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NANOEMULSIONS AS OPTHALAMIC DRUG DELIVERY SYSTEM

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Abstruct:

Nanoemulsions are liquid-in-liquid dispersion with a droplet size of about 100 nm. They have a transparent appearance, high rate of bioavailability, and increased shelf life. Nanoemulsions mainly consist of oil, water, surfactant, and cosurfactant and can be prepared by high- and low-energy methods. Diluted nanoemulsions are utilized for the delivery of ophthalmic drugs due to their capability to penetrate the deep layers of the ocular structure, provide a sustained release effect, and reduce the frequency of administration and side effects. These nanoemulsions are subjected to certain tests, such as safety, stability, pH profile, rheological studies, and so on. Cationic nanoemulsions are prepared for topical ophthalmic delivery of active ingredients from cationic agents to increase the drug residence time on the ocular surface, reducing their clearance from the ocular surface and improving drug bioavailability. This review article summarizes the main characteristics of nanoemulsions, ophthalmic nanoemulsions, and cationic nanoemulsions and their components, methods of preparation, and the evaluation parameters for ophthalmic nanoemulsions.

Key words: Nanoemulsion, cationic nanoemulsions, ophthalmic drug delivery.

Introduction:

Ophthalmic drug delivery system is one of the most important routes of drug administration, but it is regarded as a challenging attempt encountered by pharmaceutical scientists. Most ophthalmic diseases are treated by topical eye drop instillation; however, several problems, such as poor bioavailability, are associated with these formulations. The drug is removed from the precorneal area within several minutes after instillation due to lacrimal secretion and nasolacrimal drainage. Various problems, including the issue on stability, high cost, and tedious preparation methods, are associated with the scaling up of nanoemulsions. For the above reasons, pharmaceutical scientists attempt to formulate ophthalmic preparations that can overcome such problems. Although the incorporation of drugs in different pharmaceutical vehicles, such as ointments, suspensions, and emulsions, can improve the bioavailability and provide sustained drug release, they cannot be regarded as the formulation of choice given their ocular adverse effects, including irritation, redness of the eye, interference with vision, and low product stability. In addition, chronic administration may increase systemic availability and cause severe systemic

complications. Formulations containing preservatives also induce adverse reactions upon systemic absorption.

Barriers for intraocular drug transport: Each layer of the ocular tissue has distinct features and poses a diverse barrier following drug administration via a certain route .

Tears:

Tears can influence the administration of ophthalmic drugs through binding with the administered drug, resulting in enhanced clearance and drug dilution. Tear turnover is one of the dynamic barriers that significantly decrease drug availability, leading to inhibition of therapeutic effect.

Cornea:

The cornea, which is a non-vascular structure, consists of three main layers: the outer epithelial layer which is a lipophilic layer, the middle stromal layer which is hydrophilic in nature, and the inner endothelial layer that separates the aqueous humour and the stroma. The corneal epithelium forms the most important barrier to drug absorption by topical administration; the corneal cells of glycosyl amino glycans lining the ocular surface are negatively charged at physiological pH. When applying a positively charged formulation to the eye, an electro staticattraction will possibly occur, which will prolong the residence time of the formulation on the ocular surface.

Conjunctiva:

The conjunctiva of the eye is a thin layer that lines the inside of eyelids and maintains the tear film. The stroma between the outer conjunctival epithelium and inner sclera has an abundance of blood and lymphatic vessels throughout the subconjunctiva, and it acts as a dynamic barrier to hydrophobic drug absorption. Given the rich capillaries and lymphatic vessels in the stroma, the drug administered to the conjunctival sac can be rapidly cleared. The conjunctival epithelium is more penetrable to larger molecules and has 20 times larger surface area than the cornea because of its wider intercellular spaces. The conjunctival pathway favors the absorption of large hydrophilic molecules (with molecular weight nearly less than 20 k Da), such as proteins and peptides, different from the corneal route which favors lipophilic small molecules (the majority of drugs). Meanwhile, the retardation of the passive pathway can occur by the tight junctions present in the conjunctival epithelium. Therefore, if drug absorption through the conjunctiva is compared with that through the cornea, the former is considered as non-productive, leading to the low bioavailability of ophthalmic drugs.

Sclera: The sclera is the outer layer of the eyeball and is known as the white of the eye. This part can maintain the eye shape through its fibrous structure. The hydrophobic nature of drugs affects the permeability of sclera; when the lipophilicity of a drug increases, the permeability across the sclera will decrease, and vice versa. Moreover, the permeation of therapeutic molecules, including drugs, depends on the hydration degree of sclera and its intraocular pressure. Intraocular pressures in the normal range of 15-20 mmHg have negligible effects on permeability, whereas the trans-scleral permeability of solute molecules is affected by their high intraocular pressure up to (>20-60 mmHg).

Choroid/ Bruche's membrane:

This part of the eye is regarded as the most vascularized part of the body. The choroidal thickness decreases with age. By contrast, the thickness of Bruch's membrane increases with age, and the changes in the thickness of choroid and Bruch's membrane may affect drug penetration into the retina.8 With aging, the choroid becomes thinner, and the Bruch's membrane becomes thicker, leading to alteration in the barrier property which in turn alters drug permeation of drug molecules over the years.

Retina:

The retina is located at the back of the eye, on which an image is formed from the light that enters the eye from the cornea, passing across the anterior part until it reaches the retina in the posterior part of the eye, where it can then be interpreted in the brain. The retina may be subjected to diseases that affect the posterior segment of the eye, such as age-related macular degeneration and diabetic retinopathy. All of the drugs in

the vitreous can be eliminated by anterior and posterior route; the drugs can be eliminated across the retina after passing through the internal limiting membrane that separates the retina and the vitreous.[1]

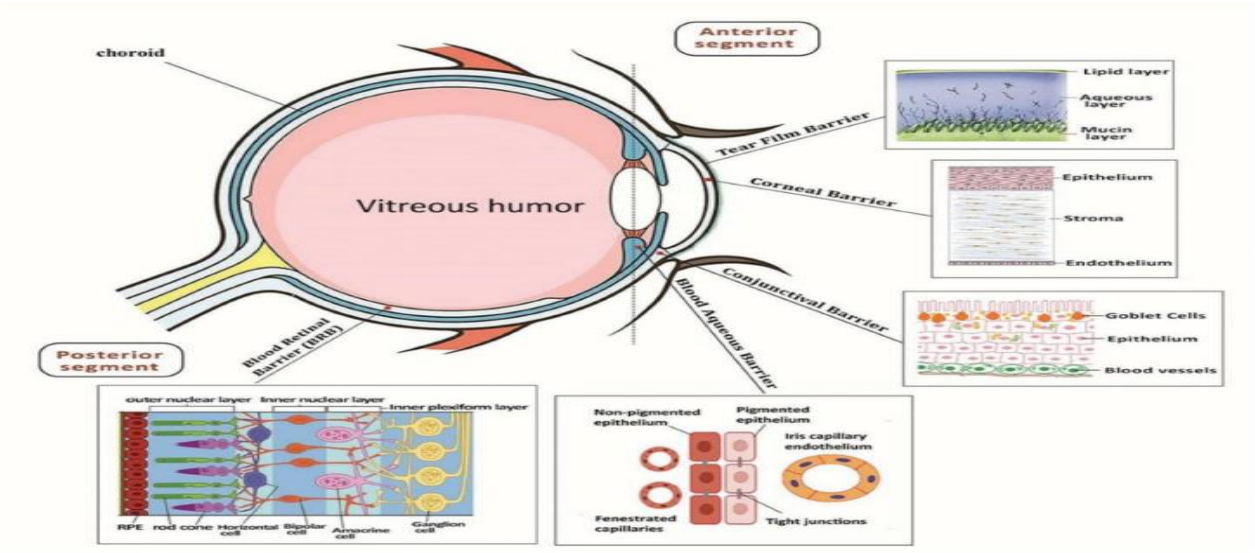

Figure 1. Ocular barriers for drug transport

Approches:

The various approaches attempted in the early stages can be divided into two main categories: bioavailability improvement and controlled release drug delivery. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on maximizing corneal drug absorption and minimizing precorneal drug loss through viscosity and penetration enhancers, prodrug, gel, and liposomes. The second one is based on the use of sustained drug delivery systems which provide the controlled and continuous delivery of ophthalmic drugs, such as implants, inserts, nanoparticles, micro particulates, and colloid.

Approaches to improve ocular bioavailability:

Viscosity enhancers:

Viscosity-increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should correspond to a slower elimination from the preocular area, which lead to improved precorneal residence time and hence a greater transcorneal penetration of the drug into the anterior chamber. It has minimal effects in humans in terms of improvement Figure 3: Precorneal factors that influence bioavailability of topically applied ophthalmic drugs. The polymers used include polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose.

Eye ointments:

Ointments are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to body temperature and are non irritating to the eye. Ointments may be simple bases, where the ointment forms one continuous phase, or compound bases where a two-phased system (e.g., an emulsion) is employed. The medicinal agent is added to the base either as a solution or as a finely micronized powder. Upon instillation in the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods. Ointments are therefore useful in improving drug bioavailability and in sustaining drug release. Although safe and well-tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation. Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers which leads to slight prolonged precorneal residence time. It has advantage like reduced systemic exposure. Despite the extremely high viscosity, gel achieves only a limited improvement in bioavailability, and the dosing frequency can be decreased to once a day at most. The high viscosity, however, results in blurred vision and matted eyelids, which substantially reduce patient acceptability. The aqueous gel typically

utilizes such polymers as PVA, polyacrylamide, poloxamer, HPMC, carbomer, poly methyl vinyl ethermaleic anhydride, and hydroxypropyl ethylcellulose.

Prodrug:

The principle of prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound. Thus, the ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility. Enzyme systems identified in ocular tissues include esterases, ketone reductase, and steroid 6-hydroxylase. Prodrug is considered as a new drug entity; so, extensive pharmacokinetic and pharmacologic information is required for proper design.

Penetration enhancers:

The transport characteristics across the cornea can be maximized by increasing the permeability of the corneal epithelial membrane. The stratified corneal epithelial cell layer is a 'tight' ion-transporting tissue, because of the high resistance of 12 to 16 kΩcm2 being exhibited by the paracellular pathway. So, one of the approaches used to improve ophthalmic drug bioavailability lies in increasing transiently the permeability characteristics of the cornea with appropriate substances known as penetration enhancers or absorption promoters. It has disadvantages like ocular irritation and toxicity.

Liposomes:

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. Liposomes possess the ability to have an intimate contact with the corneal and conjunctival surfaces, which increases the probability of ocular drug absorption. This ability is especially desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility, or those with medium to high molecular weights. The behavior of liposomes as an ocular drug delivery system has been observed to be, in part, due to their surface charge. Positively charged liposomes seem to be preferentially captured at the negatively charged corneal surface as compared with neutral or negatively charged liposomes. It is droppable, biocompatible, and biodegradable in nature. It reduced the toxicity of the drug. It provides the sustained release and site specific delivery. Liposomes are difficult to manufacture in sterile preparation. It has limitation like low drug load and inadequate aqueous stability.

Niosomes:

Niosomes are bilayered structural vesicles made up of nonionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time, which leads to increase ocular bioavailability. They are nonbiodegradable and non biocompatible in nature. In a recent approach to deliver cyclopentolate, niosomal formulation was developed. It released the drug independent of pH, resulting in significant t IOP lowering effect in rabbits as compared with timolol solution. enhancement of ocular bioavailability. Niosomal formulation of coated (chitosan or carbopol) timolol maleate exhibited significant IOP lowering effect in rabbits as compared with timolol solution.

Nanoparticles/nanospheres:

These are polymeric colloidal particles, ranging from 10 nm to 1 mm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed. Encapsulation of the drug leads to stabilization of the drug. They represent promising drug carriers for ophthalmic application. They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nano capsules. found that the nano capsules show a better effect than the nanospheres, probably because the drug is in a unionized form in the oily core and can diffuse at a greater rate into the cornea. Several authors suggest that the better efficiency of nano capsules is due to their bio adhesive properties, resulting in an increase in the residence time and biological response. Hence, it improved the ocular bioavailability of the drug and reduced dosing frequency. Alonso et al. have also reported that the nanoparticles of poly-e-caprolactone containing cyclosporin show a better corneal absorption with respect to the oily solution of the drug.

Nanosuspension:

This can be defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspension usually consists of colloidal carriers like polymeric resins which are inert in nature. Nanosuspension improves the ocular bioavailability of the drug by prolonging the contact time. Charge on the surface of nanoparticles facilitates its adhesion to the cornea. Cloricromene (AD6) was formulated in nanosuspension by using Eudragit RS100 and RL100. AD6-loaded Eudragit retarded nanoparticles suspension offered a significant edge in enhancing the shelf life and bioavailability of the drug.[2]

Nanoemulsion:

Nanoemulsions can be defined as a clear and stable dispersion of oil and water. They are mainly composed of the internal, dispersed, and external phases or the dispersion medium. The surfactant and cosurfactant molecules play an effective role in the formation of nanoemulsions due to their capability to reduce the interfacial tension and create a small particle size due to their function in the formation of stable preparations as a result of the repulsive electrostatic interaction and steric hindrance. In general, surfactants are molecules that have a bipolar structure composed of hydrophilic and hydrophobic parts.8,19 Nanoemulsions are colloidal carriers of drug molecules with a droplet size in the range of 500-1000 nm (preferably from 100 nm to 500 nm). As a drug delivery system, they increase the therapeutic efficacy and minimize the adverse effects and toxic reactions of the administered drug.[3]

Advantages of nanoemulsions:

1. It may be used as substitute for liposomes and vesicles.
2. It improves the bioavailability of drug.
3. It is non-toxic and non-irritant in nature.
4. It has improved physical stability.
5. Nanoemulsions have small-sized droplets having greater surface area providing greater absorption.
6. It can be formulated in variety of formulations such as foams, creams, liquids, and sprays.
7. It provides better uptake of oil-soluble supplements in cell culture technology.
8. It helps to solubilize lipophilic drug.
9. Helpful in taste masking.
10. Less amount of energy is required.

Disadvantage of nano emulsion:

1. E is limited ability to dissolve highly melting Compounds.
2. he high surfactant and cosurfactant concentration Required for stabilising the nanodroplets.
3. Environmental factors like pH and temperature affect NE stability.
4. A nontoxic surfactant is required for use in pharmaceutical applications.
5. The creation of nanoemulsions is an expensive Operation because the droplet size reduction needed Specialised equipment and manufacturing techniques.
6. The stabilisation of the nano droplets requires the use of Cosurfactants and surfactants at high concentrations.
7. Low solubility capability for compounds with high Melting points.
8. The surfactant used in medicinal applications must not Be harmful.
9. Environmental factors like temperature and PH have an Impact on Nano emulsion stability.[4]

Components of nanoemulsions:

The main components of nano emulsion are oil, emulsifying agents, and aqueous phases Oils can be of any type like castor oil, corn oil, coconut oil, evening primrose oil, linseed oil, mineral oil, olive oil, peanut oil, etc. A mixture of oil and water may yield a crude temporary emulsion, which upon standing, will separate in two distinct phases due to the coalescence of the dispersed globules. Emulgents or emulsifying agents can impart stability to such systems. Emulgents are broadly classified as surfactants like spans and tweens, hydrophilic colloids such as acacia and finely divided solids, e.g., bentonite and veegum. An emulgent, in addition to its emulsifying properties, should be nontoxic and its taste, odour and chemical stability should be compatible with the product. Some of the desirable properties of an emulgent are:

1. it should be able to reduce the surface tension to below 10 dynes/cm,
2. it should be adsorbed rapidly around dispersed phase globule to form a complete and coherent film to prevent coalescence,
3. it should help in building up an adequate zeta potential and viscosity in the system so as to impart optimum stability, and
4. it should be effective in a fairly low concentration. Emulgents form monomolecular, multimolecular or particulate films around the dispersed globules.(5)

Monomolecular films:

Surfactant type of emulgents stabilizes a nano emulsion by forming a monolayer of adsorbed molecules or ions at the interface reducing interfacial tension. In modern day practice, combination of emulgents is preferred over single emulgent. The combination consists of a predominantly hydrophilic emulgent in the aqueous phase and a hydrophobic agent in the oily phase to form a complex film at the interface.

Multimolecular films:

Hydrated lyophilic colloids form multimolecular films around globules of dispersed oil. Hydrated colloids do not cause any appreciable lowering of surface tension and their ability to form strong, coherent multimolecular films. Their tendency to increase the viscosity of the continuous phase enhances the stability of emulsion.

Solid particulate films:

The emulgents forming particulate films are small solid particles that are wetted to some degree by both aqueous and non-aqueous liquid phases. They are concentrated at the interface where they produce a film around the dispersed globules thus preventing coalescence.(6)

Types of nano emulsion:

1. Water in oil(W/O)

2. Oil in water(O/W)

3. Bi - continuous nano emulsion

1. Water in oil (W/O): A form of emulsion known as a water in oil nano emulsion (W/O) occurs when surfactants scatter tiny droplets of nanoscale in unprocessed form . The associated with extreme balance must be considered while creating any kind of emulsion. A nearly fully measure called the Initial ph scale aids formulators in choosing surfactant . It explains how to create the "optimal emulsion" and prevent flocculation or coalescence by balancing the both lipophilic and hydrophilic parts of a nonionic surfactant . The HLB values recommended for various kinds of emulsion are listed. For the creation of W/O nanoparticles, surfactants with a final Hlb of 4-6 work well . In segments and sub, W/O nanoemulsions are used to regulate the formation of nanoparticles like Compact discs and titanium dioxide nanoparticles. As reaction medium, different W/O emulsions are employed to produce ceramic nanoparticles. W/O emulsions are helpful in the pharmaceutical business as additives for vaccinations that include unique antigens such synthesized proteins, protein production, or DNA.(7)

2. Oil-in-water (O/W): Small lipid droplets scattered inside an aqueous phase make up oil-in-water, or water-based, nanoemulsions, with a typical mean droplet diameter of about 200 nm. The homogenized process employed in the manufacture of nanoemulsions and conventional O/W emulsions determines the droplet sizes even though both are supersaturated systems. The four emulsion phases identified by Winsor as being in equilibrium are known as Winsor phases. An O/W type is categorised as Winsor I, a 2 different system in which the top oil layer and the bottom nano emulsion exist in balance.[8]

3.Bi-continuous nano emulsion: Water and oil are both continuous phases with comparable amounts. They are found in microemulsions, mesophases, and even relatively diluted surfactant solutions. As indicated by the average mean curvature zero, a hexagonal liquid crystalline structure may also exist.[9]

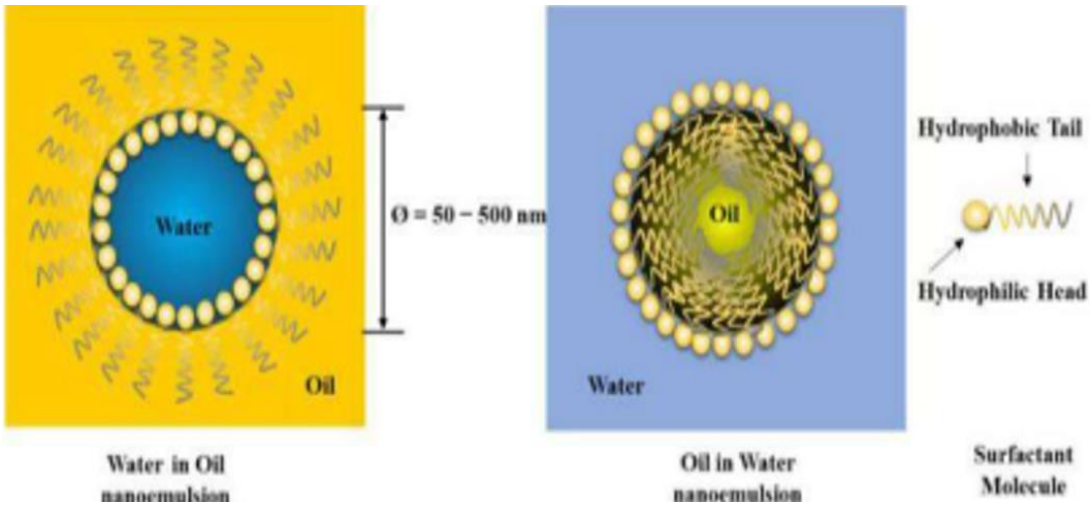

Fig:2 Nanoemulsions

Methods of ophtalamic nanoemulsions:

1. High-energy emulsification method
2. Low energy emulsification method
3. Spontaneous nanoemulsions
4. Phase inversion composition

1. High-energy emulsification method:

Given that nanoemulsions cannot naturally form and need additional mechanical or chemical energy to do so, they are regarded as non-equilibrium systems. Ultrasonic generators, high-pressure homogenizers, and elevated stirring are used to use physical energy input to make high-energy nanoemulsions. When the oil and water phases are disrupted by these mechanical devices, a nano emulsion is created. It is extensively used to prepare nanoemulsions because homogenizers deliver energy in the shortest amount of time while operating under high pressure to make homogeneously tiny droplets.[10]

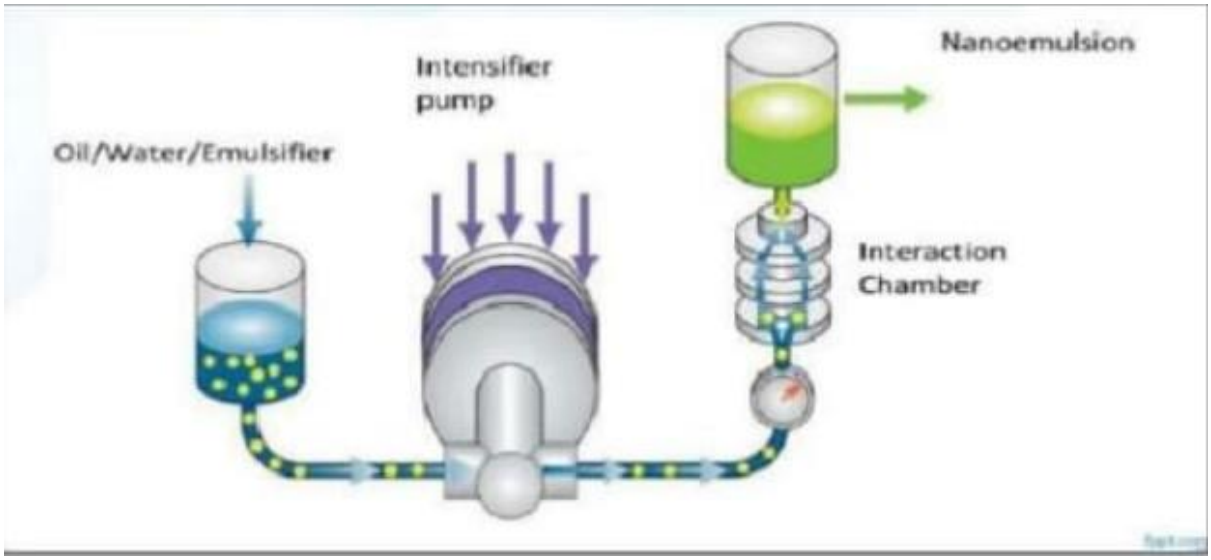

Fig:**3** High-energy emulsification method

2 low energy emulsification method:

By using the system's physicochemical characteristics, this approach produced droplets that were smaller and more uniform. This approach has several restrictions on the sorts of oils and emulsifiers it may use, including proteins and polysaccharides. Synthetic surfactants are utilised in high concentrations together with low-energy methods to Overcome this issue, but this is limiting the range of Applications, particularly for food processing. Using a low energy emulsification technique, coarse W/O Macroemulsion was converted into nano emulsion phase

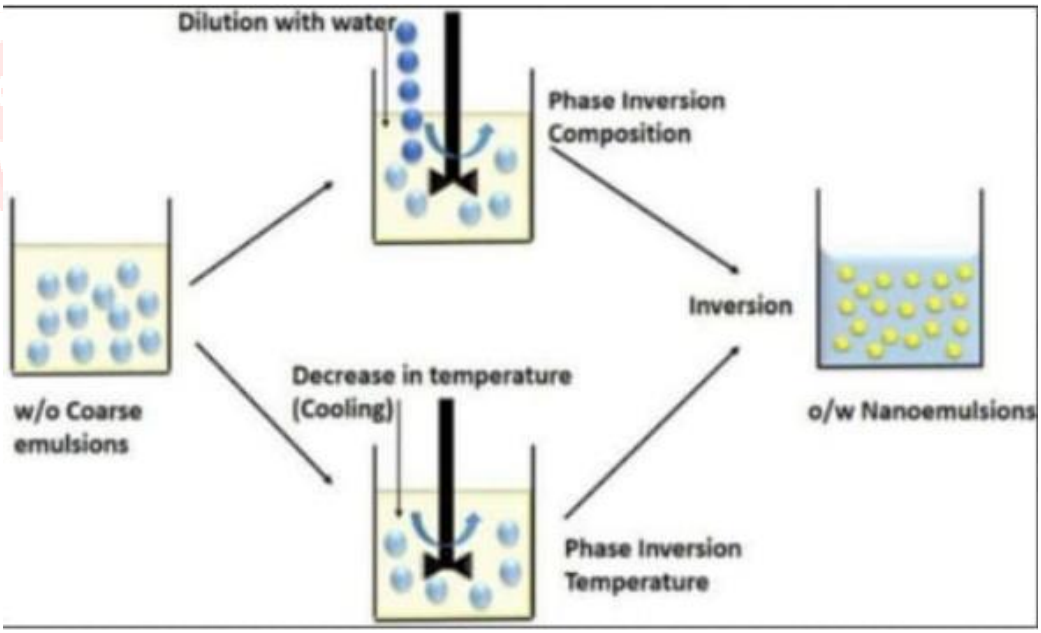

Fig:4 Low energy emulsification method

Inversion occurs. When composing the phase inversion Approach, diluting by water causes a phase inversion, whereas chilling or a temperature drop causes a phase Inversion in the optical inversion technique. They are Employed to supply the nano emulsion with input power from the reaction rate of the component. The alternative Technique involves keeping the temperature constant while altering the composition and interfacial characteristics.(11)

3.Spontaneous Nanoemulsion:

In this method, water and oil are slowly stirred together with an emulsifier at a specified temperature to create Spontaneous emulsions. The emulsifier enters the aqueous Phase as a result of gentle magnetic agitation, increasing the Oil-water interfacial area and producing oil droplets. As a result, the oily phase and unique surfactant biophysical Features are crucial to the low energy approach of Nanoemulsion generation and are easily scaleable. However, Components may deteriorate and production procedures Cannot be scaled up. Mechanical devices and high-energy Techniques can be used to regulate the size distribution and Composition of nanoemulsions.

4.Phase inversion composition:

By changing the elemental composition, the amorphous Ability of the emulsion is changed in this process. When salt Is added to an oil-in-water nano emulsion with an ions Emulsifier, the electric charge of the surfactant changes, Resulting in a water-in-oil emulsion. Similar to this, dilution with water can convert an oil-in-water emulsion into a Moisture emulsion with a high sodium content. This method Is inexpensive, doesn't need organic solvents, and is very Thermodynamically stable. It is difficult to use the phase Inversion method with very hydrophobic materials. The Phase inversion formulation method was used to dining Sector nanoemulsions with an average crystal diameter of Nm that were improved with vitamin E acetate. This strategy Delivered better results.[12]

Applications:

1.Pharmaceutical drug delivery via nano emulsion has grown to be quite appealing. Additionally, nano emulsion has a Strong benefit in the cosmetics industry. The following are the main benefits of using nano emulsion formulation in Medicines and cosmetics.

2.When compared to microemulsion, nano emulsion has a far Higher dispersibility because the smaller droplet size Precludes droplet flocculation, which permits the system to Dispersion without separation.

3.Because there are no thickening agents or colloidal Particles present, nanoemulsions are clear and fluid, improving formulation patient compliance and making them Safe to administer.

4.It has also been reported that nanoemulsions could be used for targeted delivery of active ingredients, particularly in Cancer therapy.

5.Nanoemulsion formulation may be supplied by a variety of Bodily pathways, making it a stable alternative to liposomes and vesicle-based delivery methods.[13]

CONCLUSION:

Owing to the innovation of nano formulations, which is preferred Over the systemic route, a significant improvement has been Achieved in ocular disease therapy. Heating and/or mixing must Be used in the preparation of nanoemulsions, whereas phase Separation may occur after preparation. Thus, nanoemulsions Are thermodynamically less stable than microemulsions. The translucent appearance of nanoemulsions is due to A droplet size of less than 100 nm. As a result of this small Droplet size, nanoemulsions exist as thermodynamically Unstable dispersion. A high concentration of surfactants is Required, resulting in the sticky texture of the formulation. A yellowish appearance and rancid odor occur after storage Due to the presence of phospholipids, which are generally Used to stabilize nanoemulsions. Nanoemulsions are easily Manufactured system prepared by methods which may or may Not rely on energy.

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