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Research Article

Nano emulsion: formulation technique and Application

Akriti Rai*[1], Dr. Keshav Bansal[2], Prof. Meenakshi Bajpai[3]

[1,2,3] Institute of Pharmaceutical Research, GLA University, Mathura-281406, Uttar Pradesh, India.

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Corresponding Author:
akritirai154400003@gmail.com

Abstract

Nanoscale emulsions have sparked a lot of attention in recent decades due to their unique characteristics such as high consistency, beautiful appearance, excellent performance, and sensory benefit. Nanoemulsion are, in fact, one of the most widely used formulation techniques in the pharmaceutical and cosmeceutical industries. Nanoemulsion' fast growth as a method for delivering bioactive substances/drugs in cosmetics and dermatological treatments has been fuelled by their thermodynamic and kinetic stability, as well as their minute droplet size. The quality of Nano emulsions is largely determined by their composition and production process. They are primarily aimed at high performance, consumer product distribution, and the possibility of mass manufacturing. However, formulators encounter several constraints, particularly when it comes to the dispersion of active substances into human skin. The common procedures utilised by formulators to create Nano emulsions as final application products for cosmeceutical applications have been described in this study. This study also includes an overview of characterisation tools for distinguishing among micro and Nano emulsions, as well as their standards in terms of the physical and thermodynamic stability.

Introduction:

Nano emulsion is a system of colloidal particulates in the size range of submicron's acting as drug molecules carrier. [1] Nano emulsion is a liquid preparation there are two phases; one phase oil is occurred and the other is water phase. If the Oil in Water (O/W) type is Nano-emulsion, then it will be dispersed phase which also says external phase and water is continuous phase which also says internal phase. Emulsion is a biphasic liquids dosage form system, which make help of emulgent or stabilizer to create miscible liquid that stabilized to emulsion, it is thermodynamically unstable. A Nano emulsion could be regarded to also be a traditional emulsion containing emulsion quite small particles. [2] It on the order are droplet scale emulsions a hundred nm. it made up of oil, Water & emulgent for both the development of tiny droplets, the use of an emulsifier is important as it reduced interfacial tension. Widely categorised into two main Groups for the preparation of Nano emulsion by diff-methods: higher energy methods and Lower energy methods, High-energy processes, like mechanical stirring and ultrasonic. The kinetically stable Nano emulsion. [3] Nano emulsion formulation using diff-method a dosage form has been categorised according to energy requirements, the essence of surface modification or emulsification of oneself. Using Higher energy methods like HPH, Micro fluidizing. Ultrasonic and Lower Energy Methods-Inversion steps Alteration of phase, Method of emulsification of phase inversion, Phase inversion temperature (PIT), composition of phase inversion (PIC), inversion of Disastrous process (CPI), inversion point of emulsion (EIP) and the process of self-Nano emulsification. [4] Nano emulsions have emerged as a novel system of drug delivery that allows for controlled and sustained release. The size of tiny droplets, Nano emulsion have stability against Nano emulsion, sedimentation or creaming with the maturation of the Ostwald forming the primary Nano emulsion pathway the failure. The order of component to be mixed is normally since Nano emulsion are not considered important, spontaneously are created. [5] The substantial property that distinguishes that is, Nano emulsions from other emulsion system exhibit various physical and physical patterns. Rheological characteristics with lower droplet size. Few Nanoemulsion have also been developed in industrial with oral, ophthalmic, topical, and even intravenous (IV) dosage form. [6] For cancer diagnostics, Imaging and therapy Nano emulsion have been widely used in particular because of their favorable properties for the efficient solubilization of poorly aqueous soluble drugs. Biocompatibility, high in-vitro and in-vivo stability and their ability to accumulate defective vasculature in pathological areas. [7]

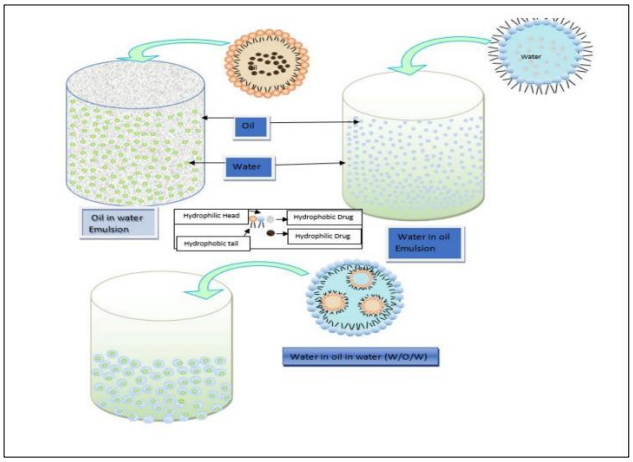


Figure 1 Types of Nano emulsions

Types of Nano emulsions

There have been 3 types' forms Nano emulsions based upon composition

(1) (o/w) Oil in the Nano emulsion of the water type that the oil is dispersed phase or water are continuous phase; oil distributed in water forms a NEs oil in the water type.

(2) (W/o) Water in oil type's Nano emulsion at which water is dispersed phase and oil is continuous phase; In oil type Nano emulsion, water is distributed in oil that forms a water.

(3) W/O/W type Nano emulsion is multiple phases, water into oil into water, o/w/o type Nano-emulsion.[8]

Methods of preparation of Nano emulsion

(1) Methods for High energy:

a. Homogenization at high pressure
b. Micro fluidizing
c. Ultrasonic Application

(2) Methods for low energy:

a. Method of phase inversion emulsification
I. Temperature of phase inversion –(PIT)
II. Phase inversion composion –(PIC)
b. Solvent –diffusion/displacement methods
c. Self nanoemulification/spontaneous methods [9]

(1)methods for high energy: To formulate Nano emulsion , high energy technique are commonly used, high mechanical energy is used to get powerful disruptive forces that break down big droplets into Nano-size droplets and generate large kinetics energy Nano emulsion[10],normally Nano emulsion are formed by used high-energy methods in which high pressure homogenizers, high shear stirring and ultrasonic generate apply mechanical energy input[11],the emulsion is produced by mechanical system use in high energy emulsification methods given the success of this high- energy techniques in minimising globule size such drugs likes thermolabile drugs and macromolecules [12].

(a) Homogenization at high pressure : This technique used a higher-pressure homogenizer/ piston homogenizer to create exceedingly low globule scale NEs (until 1nm) depending on the size of globule an number of cycle of homogenization lead to small globule size [13],the dispersal of the two of the liquids(Aqueous phase and phase of oil) was done by pressing this mixture, by forcing their mixture at extremely high pressure(500 to 5000 psi) through the narrow inlets orifice, which is subject to the mixture, intense turbulence and hydraulic shear product that results in extremely fine emulsion globules[14]In order to improve the efficiency for process of emulsion formation when creating Nano emulsions, several procedures can be applied, Even so, at emulsification, very higher phase volume ratio can resulting coalescence, but also more surfactants could be added to produce a small reduction in efficient surface tension and probably a decrease in recoalescence.[15]NE formulation to generate very high shear rate range 100 to 1000 per.

Minute generally a room temperature but control the temperature use thermostat, at these higher rotor rpm. [16] To obtain the optimized formulation, the follow control parameters should be investigated

(a) Pressure of Homogenizer: high pressure of homogenizer can be applied that found to small size of globules, range approximately 1450.4 -2175.6 psi.

(**b) cycle number of Homogenization:** no of cycle is an important to globule size formation, more no of cycle to small size globule formation [17]. To achieve micronization and membrane lysis, high-pressure homogenization utilizes various mechanical forces (such as turbulence, cavitation, and shear) along with extreme pressure. High-pressure units work automatically and are mostly adapted from laboratory research to manufacturing.

Benefits:

(1) An increased rate of dissolution includes the advantages of high-pressure homogenization.

(2) Ease of service, cost and time quality, consistency in product composition.

(3) Due to a stable emulsion and improved scalability and repeatability, higher stability of final products.

(4) High-pressure homogenization now has the capacity to decrease the size of globules to levels that most other mixing processes do not achieve [18]

(5) Improve of scale-up or less difference in batch-to-batch Improve of scale-up or less difference in batch-to-batch.

(6) Narrow scale of Nano size drug delivery.

(7) Flexibility with managing the safety of medications.

(8) Efficiently often used thermo-labile compounds [19]

Disadvantages:

(1) HPH is high costly.

(2) It also Cross-contamination in order to avoid.

(3) Every time it is used, the whole unit needs cleaning.

(4) The homogenizers of high-pressure appear to be large and extremely strong.

(5) No substance is deposited into the sample by high-pressure homogenizers its damage to system.

(6) Consider the complexity of cleaning the homogenizer, since it will need to be cleaned after each usage for most applications [20]

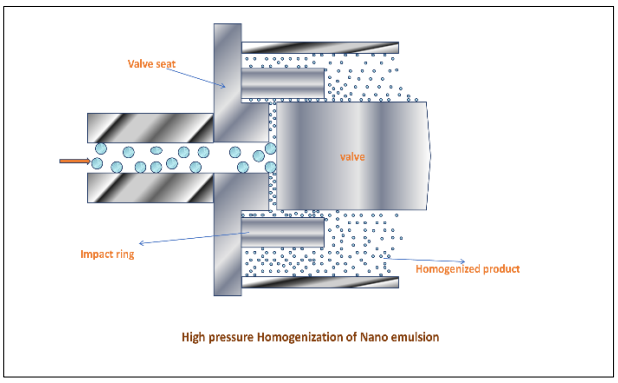


Figure 2 High pressure of Homogenization of Nano emulsion

(B) Microblading Technique:

Micro fluidizing technique is a form of higher-energy homogenization that is applied to Nano emulsions in industry operations. Its capacity to create perfect emulsions from some kind of wide range of components like supplements, vitamins , bioactive lipid medicines, anti-oxidants and flavourings, A micro fluidizer was used to create Nano emulsions on the bases of the Activity of concomitant deformation, collision, or cavitation forces.[21]The coarse emulsion previous prepared is also transferred via an air-driven of micro fluidizer (Version 110 L, Microfluidic devices,) functioning between 21 and 125 Multiple of the Pascal, A hydraulic pump, filters and a contact chamber were included in this equipment, A pressure of near to 125 Multiple of the Pascal from of pressurized air supply can be produced by the pump, Emulsions were homogenized at various pressures and periods, The micro fluidizer interaction chamber is cooled with water from the tap to relieve the increase in temperature a thermometer was mounted just after the discharge port in the sample reservoir to monitor temperature variations during micro fluidization[22]Micro fluidization is a method of mixing which uses a device called a mixer. A higher-pressure an positive pressure pump (5 hundred to20000psi) is used by this system, which drives the item through to the interaction chamber, which results in smaller sections called 'micron-channels[23] A coarse emulsion is transferred repeatedly to the touch chambers micro fluidizer till the required particle size is reached is acquired Start preparing coarse emulsion initial by combining water and oil phase mixing Area for forming small particles of Nano size, accompanied by filtering to achieve a uniform droplets[24,19] A micro fluidizer operates also on concept of a pressure stream dividing in two pieces, Going to pass through small orifice with each part.

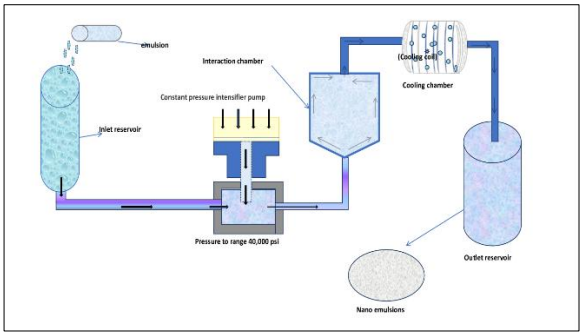


Figure 3Micro fluidizing technique Nanoemulsion

As in core of a micro fluidizer and directing an inflow at each other this is the chamber of contact to direct a flows streams via microchannel towards the impingement region the micro fluidizer requires high pressure, This causes a very strong shearing effect which provides an extremely fine emulsion, Inside a chamber for interaction, In addition to shear and impact, cavitation's reduces the size of emulsion droplets[25]A only one intensifier pump is fitted with scale machines and provides a pressure distribution which uses cyclical suction & compression movements, Except for the use of two intensifier pumping rather than one to reduce cycle lag, machines, Multi-intensifier pumps are often integrated into the constant pressure setting on a scale-up divisions and a constant variable differential capacitor (LVDT) is used to provide continuous electronic regulation of the constant pressure profile (FP) pumps, during the process control variable major 5 points –chamber types, size, pressure, of cycle and last temperature of reservoir system[26] ,a double-channel micro fluidization is used to push the scattered and continuous stages into an air-driven greater pressure microfluidizer, double channel process under two separate glass reservoirs are fed into the a double channel system, the lipid and aqueous phases, after that, emulsion formation takes place continuously by pushing the lipids and aqueous stages to move via the micro fluidizer In a single

stage, oil-phase amounts (approximately 50 percent) ,Lowering manufacturing costs and time using double-channel system, Organic emulsifiers like whey protein concentrate and Q-Natural (organic emulsifier derived from Quillaja tree) have been more efficient in generating Nano emulsions in lower emulsifier concentration by double-channel micro fluidization, In a single-channelling system operating (traditional phase of Nano emulsion elaboration) ,When combining a lipids phase with the aqueous phase, a prefusion (coarse emulsion) is produced that used a high-speed mixture, which may be transferred through the storage tank to the micro fluidizer[27,21]

Benefits:

(1) The key benefits of a methods provide greater stability with such a small size of the particles.

(2) Development for Nano delivery systems for greater repeatability on a larger level.

(3) Non accumulation for reduced fusibility of existing Nano delivery technologies.

(4) High efficacy of encapsulation for smaller use of some of the solvents.

(5) To decreased particle size and greater bio accessibility, micro fluidized Nano delivery technologies.

(6) Higher bioavailability and continuous release of oral drug delivery.

Disadvantages:

(1) Technique of formulation or improvement of extended release of such active compounds.

(2) The channel has several drawbacks, such as excess energy and much more costly lipid & oil waste to initial generating coarse emulsion to also be forced into micro fluidizer.

(3) Micro fluidization singular step double –channel the stable Nano emulsion for maximum loading capabilities is therefore prepared.

(4) In the production of SLNs, the main drawbacks of the above systems involve lipid separation, lower stability or greater need for organic solvents.

(5) Disadvantage a formation of phytochemical for the Nano emulsion-loaded plant.

(6) These approaches include the use of organic solvents, surfactants & oils, bioavailability & possible solvent toxic effects, and oral delivery stability.

(7) In the preparation process, Nano liposome growth and improvement of its extended release of these bio-active compounds.

(8) Drawbacks as in production of PLGA-based nanoparticles and drug loading potency as no uniformity & high processing difficulties are the main limitations in most techniques.

(9) Drawbacks that use chemotherapeutic agents or plant-based bioactive components produced during the development of such Nano delivery systems [28]

(C) Higher energy Ultra sonication:

Ultrasound is a kind of energy created by sound waves with frequencies that are scarcely audible to the human ear, i.e., frequencies greater than 16 kHz. When ultrasound is applied to a biological structure, it compresses and depresses the medium's constituent elements. Numerous physical, organic, and pharmacological functions can be seen in proportion to the magnitude of the sound wave and the rate employed, allowing for a variety of applications. The initial ultrasonic application was inspired by nature, since bats use ultrasound to navigate in the dark. Many cetaceans also generate ultrasound via their vocal systems to identify prey or obstacles using echolocation. [29]

Ultrasound has been utilised for several purposes, including animal communication, flaw detection, chemical amalgamation, disease diagnosis and treatment, and measuring. Ultrasound is a burgeoning branch of research, despite its wide-ranging uses and thought-provoking breakthroughs. Several academics have published a substantial quantity of material to explain the global uses of ultrasonography in various industrial areas. There has been rising research that examines the possibilities of ultrasound in large-scale applications recently. [30]

Probe Sonication

Probe Sonicators (Ultrasonic Homogenizers) provide precise engineering and all of the characteristics required to construct a complete ultrasonic disruption system. Most cells, germs, spores, and tissue could be disintegrated by them. They can homogenise "immiscible" liquids, accelerate enzymatic and chemical processes, promote bacterial activity, scatter particles in liquids, and degas liquids. [79]

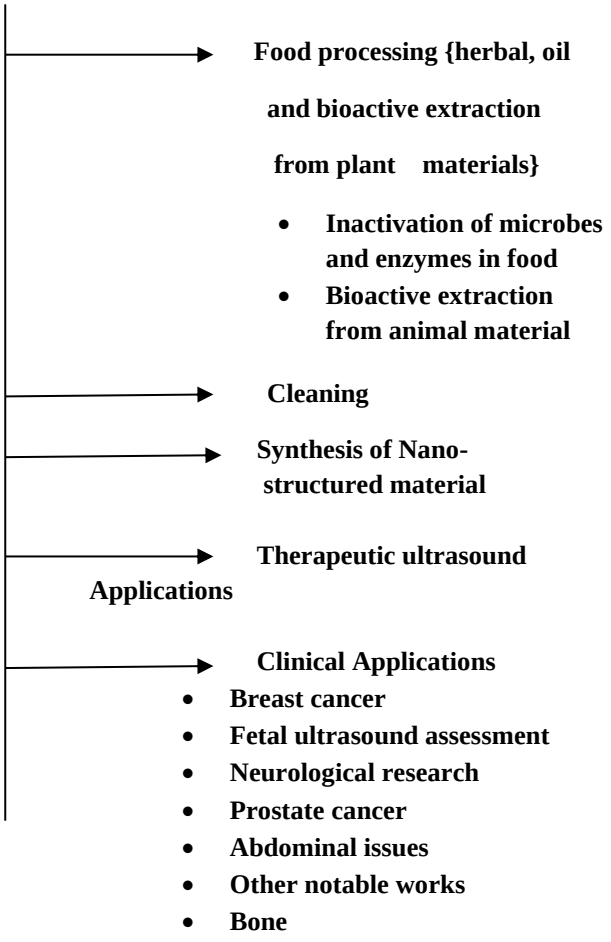
Bath Sonication-

An ultrasonic bath disperses energy evenly across a broad area. Cavitation, or the formation and collapse of bubbles, is the process for energy transmission. This can cause impurities on the surface to escape, making these baths excellent for cleaning and sterilisation preparation. They might also be used for degassing liquids, cell separation, or cell lysis (of fragile cells). [79]

Probe Sonicator vs Bath Sonicator

Content	**Probe Sonicator**	**Bath Sonicator**
Definition	Probe sonication is an instrument which is direct method in this probe is inserted into the sample	Bath sonication is an instrument which is indirectly method in this water bath is involved to provide energy into the sample
Direct or indirect method	Direct sonication method	Indirect sonication method
Contact with the sample	Sample is directly contact	Sample is isolates from the energy source
Energy is delivered through	Probe	Water bath
Input energy	Low input energy is sufficient	Supplied more input energy
For small samples	Not suitable	More effective
Sample cross contamination	Higher possibility	Cross contamination reduces
Number of samples	One sample used at only one time	At one time so many sample used in tubes

Ultrasonic application:



Applications of ultrasound in food technology-

Applications	References
Food-grade oil deterioration	31
Meat tenderization and chilling	32

The concentration of a simple solution and the content of the meat were measured.	33
Degassing, crystallisation of fats and sugars, elimination of foams, extraction of flavourings, freezing, filtering, drying, mixing, and homogenization, meats tenderization	34
Milk purity regulation by microorganisms	35
Foreign bodies are identified.	36
The cellular structure of bread crump is classified.	37
Meal chilling surveillance	38
Fruit and vegetable drying	39
Fruits are dried.	40
Changes in the diffusivity of water and dry materials	41
Absorption chilling with the use of ultrasound	42

FDA- Approved Mode for Ultrasound Therapy-

Therapy Method	Therapeutic Outcome	Bio effect Mechanism	Applicator	Frequency	Delivery	Reference
Beam that is not focused	Warming of the tissues	Heating	Portable handheld	1-3MHz	Continuous or repeated burst	43
Hyperthermia	Cancer treatment	Regional heating	Multi-element applicator	1-3.4 MHz	1h	44
Ultrasound with a higher intensities concentrated beam	Ablation of Uterine fibroid	Thermal lession	Computer directed	0.5-2 MHz	Long burst	45
Ultrasound with a higher intensities concentrated beam	Relief from Glaucoma	permeabilization	Fixed probe with water bath	4.6 MHz	1-3s	46
Ultrasound with a higher intensities concentrated beam	Tissue ablation by laparoscopy	Thermal lesion	Handheld	4 MHz	Long burst	47
Ultrasound with a higher intensities concentrated beam	Tissue ablation by laparoscopy	Thermal lession	Handheld	3.8-6.4 MHz	Long burst	48
Focussed ultrasound	Tightening of Skin tissue	Thermal lesion	Treatmen-t and Handheld imaging	4.4-7.5 MHz	20-50ms Burst	49
Extracorporeal lithotripsy (outside the body)	Communicati on between kidney stones	Mechanical stress, cavitation	Mainframe with image guidance	150kHz	Shock waves	50

Intracorporeal lithotripsy (inside the body)	Communicati on between kidney stones	Mechanical stress, cavitation	Probes of Percutaneous	25kHz	Prolonged	51
Extracorporeal shock wave treatment (ESWT) is a kind of extracorporeal	Epicondylitis, plantar fasciitis	Unknown	Mainframe with applied cator head	150kHz	Shock waves	52
Phacoemulsification	Taking out the Lenses	cavitation, vibration	Generator with probe	40kHz	Endless	53
Liposuction with ultrasound assistance	Removal of adipose tissue	Fat liquefaction, cavitation	Probe with Generator	20-30kHz	Continuous	54
Tissue removal and vessel closure	Open surgery vs. laparoscopic surgery	Vibration, Thermal lesion	handheld	55.5-5kHz	Steady	55
Ultrasound imaging of the blood vessels	Dissolution of thrombus	Gas body activation, unknown	Intravascular catheter	2.2MHz	Continuous	56
Permeability of the skin	Drug distribution via the skin	Unknown	handheld	55kHz	Continuous	57

Methods for low energy:

Low-energy emulsification works by using low-energy obtained from the formulation's ingredients, eliminating the use of high-energy external equipment. The emulsion droplets are transformed into micro by the low energy from the dosage form. This technique is used in a variety of Nano emulsion preparation processes, along with the SE, PIC, and PIT procedures.

Advantages of low energy method-[78]

- When utilising the method, it's a good idea to double-check the emulsification temperature. In many cases, lowering the emulsification temperature without compromising emulsion quality is achievable.
- To enhance emulsions, it may be advantageous to maintain the emulsions degree above the PIT (phase inversion rate) in some emulsions stabilised by non-ionic surfactants.
- Changing the emulsification process can result in significant reductions in kinetic energy consumed in mixing or homogenising in some situations.
- By improving emulsification conditions, it is usually possible to eliminate energy-intensive high-shear equipment.
- Controlling the emulsifier position and resolubilizing the oil droplets, for instance, can sometimes considerably improve emulsification without altering the formulation.
- In some cases, the low-energy approach can produce a thinner emulsion than the traditional method.

Limitation of low energy method-

- If the viscosity of the concentrate is too high, mixing becomes problematic. Like a result, there is a limit to how much external phase one can ignore.
- Fortunately, most emulsions, even those that are quite concentrated, are flowable at the high temperatures used for emulsification.
- A stable emulsion with the appropriate characteristics must be obtained after dilution. The right texture, opacity, or rheological characteristics may be the required properties. Of course, from a marketing standpoint, this criterion is critical.
- However, because emulsion is such a complicated system with so many physical variables that may alter its characteristics, defining the circumstances that would meet these criteria is difficult.

Spontaneous emulsions (SE)

The diffusion of water-miscible components (solvent, surfactant, and co-surfactant) from an organic phase into an aqueous medium when the combination is diluted is the basis for this technique. SE usually involves combining an organic component (oil plus a hydrophilic surfactant) without an aqueous solution (carrying water and co-surfactant) [58-61].

Water-miscible components migrate quickly into the aqueous phase which generates tremendous disturbance at the multiple interfaces, as well as a significant increase in the oil-water surface area. Through a budding process, it results in the natural production of oil particles enclosed by aqueous phase [62,63].

Stock solution of nanoemulsions or cube liquid metals with freshwater can also be used to make nanoemulsions [64,65].

Co-surfactants pass across the oil-water contact and into the aqueous layer upon dilution with water. As a result, the micelles become thermodynamically unstable, resulting in nanoemulsions. The SE technique is also utilised in the pharmaceutical sector to make nanoemulsions that may be used as carriers for lipophilic medicines in aqueous environments. Self-nanoemulsifying drug delivery are the term used in the order to describe systems made this way (SNEDDS) [66, 67].

Phase inversion composition (PIC)

The PIC approach relies on a shift in emulsion mixture phase (namely, from o/w to w/o or directly proportional) because of emulsified mixtures changing at a fixed temperature. Pouring one of the constituents (water or oil) into a combination of the other two is what it implies (oil-surfactant or water-surfactant, respectively). By slowly adding water to w/o nanoemulsions, for instance, they become o/w nanoemulsions. As the moisture concentration in the system rises, so does the hydration of the surfactant's polyoxyethylene chain. Mostly as response, the surfactant sudden curvature goes from negative to zero.

The surfactant's hydrophilic and lipophilic properties are now equal, so adding water shifts the nanoparticle curve from negative to positive, converting w/o micro emulsions to o/w nanoemulsions. [68, 69].

The PIC procedure for making micro emulsions consists of three main steps: blending the organic solvent (oil + surfactant), titration of the aqueous medium into the organic phase, and further mixing. [70, 71, 72].

Phase inversion temperature (PIT)

Phase inversion technique is a low-energy emulsification technique for producing micro-emulsions that involves altering the degree to modify the optimal curvature of surfactants at fixed volume. It has a benefit over the Spontaneous emulsification technique in that it does not contain an aqueous solution that is a necessary component of the Spontaneous emulsification method [73, 74].

The Phase inversion technique also outperforms the Phase inversion composition technique because the Nano emulsion droplets are smaller and have a smaller polydispersity index (PDI). The Phase inversion technique's emulsions effectiveness was likewise shown to be greater (1) than the PIC approach (0.35) [75].

Micro emulsions

Micro emulsions are a thermodynamically stable solution containing a high surfactant-to-oil ratio (typically water, oils, and emulsifiers, with a co-solvent thrown in for good measure). Micro emulsions can theoretically be made spontaneously by just mixing all of the elements together at a certain temperature without any additional energy. Depending on the quantities, type, and configurations of the molecules present, these phases may be water-continuous, oil-continuous, or discontinuous. As a result, micro emulsions can have spherical, lamellar, or discontinuous shapes [76, 77].

While nanoemulsions are chemically inert, they can destabilise if one or more of the components undergo chemical reactions, preservation or if the ambient circumstances change to a point where the system is no longer constant [77-79].

Conclusion

For the delivery of pharmaceuticals, biological, or diagnostic agents, Nano emulsions have various advantages. NEs have been utilised as complete parenteral nutrition solutions in hospitals for more than four decades. Diprivan, Liple, and Ropion are just a few of some other medication delivery devices that have made it to market. Although NEs are most used to transport aqueous insoluble medicines, they have lately gained popularity as colloidal carriers for the targeted administration of anticancer medications, photosensitizers, neutron capture therapy agents, and diagnostic agents. It can really be easily targeted to the tumour region due to their micrometre range. Several research articles have recently been published for the enhancement of drug delivery, but more attention on its characterisation, including in-vitro assessment, is still needed. Furthermore, research papers show that a higher proportion of surfactant (far higher than CMC level) is used for the structure of Nano emulsion, regardless of the systemic delivery, but toxicological assessment of the prepared Nano emulsion is lacking, which could be a broad research area in the future.

Conflict of Interest: Nil

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