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Recent advances in Nanoemulsions as Targeted Drug Delivery: Detail insights of Formulation and Stability aspects

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ABSTRACT:

Nanoemulsions are kinetically stable isotropic systems which are formed at an ultralow energy interface. The ease of preparation, high scalability, translational status and wider acceptability makes this nano-carrier a first-choice system for lipophilic molecules. Nanoemulsions have been widely investigated for lipophilic entities for improving their bioavailability. The current review focuses on recent trends in formulation aspects and stability insights of nanoemulsion systems. The present review highlights the typical features of nanoemulsion formulation and also gives detailed features of lipid excipients used in their preparation. Furthermore, the preparation methods are also explained on the basis of their selectivity and critical process parameters with their case studies. In a nutshell, this review article provides a critical appraisal of nanoemulsion based strategies along with their future prospective.

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INTRODUCTION:

An emulsion is defined as a system containing two immiscible phases, which consist of a dispersed phase as droplets [internal phase] and a continuous phase [external phase] in which these droplets are dispersed [1]. Historically, the term microemulsion was first used by Schulman, *et al.* [2] in 1959 to describe a transparent solution of a multiphase system consisting of water, oil, surfactant, and alcohol, although it is not systematically used. Some researchers use words like “micella” or “swollen micelles" [3] for emulsions as their synonyms. Research on microemulsion was unknown to the

scientific community until a work by Hoar and Schulmann was published in 1943 [4]. They described a spontaneous formation of an emulsion of oil and water upon the addition of a strong surface-active agent. The developed emulsion was kinetically stable but thermodynamically unstable. Nanoemulsion drug delivery systems are a promising tool for improving the bioavailability of hydrophobic drugs. The majority of drugs are hydrophobic (lipophilic) in nature, leading to low solubility, low oral bioavailability, uncertain absorption profiles, dose variations, wide intra and inter-subject variability. Hence, we can conclude that drugs with low solubility and low bioavailability express poor therapeutic efficacy. United State Food and Drug Administration (US-FDA) in its biopharmaceutical classification system (BCS) for drug substances has been categorized (Table 1).

Table 1. Biopharmaceutical Classification System.

BCS Class	Properties
Class I	High Solubility High Permeability
Class II	Low Solubility High Permeability
Class III	High Solubility Low Permeability
Class IV	-Lo Low Solubility Low Permeability

Class II medications have low solubility and high permeability over the gastrointestinal membrane, while class IV drugs have poor solubility and permeability across the gastrointestinal membrane, according to the BCS. As a result, when medications from classes II and IV are used orally, their absorption is unpredictable. Lipid based formulation is now a good alternative for delivering drugs with low oral bioavailability and other formulation issues. Solutions, suspensions, emulsions, nanoemulsions, solid-lipid nanoparticles (SLN), liposomes, lipoplexes, and other lipid-based dosage forms are examples of lipid formulations.

Among all of the options discussed, nanoemulsion drug delivery systems have proven to be the most effective in increasing the solubility, absorption, and bioavailability of hydrophobic medicines with low oral bioavailability and other formulation issues. A nanoemulsion drug delivery technology can also be used to deliver food bioactive ingredients. Food bioactive substances such as flavonoids (flavanols, flavones, flavanones, and isoflavones), non-flavonoids (hydroxybenzoic acids, stilbenes, and curcuminoids), and carotenoids (carotenes and xanthophylls) have been successfully encapsulated as nanoemulsion formulations. The nanoemulsion systems have a large interfacial area and stability, allowing them to shield molecules from harsh environmental conditions while also increasing their stability. Drugs can be delivered via transdermal and transmucosal channels with this drug delivery method. One media act as the dispersed phase, while the other medium acts as the dispersing medium in the system. Oil, water, surfactant, and other mediums can be used. Each droplet in a nanoemulsion contains a protective coating of emulsifier molecules with a diameter ranging from 10 to 200 nm.

Self-emulsifying formulations:

Self-Emulsifying Drug Delivery Systems (SEDDS) and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) are two types of self-emulsifying formulations (SNEDDS). SEDDS produces coarse emulsions, whereas SNEDDS produces nano-sized emulsions. Isotropic mixes of oil, surfactant, and co-surfactant are utilized in the systems. These systems form emulsions (in the case of SEDDS) or fine or optically clear nanoemulsions (in the case of SNEDDS) with modest agitation, which is caused by gastrointestinal tract (GIT) motility. Because the emulsion or nanoemulsion is generated *in vivo* by dilution with aqueous media, SEDDS and SNEDDS are commonly referred to as emulsion or nanoemulsion pre-concentrates.

For self-emulsifying formulations, a lipid formulation classification system is used:

Pouton created a four-category lipid formulation classification system (LFCS) to better understand the composition of self-emulsifying formulations. Table 2 shows the lipid formulation classification scheme. There are no water-soluble components in the system. Type II formulations also have a number of advantages over the other three classes, including a high solvent capacity for the drug after dispersion and the ability to form a fine oil-in-water emulsion with droplet size (less than 300 nm) under gentle agitation through efficient self-emulsification in the GIT fluid. Type III formulations, also known as Self-Nano Emulsifying Drug Delivery Systems, incorporate water-soluble components such as hydrophilic surfactant (HLB greater than 12) and water-soluble co-solvent (SNEDDS). It comes in two varieties:

Table 2. Categories of lipid formulation classification system.

Composition (%)	Type I	Type II	Type III		Type IV
			III A	III B	
Glycerides (Mono-, di, -tri-Glycerides)	100	40-80	40-80	<20	0
Lipophilic surfactants (HLB<12)	0	20-60	0	0	0-20
Hydrophilic surfactants (HLB>12)	0	0	20-40	20-50	20-80
Co-solvents	0	0	0-40	20-50	0-80
Characteristics features	Simple oil solutions	SEDDS	SNEDDS	SNEDDS	Spontaneous formation of micellar dispersion

Table 3. Oils used in the formulation of nanoemulsions system.

Types of oils	Examples
Fixed oils (Long chain tri-glycerides)	Soyabeanoils,arachisoil,castoroils,cottonseedoil,maize (corn) oil,oliveoil,sesameoil,sunfloweroil,palmoil,peanutoil,triolein
Medium-chain triglycerides and Relatedeasters	Caprylic/capric triglycerides, (AkomedE,AkomedR,Miglyol 810,and captex 355,Neobee M5®,crodamol,GTCC®),fractionated coconut oil, (Miglyol 810),Captex 300,Labrafac CC, Triacetin
Medium-chain mono and di-glycerides	Mono and di glycerides of capric/caprylic, Acid (Capmul MCM and imwitor)
Long-chain mono glycerides	Glyceralmonooleate (peceol),capmul, (GMO),glyceralmonolinoleate, (Maisine-35)
Propylene glycol (PG) fatty acid easters	PG diester of caprylic/ capric acid, (Labrafac PG), PG monocaprylic ester (Sefsol-218) PG monolaurate, (Lauroglyc FCC, Lauroglycol 90, Capmul PG-12) PG dicaprylate, (Miglyol 840)
Caprylic/capric/diglycerol succinate	Miglyol 829
Fatty acids	Oleic acid, (crossential 094), Caprylic acid
Fatty acid esters	Ethyl oleate,croadamol EO,ethyl butyrate,Isopropyl myristate, Isopropyl palmitate
Vitamins/Mineral oils	Vitamin E/Liquid paraffin

Table 4. List of polyoxyethylene surfactants used in the formulation of nanoemulsion.

Chemical name	Commercial name	HLB
POE SorbitanMonolaureate	Tween 20	16.7
POE SorbitaMonopalmitate	Tween 40	15.6
POE Sorbitan Monostearate	Tween 60	15
POE Sorbitan Monooleate	Tween 80	15
POE SorbitanTristearate	Tween 65	10.5
POE Sorbitan Trioleate	Tween 85	10
POE glycerol Trioleate	Tagat TO	10.5
POE-40 Hydrogenated castor oil	Cremophore RH 40 (solid)	14-16
POE-35 Castor oil	Cremophore EL (Liquid)	12-14
POE Oleyl ether	Brij 96	12.4
POE Lauryl ether	Brij 35	16.9
POE-Vitamin-E	Alpha-Tocopherol TPGS	13

III A and III B. SNEDDS is a mixture of oil, surfactant, co-surfactant, and medication that is isotropic. When this mixture is diluted with aqueous fluids *in vivo*, it produces a thin and optically transparent O/W nanoemulsion, which is helped along by mild agitation produced by the GIT tract's peristaltic movement. Because they form after dilution in aqueous media, SNEDDS are commonly referred to as nanoemulsion pre-concentrates. Type IV formulations are exceptionally hydrophilic and do not include any oil. After dilution with aqueous media, it forms a colloidal micellar dispersion consisting of hydrophilic surfactants and hydrophilic co-solvents.

Nanoemulsion Components:

Oil, lipids, surfactant, water-soluble co-solvent, and water are all components of nanoemulsion systems. The oil phase (As given in Table 3) of nanoemulsions can include triglycerides such as tri-di- or monoacylglycerol, vegetable oils, mineral oil, free fatty acids, and so on. The solubility of the medicine is usually the deciding factor when choosing an oil-based formulation. For the development of nanoemulsions, oil phases with high drug loading are commonly utilized. SPAN (Sorbitol Fatty Acid Esters) and tween (polyoxyethylene - POE derivatives of sorbitan fatty acid esters) are common surfactants utilized in the nanoemulsion system in medication delivery systems and food additives. Polysaccharides (gum and starch derivatives), phospholipids (egg, soy, or dairy lecithin), and amphiphilic proteins like whey protein isolate and caseinate. Cremophor EL, lauroyl, macrogol glycerides (Table 4) cover the most widely utilized oils and surfactants in nanoemulsion systems formulation. Co-surfactants or co-solvents are employed in the development of nanoemulsions to obtain ultra-low negative interfacial tension. Polyethylene glycol, propylene glycol, ethanol, and transcutol-P are among them (diethylene glycol monoethyl ether).

Techniques For formulation of Nano emulsion Drug Delivery Systems:

The techniques employed in the formulation of nanoemulsion drug delivery systems arediverse and show a large degree of overlapping. Different methods for the preparation ofnanoemulsion drug delivery systems have been classified based on energy requirements, nature of phase inversion, and self-emulsification. The detailed method of preparing nanoemulsion is mentioned below:

High energy methods:

High energy methods are extensively used to formulate nanoemulsion. High mechanical energy is used that provides strong disruptive forces, which break up large droplets into nanosized droplets and produce nanoemulsions with high kinetic energy. The disruptive forces are created by using mechanical devices such as ultrasonicator, micro fluidizers, and high-pressure homogenizers. By using these methods, we can achieve greater control of particle size with a choice of formulation composition. It also provides control for stability, rheology and color of the emulsion.

High-pressure homogenization:

One of the most often used methods for preparing nanoemulsions is high-pressure homogenization [6]. The cavitation phenomenon is used to disrupt and produce smaller oil droplets in this technique. Other variables, such as homogenization pressure and the number of cycles, can have a significant impact on the mean droplet size and particle dispersion [6]. A high-pressure homogenizer is a device that applies high pressure to a mixture of oil, water, and surfactant or co-surfactant [7]. While HPH procedures are popular, they are also associated with low productivity and component damage as a result of excessive heat. It is only suited for the preparation of oil/water liquid nanoemulsions with less than 20 % oil phase. In some circumstances, such as when biopolymers are utilized as an emulsifier, severe homogenization might result in a nanoemulsion with larger particles. Small-molecule surfactants, rather than biopolymers, should be employed as emulsifiers in high-pressure homogenizers because they are more successful at creating nanoemulsions.

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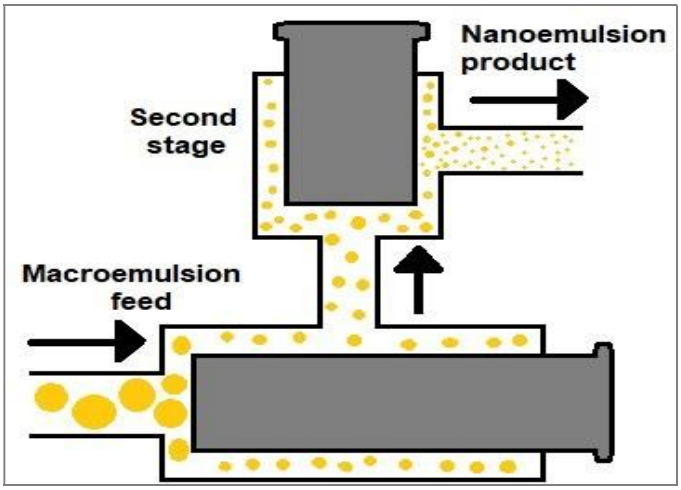

Fig 1. Schematic representation of high-pressure homogenizer.

Fig 1 shows a schematic illustration of high-pressure homogenization, which is commonly employed to create nanoemulsions in culinary, pharmaceutical, and biotechnological ingredients.

Microfluidization:

Microfluidization is a mixing technology (Fig 2) at a micro size level that uses a device called a microfluidizer. In microfludization, fluids are forced to pass through the micro channels under high-pressure (500~20,000 psi). Micro channels are generally micro-sized channels that allow mixing at micro-size level. The phases of microemulsion (aqueous and oil phases) are mixed and then passed through the microfluidizer. The macro-emulsion is guided through the micro channels under high pressure towards the interaction chamber. In the interaction chamber, two streams of macro-emulsions strike with each other at high velocity. This collision creates forces like shearing, cavitation and impact, which produce stable nanoemulsions.

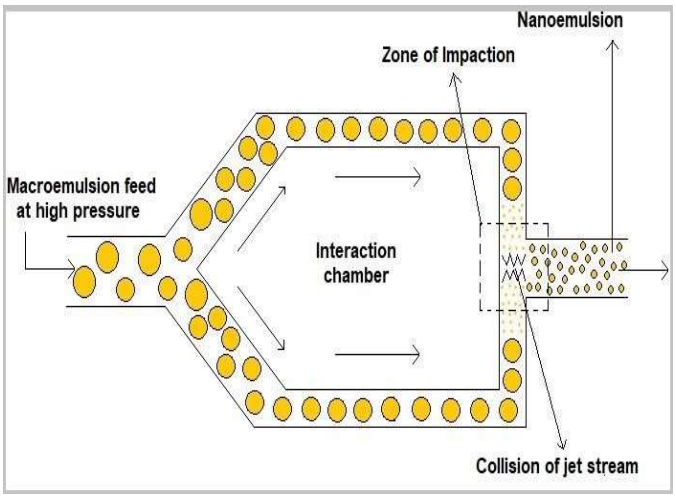

Fig 2. Schematic representation of micro fluidization technique.

Ultra-sonication generator/ Sonicator:

Ultrasonic nanoemulsion preparation (Fig 3) is gaining popularity among formulators due to its high energy efficiency, minimal necessity for high-end mixing tools, ease of system manipulation, and, most importantly, low production cost [9,10]. To distribute one liquid into another immiscible liquid through an opening, researchers employed ultrasound emulsification using changing acoustic fields [11]. Ultrasound's main effect is cavitation, which is the fast creation of vapor bubbles in a liquid under lowered pressure at room temperature [12]. The created bubble bursts quickly, releasing compressed shock waves that cause highly localized turbulence and substantial shear forces [13] that traverse the liquid, resulting in high-velocity liquid jets [14]. In the vicinity of a collapsing bubble, the perturbation of the droplets enhances the mixing of the emulsions [11]. Ultrasonication outperforms other high-energy technologies in terms of operation and cleaning.

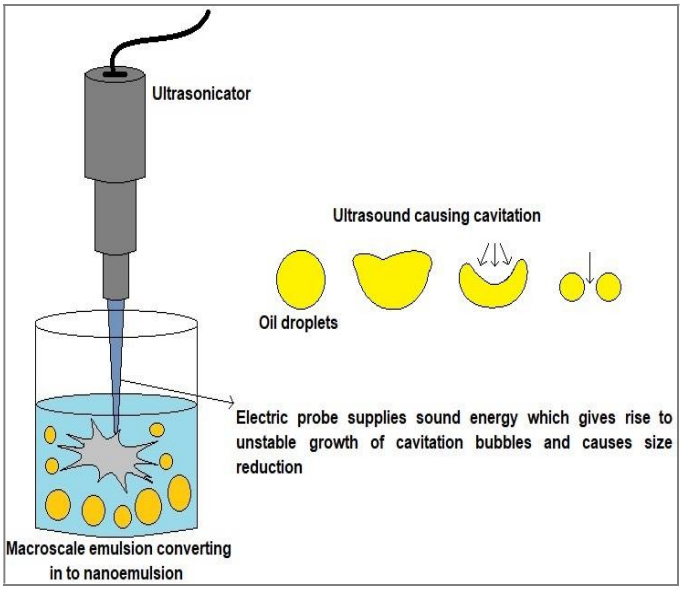

Fig 3. Ultrasonication techniques.

Low energy method:

Using these methods, creating a nanoemulsion system consumes relatively little energy. Low–energy emulsification methods are more efficient because they take advantage of a system's inherent chemical energy and create nanoemulsions with just minimal whirling. Low-energy emulsification methods include phase inversion emulsification and self-emulsification [15, 16]. Table 5 depicts comparison of low and high energy methods for preparing nanoemulsions.

Methods for determining the emulsion inversion point (EIP):

In the emulsion inversion point (EIP) approach, phase inversion occurs through catastrophic phase inversion processes. The catastrophic phase inversion is caused by changing the fractioned volume of the dispersed phase rather than the surfactant properties. The system begins to behave like a W/O nanoemulsion when water is added to the oil-surfactant mixture. When increasing volumes of water are added over particular water content [17-21] while continually stirring, water droplets mix and the phase inversion point is reached, resulting in the production of bi-continuous or lamellar structures. Further dilution with water causes phase inversion from a W/O to an O/W system via intermediate bi-continuous microemulsions. The size of the nanoemulsion droplets

produced is determined by process variables such as the rate at which water is added and the speed at which the nanoemulsion is stirred. For catastrophic phase inversion to occur, the surfactant must be largely present in the dispersed phase, resulting in a high rate of coalescence and rapid phase inversion [22, 23]. Small molecule surfactants can be used in catastrophic phase inversion. These surfactants can be used to stabilize both W/O and O/W emulsions. During catastrophic phase inversion, the surfactant is predominantly present in the dispersed phase; therefore, it behaves as an unusual emulsion [unstable emulsion] that violates Bancroft's criterion [24]. For a stable emulsion [normal emulsion], according to Bancroft's principles, the emulsifier should be predominantly present in the continuous phase. As a result of the catastrophic phase inversion, the abnormal emulsion transforms into a more stable normal emulsion.

Method of self-nano emulsification:

The self-emulsification method is used to create nano emulsions without compromising the surfactant's spontaneous curvature. Turbulence and the development of nano-sized emulsion droplets are aided by the rapid diffusion of surfactant and co-solvent molecules from the dispersed phase [27]. The self-emulsification procedure is also known as spontaneous emulsification technique. SNEEDS use more hydrophilic surfactants and co-surfactants (co-solvents), as well as less lipid, and are based on the self-emulsification phenomena. SNEDDS is an isotropic mixture of oil, surfactant, and co-surfactant, as well as a medicine [28]. When this

Table 5. Comparison between high and low energy methods to formulate nanoemulsions.

Emulsification process	Mechanism of emulsification	Advantages	Disadvantages
Low energy phase inversion composition	Progressive dilution of the dispersed phase to change the interfacial film curvature	Allows scale up production low coat and no heating required in the production process	Requires the presence of liquid crystals [LC] or mid-range microemulsion phases, requires gradual addition of one phase into another
Phase inversion temperature	Temperature variation to change the interfacial film curvature	Allows scale-up production and low cost	Requires the presence of LC or MC phases; Heat energy is required
High energy, high shear stirring using a rotor/stator system	Generate very high shear stresses due to focused energy of delivery,high localized energy disipilation rate near the mixing head	Allows scale-up production, allowing continous production of emulsion with a stirring speed of up to 36,000rpm	High power consumption than conventional mechanically stirred vessels
High-pressure homogenization	Shear, collision, and cavitation	More flexibility for selecting surfactant and internal structure of emulsion than low energy process.	Not suitable for thermal or shear sensitive compounds and more expensive than other equip.
Ultrasonication generator/ sonication	cavitation	More flexibility for selecting surfactant and internal structure of emulsion than low energy processes, as well as less costly equipment.	Can only process small batches of emulsion at a time
Microfludization	High-pressure injection		Not suitable for large scale manufacturing and more expensive than other equipment

mixture is diluted with aqueous fluid *in vivo*, it forms a thin and optically transparent O/W nanoemulsion, which is aided by modest agitation caused by digestive motility in the stomach and intestine (Fig 4). Diffusion of the hydrophilic co-solvent or co-surfactant from the organic phase into the aqueous phase induces turbulence and the formation of nano-size droplets at ultra-low interfacial tension, resulting in the formation of SNEDDS nanoemulsion [29,30]. SNEDDS is the most popular and promising approach for delivering hydrophobic medications with low bioavailability.

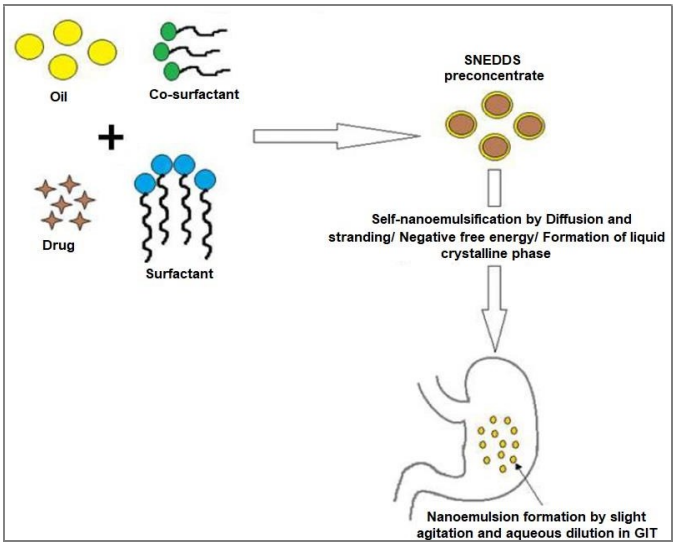

Fig 4. Self-nano emulsification method to prepare nanoemulsions.

Stability of Nanoemulsion Systems:

Due to factors of instability such as flocculation, sedimentation, coalescence, and Ostwald ripening, nanoemulsion may become turbid or phases of nanoemulsion may separate during storage [31]. Destabilization of nanoemulsion systems is relatively gradual [months], hence nanoemulsion systems are kinetically stable. Because nanoemulsion systems create smaller droplet sizes than typical macro emulsions, the Brownian motion effect dominates gravitational forces and provides improved gravitational separation stability. The attraction forces between the droplets, which are normally relatively modest in nano-sized emulsions systems, cause flocculation and coalescence [32]. As a result, nanoemulsions are far more resistant to flocculation and coalescence. Ostwald ripening is another type of nanoemulsion instability that happens often in food-grade nanoemulsions with essential oils and tri-glyceride food chains [33]. Due to the existence of insoluble long chain triglycerides oils, dairy-based nanoemulsions are generally resistant against Ostwald ripening. Ostwald ripening can be avoided by including more hydrophobic oil into the formulation.

Advantages of Nanoemulsion Drug Delivery Systems:

Nanoemulsion drug delivery systems are good in solubilizing active lipophilic substances, and as a result, they have a variety of uses. Nanoemulsion drug delivery systems have a prospective advantage over traditional emulsions in terms of particle size; as a result, this system has an optically clear look and is more resistant to droplet flocculation and coalescence [34]. The oral, parenteral, ocular, and topical administration of active compounds such as food additives and lipophilic medicines using the nanoemulsion drug delivery method has showed promise [35]. The solubilization of these hydrophobic bioactive food components in the GIT is facilitated by O/W vitamin nanoemulsion and nutraceuticals, resulting in increased bioavailability. The physico-chemical stability of bioactive substances is also improved by nanoencapsulation of food components in nanoemulsion systems [36]. Furthermore, the Nanoemulsion food component method improves bioactive chemical delivery to the intradermal layers by diffusion, which aids in the development of herbal cosmetics [37]. Nanoemulsion systems have aesthetic uses due to features such as nano-sized droplets, low viscosity, and transparency. Nanoemulsion drug delivery systems are promising methods of formulation of drugs, food ingredients, and cosmetics agents because their physic-chemical properties improve the bioactivity of encapsulated components and have wide application for delivery of antibiotics, anticancer agents, disinfectants, and antiseptics [38-40].

Ideal characteristics of Nanoemulsions:

Zeta potential:

A zeta sizer is used to measure the parameter, which describes the surface charge of droplets. The nanoemulsion sample is put in a zeta cuvette, and the droplet reading is recorded in mV [41]. Because it compensates for the adsorption of any charged counter ions, zeta potential is generally a better depiction of an emulsion droplet's electrical properties. As a result, it is a reflection of a colloidal dispersion's electrokinetic potential [42]. Values between -5 Mv and +5mV suggest quick aggregation, -20 or +20mV corresponds to short-term stability, while readings surpassing +30mV or below indicate a stable nanoemulsion, according to the zeta potential rule of thumb. Zeta potentials of well stable nanoemulsions are greater than +60mV or lower

than -60 mV. When non-ionic surfactants were included in the formulation, Marino and Rocha- Filho [43] noticed a considerable increase in negative zeta potential. This was most likely owing to the polyoxyethylene chain in the surfactant employed to make the nanoemulsion having certain advantageous chemical characteristics. In any instance, zeta potentials larger than -30Mv before and after the electro kinetic potential test suggest that the formulations were sufficiently stable to withstand the subsequent accelerated stability test [44]. This absolute value range (> -30Mv) is a hypothesis for stability and imparts improved homogeneity, which is a result of the repellent force between particles in nanoemulsions, which prevents aggressions. When more hydrophobic domains are exposed on the nanoemulsion's surface, the absolute value of zeta potential rises, enhancing inter-droplet repulsive forces [45].

Droplet size and polydispersity [intensity-based size distribution] index:

The polydispersity index and particle size distribution are critical indices that reflect the quality, stability, homogeneity, and dispersibility of nanoemulsion. Droplet size is a significant aspect in self-nano-emulsification performance since it impacts the pace and degree of active ingredient release and absorption. To determine the droplet size of a nanoemulsion, photon correlation spectroscopy and light scattering techniques such as static light scattering (SLS) and dynamic light scattering (DLS) are commonly used [45]. Because of the strong curvature and Laplace pressure that resists the deformation of big droplets, small droplet size prevents flocculation. A thick multilamellar surfactant coating deposited on the droplet interface can also inhibit droplet coalescence in nanoemulsion. The destabilization of this system, as with other nanoemulsions, is caused by Ostwald ripening [46]. When tiny droplets with a large radius of curvature are turned into bigger droplets, the process of destabilization occurs, and they spread into one huge droplet. The droplet size distribution increases to bigger sizes with time, and the nanoemulsion becomes progressively turbid [47].

Polydispersity in a nanoemulsion, on the other hand, refers to the ratio of standard deviation to mean droplet size, which indicates droplet size homogeneity within the formulation; PDI indicates departure from the average size. A PDI of less than 0.22 is preferable since it indicates that the nanoemulsion droplets are well disseminated and, for the most part, devoid of adhesion and aggressiveness. A high PDI suggests an unfavorable aspect of less uniform droplet size [50], whereas a PDI of 0.25 indicates strong emulsion stability [48,49]. Most significantly, a PDI closer to zero suggests a monodisperse droplet population, whereas a PDI closer to 1 indicates a droplet population with a wide range of sizes [51]. A homogenous droplet population in the formulation is indicated by a PDI that remains reasonably constant at 0.2 across time [52]. The size distribution of a nanoemulsion with a tiny particle size (P>0.05) and low PDI is likely to be narrow. Nonetheless, a significantly narrower size distribution is advocated by a nanoemulsion with somewhat smaller particle size (P 0.05) and lowers PDI [53, 54].

Viscosity:

In addition to the effective release of active chemicals from the carrier in formulations, viscosity is an important metric for exemplifying and gauze stability of liquid and semi-solid medicines. The compositions of the surfactants, water, and oil components of the emulsion, as well as their concentrations, have a significant impact on the viscosity. Viscosity is normally reduced by increasing the water content during the formulation process. Reduced surfactant and co-surfactant concentrations, on the other hand, might result in an increase in interfacial tension between water and oil, resulting in a more viscous emulsion. The viscosity of any particular nanoemulsion is typically tested using a Brookfield type rotatory viscometer submerged in a thermal bath at 37° c. at various shear rates and temperatures [56-60].

Furthermore, metrics such as viscosity conductivity and dielectric techniques provide crucial information about the created emulsion's macroscopic level. These properties may be used to detect the existence of rod-like or worm-like reverse micelles, as well as determine whether the nanoemulsion is oil-continuous or water-continuous. This enables phase inversion occurrences to be monitored during the formulation process [61]. To assess the rate of release of active substances, nanoemulsions containing o/w typically have on the rheological characteristics of nanoemulsion carriers [62]. Manufacturers and users prefer lower viscosity emulsions because they are easier to handle and pack, especially if the nanoemulsion is intended for oral use [63]. It's worth mentioning that when more oil is added to

an emulsion, the viscosity of the emulsion rises as well [64]. This may have an impact on the sensory quality of the final product.

Entrapment efficiency:

The entrapment efficiency (EE) of a nanocarrier is used to measure its efficacy in retaining the drug/active ingredient and ensuring appropriate delivery of the component to the intended site [65]. The method of formulation, the kind of formulation components, and the nature of the encapsulated bioactive substance in the vesicles are all important factors that can have a significant influence on EE [66]. Furthermore, particle size expands when the active components are loaded into the nanoemulsion [67], lowering the nanoemulsion's EE. The determination of EE for nanocapsules, nanospheres, and microemulsions was effectively proven utilizing a microdialysis approach [68]. Gel filtration, dialysis bag filtration, and ultracentrifugation are some more methods for determining the EE of various nanocarriers.In reality, EE estimation by gel filtration is a form of exclusion chromatography. The nanoparticles are separated by molecular weight using an aqueous solution of porous gel particles. Dialysis, on the other hand, can separate nanoparticles from slurry of other free drug nanoparticles. The nanoparticles are kept within the dialysis bag while the free active component diffuses out. The centrifugation approach, on the other hand, distinguishes free molecules from micelles based on their capacity to pass through membranes of varying pore sizes. during the centrifugation process [69]. The following is the general formula for calculating the EE.

$$EE = \frac{W1 - W2}{W1} \times 100 \quad \ldots\ldots(2)$$

Where W_1 is amount of active ingredient added in the formulation and W_2 is the amount of active ingredient in the supernatant.

Applications:

Cosmetic applications:

Nanoemulsions have sparked a lot of interest because they can be used in personal hair products. They've been shown to be useful for enhancing skin dispersion and spreading cosmetics in a controlled manner. They are highly regarded in skin care due to their strong sensory and biophysical characteristics, particularly their ability to moisturize [70]. The effect of lipid content and charge of nanoemulsions on skin hydration, elasticity, and erythema was proven by Yilmaz and Borchert [71]. A total of 14 healthy females were tested with positively charged nanoemulsions with stratum corneum lipids, positively charged nanoemulsions without stratum corneum lipids, and negatively charged nanoemulsions with stratum corneum lipids [72]. To improve the nanoemulsions' low viscosity, high-pressure homogenization was used, followed by the use of Carbopol 940 as a thickening. The addition of the co-surfactants phytosphingosine (PS) and myristic acid made the formulations stable, with zeta potential values of +354 mV for PNSC creams, +385 mV for PN creams, and 435 mV for NNSC creams. The nanodroplets are repelled by these high zeta-potentials, which hinder aggregation, flocculation, and coalescence. In terms of ceramide content, PNSC cream was compared to Physiogel® cream with equal components. Corneometer® 825 and Cutometer® SEM 575 were used to measure the skin humidity and elasticity of both formulations [73]. When PNSC creams were compared to PN creams, all of the PNSC creams' values were much higher, suggesting the necessity for SC lipids to extend their influence on skin features and improve skin barrier function by improving skin moisture and hence skin flexibility. All of the PNSC creams had much greater results than the NNSC creams, demonstrating that PS, which provides a positive charge, is necessary for improved skin hydration and flexibility [74]. In terms of ceramide content, PNSC cream was compared to Physiogel® cream with equal components. Corneometer® 825 and Cutometer® SEM 575 were used to measure the skin humidity and elasticity of both formulations. When PNSC creams were compared to PN creams, all of the PNSC creams' values were much higher, suggesting the necessity for SC lipids to extend their influence on skin features and improve skin barrier function by improving skin moisture and hence skin flexibility.

Improving permeation via the skin:

Wu, *et al.* [75] used a w/o nanoemulsion containing sorbitan monooleate (Span®80), polyoxyethylene 20 sorbitan monooleate, olive oil, and water to study topical transport of hydrophilic chemicals. After topical *in vitro* administration, nanoemulsions were examined for their ability to increase the transport of a model hydrophilic solute, inulin, over hairless and hairy mouse skin and hairy rat skin. The uniformity of inulin permeation profiles in hairy, hairless, and hairy mouse skin demonstrates that stratum corneum thickness and follicle type have no effect on inulin transport from

nanoemulsions. Furthermore, they discovered that the rate and extent of inulin transport through hairy mouse skin were substantially reliant on the surfactant combination's hydrophile-lipophile balance (HLB). The rate and extent of transfer were significantly higher in Nano emulsions made with less HLB combinations [76]. The researchers concluded that skin transport of large hydrophilic molecules dissolved in the aqueous core will be easily promoted by water-in-oil nanoemulsions generated with a lipid phase whose HLB is compatible with normal sebum, and that such transport is predicted via a trans-follicular pathway.

Mou, *et al*. [77] created a hydrogel-thickened nanoemulsion system to deliver lipophilic medicines like camphor, menthol, and methyl salicylate topically. The nanoemulsions were made by homogenizing them under high pressure before dispersing them in a carbomer 940-based gel matrix with no influence on droplet size. The formulation featured a spherical shape, tiny diameters (50 to 60 nm), and a high penetration rate, containing 5 % medication, soy lecithin, Tween 80, Poloxamer 407, and propylene glycol.

A number of variables have been blamed for the formulations' high penetration rates. The high drug concentration (5 %) resulted in a substantial concentration gradient, which could be the main drug penetration mechanism into the skin, with drug reservoirs releasing medications from the inner phase to the outer phase and then onto the skin. Furthermore, due to their small droplet sizes, oily droplets may embed in the stratum corneum, allowing drug molecules to be transported directly from the oily droplets to the stratum corneum without passing through the hydrophilic phase of nanoemulsions.

Drug molecules will have an easier time penetrating the stratum corneum. Among the compounds explored for nanoemulsion formulations with better topical and transdermal dispersion include steroids, nonsteroidal anti-inflammatory medicines, and cytotoxic drugs [78].

Delivery of a gene to a specified location:

Wu, *et al*. [79] developed water-in-oil nanoemulsions with expression plasmid DNA that appear to enhance follicular transfection in vivo after topical therapy. The nanoemulsions without DNA had 14.6 to 42.3 nm mean particle sizes, while the nanoemulsions with DNA had 20.2 to 32.1 nm mean particle sizes. Chloramphenicol acetyltransferase (CAT) or human interferon-2 cDNA expression plasmids were produced in water-in-oil nanoemulsions and applied to mouse skin. Plasmid DNA was discovered primarily in follicular keratinocytes. Transgene expression peaked 24 h after a single dosage of water-in-oil nanoemulsion containing plasmid DNA was applied topically, as measured by RT-PCR and ELISA. In the comparison of normal and atrophic hair follicles, nanoemulsion-mediated transfection was the most effective.

Photodynamic treatment:

For actinic keratosis and neoplastic skin disorders, photodynamic therapy has been considered as a first-line treatment. Topical nanoemulsions of 5-aminolevulinic acid (ALA) and temoporfin (Foscan®) have been used for photodynamic therapy of skin diseases. Zhang, *et al*. [80] used high-pressure homogenization and probe ultrasonication to generate o/w and w/o nanoemulsions of ALA and the methyl ester. The researchers utilized negatively charged nanoemulsions with a diameter of less than 256 nm.

The methyl ester in soybean oil o/w nanoemulsions could be loaded up to 68 percent, according to research. Skin penetration was higher for o/w nanoemulsions than for w/o nanoemulsions. For effective topical administration of ALA, the o/w nanoemulsion beat the aqueous solution, which required an extended-release of roughly 24 to 48 h. Furthermore, the o/w nanoemulsions had the maximum in-vitro flow without impairing skin barrier function. According to Dirschka, *et al*., an ALA nanoemulsion-based gel formulation (BF-200 ALA) has better skin penetration and stability than an ALA solution. In an *ex-vivo* skin model, the nanoemulsion outperformed the methyl ester cream. Primo, *et al*. investigated the use of o/w nanoemulsions for *in vitro* Foshan administration and found promising results [80,81].

CONCLUSION:

Nanoemulsions are dynamic in nature, as isotropic lipid systems, in terms of ease of manufacture and delivery methods. However, the stability of these systems is still a study area. We discuss new developments in nanoemulsion delivery systems, as well as their preparation methods and optimum characteristics. Prior, on the other hand, validates the main postulates and mechanisms involved in the kinetic and thermodynamic stability of nanoemulsion formulation. However, further objects and ideas must be proposed in order to prove the concept of Nanoemulsions for significant use in the drug delivery system for the therapeutic more benefit by the API for the pationes.

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