INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Nanoemulsion Formula Design and Development: A Review

Aditya Sherekar*, Sahil Shewale, Vaibhav Pawar, Musfera Jabeen Ansari Shakeel Ahmed, Rehan Khan, Dr. Vinod Bairagi

K.B.H.S.S.T's Institute Of Pharmacy, Bhaygaon Road, Malegaon-Camp, Malegaon 423203, Dist-Nashik. (Ms).

ARTICLE INFO

Published: 25 Apr 2026
Keywords:
Nanoemulsions, Small droplet size, Drug delivery system, Solubility enhancement, Kinetic stability, High surface area.
DOI:
10.5281/zenodo.19785407

ABSTRACT

The physical stability of nanoemulsions is greater than that of traditional emulsions due to their extremely small droplet size that enables the penetration of the droplet into delicate capillaries and deep into the tissues. Consequently, they have raised a lot of interest as potential medication delivery systems that can deliver a specific area in the body. The innovative delivery strategy enhances the first pass solubility and solubility of insoluble medicines in water. The special characteristics of the nanoemulsions such as small size of droplets, high solubilization ability, high interfaces area, low viscosity, optical transparency or translucency, and unparalleled kinetic stability make nanoemulsions have a diverse array of applications. They offer long stability and homogeneous dispersion in the continuous phase. In this review, the formation of nanoemulsions, the choice of excipients, formulation procedures, and optimization parameters will be fully understood..

INTRODUCTION

Nanoemulsions have become one of the most efficient dosage forms in the pharmaceutical industry to deliver medication to the specific area, and recently, they have gained significant interest as to the possible ways to use them in different domains. Nanoemulsions as versatile drug delivery systems can be administered via a broad variety of routes, such as oral, topical and parenteral. [1].

The definition of a nanoemulsion is a transparent and thermodynamically stable blend of two immiscible liquids - usually oil and water - that is stabilized by a surfactant and co-surfactant interfacial film. These systems have droplet sizes that are in the range of 50 to 1000 nanometers (nm), and thus are a new and effective platform in the delivery of drugs. The major difference between standard emulsions and nanoemulsions is the size and dispersion of the dispersed particles. Although traditional emulsions tend to have

***Corresponding Author:** Aditya Sherekar
Address: *K.B.H.S.S.T's Institute Of Pharmacy, Bhaygaon Road, Malegaon-Camp, Malegaon 423203, Dist-Nashik. (Ms).*
Email : pharmaeditorpvt@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

droplet sizes of between 1 and 20 micrometers (um), nanoemulsions have very small droplets, with the mean diameter ranging between 10 and 200 nm. [2].

Nanoemulsions are therefore regarded as submicron colloidal systems that consist of two immiscible phases, oil and water and stabilized by an interfacial film of surfactants and co-surfactants. They are the ideal choice to increase the bioavailability and therapeutic efficacy of poorly soluble drugs in that they have a small droplet size, high surface area, and high solubilization capacity due to their distinct physicochemical properties.

Nanoemulsions are a homogenous single phase and so referred to as submicron emulsions, ultrafine emulsions, or mini-emulsions. They may be developed in terms of numerous surfactants and their varying qualities, such as ionic and non-ionic. [3]. Nanoemulsions may be made using high-energy and low-energy approaches, with their functionality being maximized by altering different formulation factors. Nonetheless, the formulations might cause chemical and physical instabilities that can occur throughout or after the formulation, affecting their stability and efficacy. This review will comment on the methods of preparation, optimization, stability issues, and broad applications of nanoemulsions in various industries.

1.1 NANOEMULSION TYPES:

I. Water-in-Oil (W/O) Nanoemulsion: In this type, water droplets are dispersed within a continuous oil phase. [4]

II. Oil-in-Water (O/W) Nanoemulsion: In this system, oil droplets are dispersed within a continuous aqueous phase.

III. Bi-Continuous Nanoemulsion: In this type, both oil and water phases are continuous, with the surfactant being soluble in both. As a result, droplets of each phase are interspersed throughout the system. [5]

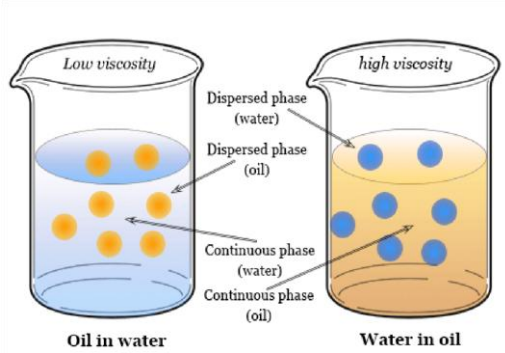

Figure 1: Types of Emulsions

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

In order to maximize the solubility of a drug candidate in a nanoemulsion formulation, the choice of the proper phase of an oil is essential. Oil phase is also influential in drug loading capacity which is usually the most important in the

attainment of a successful formulation. The oil component is commonly triglyceride, which is a compound that comprises of long-chain fatty acids; they are derived naturally and also artificially. Another type of lipid molecule which gives rise to better formulation properties is short-chain triglycerides. Triglycerides with about 12 carbon atoms are also beneficial in reducing the level of unsaturation and oxidative degradation, which increase formulation stability.

The solubility of the pharmaceutical compound is the main factor that defines the choice of oil phase. In nanoemulsion, there is increased mobility of molecules and interfacial friction which facilitates the introduction of drugs into intracellular compartments and therefore increases the solubility of drugs that are insoluble in water. It is of paramount importance to find the best compromise between drug loading capacity and emulsification efficiency especially when working with a combination of fatty oils and medium-chain triglycerides (MCTs).

In the process of creating self-microemulsifying drug delivery systems (SMEDDS), the saturation level of the long and medium-chain triglycerides is imperative. Triglycerides are very lipophilic substances, thus their solvent capacity is proportional to the concentration of the ester functional groups. It is important to note that MCTs have higher solvent capacity as well as oxidative stability than long-chain triglycerides (LCTs).

In contemporary formula, the oil phase is usually improved by incorporating digestible or non digestible oils and fats like olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil and hydrogenated oil in an effort to increase the property of solubility. The introduction of new semi-synthetic analogues to replace the traditional MCTs has also been very successful with respect to the increase of water solubility of poorly soluble drugs. [6].

2.2. SURFACTANT

The word surfactant is used to describe molecules or ions, which are adsorbed at an interface, and are capable of decreasing or stabilizing interfacial tension between two immiscible phases. Surfactants are important in the creation and stabilization of nanoemulsions. Their self-nanoemulsifying, self-emulsifying and self-microemulsifying properties are credited with their solubility of drugs that are not readily soluble in water. Most of the compounds have surfactant-type properties and this property is useful in the formation of emulsifying systems. In oral preparations, it is only suitable to use surfactants with acceptable toxicity and minimal systemic absorption ability Non-ionic surfactants with high Hydrophilic-Lipophilic Balance (HLB) are generally favoured in this case because of their low toxicity and excellent biocompatibility. Optimal surfactant concentration is necessary to prepare nanoemulsions successfully-when the concentration is too small, the nanoemulsions become unstable but when it is too large, the surfactant becomes toxic be it chemically or biologically. Thus, the formulation design is largely dependent on the consideration of the safety and compatibility of the surfactant. The source of the surfactant molecules is either natural or synthetic. [7].

The non ionic surfactants are typically thermodynamically stable and less toxic than the ionic surfactants and hence are most suitable in pharmaceutical nanoemulsion systems. During emulsification and nanoemulsification processes, the concentration of the surfactant has a great effect on the size of the droplets. The concentration is suitable and stabilizes oil droplets within the continuous phase and allows centrally dispersed droplets to remain uniform. Normally, the further the concentration of a surfactant increased, the smaller the droplets, which increases the stability

and solubilization ability of the system. Surfactant selection and optimisation therefore plays a major role in the design of nanoemulsion formulations aimed at enhancing the solubility and bioavailability of drugs that are poorly soluble to water. [8].

2.3. CO-SURFACTANT

The co-surfactant acts just like the surfactant molecule to increase its efficacy as well as the water solubility of drugs that are poorly soluble in water. In order to enhance the interfacial film and augment drudissolution, co-surfactants are either used together with or in conjunction with the surfactant. They are usually single chain molecules that are amphiphilic in nature, which reduces interfacial rigidity and is used to decrease fluidity between surfaces. In the surfactant monolayer the co-surfactant is placed in between the surfactants, oil, and water molecules to form a structured layer commonly known as the liquid crystalline film.In the case of self-nanoemulsifying drug delivery systems (SNEDDS) the primary role of co-surfactants is to stabilize the oil-water interface and to inhibit the undesirable interfacial phenomena that may cause phase separation. They enhance the formation and stabilization of nano-sized droplets by the means of their spontaneous formation and stabilization. The most common co-surfactants are short chain alcohols and polyols like ethanol, methanol, pentanol, glycol and propylene glycol. [9].

3. METHOD OF PREPARARTION

The Nanoemulsions may be prepared by a number of methods, which utilize high-energy and low-energy emulsification methods. The common methods of high energy stirring, ultrasonic emulsification, high-pressure homogenization, and microfluidization, and membrane emulsification are frequently used because they provide fine and uniform droplets. Low energy techniques, however, involve phase inversion temperature (PIT) technique, emulsion inversion point (EIP) technique, and spontaneous emulsification. Hybrid processes which combine high-energy and low-energy processes can also be used to prepare the reverse nanoemulsions in highly viscous systems. The strengths and weaknesses of these procedures are assessed to identify that they are suitable in different applications and future innovation in the use of nanoemulsion based formulae. [10]The self-emulsification technique allows the creation of nanoemulsions without any modification of the natural curvature of the surfactant film. The nano-sized droplets are formed in the process when the molecules of surfactant and/or co-solvent in the dispersed phase diffuse at a rapid rate into the continuous phase and form localized turbulence. This is also known as spontaneous emulsification technique. Self-nanoemulsifying drug delivery systems (SNEDDS) are usually characterized by a reduced amount of lipids and a higher concentration of hydrophilic co-surfactants/co-solvents, which are known to self-assemble into a fine oil-in-water (O/W) nanoemulsion when diluted with aqueous fluids. [11]The name SNEDDS is used to denote an isotropic blend of oil, surfactant, co-surfactant, and drug that spontaneously forms a fine oil-in-water (This process is facilitated by mild agitation brought about by gastrointestinal motility which results in transparent and stable emulsion. The two main pathways put forward as the basis of nanoemulsion formation in SNEDDS include: (i) diffusion of hydrophilic co-solvent or co-surfactant molecules into the aqueous phase out of the organic phase, and (ii) the creation of temporary negative or ultralow interfacial tension, which results in negative free energy of formation. SNEDDS are identified as one of the most promising and popular delivery systems of hydrophobic, low

bioavailability drugs, as well as have been used in delivering bioactive foodstuffs. [12].

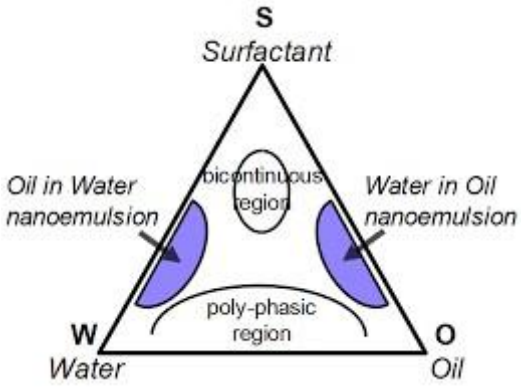

Figure 2: Ternary Phase Diagram

3.2.1. Phase Inversion Emulsification Method:

In this method, phase transition takes place in the course of emulsification as a result of variation of spontaneous curvature of the surfactant molecules. These spontaneous curvature may be affected by variations in parameters like temperature, composition and concentration, which will affect the emulsion formation. There are two major classifications of phase inversion emulsification techniques, Transitional Phase Inversion (TPI), consisting of Phase Inversion Temperature (PIT) and Phase Inversion Composition (PIC), and Catastrophic Phase Inversion (CPI), consisting of the Emulsion Inversion Point (EIP) method. In TPI, the inversion is due to the changes in the affinity or spontaneous curvature of the surfactant due to changes in temperature or composedness. On the other hand, CPI is a process whereby dispersed phase droplets are continuously added to the system resulting in the coalescence and formation of bicontinuous or lamellar structural phases. [13]The term catastrophe is used to denote an abrupt change of behavior in a system due to a change in conditions. To achieve catastrophic phase inversion, the surfactant has to be concentrated in the major part at the interface of the dispersing particles leading to a high rate of coalescence and abrupt phase inversion. Conversely, in transitional phase inversion, gradual changes in surfactant affinity or spontaneous curvature cause the inversion, whereas in catastrophic phase inversion these properties are constant and the inversion comes about through hydrodynamic and compositional instabilities. [14].

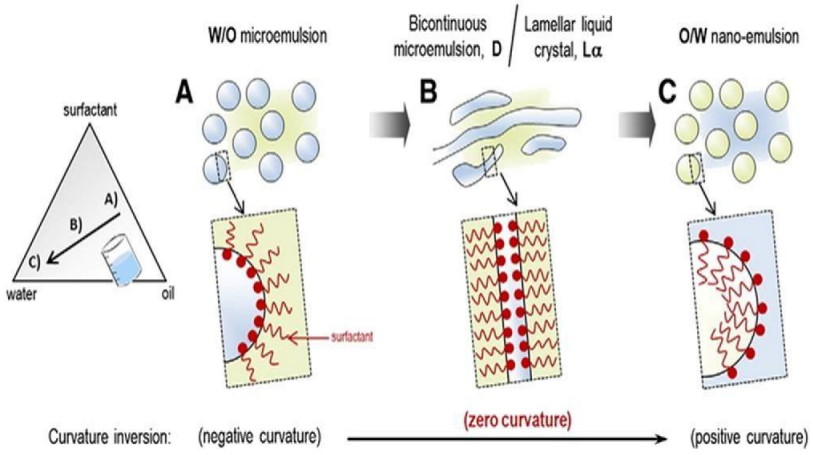

Figure 3: Phase Inversion Emulsification Techniques

A. Phase Inversion Composition (PIC):

Like Phase Inversion Temperature (PIT) method, the Phase Inversion Composition (PIC) technique triggers phase inversion by changing the composition of the system instead of its temperature. In PIC, inversion is triggered by slowly adding one of the constituents of the mixture, typically water, or adding oil to a water-surfactant complex. Although other types of surfactants can be used, non-ionic surfactants of the polyoxyethylene (POE) type are usually preferred in nanoemulsions formation. With the addition of more and more water, the POE chains are hydrated, and the volume fraction of the aqueous phase rises. This results in an equilibrium between the hydrophilicity and lipophilicity of the surfactant so that its spontaneous curvature goes towards zero, which is similar to the hydrophilic-lipophilic balance (HLB) point of the PIT method. In this transition a bi-continuous or lamellar structure is created.As the water is added beyond the transition composition the surfactant layer at zero curvature at the transition develops a significant positive curvature and the process of phase change by inversion to create nano-sized droplets is accomplished. Therefore, the PIC method is phase inverted as a result of changes in system composition. There can also be similar compositional factors which can affect the process like salt concentration and pH. The phase inversion which can be attributed to transitional phase inversion leads to the production of nanometer size droplets during the emulsification process. [15].

B. Emulsion Inversion Points (EIP):

Phases inversion in the Emulsion Inversion Point (EIP) method is done through the Catastrophic Phase Inversion (CPI) mechanisms. CPI, in contrast to transitional phase inversion, is controlled by variations in the volume fraction of the dispersed phase, and not surfactant properties. In the case of a slow addition of water to an oil-surfactant mixture system, the system will initially act as a water-in-oil (W/O) nanoemulsion. With further dilution of water under constant stirring, water droplets merge to the extent of phase inversion point creating bicontinuous or lamellar phases. Additional dilution transforms the system into W/O to oiledin water (O/W) by a transitional bi-continuous microemulsion.Such parameters as the addition rate at which the water is added and the stirring rate affect the final size of the dropletes of the nanoemulsion. To achieve CPI, the surfactant should mainly be found at the interface between the dispersed particles leading to high rate of coalescence and quick inversion. Surfactants that are low-molecular-weight are typically used because they are able to stabilize both W/O and O/W emulsions. As catastrophic inversion sets in the surfactant is concentrated in the dispersed phase forming an unstable emulsion that does not follow the Bancroft rule that dictates that the emulsifier should be located in the continuous phase to attain the highest stability. This abnormal emulsion is then transformed to a normal emulsion, which becomes more stable and homogenous, by CPI process. [16].

C. Phase Inversion Temperature (PTI):

In Hell technique, the spontaneous curvature of the surfactant is changed using temperature variation and induces phase inversion. The non-ionic surfactants have dehydrated polyoxyethylene (POE) groups that enhance the lipophilicity of the surfactant, altering its curvature, and allowing it to invert the phase, leading to the formation of nanoemulsions. Firstly, the emulsions, which are oil-in-water (O/W), are made by mixing oil, water and non-ionic surfactants. The non-ionic surfactant has zero curvature and an equal affinity with the aqueous and oil phases at the hydrophile-lipophile balance (HLB) temperature, which forms

the intermediate point in phase inversion.As the temperature rises, dehydration of the POE groups causes the surfactant to switch its affinity to the oil phase, necessitating an intermediate phase in-between the initial O/W emulsion and a water-in-oil (W/O) nanoemulsion. The HLB temperature will require rapid heating or cooling to accomplish effective phase inversion and resulting kinetically stable nano emulsions to tend towards O/W or W/O emulsions, respectively, depending on the direction of the temperature variation. [17].

3.3. High energy methods:

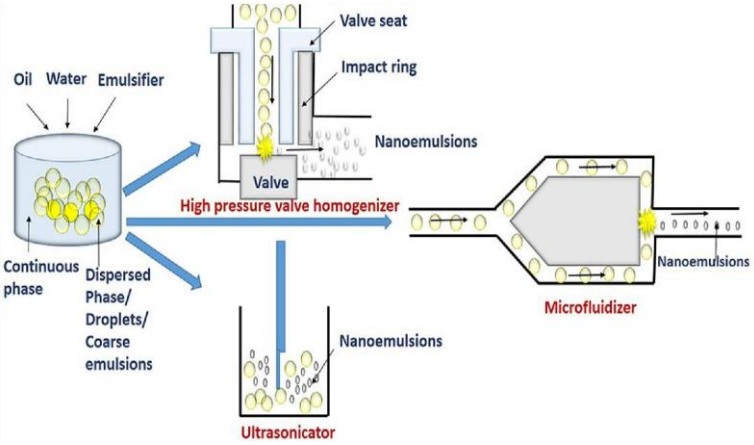

Figure 4: Method of Preparation of Nanoemulsion

3.3.1. Ultra-sonification:

Ultrasonication is the best high-energy technique that is easy to operate and controlled. In ultrasonic emulsification, macroemulsions are disrupted into nanoemulsions by ultrasonic wave generated cavitation forces. Ultrasonicators are used in this process and produce high frequency waves to the system. The stability and size of the desired droplet can be attained by modifying the input of ultrasonic energy and exposure time. Acoustic cavitation gives the physical shear needed in disruption of droplets. Cavitation is the process whereby microbubbles develop, grow and burst under pressure changes caused by sound waves generating strong local turbulence that forms nanoemulsions. Nanoemulsions may sometimes be prepared by ultrasonication without the assistance of surfactants. In recent research, it was found out that the effectiveness of this technique relies on the intensity of ultrasonication, duration of ultrasonication, and the surfactant that can be utilized. The application of ultrasonication in making food grade and pharmaceutical nanoemulsions has seen extensive usage because it has proven to have benefits of smaller droplet sizes, increased stability, and reduced energy usage than the traditional high energy techniques. [18,19].

3.3.2. Micro fluidization:

Micro Fluidizer is a device that is used in the microfluidization technology. The pump used in this process is a high-pressure positive displacement pump (forced at 500-200 PSI) and forces the product into an interaction chamber that consists of highly narrow channels called microchannels. Due to the flow of the formulation through these microchannels and converging in the impingement zone, intense forces in shear and impact are exerted leading to the development of submicron size particles. First, the oil and aqueous phases are mixed in an inline homogenizer to make a crude emulsion of the mixture after which it is sent to the Micro Fluidizer to produce a stable nanoemulsion with a fine distribution of droplets. [20].

3.3.3. High-Pressure Homogenization:

This technique implies high pressure treatment of an oil phase, aqueous phase, and a surfactant or co-surfactant, using a homogenizer. The pressure in use promotes the droplet disruption and dispersion, creating fine emulsions. Nevertheless, the drawbacks of this method are low productivity and degradation of components as a result of too much heat being generated in the process. Furthermore, high-pressure homogenization is mostly only applicable to the preparation of liquid oil-in-water (O/W) nanoemulsions that have a low oil phase content (less than 20%); high-pressure homogenization fails to yield cream-like nanoemulsions with high viscosity, rigidity, or mean droplet sizes under 200 nm. [21].

4. INSTABILITIES IN NANOEMULSION: [22]

1.1 Physical Instabilities:

4.1.1 Coalescence:

Coalescence is the irreversible process that consists of dispersed droplets combining to produce bigger droplets. This activity carries on to the point when the oil and water layers are entirely separated to cause emulsion disintegration or cracking. When the repulsive energy barrier is surmounted by the emulsion droplets, the droplets are said to have coalescence when they are close to the primary minimum of interaction. At this point, the droplets are very close to each other and the resistance to rupture of the interfacial film is the major factor of stability against coalescence. The continuity of the phase liquid film that is present between the droplets of oil is drained as they approach each other and deform and finally, the rupture of the film happens. Thick multilayered films created by some polymers and rigid and closely stacked elastic films created by some combinations of emulsifiers provide stability against coalescence, which are highly resistant to film rupture.

4.1.2 Flocculation:

Flocculation is a weak reversible interaction between droplets of the emulsion, which are still separated by a thin film of the continuous phase. Every cluster of the droplets has its own identity but acts as one kinetic unit. Such floccules can easily be redispersed by mild agitation, e.g. by gentle shaking. Flocculation is also a possibility which can be reduced by selecting emulsifiers in an appropriate manner. Though adsorbed layers made of emulsifiers can have a tendency to increase the time lag before coalescence can take place, flocculation is usually undesired since flocculated droplets in a emulsion will cream more quickly under gravity compared to individual emulsion droplets.

4.1.3. Creaming:

Creaming involves separation of dispersed droplets under the action of gravity into a concentrated or creamier layer in the emulsion. Any dilute emulsion with relatively large droplet sizes (~1 mm) is bound to cream in the event that there is a density difference between the oil and water phases. As the majority of oils are lower density than water, they generally ascertain and create an upper cream layer in oil-in-water (O/W) emulsions and water droplets assemble to create a lower layer in water-in-oil (W/O) emulsions. Even though a creamed emulsion can easily be redispersed through gentle agitation to its original homogeneity, this does not make it good aesthetically and also may result in erroneous dosing in the case that the emulsion was not properly mixed prior to administration. The most viable ways of minimizing the creaming are by decreasing the size of the droplets and enhancing the viscosity of the continuous phase using viscosity enhancers. Comparatively few efforts have been made, on the other hand, to adjust the

density difference between the two phases in order to reduce creaming.

4.1.4. Emulsion Inversion:

In certain circumstances there is a phenomenon called emulsion inversion in emulsions. With oil in water (O/W) emulsion, a phase inversion can be observed between the water-in-oil (W/O) and oil-in-water (O/W) emulsion at a specific temperature, a process that is generally applied to the preparation of nanoemulsions using low energy. This reversal is seen as a result in large part of the alteration in the solubility of the emulsifier which is no longer water soluble at low temperatures but turns to be oil soluble at high temperatures as is the case with some nonionic surfactants. The interaction with other formulation components may also cause emulsion inversion. As an example, an O/W emulsion stabilized by a sodium salt could be inverted to a W/O emulsion by the addition of divalent ions such as Ca2+ which form calcium salts, which preferentially stabilize the W/O system.

4.1.5. Ostwald Ripening:

Ostwald ripening - this is a physicochemical process that takes place automatically, in which larger droplets increase at the cost of smaller ones. This effect continues in emulsions with submicron sized droplets (usually less than 600 nm) provided that the dispersed phase has some degree of solubility in the continuous medium. This can be attributed to the Kelvin effect which states that a partially miscible droplet is much more likely to dissolve as its radius reduces. Accordingly, small droplets are more soluble than big droplets. These minute droplets are dissolved to create equilibrium, and the molecules are diffused into the continuous media to deposit again on larger droplets, which results in a progressive increase in the size of the droplets and a net increase in the average size of the droplets. In contrast to coalescence, Ostwald ripening does not need the droplets to be in physical contact. It is known as the major instability process in most oil-in-water fat and perfluorocarbon emulsions. Even though interfacial surfactant films inhibit the process of flocculation and coalescence, the existence of micelles can also hasten the process of Ostwald ripening by increasing the process of solubilizing oil. This can be reduced by lowering the molecular diffusion of the dispersed oil phase, which is usually by incorporation of small amounts of a second, more immiscible oil. As an example, the stability of perfluorodecalin contrast emulsions based on the addition of perfluorotributylamine, and fat emulsions based on the addition of less soluble hydrophobic oils are more resistant to instability. Moreover, the strong adsorbing surfactants like Pluronic F68(r), which are not micelle-forming and do not adsorb at the oil-water interface in the continuous phase, are able to suppress Ostwald ripening. In the same manner, polymers that raise the viscosity of the external phase are useful in preventing ripening by blocking the diffusion of the molecules.

4.2 Chemical Instabilities:

The ideal is to have all the elements of an emulsion, which are chemically inert during the emulsification. Nonetheless, this does not happen as a rule, and, therefore, it is critical to study the chemical makeup of all ingredients before formulation. Differences in composition may cause an unsteady situation. Special care is demanded when using therapeutic oils because they are easily oxidized by atmospheric oxygen or microorganisms, thus, possessing a rancid odor and being unappealing in taste. Antioxidants and preservatives are usually added to the formulation in order to overcome such effects. Polymer emulsifiers can also lose their ability to emulsify and the consistency because of hydrolysis or microbial breakdown. More so, chemical reactions

of the emulsifying agent with other components of the formulation are able to impair emulsifying performance and cause emulsion breaking. As an example, nonionic emulsifiers, polyoxyethylene (POE), have the ability to form hydrogen bonds when exposed to phenolic preservatives and certainly decrease preservation efficacy and emulsifying capacity. In the same way, ionic emulsifiers do not frequently coexist with oppositely charged substances. It is noted to occur with cationic reagent like cetrimide, neomycin sulfate together with an anionic emulsifier like sodium lauryl sulfate and it becomes destabilized. The repulsive forces may be suppressed and the lamellar structures in the continuous phase may be disrupted due to this kind of interaction during storage and the emulsion consistency ultimately lost.

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 of the formulation between [?]21degC and +25degC under standard laboratory conditions were performed to determine the thermal stability of this formulation. These were carried out in three months. Besides, three formulation batches were placed in accelerated temperatures of 30degC, 40degC, 50degC and 60degC and at ambient humidity. Samples were sampled at set time intervals of 0, 1, 2, and 3 months with the chemical and physical integrity of the drug measured using an approach of stability that was an UV-indicating or HPLC method to determine the drug content. [23

5.4. OPTIMIZATION OF NANO-EMULSION PREPARATION

5.5. Experimental Designs For Optimization:

Experimental designs enable the systematic investigation of multiple variables with a limited number of experiments. Through statistical analysis, polynomial equations can be applied to correlate independent variables with the desired responses. The purpose of the experimental design is to determine the influence of two qualitative independent factors—the type of oil and the type of lipophilic emulsifier—on the formulation outcome. References cited on both sides originate from the same research group. In the incorporation of retinol into a self-nanoemulsifying system, three independent formulation variables—oil, surfactant, and co-surfactant concentrations—were evaluated, while four response variables—mean droplet size, turbidity, dissolution rate, and another relevant parameter—were analyzed. [24] Optimization of the system was performed for the dissolution rate at 30 minutes using the remaining three responses as constraints, and response equations were generated. Six response factors were analyzed through surface response methodology, providing additional insights. [25] A comparable evaluation was conducted for the characterization of nanoemulsions produced via ultrasonication, with extensive discussion on the application of experimental design. The phase inversion composition (PIC) technique was applied for low-energy emulsification, and the effects of compositional factors were

systematically compared. The response surface for droplet size was minimized separately with respect to both compositional and preparative variables. Results indicated the existence of an optimal surfactant mixing ratio—or optimal HLB—demonstrating that increasing the oil-to-surfactant ratio led to larger droplet sizes. For preparative parameters such as addition rate and agitation speed, minimal yet statistically significant effects were observed. In ionic surfactant-based nanoemulsions prepared by the PIC method, experimental design optimization again revealed an ideal surfactant ratio, with similar trends in droplet size behavior. Preparative factors showed negligible influence on droplet size. Additional unpublished findings from the same authors using the phase inversion temperature (PIT) method confirmed that parameters such as cooling rate and agitation speed had limited effects on droplet size. Overall, studies employing experimental design consistently conclude that this approach is a powerful tool for investigating and optimizing nanoemulsion formulation processes. [26]

6.2. Phase Behaviour Studies For Optimization:

In condensation or low-energy emulsification methods, studies of phase behavior are often critical for optimizing nanoemulsion properties, as the phases present during emulsification strongly influence droplet size and polydispersity. In contrast, shear-based methods do not follow a compositional emulsification pathway, and only the phases at the final composition are relevant. Recent reviews emphasize the importance of phase behavior, particularly the crossing of microemulsion regions—bicontinuous (D) or lamellar liquid crystalline phases—during emulsification. [27]This principle has been experimentally demonstrated in several recent studies producing nanoemulsions via the phase inversion temperature (PIT) method, phase inversion composition (PIC) method, [28] or self-emulsifying techniques. For self-emulsification, only bicontinuous (D) or oil-in-water (O/W) microemulsions are considered suitable. Lamellar liquid crystalline phases generally fail to self-emulsify upon dilution, likely due to their high viscosity. [29]Comparisons of experimental data indicate that slow addition of water to a lamellar liquid can yield nanoemulsions with smaller droplet sizes, whereas rapid dilution tends to produce emulsions with larger droplets, as observed in self-emulsifying methods. [30] In ionic surfactant systems, emulsification paths that traverse micellar cubic or liquid crystalline phases upon aqueous addition result in nanoemulsions with extremely small droplet sizes. Overall, the requirements for producing O/W nanoemulsions with minimal droplet size and low polydispersity are well established: in PIT or PIC emulsification, an aqueous continuous phase—O/W or bicontinuous—with fully solubilized oil must be crossed immediately prior to reaching the final two-phase region where nanoemulsions form. These compositional conditions are necessary but not sufficient, as preparative factors, such as the rate of aqueous phase addition in PIC or the cooling rate in PIT, significantly influence the efficiency of oil incorporation into the continuous phase and the formation of nanoemulsion droplets. [31]

6.3. Optimization By Selective Variation Of Parameters:

Factors influencing nanoemulsion properties are commonly classified as either composition or preparation variables. In low-energy emulsification, composition variables typically exert a greater effect, whereas in shear-based emulsification, preparation variables are often decisive. Recent studies on shear-produced nanoemulsions have examined the relationship between droplet size and various influencing factors. [32]High-pressure microfluidizers are

frequently used to emulsify food systems, with surfactants and polymers stabilizing the resulting emulsions. These studies often consider the interplay of droplet breakup and coalescence alongside the role of stabilizers. [33] Optimization of nanoemulsion formation can also be achieved by subjecting coarse emulsions to subcritical water conditions, with careful adjustment of composition parameters (e.g., surfactant and oil concentrations) and preparation variables such as temperature. This approach can yield droplets as small as 40 nm. The surfactant-to-oil ratio, and in the case of surfactant combinations, the relative proportions of surfactants, are frequently investigated in alternative condensation processes. Numerous studies have reported optimization of nanoemulsions prepared via the phase inversion temperature (PIT) method, demonstrating that increasing the oil-to-surfactant ratio generally leads to larger droplet sizes, whereas droplet size is often independent of surfactant mixing ratio when cooling from the HLB temperature. Similar trends have been observed in nanoemulsions produced via the phase inversion composition (PIC) method, where variations in droplet size with oil-to-surfactant ratio and preparation parameters are systematically analyzed. [34]Further research has explored multiple emulsification techniques, reporting droplet size fluctuations in relation to HLB, water fraction, and surfactant concentration. These studies generally indicate the existence of an optimal HLB, with droplet size increasing as the oil-to-surfactant ratio rises. Optimization of W/O nanoemulsions involves selecting ideal surfactant compositions, such as specific Span-Tween combinations, to maximize water solubility while evaluating droplet size variation with water fraction. [35] Consistent with these observations, higher water concentrations are associated with larger droplets in W/O systems. Extensive work has also addressed optimization of self-emulsifying nanoemulsions, investigating the effects of surfactant HLB, solvents, and oil content on droplet size. Results indicate the existence of optimal HLB and solvent ratios. Additional studies have examined the influence of sucrose-based surfactants on percutaneous penetration, demonstrating improved efficacy of a schistosomicidal agent when incorporated into optimized nanoemulsions, highlighting the functional benefits of this approach. [36]

7. APPLICATIONS:

One of the most promising applications of nanotechnology is the cell-specific delivery of therapeutic agents. By encapsulating toxic compounds and minimizing off-target interactions, delivery systems composed of smart materials with tunable physical and biological properties can enhance current therapies. Such systems also improve the bioavailability of poorly soluble drugs, confer tissue or cell specificity, and facilitate or enable intracellular delivery. [37] Nanoemulsions are colloidal dispersions consisting of an oil phase, an aqueous phase, a surfactant, and a co-surfactant in precise proportions. Unlike conventional emulsions, nanoemulsions are stabilized by low interfacial tension, often achieved through the addition of a co-surfactant, which promotes spontaneous formation of a thermodynamically stable system. Emulsions with internal droplet sizes below 1000 nm are commonly referred to as nanoemulsions; they are also described as ultrafine emulsions, submicron emulsions, or microemulsions. Studies on phase behavior indicate that at the inversion point, induced by temperature or composition, the surfactant phase structure—bicontinuous microemulsion or lamellar—determines droplet size. Investigations using the phase inversion temperature (PIT) method show that the smallest droplet sizes are achieved when total oil is solubilized within a bicontinuous microemulsion

phase, irrespective of whether the initial phase equilibrium is single- or multiphase. Due to their small droplet sizes, nanoemulsions are resistant to sedimentation and creaming, with Ostwald ripening representing the primary mechanism of instability. [38]The fundamental difference between emulsions and nanoemulsions is that emulsions are physically opaque and kinetically stable but thermodynamically unstable, whereas nanoemulsions are highly transparent and exhibit greater stability. Nanoemulsions have diverse potential applications, including vaccine delivery, prophylaxis against bioterrorism, non-toxic disinfectants, cell culture technologies, enhanced oral delivery of poorly soluble drugs, and ocular or optic nerve targeting. They are also utilized in intranasal, parenteral, transdermal, cancer, and pulmonary drug delivery. [39]

7.1 ADVANTAGES OF NANOEMULSIONS

- Nanoemulsions enhance the water solubility and bioavailability of lipophilic drugs.
- They aid in the stabilization of lipophilic pharmaceuticals and help mask unpleasant tastes.
- Encapsulation of drugs within oil droplets protects them from hydrolysis and oxidation.
- Nanoparticle-sized droplets with high surface area and rapid absorption improve transdermal drug penetration.
- Nanoemulsion-based delivery systems can increase therapeutic efficacy, allowing dose reduction and minimizing adverse effects. They are also capable of transporting peptides susceptible to enzymatic hydrolysis in the gastrointestinal tract.

7.2 DISADVANTAGES OF NANOEMULSIONS

- Stabilization of nanoparticles requires the use of very high concentrations of surfactants and surfactants.
- Specialized equipment is necessary for nanoemulsion preparation.
- High-melting compounds have limited solubility in the formulation.
- Surfactants employed in pharmaceutical applications must be non-toxic and safe.
- Environmental factors, including temperature and pH, significantly influence nanoemulsion stability.

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.

CONCLUSION

An oil-in-water nanoemulsion is a colloidal dispersion of two or more immiscible phases. Recently, they have garnered considerable attention as colloidal carriers for the targeted delivery of anticancer drugs, photosensitizers, neutron capture therapy agents, and diagnostic compounds. Hydrophobic drugs and bioactive food ingredients with high first-pass metabolism often exhibit limited bioavailability, which can be effectively improved using nanoemulsion-based delivery systems. High-energy techniques are frequently employed to enhance the delivery of such pharmaceuticals and bioactive compounds. Optimization studies, including selective parameter variation and experimental designs, indicate that there is generally an ideal surfactant mixture, or HLB, where increasing the oil-to-surfactant ratio corresponds to larger droplet sizes. The stability of nanoemulsion formulations can be improved by controlling factors such as the type of oil phase, preparation methods, process parameters, and the inclusion of additives at the interface. However, physical and chemical instability continues to limit their applications. This study discusses novel strategies and key factors for successful nanoemulsion formulation, aiming to provide a framework for future advances in the field.

REFERENCES

1. Suyal J. An Introductory review composition 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 preface to styles of medication, operations and characterization of nanoemulsion medicine 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 expression and characterization ways Indian J Pharm Sci 2018; 80(5) 781- 789Rajalakshmi R, Mahesh K, Ashok Kumar C K. A Critical Review on Nano Emulsions, International Journal of Innovative Drug Discovery, 1(1), 2011, 1-8.
4. 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.
5. 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.
6. Pallavi M. Nigade, Swapnil L. Patil, Shradha S, Tiwari. Self-Emulsifying Drug Delivery System (SEDDS), A Review, IJPBS, 2(2), 2012, 42-52.
7. 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.
8. Lifshitz IM, Slyozov VV. The kinetics of precipitation from supersaturated solid solutions. Journal of Physics and Chemistry of Solids 1961; 19:35–50.
9. 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.
10. 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.

11. Ishak KA, Annuar MSM. Phase inversion of medium-chain-length poly-3-hydroxyalkanoates (mclPHA)-incorporated nanoemulsion: effects of mcl-PHA molecular weight and amount on its mechanism. Colloid Polym Sci. 2016. 294:1969-1981.
12. 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.
13. Solans C, Solé I. Nano-emulsions: formation by low-energy methods. Curr Opin Colloid Interface Sci. 2012. 17:246-254.
14. 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.
15. Vandamme TF, Anton N. Low-energy nanoemulsification to design veterinary controlled drug delivery devices. Int J Nanomedicine. 2010. 5:867-873.
16. 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.
17. 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.
18. 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.
19. Wang Y. Preparation of nano- and microemulsions using phase inversion and emulsion titration methods. Master's thesis. Massey University, Auckland, New Zealand. 2014.
20. Alton's pharmaceuticals: The Design and Manufacturing of Medicinie.5th Edition; Chapter 27; Page No. 470-473.
21. 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
22. 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.
23. 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
24. 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
25. Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nanoemulsions. Advances in Colloid and Interface Science 2004; 108–109:303–18.
26. 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
27. 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.
28. 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.
29. 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
30. Seekkuarachchi IN, Tanaka K, Kumazawa K. Formation and characterization of submicrometer oil-inwater (O/W) emulsions, using high energy emulsification. Industrial and Engineering Chemistry Research 2006; 45: 372–90.
31. Seekkuarachchi IN, Tanaka K, Kumazawa K. Formation and characterization of submicrometer oil-inwater (O/W) emulsions, using high energy emulsification. Industrial and Engineering Chemistry Research 2006; 45: 372–90.
32. 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.
33. Porras M, Solans C, González C, Martínez A, Guinart A, Gutierrez JM. Studies on W/O nanoemulsions. Colloids and Surfaces A, Physicochemical and Engineering Aspects 2004;249:115–8.
34. 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.
35. Frank Sainsbury, Bijun Zeng and Anton PJ Middelberg Current Opinion in Chemical Engineering 2014, 4:11–17 Elsevier publications
36. 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
37. Haritha, Syed Peer Basha, Koteswara Rao P, ChakravarthiVedantham 2010 Indian Journal of Research in Pharmacy and Biotechnology vol 1 issue1 pg.no 25-18.
38. P. Bhatt and S. Madhav A Detailed Review on Nanoemulsion Drug Delivery System IJPSR, 2011; Vol. 2(10): 2482-2489
39. Sarvardekar P. Nanoemulsion-A Review.Int J of Res in Pharam Chem.2016;6(2):312-322.

HOW TO CITE: Aditya Sherekar, Sahil Shewale, Vaibhav Pawar, Musfera Jabeen Ansari Shakeel Ahmed, Rehan Khan, Dr. Vinod Bairagi, Nanoemulsion Formula Design and Development: A Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 4, 4330-4345, https://doi.org/10.5281/zenodo.19785407