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REVIEW ARTICLE

Recent Trends in Nanoemulsion Formulations for Solubility Enhancement of Poorly Water-Soluble Drugs

Shyam Narayan Mishra[1*], Navneet Kumar Verma[2] and Keshav Kumar Gupta[3]

[1]Shri Baijnath Shivkala Mahavidyalaya, Mangalpur Barabanki, Uttar Pradesh, India
[2]Suyash Institute of Pharmacy, Hakkabad, Gorakhpur, Uttar Pradesh, India
[3]RCC College of Pharmacy, Basti, Uttar Pradesh, India

Corresponding authors:
Shyam Narayan Mishra

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ABSTRACT

Nanoemulsions are thermodynamically stable colloidal dispersion systems composed out of two immiscible liquids that incorporate emulsifying agents (surfactants and co-surfactants) to create a single phase. The utilisation of nanoemulsions as means of delivering medicines has been extensively explored. Furthermore, nanoemulsions are transparent and clear. Mini-emulsion, ultrafine emulsion, and submicron emulsion are other names for nanoemulsion. These emulsions are of the oil-in-water variety, and their typical droplet size ranges from 5 to 100 nm. Transparent or translucent dispersions of water and oil that are thermodynamically stable and regulated by an interfacial coating of surfactant and co-surfactant molecules have droplet sizes smaller than 100 nm are referred to as nanoemulsions.

Keywords; Nanoemulsions, Emulsifying Agents, Surfactants, Co-Surfactants.

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.

COMPOSITION OF NANOEMULSIONS:

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

1.1. 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. [4]

1.2. 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. [5] 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. [6]

1.3. 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. [7]

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. [8]

1.4. 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. [9] 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. [10]

1.5. 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. [11]

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. [12]

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. [13]

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/Oand 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. [14]

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. [15]

3.3. High energy methods:

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. [16]

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.

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. [17]

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. [18].

4. Stability in Nanoemulsions

Nanoemulsions have a kinetic stability due to their unique combination of small droplet size (usually 20–200 nm) and high interfacial area. They are less likely to cream or sediment because their finely distributed droplets resist gravitational separation. Surfactants and co-surfactants, which lower interfacial tension and form a steric or electrostatic barrier around droplets, further improve stability.

Over long periods of storage, a well-designed system maintains uniform dispersion, inhibits microbial growth, and retains sensory attributes like color, clarity, and odor. Droplet integrity may occasionally be strengthened by structural configurations such as encapsulating films or liquid crystal layers. If composition, pH, and temperature are appropriately regulated, nanoemulsions can maintain their structure for months or even years because they are metastable rather than in true equilibrium.[19]

5.Instability Mechanisms[20]

Despite their durability, physical and chemical pathways can cause nanoemulsions to destabilize over time:

5.1 Flocculation: When droplets group together without combining, the rate of creaming or sedimentation is accelerated.

5.2. Coalescence: When the interfacial film breaks down, smaller droplets combine to form larger ones, which ultimately split off as a separate phase.

5.3. Ostwald Ripening: Oil molecules diffuse through the continuous phase, causing droplet growth and eventual phase separation, driven by the solubility differences between larger and smaller droplets. In nanoemulsions, this is frequently the most prevalent mechanism of instability.

5.4. Creaming/Sedimentation: Vertical separation results from density differences between the continuous and dispersed phases. This process can still happen in some circumstances, even though droplet size reduction slows it down.

5.5. Unlike creaming, cracking (also known as breaking) is an irreversible phase separation in which the dispersed phase forms a distinct layer that cannot be reversed by agitation.

5.6. Chemical degradation: Lipids' oxidation or hydrolysis, particularly in unsaturated oils, can change their composition and cause the system to become unstable.

6. Factors Affecting Stability[21]
Important factors influencing stability include:

6.1 Distribution of droplet sizes: Uniform, narrow distributions fend off ripening and flocculation.

6.2 Type and concentration of surfactant: High-HLB non-ionic surfactants frequently provide superior thermal and pH stability; sufficient coverage at the oil–water interface is crucial.

6.3 Oil phase composition – Oils with lower water solubility and appropriate chain length reduce Ostwald ripening.

6.4 Environmental factors: Variations in temperature, pH, and ionic strength can all cause interfacial films to break.

6.5 Processing technique: Phase inversion techniques rely on optimizing interfacial tension to achieve stability, whereas high-energy techniques (such as high-pressure homogenization and ultrasonication) typically result in smaller, more uniform droplets.

7. Stability and functionality in balance[22]
In real-world applications, the goal of nanoemulsion design is to minimize instability triggers while optimizing functional performance (drug delivery effectiveness, cosmetic feel, or food sensory appeal). This entails choosing appropriate oil–surfactant systems, processing to regulate droplet size, and adding additives like ripening inhibitors or antioxidants. In the end, true nanoemulsions cannot achieve thermodynamic stability, but their kinetic stability can be designed to satisfy shelf-life specifications without sacrificing performance noticeably.

8. Characterization of Nanoemulsions
8.1. Droplet size
Transmission electron microscopy
To investigate form and size of nanoparticles transmission electron microscopy is used. For this we use 300 mesh copper/carbon Transmission electron microscopy (TEM) grid with glow discharge. Samples are prepared by incorporating dilute solutions and then drying at room temperature. For TEM only most stable emulsions can be utilized [23]. The specimens were positioned on a polycarbonate base, and any surplus water was allowed to evaporate naturally at room temperature (25 ± 8 °C). Subsequently, they undergo drying in a critical point dryer utilizing carbon dioxide, followed by sputter coating with gold using a metallizer. Finally, the samples were scrutinized using a scanning electron microscope with an operational accelerating voltage of 20 kV.

8.2. Interfacial tension
Interfacial tension is used to study formulation and characteristics of Nanoemulsions. When surfactant phase is in equilibrium with oil and aqueous phases, ultralow levels of interfacial tension are indicated with phase behaviour. Extremely low levels of interfacial tension can be determined by spinning drop equipment [32]. Nanoemulsions droplet size is measured by photon correlation spectroscopy. It is done by using a volumetric flask in which 0.1ml formulation and 50ml water is added and mixed by inverting flask gently. Measurements are taken by setting zeta sizer and light scattering monitor at 25 °C at specific angle (90° or 180°) [27].

8.3. Zeta potential
Zeta potential is a measure of particle charge which is important characteristic to determine stability of Nanoemulsions. High zeta potential indicates stability which means solution show resistance to aggregation. Low potential indicates attraction exceeds repulsion and dispersion flocculates. This measure indicates forces between particles at Nanoemulsions surface which helps in stabilization of Nanoemulsions. For electrostatically stable emulsions zeta potential must be 30 mV. For nano scaled particles zeta potential influenced by manufacturer such as particle source, electrolyte concentration, pH, hydration, particle morphology [25]. Zeta potential was determined by using the Electrophoretic mobility of particles in an electric field using Zeta sizer Nano ZS Apparatus. Zeta potential of the formulation was measured using Beckman Coulter Delsa Nano C Particle analyzer, USA. Through the determination of the electrostatic magnitude and the repulsion or attraction charge between particles, the potential value of zeta gives an indication of the stability of the Nanoemulsion. To maintain stability, an emulsion has to attain a minimum of 30 mV (positive or negative) of zeta-potential value [29].

8.4. Refractive index
Refractive index is the net value of the components of Nanoemulsion and indicates the isotropic nature of formulation. It is the technique for assessing whether formulation is transparent or not also thermodynamic stability analysis of sample

[32]. It is determined by putting sample drop on slide and then comparing with water having RI 1. 33 using refractrometer. If comparison of system's RI is relatable to water's RI, then formulation is transparent. Refractive index was determined by using refractometer [27].

8.5. Conductance

Conductometer is used to determine conductance of sample i.e., Nanoemulsions. An EC Tester 11+, USA conductance meter was used to test the electrical conductance of the Nanoemulsion at 25 degrees. Three runs of this test were conducted to ensure uniformity [26]. In this method electrodes immersed in emulsion system which is supplied with electric source and lamp. If o/w type emulsions then water conducts current and lamp lights up due to flow of current between electrodes. In case if oil is exterior phase so lamp is dark because emulsion is absent [27].

8.6. Viscosity

It is key characteristic of Nanoemulsion. The resistance to flow of fluids is termed as viscosity, or the friction that exists within fluids. The most frequently employed instrument to measure viscosity is Brookfield viscometer. The viscosity of the produced Nanoemulsion was measured using the Brookfield DV-II+ Pro viscometer at 25 °C without dilution by taking average of three data points at specific shear rate. After the mixture had been in the beaker for five minutes, spindle readings were taken at 0.5, 1, 2.5, and 5 rpm at maintained temperature and at room temperature for 12 weeks which suggests that the lower the storage temperature, there is increase in viscosity of Nanoemulsions. The viscometer's accompanying dial was read and recorded. According to power law model, emulsions exhibit shear thinning behaviour under shear rate. It gives three ranges for n (flow behaviour index): n1 for shear thickening fluids. An emulsion shows less than 1 n value [26]. Viscosity= mass/volume (1) The viscosity of Nanoemulsions can be determined at various shear speeds [27].

8.7. Dye test

Microscopic analysis is done for clear understanding. If o/w emulsions type then it continuously absorbs water soluble dye. Conversely, if w/o emulsion it only uptakes water soluble dye in dispersion phase and the colour is not uniform [27].

8.8. Creaming test Following homogenization, 10 milliliters of the Nanoemulsions were immediately put into a test tube, firmly sealed, and kept at room temperature (25 ± 2 °C) for seven days. The creaming stability was determined by visually examining and then calculating the creaming index percent Creaming index percent= (HL/HE) × 100% (2) where HL is the entire height of the cream layer and HE is the overall height of the emulsions [34].Increased creaming index indicates the presence of emulsion instability, which can be attributed to flocculation, aggregation, coalescence, or high particle size [25].

8.9. pH values and total soluble solid content

At −20 °C, the total soluble solid content was measured in Brix is the result of triplicate measurements made with a Pocket Pal-1 refractometer. The pH was calculated using the pH meter by submerging the instrument bulb into 30 ml of each produced formulation [29].

8.10. Texture Analysis

The Nanoemulsion samples were kept in plastic containers at -20 °C for a whole day in order to conduct the texture analysis. At room temperature (25 ± 2 °C), measurements of firmness, hardness, consistency, cohesiveness, and viscosity index were made using a texture analyzer TAXT2i fitted with a 2-mm-diameter acrylic cylindrical probe. The samples' geometrical centers had a penetration depth of 10 mm, and their penetration rates were 1 mm/s. After being hardened at -30 °C, the Nanoemulsion was sliced to fit into a tiny cylindrical cup with a diameter of 4.5 cm and a depth of 30 mm. It was then tempered overnight to -15 °C in preparation for the analysis. The penetration speed of the probe was 2 mm/s up to a 20 mm distance [29].

8.11. Creaming and cracking

Each multiple Nanoemulsion (MNE) was sampled in 30 ml and placed in a glass bottle with a screw lid (height 65 mm and inner diameter 25 mm). The container was then allowed to stand at 25 ± 2 °C for a day before being checked for physical changes. The permanent/irreversible division or separation of the internal/dispersed phase (where oil and water are clearly separated) at the top of the emulsion is known as cracking, which is a physical instability. The given Equation was used to calculate the cream layer height (top layer) and the overall emulsion height in the event that the emulsions are divided into cream and serum layers. This allowed for the determination of the percentage of creaming. Creaming (%) [28]= 100 × Height of cream layer/Total height of emulsion [32].

8.12. Entrapment efficiency

To determine the percentage drug encapsulation efficiency, the concentration of unentrapped drug, or free drug, in the formulation was assessed. This concerns since it has an impact on the medication molecule's release characteristics. Equation was used to determine the quantity of drug encapsulated per unit weight of formulation after the entrapped drug

was separated from the Nanoemulsion formulation. %EE = (amount of drug added − free (unentrapped) drug)/(amount of drug added) × 100 [32].

4.13. Differential Scanning Calorimetry (DSC)

It is a thermo analytical technique which measures difference in amount of heat needed to increase temperature of sample and reference. Both reference and sample are maintained at same temperature throughout experiment. The sample should have well defined heat capacity over the range of temperature. This technique is employed to detect phase transitions as melting of crystalline agents and analyze proportion of solid fat or ice crystals in emulsion. It is also used to detect crystallization temperature of mixture of surfactants [25].

4.14. Fourier Transform Infrared Spectroscopy (FTIR)

It is based on infrared radiations that are absorbed by sample. It gives spectrum that represent molecular absorption and transmission forming molecular finger print of sample. This fingerprint represents characteristic absorption peaks corresponding to frequencies of vibration between atoms of material. The size of peaks in spectrum is direct indication of amount of material in sample. Advantage of FTIR is to determine amount of component in mixture and to determine quality and consistency of sample. It gives accurate and reproducible measurements [25].

4.15. In vitro dissolution profile

4.15.1. United State Pharmacopoeia (USP) type-II apparatus

A dissolution apparatus type II was used for a drug release investigation. 900 milliliters of pH 1.2 simulated gastric fluids served as the dissolving medium. Every Nanoemulsion formulation has gone through this investigation at various pH levels by being placed in a dialysis membrane bag and replaced with fresh medium. At certain intervals, a 5 ml sample was taken and replaced with new media. Each sample was examined to determine drug concentration using a UV-Vis spectrophotometer set to analyze at lambda max of 210nm after being filtered with a syringe filter of 0.45 µm. Then samples are analyzed in HPLC or by other methods for determining release behaviour which is then compared with standards [31].

4.15.2. Franz cell apparatus method

The Franz cell device with a diffusion area of 1.79 cm2 and a receiver chamber volume of 16 ml was used for in vitro drug release. A synthetic cellulose acetate membrane (Merck, Brazil) was used, which had been previously moistened. The donor and receiver compartments were then separated by the membrane. To maintain sink conditions, the receiver chamber was filled with a physiological solution containing 1% -cyclodextrin as a solubilizer (maximum MS solubility = 2.13 mg/ml). A Peltier-Type Temperature Control Equipment was used to keep the receptor compartment at 32 °C by employing an external thermal bath. Throughout the experiment, continuous stirring was maintained. Bubbles were avoided by sonicating the receiver solution before to the experiment. On top of the membrane, the equivalent of 10 mg of formulation was deposited. The donor compartment was secured to the receiving compartment, which was then sealed with Parafilm®. Aliquots of 500: l was collected after 30 minutes, 1, 2, 3, 4, 6, 7, 8, and 24 hours. An equivalent volume of new medium was poured to maintain the washbasin condition. A validated HPLC method was used to find the concentration of MS in each sample [32].

4.15.3. Membrane diffusion method

Drug release studies were carried at temperature 32 °C by using (standard regenerated cellulose and Spectra). For Experiment of release take 5g of Formulation along with the receptor solution filled in dialysis chamber for 24 hours. By using UV-Visible Spectroscopy the concentration of drug in receptor solution was analyzed by wavelength in 350 nm. Surfactant was added in solution to increase solubility in receptor solution. The receptor solution consists of 1.5% w/w polysorbate buffer at pH (7.4) [33].

APPLICATIONS OF NANOEMULSION IN DRUG DELIVERY[34, 35,36]

5.1. Parenteral Delivery

Parenteral administration of medications with restricted solubility (particularly via the IV route) is a significant concern in the business due to the highly poor drug delivery to a specific spot. Nanoemulsion formulations differ from macroemulsion systems when administered parenterally because nanoemulsions of small particles are excreted from the body slower and more gradually than emulsions of large particles and stay there for a longer period of time. Parenteral delivery can be performed using either o/w or w/o nanoemulsion. Several of the nanoemulsion systems described in the literature can be employed for parenteral administration due to surfactant toxicity and parenteral use. By substituting parenterally acceptable co-surfactants, such as polyethylene glycol (400)/polyethylene glycol (660)/12 hydroxystearate/ethanol, for C3-C4 solvents, Von Corsewant and Thoren were able to create an almost balanced middle phase nanoemulsion while maintaining a versatile emulsifier film and impulsive curvature close to zero. The intermediate phase formation was selected for this application because it could integrate substantial amounts of water and oil with only a small amount of surfactant.

5.2. Oral Delivery

For oral delivery, nanoemulsion formulations provide a number of advantages over traditional oral formulations, including increased clinical potency, improved absorption, and reduced drug toxicity. Therefore, it has been suggested that nanoemulsion is the good delivery system for medications like steroids, hormones, diuretics, and antibiotics. Pharmaceuticals using peptides and proteins have very high potencies and are very targeted in their physiological effects. The majority, though, are challenging to provide orally. They are typically not therapeutically active when administered orally since their oral absorption in conventional formulations—those that don't include nanoemulsions—is below 10%. The majority of protein medicines are only offered as parenteral formulations the result of their negative oral bioavailability. However, because parenterally given peptide medications have a very short biological half-life, several doses are necessary. Neoral®, a cyclosporine nanoemulsion preparation, has taken the place of Sandimmune®, a mediocre cyclosporine oil-in-water emulsion preparation. Due to its increased dispersion, Neoral® absorbs more quickly, reliably, and with less fluctuation between and within individuals.

5.3. Topical Delivery

The avoidance of the drug's hepatic first pass metabolism and associated adverse consequences is just one of the benefits of topical drug administration over other approaches. Another is the drug's capacity to distribute itself straight on the skin or eyes that are afflicted. For the administration of prostaglandin E1, In a hairless mouse model, both o/w and w/o nanoemulsions have been tried. The nanoemulsions were built on oleic acid, or Gelucire 44/14, and stabilised with a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and PlurolOleique CC 497 as a surfactant. Regardless of the O/W nanoemulsion. there were observed delivery rates to be boosted, the authors came to the conclusion that neither system's penetration rates were sufficient for practical application. It has also been claimed to use a lecithin/IPP/water nanoemulsion to deliver indomethacin and diclofenac transdermally. As per FTIR spectra and differential scan calorimetry (DSC), after a day of incubation, the IPP organogel had changed the lipid composition in the mammalian stratum corneum. It has also been investigated how the hydrophilic drug diphenhydramine hydrochloride is distributed transdermally into excised human skin from a w/o nanoemulsion. The formula was created using Tween 80 and Span 20 in combination with IPM. However, two other formulationsthat contained oleic acid and cholesterol, respectively, were evaluated. Although oleic acid had no detectable effect and cholesterol improved medication penetration, scientists have shown that compositional choices can change the parameters of penetration.

5.4. Ocular and Pulmonary Delivery:

The majority of drug delivery to cure eye disorders occurs topically. For ocular delivery, poorly soluble drug dissolution, increased absorption, and prolonged release profiles of o/w nanoemulsions have been studied. Lecithin, propylene glycol, and PEG 200 were used in the formulation of the pilocarpine-containing nanoemulsions, with IPM serving as the oil phase. The formulations' a favourable refractive index and low permeability made them suitable for ophthalmologic uses. a non-ionic fluorocarbon surfactant that stabilises a water-in-HFA propellant nanoemulsion that is meant for pulmonary distribution.

5.5. Nanoemulsions in Biotechnology:

Aqua-organic or purely organic media are used for many enzymatic and biocatalytic processes. These kinds of reactions also include biphasic media. Biocatalysts' denaturation is caused using only pure polar media. The usage of water-resistant media has some advantages. Low water content enzymes detect and have-

- An increase in solubility in reactants that are non polar.
- Thermodynamic equilibrium modifications that would encourage condensations.
- Improvements in the enzymes' thermal stability make it possible to conduct reactions at high temperatures

Numerous enzymes typically function in hydrophobic environments within cells, including hydrolytic enzymes, esterases, aldehyde dehydrogenases, and oxidases. In biological systems, many enzymes function at the interface where the hydrophilic and hydrophobic domains converge. Polar lipids and other naturally occurring amphiphiles often serve to stabilise this interface. Enzyme catalysis has been employed in nanoemulsions for a number of reactions, including the production of esters, peptides, and sucrose acyl transesterification; various degradation processes; and the modification of steroid molecules. The lipase family of enzymes is the one that is most frequently used in microemulsion-based processes.

Advantage of Nanoemulsions [37]:

- They can easily be the administration to mucous membranes and skin because they are non-toxic and non-irritating.
- The nanoemulsions' small size allows them to penetrate the "rough" skin surface, which improves the penetration of active ingredients.
- If the formulation includes biocompatible surfactants, it can be taken orally.
- It is the first stage in the manufacture of nanocapsules and nanospheres employing condensation and nanoprecipitation. interfacial poly
- Nanoemulsions have a high surface area and low free energy, making them an effective transport mechanism.

- It could be used for vesicles and liposomes, and lamellar liquid crystalline phases can be created around the nanoemulsion droplets.
- It enables toxicity studies of oil-soluble medications and greater uptake of oil-soluble nutrients in cell cultures to increase the proliferation of cultured cells.
- The setup of the homogenizer, a necessary tool for the formulation of nanoemulsions, is a costly process. Additionally, ultrasonication and microfluidization (producing processes), They need significant financial support.
- Nanoemulsion formulation storage is a significant problem. The delivery of nanoemulsions is said to be expensive in the cosmetics business.
- The cosmetics sector is particularly affected by the high cost of production due to the use of emulsifiers in high concentrations during commercial manufacture. Method of Preparation of Nanoemulsions: The best technique to create nanoemulsions, which have a very limited range of particle sizes, is with high-pressure equipment. Microfluidization and high-pressure homogenization are the most common processes for making nanoemulsions at laboratory and industrial scales. The creation of nanoemulsions can also be accomplished using ultrasonification and in-situ emulsification.
- The issues with natural creaming, flocculation, coalescence, and sedimentation are not displayed.
- It is possible to create it in a variety of ways, including foams, creams, liquids, and sprays.
- It is acceptable for both veterinary and human therapeutic reasons, because it does not harm both healthy animal and human cells.

Disadvantages of Nanoemulsions [38]

- Although pH and temperature have an effect on the solidity of surfactants and cosurfactants, extensive grouping of these substances is necessary for adjustment, and uncertainty can be brought about by impact of Oswald's maturation, which is expensive because of the size of the droplets reduces.
- Due to the tiny reduction of the droplets, which necessitates a special set of instruments and procedural techniques, the creation of nanoemulsionsis a costly process.
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CONCLUSION

Pharmaceutical systems make extensive use of nanoemulsions. Drug, biological, or diagnostic agent distribution is one of the many benefits of nanoemulsion formulation. The most significant use of nanoemulsion is to cover up the unpleasant flavour of greasy liquids. The medications, which are vulnerable to oxidation and hydrolysis, may also be shielded by nanoemulsion. Nanoemulsions have recently drawn a lot of interest as a drug carrier for enhancing the administration of medicinal substances, including anticancer medications, and compounds used in neutron capture treatment. The use of nanoemulsion for transdermal medication administration has been the subject of numerous investigations in recent years. Oil, surfactants, and co-surfactants are all present in the nanoemulsion formulations, which are discovered to be transparent due to their particle size in nanometres.

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