulting formulation had high permeation rates.
- In order to achieve deep skin delivery for tackling psoriasis, a nanoemulsion containing paclitaxel has been evaluated. In vivo pharmacokinetic studies following topical application revealed very high availability of drug in the skin, with minimum systemic escape.
- Caffeine has been delivered topically via a W/O nanoemulsion for treatment of skin related cancer. Shakeel et al. dispersed caffeine in an aqueous solution and titrated it against Lauroglycol 90, Transcutol HP and isopropanol to arrive at a thermodynamically stable and safe nanoemulsion which was sized between 20 and 100 nm. Upon testing nanoemulsion against aqueous caffeine, they observed significant increase in permeability parameters, steady-state flux and permeability coefficient.
- Nanoemulsions can be employed to deliver small molecules systemically via topical route. In an illustrative study, an O/W nanoemulsion (made with high pressure homogenization using soybean oil, phosphatidyl choline, Tween 80) containing α, δ or γ tocopherol was compared with their respective Nano suspensions. It was observed that systemic bioavailability along with antioxidant activity of δ and γ tocopherol increased 2.5 times when they were delivered as nanoemulsion.
- Nanoemulsions of ketoprofen and celecoxib have been prepared with adequate stability to attain high skin permeation rate. When compared against regular drug containing gel, such formulations had substantially greater permeability and transepidermal flux.
- W/O Nano emulsions have been used to deliver proteins or plasmids via transepidermal route. Their oil component is compatible with sebum present in follicular openings which act as alternate entry points. This opens up possibility of directing and confining potentially therapeutic transgenics to clinically active skin lesions.
- Wu eta al developed a system carrying plasmid pCF1CAT in olive oil employing spontaneous emulsification which had following characteristics:

(1) Significant entrapment of highly concentrated plasmid solutions
(2) Physical conservation of plasmid DNA due to simple manufacturing technique;
(3) Extended stability and (4) an acceptable safety profile. Even a hydrophilic compound like inulin can be systemically delivered 5 to15 fold better than its aqueous or micellar counterpart using a W/O nanoemulsion. Rate and extent of inulin transport across skin is dependent on hydrophile-lipophile balance of surfactant employed and availability of trans-folicular openings.

4) OCULAR AND PULMONARY DRUG DELIVERY SYSTEM

- Ocular administration of O/W Nano emulsions has been attempted to deliver water incompatible, environmentally sensitive, poorly absorbed (via Trans corneal route) or poorly retained drugs. Special consideration is accorded to transparency, viscosity and refractive index of nanoemulsions whilst devising them for ophthalmic applications.
- Any nanoemulsion intended for ocular administration should always be titrated against different doses to evaluate its tolerability. Some drugs like antisense oligonucleotides which have shown great therapeutic potential at in vitro level in variety of ailments, but are limited by their dispositional susceptibility in vivo, are good

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candidates for localized delivery via nanoemulsions.

- Hagigit et al. have managed ocular antisense delivery using a cationic nanoemulsion made of DOTAP (a cationic lipophilic transfection agent) for treatment of retinal neovascularization. DOTAP forms a complex with negatively charged antisense nucleotide and helps in penetrating negatively charged biological membrane which otherwise is not possible due to electrostatic repulsion.
- This cationic nanoemulsion (zeta potential +56 ± 2.6 mV) with a droplet diameter of 95 ± 2 nm was adjusted to pH 7.4 to create a formulation which was ideally suited for ophthalmic delivery. Temperature sensitive ophthalmic Nano emulsions, which convert into gel upon administration, have been developed to improve permeability, retention time and overall ocular bioavailability of loteprednol etabonate.
- A nanoemulsion made by spontaneous emulsifi-cation of triacetin, isopropyl myristate, ethyl alcohol and Tween 80 has been found capable of increasing solubility, ocular retention and permeability of lutein. The drug is effective in macular degeneration but suffers from limited ocular retention and consequently warrants repeated administration.
- Pulmonary route is an important means of drug administration. Pulmonary delivery has been envisaged for direct lung delivery of amphotericin B to treat pulmonary aspergillosis. To substantiate the purported hypothesis, amphotericin B was sonicated into two commercially available nanoemulsions (Intralipid® or Clinoleic®).
- Nanoemulsions of amphotericin B when delivered by an aerosol (developed using Pari Sprint jet nebulizer) enhanced lung deposition and pulmonary retention of drug. Additionally, first pass metabolism and systemic escape was also avoided which further improved therapeutic Efficacy.

5) INTRANASAL DRUG DELIVERY SYSTEM OF NANOEMULSION

- A major hurdle in targeting brain is presence of blood brain barrier (BBB). It restricts entry of hydrophilic and high molecular weight molecules like peptides. However, olfactory vein in nasal mucosa provides a direct passage between nose and brain. This has been exploited by use of nanoemulsions loaded with anti-Alzheimer's, anti-parkinsonism, anti-psychotic drugs for targeting brain.
- Risperidone, an antipsychotic, exhibits low bioavailability due to extensive first pass metabolism. This warrants administration of huge doses, which brings about numerous side effects. To reach the brain in effective concentrations and to avoid any unnecessary side effects a strategy involving nanoemulsion has been implemented; that improves bioavailability by preventing first pass metabolism and facilitating blood–brain barrier transport. Risperidone was dissolved in capmul MCM, tween 80, transcutol and propylene glycol to (48%, w/w) to form an O/W nanoemulsion spontaneously.
- Ultra-fine globule size of the developed nanoemulsion (15.5–16.7 nm) ensured quick and effective risperidone delivery to brain following intranasal administration. Nanoemulsions as a formulation unit have been employed as carriers for antigen presentation (vaccines) to dendritic cells either infiltrating or lying underneath the epithelial cell lining of nasal mucosa. Following enhanced intracellular uptake, and processing, antigen loaded nanoemulsion induce migration of stimulated dendritic cells to regional lymph nodes within a day.
- Das et al. have encapsulated an immunoadjuvant in an intranasally deliverable O/W nanoemulsion (W805EC nanoemulsion) to complement an inactivated influenza vaccine. W805EC nanoemulsion adjuvant generated a strong immune response providing advantages over parenteral vaccination.
- Yadav et al.have encapsulated a siRNA directed against TNF α in a cationic nanoemulsion for intranasal brain delivery to treat experimental neuro inflammation. The said nanoemulsion had greater transfection capability than commercially available transfection reagents and upto fivefold greater brain uptake than naked siRNA.

6) NANOEMULSION IN COMMERCIAL AND CLINICAL PIPELINE

- Nanoemulsions available commercially and those undergoing clinical trials are pondered upon in this section. Nanoemulsions have been developed for total parenteral nutrition. Oil content (soy bean oil, egg phospholipids, peanut oil, glycerin, fat soluble vitamins) present in such parenteral nanoemulsions act

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as alternative sources of energy and supplementation to meet daily requirements of fat-soluble vitamin A, D2,E&K1 in critical patients who cannot consume fats orally (Intralipid®, Vitalipid® developed by Fresenius kabi).

- Dexamethasone palmitate a steroid used in treatment of allergic disorders, and skin conditions has been made available as a nanoemulsion (Limethasone®) by Mitsubishi Pharmaceuticals for benefit in rheumatoid arthritis.
- Flurbiprofen axetil, a non-steroidal analgesic, also indicated in rheumatoid and osteoarthritis arthritis is administered as a nanoemulsion too.
- Clevidipine a calcium channel blocker, with extremely short distribution and termination half-life is given as a nanoemulsion (Cleviprex® by The Medicines Company). Clevidipine is practically insoluble in water, but its nanoemulsification in soybean oil, egg phospholipids and glycerin yields an ultrafine milky dispersion which can be diluted infinitely and administered as a slow infusion capable of attaining therapeutic concentrations despite short half-life of drug.
- Astra Zeneca has developed a nanoemulsion Diprivan that contains 10 mg/ml propofol for inducing general anesthesia diazepam is administered delivered via an intravenous nanoemulsion under the trade name Diazemuls (by Kabipharmacia).
- Kamira, a cosmetic company and its sister corporation TRI-K industries have come up with a Nano Gel system which can accommodate variety of active constituents. They claim that Nano Gel not only enhances penetrability of active compound but also minimizes epidermal water loss and keeps the skin moisturized for a longer period.

- **PATENTED NANOEMULSION**

- Patent name: method of preventing and treating microbial infections. Assignee: Nano Bio corporation (us).US patent number: 6,506,803
- Patent name: NE based on phosphoric acid fatty acid esters and its uses In cosmetics, dermatological, pharmaceutical, and/or ophthalmological field.Assignee:loreal.US patent number: 6,274,150.
- Patent name: NE based on ethylene oxide and propylene oxide block copolymers and its uses in cosmetics,dermtological and/or opthalmological field .assignee:loreal.US patent number:6,464,990
- NE of 5 aminolevulinic acid (6,559,183).Assignee: ASAT AG Applied science and technology (Zug, CH).PCT number: CT/EP99/08711.
- NEs of poorly soluble pharmaceutical active ingredients and method of making the same. Patent no: WO/2007/103294.

II. CONCLUSION

In pharmaceutical systems, Nano emulsions are commonly employed. Nanoemulsion formulation has various advantages, including pharmacological, biological, and diagnostic agent delivery. The most common use of nanoemulsion is to cover up the unpleasant taste of greasy liquids. The medications, which are sensitive to hydrolysis and oxidation, may also be protected by nanoemulsion.Nanoemulsions are now widely employed for the targeted administration of anticancer medicines, photo sensitizers, and therapeutic agents. Nano emulsions can potentially extend the duration of a drug's activity. In general, all nanoemulsion formulations can be regarded effective, safe, and bioavailable. In the future, it is projected that more nanoemulsion research and development will be carried out. Arguments made in this review suggest increasing influence of nanoemulsions in each and every aspect of drug delivery.

Nanoemulsions are 1) inherently resistant to normal destabilizing mechanisms persistent in emulsions; 2) they are usually transparent which gives them a cosmetic appeal, and 3) present many opportunities of increasing oral bioavailability of strongly lipophilic drugs. Oral delivery was the principal concept which led to development of emulsions, and it is in this aspect that nanoemulsions are especially suited. Other routes of drug delivery are equally approachable via nanoemulsions. Their minute dimensions make them special candidates for innocuous intravenous entry. Nanoemulsions are expected to progressively become center of research and development. Nevertheless many challenges still need to be overcome, in order to ensure that nanoemulsions enter mainstream pharmaceutical market and reach from a laboratory bench side to an actual patient bed side. Principal amongst them are the cost implications for scaling up nanoemulsion production, quest for nontoxic solvents in formulation, and also enhancing toxicity

Database available for various excipients employed in fabrication of nanoemulsions

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Expected Outcomes:

- Identify the types of Nano emulsion based on internal and external phase.
- Ensure the ingredient used in formulation with their categories.
- Produce Nano emulsion by using different Nano emulsification method.
- Clear idea of the physicochemical properties of Nano emulsion.
- Rheological properties of Nano emulsion can be clear
- Ensure the stability of nanoemulsion
- Eliminate instability
- Identify the marketed formulation and patented products of nanoemulsion for various application.