IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

NANOEMULSION FORMULA DESIGN AND DEVELOPMENT: A REVIEW

Mr. Manoj Pabale[1], Miss. Vishakha Yenare[2], Mr. Mahesh Handal[3], Mr. Shounak Utage[4] Dr. Sudarshan Nagrale[5],Mr. Amit Pondkule[6]
Dr. Vishal Babar[7]

Department of Pharmaceutical Quality Assurance[1,2,3]
Department of Pharmaceutics[4,6]
Department of Pharmaceutical Chemistry[5,7]
Dattakala Collage of Pharmacy, Swami-Chincholi, Maharashtra

ABSTRACT:

Nanoemulsions are physically more stable than conventional emulsions because their small droplet sizes allow them to pass through delicate capillaries and penetrate deep into the tissues. As a result, this emulsion is being thoroughly studied for its potential as a drug delivery system and for its capacity to target particular body regions. A wholly original drug delivery system for raising first pass metabolism and water solubility of poorly soluble medicines. Nanoemulsions are employed in a variety of applications because they feature small droplets with properties such as high solubilization capacity, large interfacial area, low viscosity, transparency or translucent appearance, and high kinetic stability. A longer-lasting, thermodynamically stable nanoemulsion that maintains uniform dispersion throughout the continuous phase. We hope to provide information on the various applications used in the formulation of nanoemulsions as well as excipient selection, formulation methods, optimization parameters, and formulation instability during this review.

Keywords: Applications, Types, Methods, and Instabilities of Nanoemulsion.

1. INTRODUCTION

In the pharmaceutical industry, nanoemulsion is one of the most effective dosage forms for reaching the target and has received a lot of attention recently for its use in a variety of industries. As a medication delivery mechanism for a variety of systemic routes, including oral, topical, and parenteral, nanoemulsions are used. [1]

A transparent, thermodynamically stable mixture of two non-soluble liquids, such as oil and water, stabilised by an interfacial surfactant coating is referred to as a nanoemulsion. Using an emulsified oil and water system with a mean droplet size that spans from 50 to 1000 nanometers (nm), nanoemulsions are a revolutionary medication delivery technology. The size and shape of the particles dispersed in continuous phase are the fundamental differences between emulsions and nanoemulsions. Nanoemulsions have particles that are between 10 and 200 nm and 1 and 20 micrometres (m) in size. [2]

Nanoemulsions are submicron sized colloidal particulate systems that contain two immiscible liquids, such as water and oil, and are stabilised by an interfacial film made of an appropriate surfactant and co-surfactant to form one phase. They are also referred to as submicron emulsions, ultrafine emulsions, and mini emulsions. Nanoemulsions have been employed with a variety of surfactants, some of which have different properties (ionic or non-ionic). [3]

Nanoemulsions are created using both high and low-energy techniques. Nanoemulsion optimization through changes to various parameters. Chemical and physical instabilities are also noticed during or after formulation, and applicability in diverse sectors is explored within this review.

1.1 NANOEMULSION TYPES:

I. W/O, or water in oil nanoemulsion: A droplet of water was distributed in a continuous phase of oil during a nanoemulsion. [4]
II. O/W or oil in water nanoemulsion: Oil droplets were dispersed in a continuous phase of water during a nanoemulsion.
III. Bi-continuous Nanoemulsion: In this process, the surfactant was soluble in both the water and the oil phases, and the droplet was distributed in both. [5]

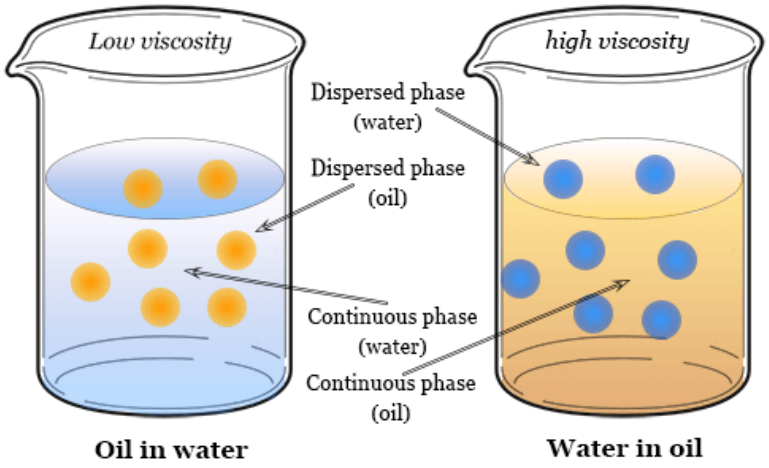

Figure 1: Types of Emulsions

2. COMPOSITION OF NANOEMULSIONS:

The Formulation Components of a Nanoemulsion Are Described in the Following Table With Examples:

Sr. No.	Components	Examples
01	Oil	Castor oil, Corn oil, Coconut oil, linseed oil, Mineral oil, olive oil, groundnut oil
02	Surfactant	Polysorbate20, Polysorbate80, Polyoxy 60, DGME, Sorbitan monooleate, Caprylic glyceride
03	Co-surfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer
04	pH Stabilizer	Sodium hydroxide or hydrogen chloride, Triethanolamine
05	Preservatives	Methyl Paraben, Propyl Paraben, Benzalkonium Chloride (0.01%w/v), Potassium Sorbate

2.1. OIL

The oil is essential for the drug candidate's maximum capacity to dissolve in the nanoemulsion formulation. With its great capacity for drug loading, this is frequently the most important strategy. Triglycerides, which are a mixture of oils and fats that can exist both naturally and artificially, contain long chain fatty acids. Short chain triglycerides are the type of lipids. To reduce the level of unsaturation and to halt oxidative destruction, triglycerides (12 carbons) are essential. The effectiveness of the solubilized pharmaceuticals determines the oil phase to be used, and nanoemulsion is essential. Increased friction is necessary to move drugs into intracellular compartments and to make less water-soluble drugs more water-soluble.

A good balance between the drug's loading capacity and emulsification or nanoemulsification is required, for instance, when fatty oil and medium chain triglycerides are combined. It is crucial to use long chain and medium chain triglyceride oils at various saturation levels while developing SMEDDS. The solvent capacity of triglycerides, which are highly lipophilic oily molecules, is a common function of their effective concentration in ester groups, with medium chain triglycerides (MCT) molecules having a higher solvent capacity and greater ability to resist oxidation than long chain triglycerides molecules.

Nowadays, oil phases are modified by oils, digestible or non-digestible oils and fats like olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, and hydrogenated oil for better solubility. The MCT are replaced by novel semi-synthetic MCT is critical to influencing the water solubility of poorly soluble drugs. [6]

2.2. SURFACTANT

The term "surfactant" refers to molecules and ions that are adsorbed at a contact. It has the power to both create and maintain interfacial tension in nature. It is a crucial ingredient in the creation of nanoemulsion. Its ability to solubilize poorly water-soluble drugs comes from its self-Nanoemulsifying, self-emulsifying, and self-Micro emulsifying agent. The majority of chemicals have surfactant-like characteristics that are useful when constructing emulsifying systems. The restricted surfactant unit is suitable for oral use. Having a high Hydrophilic and Lipophilic Balance are non-ionic surfactants (HLB). The ideal amount of surfactant is used to prepare nanoemulsions, but excessive amounts might be hazardous chemically. Therefore, a key consideration when choosing a surfactant molecule is security. The surfactant molecule can be produced synthetically or naturally. [7]

Surfactant with a restricted ability to self-emulsify. Since they are nontoxic and thermodynamically stable, non-ionic surfactant molecules are more stable than ionic surfactant molecules. The diameters of droplet molecules for preparation of emulsification and nano emulsification are notably supported by the surfactant concentration. This is frequently crucial for keeping oil droplets stable in a surfactant system area. The size of the droplet is mainly dependent on the surfactant concentration, which increased as the droplet's size also increased. It's an essential step in creating a nanoemulsion system to enhance the solubility of pharmaceuticals with poor water solubility. [8]

2.3. CO-SURFACTANT

Co-surfactant performs a similar role as the surfactant unit. In order to augment the strength of the surfactant and improve the water solubility of a medicine that was not very water soluble, co-surfactant was introduced along with the surfactant unit or in combination with the surfactant unit. The co-surfactant is a single chain surfactant unit that is prepared to stop the fluidity between surfaces. The monomolecular layer of the surfactant molecule can be used to isolate the co-surfactant molecule from the surfactant, oil, and water molecules. Surfactant molecules' monomolecular layer is known as the liquid crystal formation layer. The primary purpose of co-surfactants in self-nanoemulsifying drug delivery systems (SNEDDS) is to prevent natural phenomena that occur at the interface of oil and water. Ethanol, Methanol, Pentanol, Glycol, and Propylene Glycol are examples of co-surfactants. [9]

3. METHOD OF PREPARARTION

The creation of nanoemulsions can be done in a number of ways, including by combining high- and low-energy emulsification techniques. High-energy stirring, ultrasonic emulsification, high homogenization, including micro fluidics, and membrane emulsification are prioritised among the high-energy approaches. The phase inversion temperature method, the emulsion inversion point method, and consequently spontaneous emulsification are three low-energy emulsification techniques. Reverse nanoemulsions can be organised in extremely viscous systems by using a combination technique that combines high-energy and low-energy emulsification. The main benefits and drawbacks of various nanoemulsion preparation techniques are examined, and as a result, future applications for nanoemulsions are taken into account. [10]

3.1. The shelf-nano emulsification method:

The self-emulsification approach allows for the creation of nanoemulsions without affecting the surfactant's natural curvature. Nano-sized emulsion droplets are produced by the rapid diffusion of surfactant and/or co-solvent molecules from the dispersed phase to the continuous phase, which results in turbulence. The spontaneous emulsification method is another name for the self-emulsification technique. SNEDDS have reduced lipid content and more hydrophilic co-surfactants (co-solvents), which support the self-emulsification phenomena. [11]

The term "SNEDDS" refers to an isotropic mixture of oil, a surfactant, a co-surfactant, and a medication. In the presence of aqueous fluids, this mixture forms a thin and optically transparent O/W nanoemulsion with the help of the mild agitation brought on by the stomach and intestines digestive motility. The diffusion of the hydrophilic co-solvent or co-surfactant from the organic phase into the aqueous phase and the formation of nanoemulsion negative free energy at transient negative or ultralow interfacial tensions are the two most frequently reported mechanisms of nanoemulsion formation from SNEDDS. SNEDDS are also the most well-liked and optimistic administration method for hydrophobic medications with low bioavailability. The distribution of bioactive food ingredients has also been done using SNEDDS. [12]

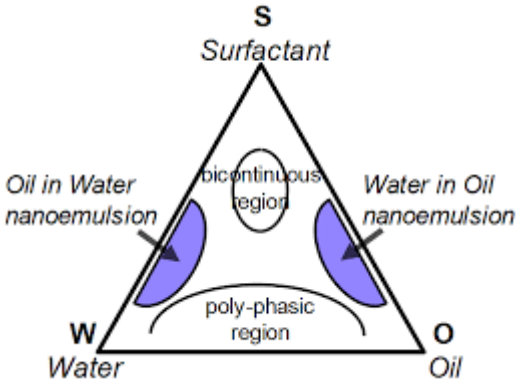

Figure 2: Ternary Phase Diagram

3.2. Low Energy Method

3.2.1. Phase Inversion Emulsification Method:

In this technique, phase change occurs during the emulsification process as a result of the surfactant's spontaneous curvature. Temperature, composition, and other changes in factors can alter the surfactant's spontaneous curvature. Phase inversion emulsification techniques fall into two categories: TPI techniques, which use PIT and PIC, and CPI techniques, which use EIP. Transitional phase inversion occurs in response to variations in the surfactant's affinity or spontaneous curvature as a function of temperature and composition. But CPI happens when dispersed particles are constantly introduced, causing the droplets of scattered particles to collect into bicontinuous/lamellar structural phases. [13]

The term "catastrophe" refers to a system's behaviour altering abruptly as a result of new circumstances. The surfactant must be primarily present among the scattered particles for catastrophic phase inversion to occur; this causes a high coalescence rate and a quick phase inversion. While spontaneous curvature or surfactant affinity are altered during transitional phase inversion, these properties remain unchanged during catastrophic phase inversion. [14]

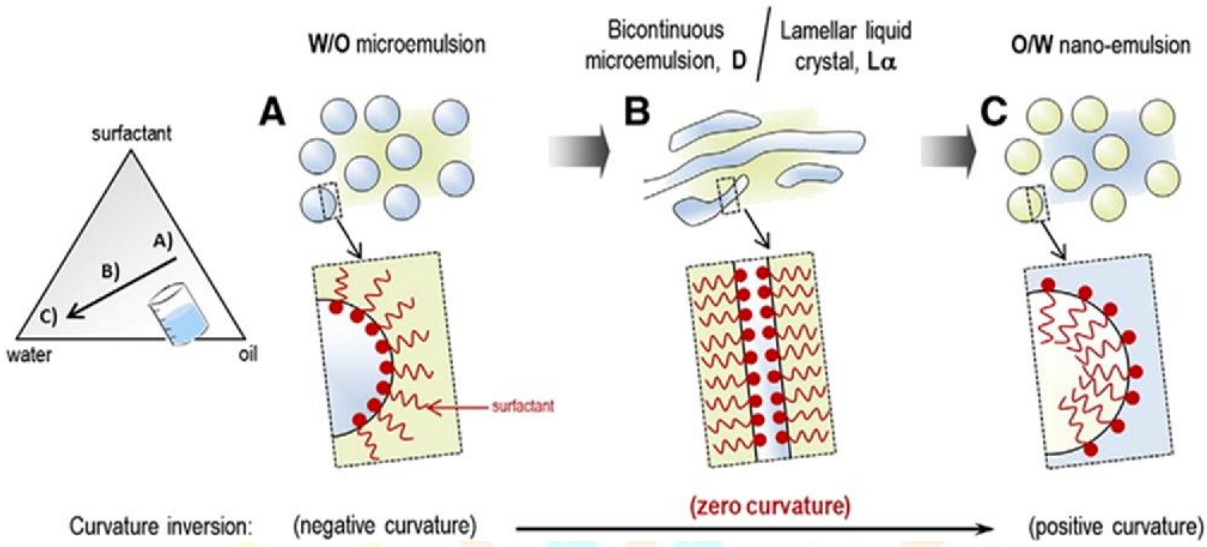

Figure 3: Phase Inversion Emulsification Techniques

A. Phase Inversion Composition (PIC):

Similar to the PIT method, the phase inversion composition (PIC) method achieves phase inversion by altering the system composition rather than system temperature. PIC involves adding one of the ingredients, such as water, to a combination and then adding oil-surfactant or oil to the water-surfactant mixture. Although other types of surfactants may also be used, the PIC method typically uses non-ionic surfactants of the POE type to create nanoemulsions. Surfactant POE chain hydration takes place when water is gradually supplied to the oil phase and because the volume of the water fraction grows. The water phase's surfactant hydrophilic and lipophilic properties will balance, and the surfactant's spontaneous curvature will change to zero, almost as at the HLB temperature in the PIT method. A bi-continuous or lamellar structure is created during this transition. The structures of the surfactant layer that had zero curvature changed to having large positive curvature as more water was introduced because the transition composition was exceeded. Phase inversion and the creation of nano-sized droplets are the results of this change in curvature. Phase inversion arises as a result of system composition changes. The addition of salt and pH are two similar compositional factors. Emulsification via Phase Inversion Changes in methods also results in emulsion droplets that are nanometer-sized due to transitional phase inversion. [15]

B. Emulsion Inversion Points (EIP):

Phase inversion occurs through CPI processes in the EIP approach. Instead of the surfactant characteristics, the Catastrophic Phase Inversion (CPI) is caused by altering the fractioned volume of the dispersed particles. The system begins to behave as a water-oil nanoemulsion when the water phase is added to the oil-surfactant mixture. Water droplets merge with one another as more water is added over a certain water content while being stirred continuously, reaching a phase inversion point that results in the formation of bicontinuous or lamellar structures. Phase inversion from a W/O to an O/W system is brought about by additional water dilution through an intermediary bi-continuous microemulsion. The technique factors, such as the rate of water addition and therefore the stirring speed, affect the sizes of the nanoemulsion droplets that are produced. The surfactant must be largely present in the dispersed particles for catastrophic phase inversion to take place; as a result, the rate of coalescence is high and rapid phase inversion takes place. Surfactants made of small molecules are frequently used in catastrophic phase inversion. Both W/O

and O/W emulsions can be stabilised by these surfactants. The surfactant is particularly concentrated in the scattered particles at the beginning of the catastrophic phase inversion, which causes it to behave abnormally as an unstable emulsion that deviates from Bancroft's laws. According to Bancroft's principles, the emulsifier should be mostly present in the continuous phase for a stable emulsion (normal emulsion). As a result, a more stable normal emulsion is created through catastrophic phase inversion from the abnormal emulsion. [16]

C. Phase Inversion Temperature (PTI):

By altering temperature, the surfactant spontaneous curvature is reversed in the Hell method. Dehydration of the POE groups in non-ionic surfactants, such as polyethoxylated surfactants, increases the lipophilicity of the substance and alters the curvature of the surfactant. Phase inversion consequently takes place, and nanoemulsion is created. In this procedure, oil-in-water (O/W) emulsions are created by heating oil, water, and non-ionic surfactants. Then, as the temperature rises gradually, dehydration of the POE groups in the surfactant occurs, making the surfactant more lipophilic and increasing its affinity for the oily phase. This results in phase inversion through intermediary liquid crystalline or bi-continuous structures from the initial O/W emulsion to the water-in-oil (W/O) nanoemulsion (e.g., lamellar phase). The non-ionic surfactant has no curvature and exhibits the same affinity to the aqueous and oily phases at hydrophile-lipophile balance (HLB) temperatures, which is an intermediate temperature. Fast cooling or heating of HLB (to produce O/W or W/O emulsions, respectively) is necessary for effective phase inversion. Nanoemulsion that is kinetically stable is produced by rapid cooling or heating. [17]

3.3. High energy methods:

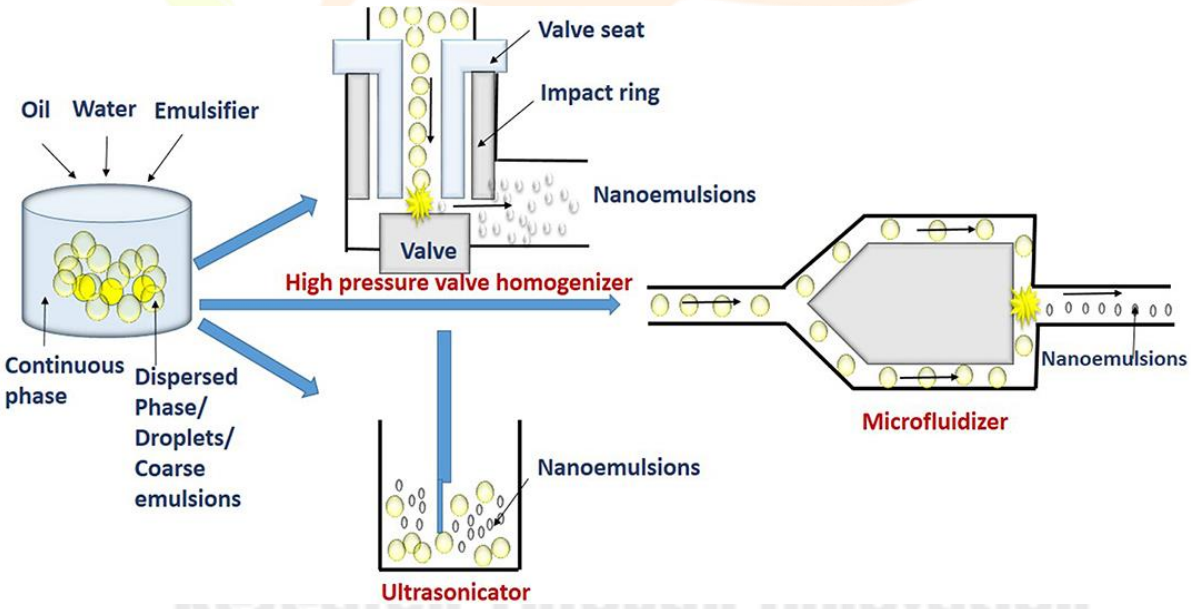

Figure 4: Method of Preparation of Nanoemulsion

3.3.1. Ultra-sonification:

When it comes to cleaning and operation, ultrasonication is superior to other high energy approaches. Ultrasonic waves produce cavitation forces during ultrasonic emulsifications, which cause the macroemulsion to separate into a nanoemulsion. This technique makes use of ultrasonicators, which have a search that emits ultrasonic waves. It will be possible to achieve the desired particle size and stability of the nanoemulsion by adjusting the ultrasonic energy input and time. The technique of acoustic cavitation specifically provides physical shear in ultrasonic emulsification. Cavitation is a phenomena that occurs when microbubbles form, expand, and then burst due to pressure changes brought on by a sound wave. [18]

Nano-sized droplets occur as a result of the extreme turbulence brought on by the collapse of microbubbles. An oil and water system is subjected to ultrasonic irradiation, which induces cavitation forces and supplies extra energy to create brand-new interface formations that result in nano-sized emulsion droplets. Nanoemulsions are frequently created by ultrasonication without the use of surfactants. Recent research has demonstrated that the effectiveness of ultrasonic emulsification varies on ultrasonication strength, time, and surfactant type. For the production of food and medicinal ingredient nanoemulsions, ultrasonication has been employed extensively. Food-grade ultrasonication produces nanoemulsions that are more stable, have smaller droplet sizes, and use less energy than methods that use high energy. [19]

3.3.2. Micro fluidization:

The "MICRO FLUIDIZER" is a tool used in micro fluidization technology. The product is pushed into the interaction chamber, which is made up of tiny channels called micro channels, using a high-pressure positive displacement pump (500–200 PSI). The product travels via the microchannels and into the impingement zone, producing very small particles in the submicron range. An inline homogenizer is used to mix the two solutions (oily phase and aqueous phase) and process them into a thick emulsion. A micro fluidizer is used to further convert the coarse emulsion into a stable nano emulsion. [20]

3.3.3. High-Pressure Homogenization:

Applying a high over a system with an oil phase, aqueous phase, and surfactant or co-surfactant is how this procedure is carried out. The homogenizer is used to help apply the pressure. Poor productivity and component deterioration that results in excessive heat generation are some issues with homogenizers. With this technique, only liquid Oil in Water (O/W) nanoemulsions with less than 20% oil phase can be created; cream nanoemulsions with high viscosities or hardness and mean droplet diameters smaller than 200 nm cannot. [21]

4. INSTABILITIES IN NANOEMULSION: [22]

4.1. Physical Instabilities:

4.1.1. Coalescence:

The irreversible process of dispersed particle droplets combining to form larger droplets is known as coalescence. The process is repeated until the oil and water phases have completely separated and the emulsion breaks (cracks). When the emulsion droplets are prepared to cross the repulsive energy barrier and get close to the initial minimum, coalescence takes place. Once during this minimum, they are quite close to one another, hence stability against coalescence is largely determined by the interfacial film's resistance to rupture. As the oil droplets approach one another and get deformed, coalescence starts with the draining of liquid films of continuous phase from between them and finishes with the breaking of the film. Droplets are protected against coalescence by thick multilayered films produced by several polymers and rigid close-packed elastic films formed by certain emulsifier mixes because they are highly resistant to film rupture.

4.1.2. Flocculation:

A weak, reversible interaction between emulsion droplets that are separated by trapped continuous phase is known as flocculation. Although each floccule of droplets preserves its identity, each floccule operates physically as a single kinetic unit. Mild agitation, such as shaking the container, frequently causes floccules to redisperse. Therefore, the potential for flocculation can be decreased by using the right emulsifier. Although the adsorbed emulsifier can frequently extend the duration between flocculation and coalescence

virtually indefinitely, flocculation is typically regarded as undesirable since floccules cream sooner under the effect of gravity than individual emulsion droplets.

4.1.3. Creaming:

Creaming is a process that creates a layer of creamier emulsion by causing dispersed droplets to separate under the action of gravity. Any diluted emulsion with relatively large droplets (~1μm) will inevitably cream if there is a difference in density between the oil and water phases. Since most oils are less thick than water, they rise to the surface to form an upper layer of cream in an o/w emulsion while water droplets settle to form a lower layer in w/o emulsions. Even though gentle agitation can often return a creamed emulsion to its original state, this is frequently viewed as undesirable due to the emulsion's unattractive appearance and, more importantly, the risk that the patient may not receive an adequate dose if the emulsion isn't sufficiently agitated before use. Organizing emulsions with small droplet sizes and thickening the exterior phase by adding viscosity modifiers are the two most practical ways to reduce creaming. Little attention has been paid to density adjustment to lessen the density difference between the two phases.

4.1.4. Emulsion Inversion:

Sometimes in emulsions, under particular circumstances, emulsion inversion happens. Phase inversion, which occurs when an o/w emulsion turns into a w/o emulsion at a specific temperature, is a phenomenon used in the low-energy preparation of nanoemulsions. This phenomenon is caused by an emulsifier's solubility changing from being water soluble at coldness to grease soluble at heat (for example, some non-ionic surfactants). Emulsion inversion may also result from certain interactions with other ingredients. If a sodium salt is used to stabilise an o/w emulsion, for instance, the emulsion may invert to a w/o emulsion by the addition of divalent ions, such as Ca2+ ions, to create the calcium salt, which stabilizes a w/o emulsion.

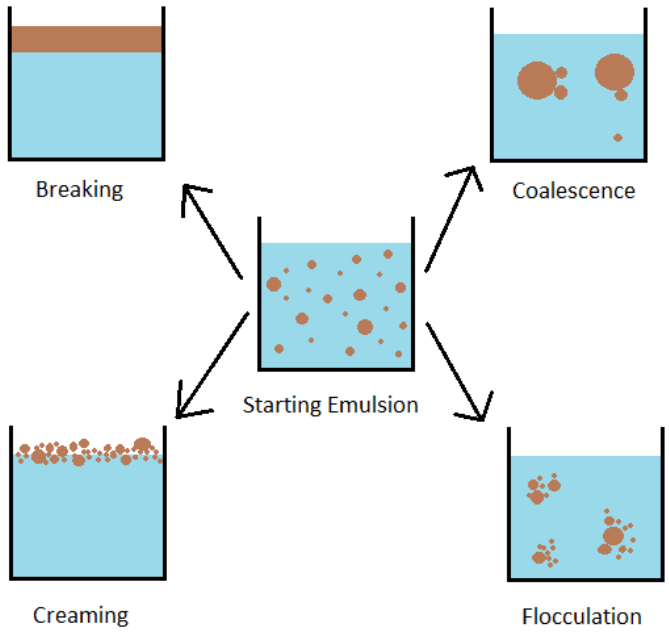

Figure 5: Instabilities of Emulsion

4.1.5. Ostwald Ripening:

Ostwald ripening is an unstoppable process that causes large droplets to grow at the expense of smaller ones. In emulsions with tiny sub-micrometer droplets (less than 600 nm), Ostwald ripening occurs as long as the dispersed particles also have a sufficient solubility in the continuous phase. The Kelvin effect, which explains how a partially miscible droplet's solubility rises sharply as its radius falls, may have a direct bearing on Ostwald ripening. As a result, smaller emulsion droplets are more soluble than bigger ones.

Tiny droplets dissolve to achieve equilibrium, and their molecules diffuse through the continuous phase and redeposit onto larger droplets, which mature and get larger overall, increasing the average droplet size. In contrast to coalescence, Ostwald ripening doesn't require any contact between the droplets. The underlying mechanism of instability in many o/w fat emulsions and perfluorocarbon emulsions is Ostwald ripening rather than coalescence. Although the characteristics of surfactant interfacial films prevent flocculation and coalescence, Ostwald ripening may be facilitated if micelles are also present to further solubilize the oil. Ostwald ripening is frequently avoided by reducing the molecular diffusion of the main partially miscible oil by adding a small amount of immiscible second oil. Perfluorodecalin contrast media emulsions are more stable when modest amounts of the insoluble perfluorotributylamine are present, while fat emulsions containing local anaesthetics or analgesics exhibit better stability in the presence of less soluble hydrophobic oils. The surfactant Pluronic F68®, which is highly adsorbed at the o/w interface and doesn't form micelles in the continuous phase, also inhibits Ostwald ripening. Ostwald ripening is also prevented by polymers that thicken the emulsion exterior phase because they impede molecular diffusion.

4.2 Chemical Instabilities:

Chemical shakiness ideally, during emulsification, every component of the emulsion should be chemically inert. Unfortunately, this is not always the case, thus it is crucial to understand the chemical makeup of every component of the emulsion before using it. Variety is produced. When choosing therapeutic oils, special care must be given because they are susceptible to oxidation by ambient oxygen or microbial contamination, generating a disagreeable odour and taste as they get rancid. To lessen these impacts, the emulsion could additionally contain antioxidants and preservatives. The emulsification power and consistency of polymeric emulsifiers might be lost as a result of depolymerization caused by hydrolysis or microbial decay. The destruction of emulsifying capabilities could also result in interactions between the emulsifying agent and other components, which would cause the emulsion to break up. Examples include the formation of hydrogen bonds between POE non-ionic emulsifiers and phenolic preservatives, which leads to poor preservation as well as a reduction in emulsifying ability. Materials having the opposite charge are typically incompatible with ionic emulsifying agents. This occurs when cationic substances, such as surfactants or medications (such as cetrimide or neomycin sulphate), are mixed with cream that already contains an anionic emulsifier like sodium lauryl sulphate. When cream is stored, its consistency is lost because the suppression of repulsive forces causes lamellar structures in the continuous phase to disintegrate.

5. THERMODYNAMIC STABILITY STUDIES:

Following stress tests, drug-loaded Nanoemulsions were found to be thermodynamically stable.

5.1. Heating Cooling Cycle:

Six cycles of nanoemulsion formulations between refrigerator temperature (4°C) and 45°C were performed. The centrifugation test was then performed on the stable formulations.

5.2. Centrifugation:

The nanoemulsion formulations that did not exhibit any phase separation after being centrifuged at 3500 rpm were chosen for the freeze-thaw stress test.

5.3. Freeze Thaw Cycle:

Three freeze-thaw cycles between 21°C and +25°C, maintained in conventional laboratory conditions, were performed on the formulation.

Three months were spent doing these studies. The accelerated temperatures of 30°C, 40°C, 50°C, and 60°Cat ambient humidity were maintained for three batches of formulations. The samples were taken out on a regular basis at 0, 1, 2, and 3 month intervals, and the drug content was determined using a stability-indicating UV or HPLC method. [23]

6. OPTIMIZATION OF NANO-EMULSION PREPARATION

6.1. Experimental Designs For Optimization:

With a small number of experiments, experimental designs enable the study of the effects of various variables. The desired answer can be correlated with the variables by using polynomial equations, which can be done through statistical analysis of the findings. The goal of the experimental design is to ascertain how two qualitative independent variables—the type of oil and the type of lipophilic emulsifier—influence the outcome. The four references on the left and right are from the same study team. Oil, surfactant, and cosurfactant quantities in the formulation are the three independent factors evaluated in the incorporation of retinol to a self-nanoemulsifying formulation, whereas mean droplet size, turbidity, and dissolving rate are the four response variables. [24]

The system is optimised for the dissolving rate at 30 minutes utilising the opposite three responses as constraints. Response equations are supplied. Six reaction factors are analysed in the surface response technology and more information is provided. [25]

A comparable evaluation process for the characterisation of nano-emulsions using ultrasonic technology. The creation of nanoemulsions is discussed together with a thorough discussion of experimental design application. The phase inversion composition approach is applied to low-energy emulsification, and the impacts of the composition factors were all compared. The response surface for droplet size was reduced separately, first in relation to compositional variables and then in relation to preparational variables. The findings show that there is an optimal surfactant mixing ratio, or, to put it another way, an optimal HLB, where the higher the oil surfactant ratio, the larger the droplet size. The optimum agitation rate is discovered for the preparation variables of addition and agitation rate, which have minimal yet considerable impact. In, nano-emulsions in an ionic surfactant system produced by the phase inversion composition method are subjected to experimental design optimization approach. There is an ideal ratio of surfactants in the combination utilised, and again, the higher the oil surfactant ratio, the larger the droplet size. The preparation factors once more have little to no impact on droplet size. The authors' other, unpublished findings on nano-emulsions made at the phase inversion temperature support the idea that preparation factors like cooling pace and agitation don't significantly affect droplet size. Papers using experimental designs generally come to the conclusion that this methodology is an excellent tool for researching how nano-emulsions are prepared. [26]

6.2. Phase Behaviour Studies For Optimization:

When the so-called condensation or low-energy emulsification methods are used, studies on phase behaviour for optimising nano-emulsion properties are frequently important because the phases involved during emulsification are crucial in order to obtain nano-emulsions with small droplet size and low polydispersity. When shear methods are employed, however, there is no composition emulsification path and only the phases at the final composition matter. Recent reviews go into great detail about the significance of the phase behaviour, specifically crossing microemulsion (bicontinuous, D) or lamellar liquid crystalline phase regions during emulsification. [27]

This conclusion has been experimentally demonstrated in a few recent original research, including those that produced nanoemulsions using the phase inversion temperature method (PIT), the phase inversion composition method (PIC), [28] or a self-emulsifying technique. The only microemulsions that are thought

to be suitable for self-emulsification are bicontinuous (D) or O/W microemulsions. Lamellar liquid crystal compositions do not self-emulsify by dilution, perhaps because of the viscosity of the lamellar phase. [29]

When comparing data from and with results from, it is frequently argued that slow water addition to a lamellar liquid can produce nano-emulsions, whereas quick dilution produces emulsions with larger droplets (as in self-emulsifying methods). [30]

When aqueous phase is added, an emulsification path that crosses a micellar cubic liquid crystalline phase produces nanoemulsions with extremely small droplet sizes in an ionic surfactant system. In reality, the requirements for producing O/W nanoemulsions with the smallest possible droplet size and, as a result, low polydispersity are frequently stated as follows: "In emulsification by phase inversion temperature or composition methods an aqueous continuous phase, O/W or bicontinuous, with all the oil solubilized must be crossed immediately before reaching the ultimate two-phase region where the nano-emulsions form. These composition conditions are necessary but insufficient because preparation factors like the rate of aqueous phase addition for the PIC method or the rate of cooling for the PIT method also affect how quickly oil is incorporated into the current water continuous phase or coalesces to form nano-emulsion droplets. [31]

6.3. Optimization By Selective Variation Of Parameters:

Factors that can be categorised as composition or preparation variables are those whose effects on nano-emulsion properties are frequently researched. Composition variables will have a greater impact on emulsification by low-energy methods than would preparation variables, but for shear emulsification, the impact of preparation variables will be decisive. Examples of recent research on the optimization of shear-produced nanoemulsions include analyses of the effects of various factors and the relationship between droplet size and those factors. [32]

A high pressure microfluidizer is used to emulsify a food system while a surfactant and other polymers are used to stabilise the emulsions. We explore the opposing processes of breaking and coalescence while taking the role of stabilisers into account. [33] By subjecting a rough emulsion to subcritical water conditions, the preparation of nano-emulsions is optimised. By carefully varying the composition parameters (surfactant and oil concentration), and preparation parameter, the optimization was analysed (temperature). Small sizes, 40 nm, are obtained with this method. The surfactant oil ratio and, consequently, the ratio between surfactants when a surfactant combination is utilised, are factors whose effects are typically explored for alternative condensation processes. Several acknowledged references of recent bibliography show optimization by selective change of parameters for nano-emulsions made by the phase inversion temperature method. When droplet size is studied in relation to oil surfactant ratio, it is clear that the higher the oil surfactant ratio, the larger the droplet size will be. However, when droplet size is studied in relation to surfactant mixing ratio, it is astoundingly clear that if nano-emulsions are made by cooling from the HLB temperature, droplet size is independent of surfactant mixing ratio. There are also a number of papers in the most recent bibliography for nano-emulsions made using the phase inversion composition approach. In optimization, variations in droplet size with oil surfactant ratio and preparation process are discussed. [34]

A number of emulsification techniques are investigated, and droplet size fluctuation with HLB, water fraction, and surfactant concentration are also reported. With the anticipated outcome that there is an optimal HLB and that the higher the oil surfactant ratio, the larger the droplet size, the effects of the variables HLB and oil surfactant ratio are independently explored in. W/O nano-emulsion preparation optimization is discussed. An ideal surfactant composition providing a water solubility maximum is selected for various Span-Tween surfactant combinations, and droplet size fluctuation is examined in relation to water concentration. [35]

Additionally, it goes without saying and is consistent with W/O nano-emulsions that the larger the droplet size, the higher the water concentration. There has been extensive work done on optimization for nano-emulsions created through self-emulsification. It was investigated how surfactant HLB, solvents, and oil affected droplet size. The findings suggested that there are ideal values for HLB and solvent proportions. The influence of sucrose surfactants on percutaneous penetration is explored, and the efficiency of a schistosomicidal agent is increased by including the agent in nanoemulsions as an example of optimising nano-emulsion function. [36]

7. APPLICATIONS:

One of nanotechnology's most promising uses could be the cell-specific delivery of medications. By encapsulating toxic agents and limiting off-target interactions, delivery systems made of smart materials with tunable physical and biological properties will enhance current therapeutic approaches. They will also increase the bioavailability of drugs with poor solubility, imparting tissue or cell specificity, and improve or enable intracellular delivery. [37]

Colloidal dispersions known as nanoemulsions are made up of an oil phase, an aqueous phase, a surfactant, and a co-surfactant in the proper proportions. Unlike granular emulsions that have been heated externally. Low interfacial tension supports nanoemulsions. This is frequently done by using a co-surfactant, which causes a nanoemulsion to spontaneously form that is thermodynamically stable.

When referring to emulsions with inner phase droplets smaller than 1000 nm, the term "nanoemulsions" is frequently used. The terms tiny emulsions, ultrafine emulsions, and submicron emulsions are also used to describe nanoemulsions. According to studies on phase behaviour, at the inversion point caused by either temperature or composition, the surfactant phase structure (bicontinuous microemulsion or lamellar) determines the size of the droplets. Independent of whether the initial phase equilibrium is one or multiphase, studies on the generation of nanoemulsions using the phase inversion temperature method have demonstrated a link between the smallest droplet size and total oil solubilization during a microemulsion bicontinuous phase. Nanoemulsions are resistant to sedimentation or creaming because of their small droplet sizes, with Ostwald ripening constituting the primary mechanism of breakdown. [38]

The main distinction between emulsion and nanoemulsion is that while emulsion is physically foggy and nanoemulsion is exceedingly transparent, whereas emulsion is kinetically stable but thermodynamically unstable. Vaccine administration, prophylaxis against bioterrorism, non-toxic disinfection cleaner, cell culture technology, formulations for enhanced oral delivery of poorly soluble drugs, and ocular and optic nerve delivery are all possible uses for nanoemulsions. Drug administration, intranasal drug administration, parenteral drug administration, transdermal drug administration, cancer therapy, and pulmonary drug administration. [39]

7.1 ADVANTAGES OF NANOEMULSIONS

- Nanoemulsion is a method for enhancing the water solubility and bioavailability of pharmaceuticals for lipophilic drugs.
- Aids in the stabilisation of lipophilic medications and taste muffling.
- Due to the medicine being enclosed in oil droplets, this method protects it from hydrolysis and oxidation.
- Enhance the drug's capacity to penetrate the skin through the use of nanoparticle-sized droplets, which have a huge surface area and a rapid rate of absorption.
- The use of Nanoemulsion as delivery systems can increase the efficacy of a drug, allowing the total dose to be reduced and limiting adverse effects. They need to have the ability to transport peptides that are vulnerable to enzyme hydrolysis in the GIT. [40]

7.2 DISADVANTAGES OF NANOEMULSIONS

- Use of extremely high concentrations of co- and surfactants is required for stabilising nanoparticles.
- Need specialist tools for preparation
- Limited ability of top melting compounds to dissolve.
- Surfactant used in pharmaceutical applications must not be harmful.
- Environmental factors like temperature and pH have an impact on nanoemulsion stability. [41]

7.3 BENEFITS COMPARED TO OTHER DOSAGE FORMS:

- Reduced variability in absorption and an increase in absorption rate.
- Defense against hydrolysis and oxidation in O/W nanoemulsions.
- Delivery of solubilized lipophilic medicines.
- Water-soluble medication is administered in aqueous form.
- Improved bioavailability for a number of medications.
- Capability of incorporating both hydrophilic and lipophilic medicines.
- Delivery methods that increase efficacy while lowering the overall dose and negative effects.
- As non-toxic and non-irritating carriers for drug penetration through liquid films, whose hydrophilicity or lipophilicity as well as thickness are frequently carefully adjusted.
- Because nanoemulsions are thermodynamically stable systems, they can self-emulsify even when their properties don't support the chosen strategy.
- Enhance a drug's effectiveness, enabling the dose to be halved while limiting negative effects.

8. CONCLUSION:

An oil and water nanoemulsion is a colloidal dispersion of two or more incompatible phases. As colloidal carriers for the targeted delivery of different anticancer medications, photosensitizers, neutron capture treatment agents, or diagnostic agents, they have recently attracted considerable attention. Drugs and food ingredients that are hydrophobic and have a high first pass metabolism suffer from limited bioavailability, which is efficiently addressed by nanoemulsion drug delivery devices. Researchers use high energy techniques to improve medication and bioactive food component delivery. With regard to composition factors, optimizations by selected parameter change or experimental designs allow for the conclusion that there is typically an ideal surfactant mixture composition, or HLB, where the larger the oil surfactant ratio, the larger the droplet size. Controlling numerous elements, such as the kind of oil phase, the methods employed, the process variables, and the addition of additives used across the inter phases of nanoemulsion formulation, could improve the formulation's stability. The physical and chemical instability of nanoemulsions restricts its uses. In this study, new approaches and factors for formulating successful nanoemulsions have been discussed in the hopes that they would serve as a model for future achievements in the field.

9. REFERENCES:

1. Suyal J. An Introductory review article on Nanoemulsion.Int J of Res in Pharm Pharma Sci.Jule 2017;4(2):35-40.
2. Haritha, Basha S P, Rao K P, Chakravarthi V. A brief introduction to methods of preparation, applications and characterization of nanoemulsion drug delivery system. Indian Journal of Research in Pharmacy and Biotechnology. 2013; 1(1):25-28.
3. K. Gurpreet and S. K. Singh: Review of Nanoemulsion formulation and characterization techniques: Indian J Pharm Sci 2018;80(5):781-789
4. Sandeep Kumar Singh, Priya Ranjan Prasad Verma and Balkishen Razdan. Development and characterization of a lovastatin loaded selfmicroemulsifying drug delivery system, Pharmaceutical Development and Technology, 15(5), 2010, 469-483.

5. Rajalakshmi R, Mahesh K, Ashok Kumar C K. A Critical Review on Nano Emulsions, International Journal of Innovative Drug Discovery, 1(1), 2011, 1-8.
6. Udaya Sakthi M., Josephine Ritashinita, Lobo F and Kiran B. Uppulurl, Self-Nano Emulsifying Drug Delivery Systems for Oral Delivery of Hydrophobic Drugs, Biomed, and Pharmacol. J., 6(2), 2013, 355-362.
7. Gade Abhishek V, Salunkhe K S, Chaudhari S R, Gadge P B, Dighe G S, Amit Asati. A Review on, Self-Micro Emulsifying Drug Delivery system, Am. J. Pharmatech Res, 5(1), 2015, 51- 66.
8. Pallavi M. Nigade, Swapnil L. Patil, Shradha S, Tiwari. Self-Emulsifying Drug Delivery System (SEDDS), A Review, IJPBS, 2(2), 2012, 42-52.
9. Shukla Jill B, Koli Akshay R, Ranch Ketan M and Parikh Rajesh K, Self-Micro Emulsifying Drug Delivery System, Pharma Science Monitor, An International Journal of Pharmaceutical Sciences, 1(2), 2010, 13-33.
10. Lifshitz IM, Slyozov VV. The kinetics of precipitation from supersaturated solid solutions. Journal of Physics and Chemistry of Solids 1961; 19:35–50.
11. Agrawal S, Giri TK, Tripathi DK, Ajazuddin, Alexander A. A review on novel therapeutic strategies for the enhancement of solubility for hydrophobic drugs through lipid and surfactant based self micro emulsifying drug delivery system: a novel approach. Am J Drug Discovery Dev. 2012. 2:143-183.
12. Kohli K, Chopra S, Dhar D, Arora S, Khar RK. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov Today. 2010. 15:958-965.
13. Ishak KA, Annuar MSM. Phase inversion of medium-chain-length poly-3-hydroxyalkanoates (mcl-PHA)-incorporated nanoemulsion: effects of mcl-PHA molecular weight and amount on its mechanism. Colloid Polym Sci. 2016. 294:1969-1981.
14. Armanet L, Hunkeler D. Phase inversion of polyacrylamide-based inverse-emulsions: influence of inverting-surfactant type and concentration. J Appl Polym Sci. 2007. 103:3567-3584.
15. Solans C, Solé I. Nano-emulsions: formation by low-energy methods. Curr Opin Colloid Interface Sci. 2012. 17:246-254.
16. Fernandez P, André V, Rieger J, Kühnle A. Nano-emulsion formation by emulsion phase inversion. Colloids Surf A Physicochem Eng Aspects. 2004. 251:53-58.
17. Vandamme TF, Anton N. Low-energy nanoemulsification to design veterinary controlled drug delivery devices. Int J Nanomedicine. 2010. 5:867-873.
18. Jayasooriya SD, Bhandari BR, Torley P, D'Arcy BR. Effect of high-power ultrasound waves on properties of meat: a review. Int J Food Prop. 2004. 7:301-319.
19. Gaikwad SG, Pandit AB. Ultrasound emulsification: effect of ultrasonic and physicochemical properties on dispersed phase volume and droplet size. Ultrason Sonochem. 2008. 15:554-563.
20. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, et al. Nanoemulsion: concepts, development and applications in drug delivery. J Control Release. 2017. 252:28-49.
21. Wang Y. Preparation of nano- and microemulsions using phase inversion and emulsion titration methods. Master's thesis. Massey University, Auckland, New Zealand. 2014.
22. Alton's pharmaceuticals: The Design and Manufacturing of Medicinie.5th Edition; Chapter 27; Page No. 470-473.
23. Ahmad Akhter, Farhan J, Jain K, Jain Neelu, Khar Roop K, Zeenat I. Khan and Talegaonkar Sushama: Investigation of Nanoemulsion System for Transdermal Delivery of Domperidone: Ex-vivo and in vivo Studies382. Current Nanoscience 2008; 382
24. Bouchemal K, Briançon S, Perrier E, Fessi H. Nanoemulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization. International Journal of Pharmaceutics 2004; 280:241–51.
25. Shah RB, Zidam AS, Funck T, Tawakkul MA, Nguyenpho A, Khan MA.Quality by design: characterization of self-nanoemulsified drug delivery systems (SNEDDSs) using ultrasonic resonator technology. International Journal of Pharmaceutics2007; 341:189–94

26. Solè I, Maestro A, González C, Solans C, Gutierrez JM. Optimization of nano-emulsion preparation by low energy methods in an ionic surfactant system. Langmuir 2006; 22:8326–32
27. Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nanoemulsions. Advances in Colloid and Interface Science 2004; 108–109:303–18.
28. Morales D, Solans C, Gutierrez JM, Garcia-Celma MJ, Olsson U. Oil/ water droplet formation by temperature change in the water/C16E6/ mineral oil system. Langmuir 2006; 22:3014–20
29. Wang L, Li X, Zhang G, Dong J, Eastoe J. Oil in water nano-emulsions for pesticide formulations. Journal of Colloid and Interface Science 2007; 314:230–5.
30. Date AA, Nagarkenser MS. Design and evaluation of self-nanoemulsifying drug delivery system (SNEDDS) for cefpodoxime proxetil. International Journal of Pharmaceutics 2007; 329:166–72.
31. Pey CM, Maestro A, Solè I, González C, Solans C, Gutierrez JM. Optimization of nano-emulsions prepared by low energy emulsification methods at constant temperature using experimental designs. Colloids and Surfaces A, Physicochemical and Engineering Aspects 2006; 288:144–50
32. Seekkuarachchi IN, Tanaka K, Kumazawa K. Formation and characterization of submicrometer oil-in-water (O/W) emulsions, using high energy emulsification. Industrial and Engineering Chemistry Research 2006; 45: 372–90.
33. Seekkuarachchi IN, Tanaka K, Kumazawa K. Formation and characterization of submicrometer oil-in-water (O/W) emulsions, using high energy emulsification. Industrial and Engineering Chemistry Research 2006; 45: 372–90.
34. Sadurní N, Solans C, Azemar N, García-Celma MJ. Studies on formation of O/W nano-emulsions, by low energy methods, suitable for pharmaceutical applications. European Journal of Pharmaceutical Applications 2005; 26: 438–45.
35. Porras M, Solans C, González C, Martínez A, Guinart A, Gutierrez JM. Studies on W/O nano-emulsions. Colloids and Surfaces A, Physicochemical and Engineering Aspects 2004;249:115–8.
36. Bouchemal K, Briançon S, Perrier E, Fessi H. Nanoemulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization. International Journal of Pharmaceutics 2004; 280:241–51.
37. Frank Sainsbury, Bijun Zeng and Anton PJ Middelberg Current Opinion in Chemical Engineering 2014, 4:11–17 Elsevier publications
38. Navneet Sharma, Sharadendu Mishra, Suryadev Sharma, Rohan D. Deshpande, Rakesh Kumar Sharma 2013 Preparation and Optimization of Nanoemulsions for targeting Drug Delivery Vol. 5 Issue 4 Scopus & Embase, Elsevier publications
39. Haritha, Syed Peer Basha, Koteswara Rao P, ChakravarthiVedantham 2010 Indian Journal of Research in Pharmacy and Biotechnology vol 1 issue1 pg.no 25-18.
40. P. Bhatt and S. Madhav A Detailed Review on Nanoemulsion Drug Delivery System IJPSR, 2011; Vol. 2(10): 2482-2489
41. Sarvardekar P. Nanoemulsion-A Review.Int J of Res in Pharam Chem.2016;6(2):312-322.