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Nano Emulsion:Novel Carrier For Drug Delivery

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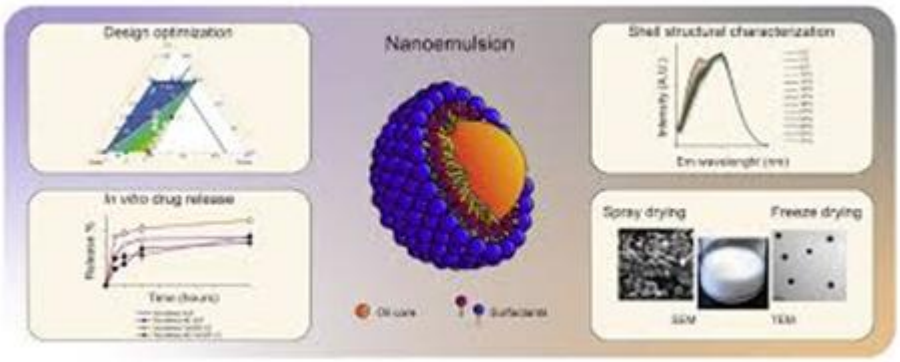
INTRODUCTION:-

An ideal drug delivery system fulfils the objective of maximizing therapeutic effectwhileminimizingtoxicitywiththeprogressinti meandadvancescienceand technology dosage forms have evolved from simple mixtures and pills, to highly sophisticated systems which are known as novel drug delivery systems. Nano emulsions are novel drug delivery systems consisting of emulsified oil and water systemswithmeandropletdiametersrangingfrom50 to1000nm.

Nano emulsions (Figs.1 and 2) are made from pharmaceutical surfactants that are generally regarded as safe (GRAS). The surfactant type and concentration in the aqueous phase are chosen to provide good stability against coalescence.Severaltypesofoils-naturalsemi-syntheticandsyntheticareusedinthe formulation of Nano emulsions. The capacity of Nano emulsions to dissolve large quantities of low soluble drugs along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal drug delivery vectors.



(Fig Drug Delivery System)

The major advantages of Nano emulsion radiations drug delivery carriers include increased drug loading enhanced drug solubility and bioavailability, reduced patient variability, controlled drug release, and protection from enzymatic degradation. Dosage forms.Arangeofnovelstrategiesarecurrentlybeingd evelopedforefficientdeliveryof poorly water-soluble drugs, such as the formulation of amorphous solid form, nanoparticles, micro emulsions, solid dispersions melt extrusion, salt formation

Types of Nano-emulsions:-

Types of Nano-emulsions based on composition:
Three types of Nano emulsions are most likely to be formed depending on the composition:

1. Oil in water Nano emulsions wherein oil droplets are dispersed in the continuous aqueous phase;
2. Water in oil Nano emulsions wherein water droplets are dispersed in the continuous oil phase;
3. Bi-continuous Nano emulsions wherein micro domains of oil and water are interspersed within the system.
4. In all three types of Nano emulsions, the interface is stabilized by an appropriate

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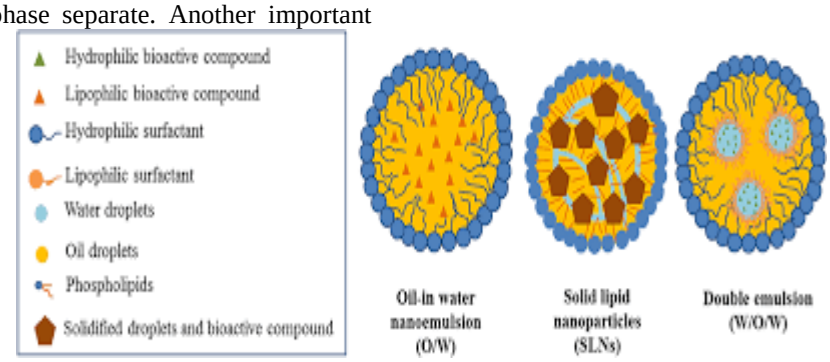
combination of surfactants and/or co-surfactants. The key difference between emulsions and Nano emulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate. Another important difference concerns their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



(Fig Type of Nano emulsion)

Types of Nano-emulsions based on drug delivery:

Self-emulsifying formulations (SEFs):

Self-emulsifying formulations (SEFs) are mixtures ofoil,surfactant, co-surfactant, and co solvents (absence of external phase water) and forms a transparent isotropic solution, which emulsify under gentle agitation similar to those which would be encountered in gastro intestinal tract (GIT). It has been recognized that this formulation when administered orally undergo spontaneous emulsification in aqueous GI fluids. This emulsified oil (triglycerides) stimulates bile secretion and drug containing oil droplets are further emulsified by bile salts. Lipid droplets are then metabolized by lipases and co lipases, secreted from the salivary gland, gastric mucosa and pancreas, which also hydrolyze the triglycerides into di-and mono glycerides and free fatty acids. Further, solubalization of these molecules occurs during the passage through the GI tract and eventually forms a range of emulsion droplets, vesicular structures.

Nano emulsions — Advances in Formulation, Characterization and Applications in Drug Delivery and mixed micelles containing bile salts, phospholipids and cholesterol Upon mixing with water the system SEFs have an ability to form fine colloidal droplets with very high surface area. In many cases, this accelerates the digestion of the lipid formulation, improves absorption, and reduces food effect and inter-subject variability. Self-emulsifying formulations distribute readily in the GI tract, and digestive motility.

The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water .This is followed by solubilization within the oil phase, as a result of aqueous penetration through the interface. Invariably, this tends to occur until the solubilization limit is attained close to the interphase. Further, aqueous penetration will lead to the formation of the dispersed liquid crystal phase.

a) Self-emulsifying drug delivery systems (SEDDS)

Self-emulsifying drug delivery system (SEDDS) is a strategy that has drawn wide research interest, basically due to its distinct capacity to solubilize and improve the bioavailability of hydrophobic drugs. This it does by ensuring aqueous solubility of the lipophilic drug. The presence of oil makes SEDDS unique and distinguishes them from ordinary surfactant dispersions of drugs. SEDDS are isotropic combination of drug, lipid/oil, co-solvents and surfactants.

On dilution by an aqueous phase they form fine stable oil-in-water (o/w) emulsions or fine lipid droplets which is the characteristic feature of these systems. When such a formulation is released into the lumen of the GIT, it disperses to form a fine emulsion generally o/w emulsion. SEDDS are generally formulated with triglyceride oils and ethylated nonionic surfactants. In general, the concentration of surfactant is greater than 25% in the formulation. The size of droplets ranges approximately less than 100 nm. SEDDS are believed to be superior compared with lipid

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solutions due to the presence of surfactants in the formulations leading to a more uniform and reproducible bioavailability.

Advantages of SEDDS include more consistent drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, protection of drug(s) from the gut environment, control of delivery profiles, reduced variability including food effects, enhanced oral bioavailability enabling reduction in dose and high drug loading efficiency. Self-emulsifying formulations spread readily in the gastrointestinal tract (GIT), and the digestive motility of the stomach and intestine provide the agitation necessary for self-emulsification.

These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. SEDDSs typically produce emulsions with turbid appearance, and droplet size between 200 nm to 5 µm while self-micro emulsifying drug delivery systems (SMEDDSs) form translucent micro-emulsions with droplet size of less than 200 nm. However, self nano emulsifying drug delivery systems (SNEDDS) produces clear or transparent emulsion with droplets size less than 100 nm].

When compared with emulsions, which are sensitive and metastable dispersed forms, SEFs are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles. SEDDS are prepared in two forms: Liquid and solid SEDDS (S-SEDDS). S- SEDDS are prepared by solidification of liquid self- emulsifying components into powder. This powder is then used to produce various solid dosage forms, for example self- emulsifying pellets, self-emulsifying tablets etc. S- SEDDS do not suffer with the problems like liquid SEDDS (L-SEDDS). It has Nano emulsions—advances in Formulation, Characterization.

Applications in Self emulsifying Drug Delivery:

The advantages like low manufacturing cost, more stability and is more patient compliance, because they are available as solid dosage form in tablets or pellet form. In many studies it have been reported that SEDDS are used for delivering and targeting hydrophobic drugs such as coenzyme Q10,halofantrine, vitamin E and cyclosporine-A. The solid SEDDS focus on the incorporation of liquid/semisolid ingredients into powders employing diverse solidification techniques like spray drying, melt granulation, molding, melt extrusion, and nanoparticle technology. The powders can then be formulated as solid dosage forms like self-emulsifying tablets and self-emulsifying pellets. Alternative approaches for the development of solid SEDDS comprise adsorption by solid carriers like microcrystalline cellulose, colloidal silica and various viscosity grades of HPMC, and use of high melting point solid excipients like Lutrol® and Gelucire.

High levels of surfactant typically present in SEDDS formulations can invariably lead to severe GI side-effects. Hence, a new class of SEDDS formulations, i.e. supersaturable SEDDS (SSEDDS) has been designed to reduce the amount of surfactant.

B)Self-Non-emulsifying drug delivery systems (SNEDDSs):

Self-non emulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in-water Nano emulsion when introduced into aqueous phases under gentle agitation. SNEDDS spread readily in the gastrointestinal tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDSs typically produce emulsions with turbid appearance, and droplet size between 200 nm to 5 µm, while self-micro emulsifying drug delivery systems (SMEDDSs) form translucent micro-emulsions withdroplet size of less than 200 nm. However, self-Nanoemulsifying drug delivery systems (SNEDDS) produce clear or transparent emulsiondroplets size less than 100 nm.

Successful formulation of SNEDDS depends on the thorough understanding of the spontaneous Nano-emulsification process and also on the physicochemical and biological properties of the components used for the fabrication of SNEDDS. The factors influencing the phenomenon of self-Nano emulsification are:

•The physicochemical nature and concentration of oily phase, surfactant and co- emulsifier or co surfactant or solubilizer (if included)
•The ratio of the components, especially oil-surfactant ratio
•The temperature and pH of the aqueous phase where Nano-emulsification would occur
•Physicochemical properties of the drug, such as hydrophilicity/lipophilicity, PKa and polarity.

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These factors should receive attention while formulating SNEDDS. In addition, the acceptability of the SNEDDS components for the desired route of administration is also very important while formulating SNEDDS. 84 Application of Nanotechnology in Drug Delivery SNEDDS offer a reduction in bioavailability and can offer reproducibility in plasma profiles of drugs. The ability of the SNEDDS in improving Cmax and oral bioavailability or therapeutic effect has been established for various hydrophobic drugs.

The improvement in bioavailability can be translated into reduction in the drug dose and dose-related side effects of many hydrophobic drugs, such as antihypertensive and antidiabetic drugs.

Advantages of Nano-emulsions as drugdeliverysystems:

T**he advantages of Nano emulsions drug delivery systems includes,**

• 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.

•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. Nano emulsions are thermodynamically stable system and the stability allows self- emulsification of the system.

•The small droplets also prevent their coalescence, since these droplets are elastic, surface fluctuations are prevented.

•Nano emulsions are suitable for efficient delivery of active ingredients through the skin. The large surface area of the emulsion system allows rapid penetration of actives. It is non-toxic and non-irritant so can be easily applied to skin and mucous membranes.

•The transparent nature of the system, their fluidity (at reasonable oil concentrations) as well

•The absence of any thickeners may give them a pleasant aesthetic character and skin feel.

•Unlike micro-emulsions (which require a high surfactant concentration, usually in the region of 20 % and higher), Nano emulsions can be prepared using reasonable surfactant concentration. For a 20 % o/w Nano emulsion, a surfactant concentration in the region of

5 – 10 % 88 Application of Nanotechnology in Drug Delivery may be sufficient. Nano emulsions are usually formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.

•Nano emulsions can be applied for delivery of fragrance, 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 crystalline phases around the Nano emulsion droplets.

•Nano emulsions can be formulated in numerous dosage foam such as creams, liquids.

•They do not damage healthy human and animal cells, so Nano emulsions are suitable for human and veterinary therapeutic purposes.

•Increase the rate of absorption, increases bioavailability and eliminates variability in absorption

•Helps solubilize lipophilic drug and masks unpleasant taste of some drugs

•Various routes like topical, oral and intravenous can be used to deliver the product.

•Better uptake of oil-soluble supplements in cell cultures. Improve growth and vitality of cultured cells. It allows toxicity studies of oil-soluble drugs in cell cultures.

•Nano emulsions could enhance the stability of chemically unstable compounds by protecting them from oxidative degradation and degradation by light.

•Possibilities of controlled drug release and drug targeting, and the incorporation of a great variety of therapeutic actives.

Disadvantages of Nano-emulsion based system:-

•Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the Nano-droplets.

•Limited solubility capacity for high melting substances.

•Nano emulsion stability is influenced by environmental parameters such as temperature and ph.

•Lack of understanding of the mechanism of production of submicron droplets and the role of

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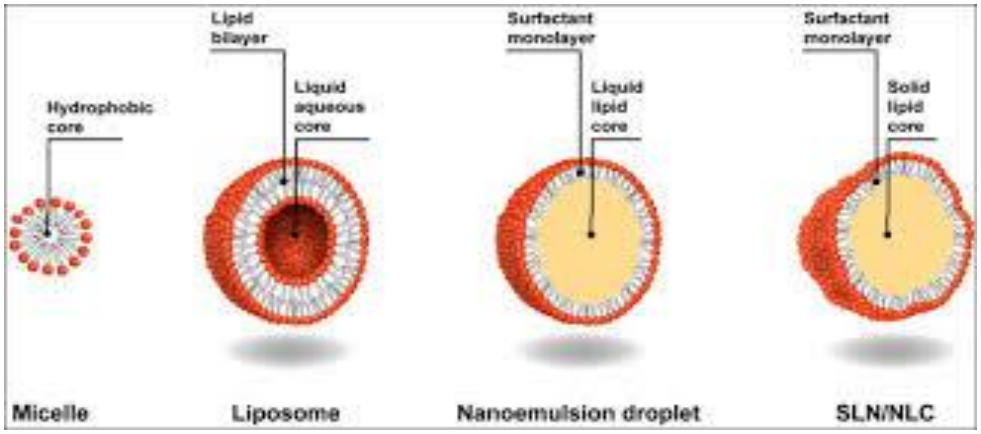
surfactants and co-surfactants.
•Lack of demonstration of the benefits that can be obtained from using Nano emulsions when compared with the classical macro-emulsion systems.
•Lack of understanding of the interfacial chemistry that is involved in production of Nano emulsions.

Theory of Nano-emulsion:-

In Nano emulsion which is categorized as multiphase colloidal dispersion which is generally characterized by its stability and clarity. There is an application of high shearGenerally obtained by micro fluid or ultrasonic approach generally used to reduce the droplet size to nanoscale. There is a marginal difference between the terms Nano emulsion and micro-emulsion also known as micellar phase or mesophase. The micro-emulsion generally forms through thermodynamic self-assembly whereas Nano emulsion requires external shear for rupturing the droplets.

In retrospect, the historical choice of the word "micro emulsion" to describe the nanoscale is unfortunate since they are structurally between 1 to 100 nm as for nanoemulsion. Micro emulsions are not the emulsions of micro scale droplets. They are formed by self-assembled equation phase in which the surface tension dose not play a significant role. The nanoemulsions underlines the basic principle in its formulation. They generally comprises of two immiscible phase with an interfacial tension between them reduced by addition ofsurfactant.



(Fg Theory of Nano Emulsion)

Materials used in preparation of Nano emulsions:-

Nano emulsions are prepared using oils, surfactants and co-surfactants and aqueous phase. Oils used in Nano emulsions preparation include Captex 355, Captex 8000, Witepsol, Myritol 318, Isopropyl myristate, Capryol 90, Sefsol-218, triacetin, isopropyl myristate, castor oil, olive oil, etc. Solubility of the drug in the oil phase is an important criterion for the selection of oils.

This is particularly important in the case of oral formulation development, as the ability of Nano emulsion to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase.

While water-in-oil Nano emulsions are better choice for hydrophilic drugs lipophilic drugs are preferably solubilized in oil-in-water Nano emulsions.

Drug loading in the formulation is a very critical design factor in the development of nanoemulsions for poorly soluble drugs, which is dependent on the drug solubility in various formulation components. An understanding of factors influencing drug loading capacity while maintaining the capability of the system to undergo monophasic dilution with water and minimizing the tendency for drug precipitation or crystallization in diluted systems is essential to the design of stable and appropriately low-volume Nano emulsion systems for drug delivery applications. Edible oils are not frequently useful due to their poor ability to dissolve large amounts of lipophilic drugs.

Formulation of Nano emulsions:-

Nano emulsion contains main three components as-
1) Oils.
2) Surfactants.
3) Co- surfactants.
Oils:-
Eg.1.Captex 355
2. Captex 200
3 .Captex8000
4. Witepsol

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5.Isopropylmyristate
Surfactants:-
Solutes or molecules that are preferentially absorbed at surface or interface of liquids reduce the surface of interfacial tension and are therefore termed as surface active agents or surfactants.
Classification of surfactants:
1) Anionic surfactants
2) Cationic surfactants
3) Non-ionic surfactants
4) Ampholytic surfactants.

1. Anionic surfactants:-
Anionic surfactants in common use consist of the soaps of alkali ,amines metals,sulphated alcohols ,and sulphonates.
Eg - Alkali soaps - pottasium and sodium sterarte. Amine soaps – ethanolamine ,diethanolamine. Metallic soaps – Calcium and Aluminium stearate.
2. Cationic surfactants:-
Eg – quaternary ammonium compounds such as cetrmide, benzalkonium chloride
,benzethonium chloride.
3.Ampholytic surfactant :
These are substances whose ionic characteristics depand on ph of the system .At intermediate ph these as zweterrionions .
Eg – Lecithin , N –Dodecyclamine. 4.Non–ionic surfactants :
The advantages of these agents include that compatibility with both anionic and cationic surfactants their resistance to ph change and effect of electrolyte and lower irritancy compared to other surfactants .
Co-Surfactants :
A surfactant that act in addition to other surfactant further reducing the surface tensionofliquids .
Eg – Transcutol P Ethylene glycol Ethanol.

Characterization of Nano emulsion:-

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the Nano emulsion. The droplet size distribution of Nano emulsion vesicles can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting Nano emulsion stability.

1.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.

2.Dilutability Test:-

O/W Nano emulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nano emulsion.

3.Conductance Measurement:-

O/W Nano emulsion 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 Nano emulsion systems was observed at low volume fractions and such behavior was interpreted as an indication of percolated behavior‟ or exchange of ions between droplets before the formation of bi-continuous structures. Dielectric measurements are a powerful means of probing both structural and dynamic features of Nano emulsion systems.

4.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.

5.Polydispersity:-

The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 25oC using a He-Ne laser.

6.Phase analysis:-

To determine the type if Nano emulsion that has formed the phase system (O/W or W/O) of the Nano emulsions is determined by measuring the electrical conductivity using a conduct meter.

7.Interfacial Tension:-

The formation and the properties of Nano emulsion can be studied by measuring the interfacial tension. Ultra-low values of interfacial tension are correlated with phase behavior, particularly the existence of surfactant phase or middle-phase Nano emulsions in equilibrium with aqueous and oil phases.

8.Viscosity measurement:-

The viscosity of Nano emulsions of

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several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37±0.2°C by a row bath, and the samples for the measurement are to be immersed in it before testing.

9.PH:-

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

10.Refractive Index:-

The refractive index, n, of a medium is defined as the ration of the speed, c, of a wave such as light or sound in a reference medium to the phase speed up of the wave in the medium. n=c/vp; It was determined using an Abbes type refractometer (Normal International) at 25±0.5°C .

11.Transmission Electron Microscopy (TEM):-

Morphology and structure of the Nano emulsion were studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of Nano emulsion droplets. Observations was performed as, a drop of the Nano emulsion was directly deposited on the holey film grid and observed after drying.

12.In Vitro Skin Permeation Studies:-

In vitro skin permeation studies were performed by using KesharyChien- diffusion cell. In vitro drug release of the formulation was performed in simulated intestinal fluid (SIF) (pH 6.8) using dialysis membrane. The membrane was activated by keeping it in SIF overnight. It was exposed to running water for few hours to remove glycerin based contents. Nano emulsion formulation (equivalent to 80 mg of drug) were loaded into the dialysis membrane and placed in a 150 ml of 1 N SIF (pH 6.8) in a shaking incubator (maintained at 50 rpm and 37 ± 0.5°C). Samples were withdrawn at predetermined intervals and replaced with same volume of the fresh medium.

Stability:-

This section describes the fundamentals behind emulsion destabilization mechanisms and systematically presents the reasons for robust stability of nanoemulsions. This section also details the research conducted on understanding and controlling nanoemulsion stability.

Destabilization mechanisms:-

Nanoemulsions are kinetically stable and given sufficient time, will separate into different phases.Summarizes the different destabilization mechanisms of nanoemulsions namely flocculation, coalescence, Ostwald ripening and creaming/sedimentation. In flocculation, droplets come closer to each other because of attractive interactions and move as a single entity. In contrast, during coalescence, the droplets merge into each other to become a bigger drop1.

The DLVO theory predicts that when the repulsive maximum of the droplet–droplet interaction potential is low (B0kBT), droplets come close to each other and fall into the primary minimum i.e., the irreversibly flocculated state. During this process, when the droplets come into 'primary' contact, they tend to coalesce. Therefore, it is hard to distinguish between flocculation and coalescence in emulsions. Typically, due to the adsorbed layer of emulsifier on the droplet, steric interactions increase the repulsive maximum which in turn stabilize the emulsions against flocculation and coalescence. The steric stabilization is stronger in nanoemulsions as the thickness of the adsorbed emulsifier layer (B10 nm) is comparable to the droplet size.

Ostwald ripening occurs due to the difference in chemical potential of solute within droplets of different sizes. Due to Laplace pressure the chemical potential of the dispersed phase is higher in smaller droplets than in larger ones, providing the driving force for mass transfer from the smaller to the larger droplets. Thus the smaller droplets become smaller and the larger droplets grow.

Controlling stability of Nano emulsions:-

Shows the summary of the work done on controlling Nano emulsion destabilization.lists various parameters that affect the destabilization rate of Nano emulsions. Dilma's ET al.showed that the Ostwald ripening rate follows an Arrhenius behavior with this happens because both solubility and diffusivity are temperature dependent. The ionic strength ofthe continuous phase significantly affects the repulsive barrier between the two droplets. Increase in the ionic strength of the continuous phase significantly reduces the Debye screening length and hence a lower repulsive barrier is observed. Thus, the emulsions have a much higher probability of flocculating coalescing.

Development in Nano- emulsion:-

Materials:-

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Cefuroxime,3-(aminocarbonyl)oxy]methyl}-7-[(2Z)-2-(2-furyl)-2(methoxyimino)acetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, was purchased from Euroasias chemical private limited (Mumbai, India).Safflower seed oil, soybean oil, sunflower oil, pine nut oil, olive oil, Cremophor EL, and sodiumoleate were purchased from Sigma-Aldrich Co. (St Louis, MO, USA). Lecithin Lipoid S75 was also purchased from Lipoid GmbH (Ludwigshafen, Germany); Tween 80 (polyoxyethylenesorbitanmonooleate) was purchased from Merck (Hohenbrunn, Germany), and glycerol was purchased from J.T. Baker (Phillipsburg, NJ, USA).

All the used oils and surfactants were analytically graded materials. Acetonitrile (high-performance liquid chromatographic [HPLC] grade, 99.9% purity) was purchased from J.T. Baker. Sodium hydroxide (analytical grade) was purchased from Merck Millipore (Billerica, MA, USA). Water was deionized and Milli-Q filtered. Centrisart tubes and dialysis membranes were from Sartorius AG (Göttingen, Germany). All other chemicals and reagents were of analytical or HPLC grade.

HPLC analysis

Waters acuity High Performance Liquid Chromatographic system (Waters Corporation, Milford, MA, USA), which was equipped with a photodiode array (PDA) detector (Waters 2998) and auto samplers, was used for cefuroxime analysis.

This method was previously validated according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines and proven specific, linear (r2>0.9995), and precise (relative standard deviation [RSD] <1.85%).

Applications Of Nano Emulsions In Drug Delivery:-

Nano emulsions could be and have been applied in various aspects of drug delivery including: cosmetics and transdermal delivery of drug, cancer therapy, vaccine delivery, prophylactic in bio-terrorism attack, non-toxic disinfectant cleaner, cell culture technology, formulations for improved oral delivery of poorly soluble drug, ocular and otic drug delivery, intranasal drug delivery, parenteral drug delivery and pulmonary delivery of drugs.

Applications in cosmetics:-

Recently importance of nanoemulsions have become increasing as good vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers. Due to their lipophilic interior, nanoemulsions are more suitable for the transport of lipophilic drug than liposomes Similar to liposomes, nanoemulsions supports the skin penetration of active ingredients and thus increases their concentration in the skin. Another advantage is the small-sized droplet with its high surface area permit effective delivery of the active to the skin.

More ever, nanoemulsions gain increasing interest due to their own bioactive effects. This may reduce the trans-epidermal water loss (TEWL), suggesting that the barrier function of the skin is strengthened. Nano emulsions are acceptable in cosmetics because there is no chance of creaming, sedimentation, flocculation or coalescence, which is observed within micro emulsions. The incorporation of potentially irritating surfactants can be avoided by using high-energy equipment during manufacturing process. PEGfree Nano emulsions for cosmetics has also been developed and formulations exhibited good stability.

Antimicrobial Nano emulsions:-

Antimicrobial Nano emulsions are o/w droplets that range from 200-600 nm. They are made of oil and water and are stabilized by surfactants and alcohol. The Nano emulsions has a broad spectrum of activity against bacteria like E. coli, salmonella,

S. aureus; enveloped viruses like HIV, herpes simplex; fungi like candida, dermatophytes,and spores like anthrax. The Nano emulsions particles are thermodynamically driven to fuse with lipid-containing organisms.

This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death. In the case of spores, additional germination enhancers are added into the emulsion. Once starting of germination takes place, the germinating spores become susceptible to the antimicrobial action of the Nano emulsions. An aspect of the Nano emulsions is their highly selective toxicity to

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microbes at concentration range that are non-irritating to skin or mucous membrane.

The safety range of Nano emulsions is because of the low amount of detergent in each droplet, yet when acting in concert, these droplets have enough energy and surfactant to destabilize targeted microbes without affecting healthy cells. Nano emulsions can get a level of topical antimicrobial activity, which can only be previously achieved by systemic antibiotics.

Prophylactic in bio-terrorism attack:-

Because of their antimicrobial activity, research has begun on use of nanoemulsions as a prophylactic medicated dosage form, a human protective treatment, to prevent the people exposed to bio-attack such as Anthrax and Ebola. The broad-spectrum nanoemulsions were checked on surfaces by the US Army (RestOps) in Dec 1999 for decontamination of Anthrax spore.

It was checked again by RestOps in March 2001 as a chemical decontamination agent. This technology has been tested on gangrene and clostridium botulism spores, and can even be used on contaminated wounds to salvage limbs. The nanoemulsions can be formulated into a cream, foam, liquid and spray to decontaminate a large number of materials.

Nano emulsions in vaccines delivery:-

This medication delivery system uses nanotechnology to vaccinate against human immunodeficiency virus (HIV). There is recent evidence that HIV can infect the mucosal immune system. Therefore, developing mucosal immunity through the use of Nano emulsions may become very important in the future fight against HIV [50]. The oil- based emulsion is admin interred in the nose, as opposed to traditional vaccine routes. Recent research results indicate that genital mucosa immunity may be attained with vaccines that are administered into the nasal mucosa.

Nano emulsions are being used to transport inactivated organisms to a mucosal surface to produce an immune response. The first applications as vaccine, an influenza vaccine and an HIV vaccine, can proceed to clinical trials. The Nano emulsion causes proteins applied to the mucosal surface to be adjuvant and it help uptake by antigen presenting cells. This results in the significant systemic and mucosal immune response due to that the production of specific IgG and IgA antibody as well as cellular immunity.

Work in influenza has shown that animals can be prevented against influenza after a single mucosal exposure to the virus mixed with the Nano emulsions. Research has also show that animals exposed to recombinant gp120 in Nano emulsions on their nasal mucosa create significant responses to HIV, thus giving a basis to use of this material as an HIV vaccine. Additional research has been ongoing to complete the proof of concept in animal trials for other vaccines including Anthrax and Hepatitis B. The University of Michigan has licensed this technology to Nano Bio.

Nano emulsions as non-toxic disinfectant cleaner:-

Nano emulsions have been employed as a disinfectant cleaner. A nontoxic disinfectant cleaner for use in routine markets that include healthcare, travel, food processing and military applications has been developed by enviro systems. They have been found to kill tuberculosis and a large spectrum of viruses, bacteria and fungi within 5 to 10 min without any of the hazards posed by other categories of disinfectants. The product requires no warning labels. It does not irritate eyes and can be absorbed through the skin, inhaled or swallowed with harmless effects.

Nano emulsions in cell culture technology:-

Cell cultures are used for in vitro assays or to produce biological compounds like an antibodies or recombinant proteins. For optimization of cell growth, the culture medium can be supplemented with a large number of molecules or with blood serum. It has been very difficult to provide the media with oil-soluble substances that are available to the cells, and only few amounts of the lipophilic compounds could be absorbed by the cells.

Nano emulsions are a new method for the delivery of oil-soluble substances to human cell cultures. The system is based on a Nano emulsions that is stabilized by phospholipids. This Nano emulsions is transparent and can be passed through 0.1 mm filters for sterilization. Nano emulsions oil droplets are very easily taken up by the cells.

Nano emulsion formulations for improved oral delivery of poorly soluble drugs:-

Nano emulsions formulation was developed to increase oral bioavailability of hydrophobic drugs. Paclitaxel was selected as a model hydrophobic drug. The o/w Nano emulsions were made with pine nut oil as the internal oil phase, water as the external phase and egg lecithin as theprimary emulsifier. Stearylamine and

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deoxycholic acid were used to give positive and negative charge to the emulsions, respectively.

The formulated nanoemulsions had a particle size range of 100-120 nm and zeta potential ranging from 34 mV to 245 mV. After oral administration of Nano emulsions, a significantly higher concentration of paclitaxel was observed in the systemic circulation compare to control aqueous solution. The results of this study suggest that Nano emulsions are promising novel formulations which can promote the oral bioavailability of hydrophobic drugs.

Nano emulsions in ocular and otolith drug delivery:-

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. It is a common knowledge that the application of eye drops as conventional ophthalmic delivery systems results in poor bioavailability and therapeutic response because oflacrimal secretion and nasolacrimal drainage in the eye. Most of the drug is drained away from the peroneal area in few minutes.

As a result, frequent instillation of concentrated solutions is needed to achieve the desired therapeutic effects. But, by the tear drainage, the main part of the administered drug is transported via the nasolacrimal duct to the gastric intestinal tract where it may be absorbed, sometimes causing side effects. In order to increase the effectiveness of the drug, a dosage form should be chosen which increases the contact time of the drug in the eye. This may then increase the bioavailability, reduce systemic absorption, and reduce the need for frequent administration leading to improved patient compliance. Nano emulsions could be employed to overcome some ofthese problems.

Nano emulsions as a vehicle for transdermal delivery:-

Drug delivery through the skin to the systemic circulation is convenient for a number of clinical conditions due to which there has been a considerable interest in this area. It offers the advantage of steady state controlled drug delivery over extended period of time, with self-administration also being possible, which may not be the case with parenteral route. The drug input can be eliminated at any time by the patient just by removing the transdermal patch.

CONCLUSION:-

Nano emulsion formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents. Traditionally, Nano emulsion have been used in clinics for more than four decades as total parenteral nutrition fluids. Several o ther products for drug delivery applications such as Diprivan, Liple and Ropion have also reached the marketplace. Although Nano emulsion 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, photosensitizer's 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 (much higher than CMC level) used for the formation of Nano emulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared Nano emulsion, which can be abroad research area in future.

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