Review Article

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A SNAPSHOT ON NANOEMULSIONS FABRICATION TECHNIQUES FOR DRUG DELIVERY SYSTEMS

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ABSTRACT

Nanoemulsions are budding from conventional emulsion and formation of nanoemulsion is occurred by reducing the interfacial phenomenon to negative and it is a mixture of oil and water which miscible by surfactants and co-surfactants where globule size in the range of 20 – 500 nm and nanoemulsions are the potential pharmaceutical carriers as it can be used for both lipophilic and hydrophilic drugs. Nanoemulsions are getting more attention because they have been shown to be very viable, non-invasive and cost-effective nanocarriers for facilitated transdermal delivery of a wide variety of active ingredients that appear to be highly metabolized or have undesirable side effects when taken orally. Increase in the skin permeation with very low skin irritancy and nanoemulsions are easy to fabricate. This review reveals the fabrication methods and theoretical aspects of nanoemulsion formation, stability problems of nanoemulsions and their prevention methods. Nanoemulsions can be employed to deliver the drug for various drug delivery systems.

Keywords: Nanoemulsion, Fabrication, Assessment, stability.

INTRODUCTION

Nanoemulsions are oil-in-water (O / W), water-in-oil (W / O) dispersion of two balanced immiscible liquids using a suitable surfactant.[1] Normally the mean droplet diameter is less than 500 nm.[2] Micro droplet size brings them a translucent or hazy look that varies from the milky colour found with the macro emulsion (whose micron-sized globules are part of multiple light dispersion).[3] Sometimes the term nanoemulsion is switchable with submicron emulsion or mini emulsion; however, microemulsion should not be messed with this. Whereas nanoemulsions have the same droplet size range as microemulsions, they differ greatly in structural facet and thermodynamic stability over the long term.[4]

Nanoemulsions, like liquids, can be rendered in several dosage forms.[5] Creams,[6,7] Sprays,[8] Gels,[9,10] aerosols,[11,12] foams,[13] and most often route of administration is Topical,[14] oral,[15]. They have a higher solubilizing capacity than simple micellar dispersions, a higher kinetic stability than coarse emulsions and cosmetic use.[16] Their long-term physical stability is a direct result of small droplet size that impairs traditional processes of destabilization such as creaming, sedimentation and coalescence. Brownian motion is often good enough to counteract kinetic instability that is caused by gravity or viscosity. Nanoemulsions were used, in parenteral form, to solubilize and protect drugs against harsh environmental factors (oxidation, pH, hydrolysis).[17] Targeting specific organs by using improved permeability and retention effect[18] and for avoiding reticuloendothelial systems.[19] Once administered orally, the small size of droplets in nanoemulsion and their ability to solubilize very hydrophobic drugs provide a mechanism to greatly increase the rate of drug degradation and the anticipated systemic bioavailability afterwards.[20] Drug release from nanoemulsion involves partitioning from oil to surfactant layer then to aqueous environment consecutively. The solubilized drug moiety while diffusing out of oil interacts with encompassing water and experiences nano precipitation. This raises drug's surface area enormously; accelerating its dissolution in accordance with Noye- Whitney's equation.[21] Several nanoemulsions have been reported to undergo direct lymphatic absorption thus avoiding first-pass metabolism to enhance bioavailability thereby reduce the amount of drug which undergo largely to hepatic transformation.[22] Nanoemulsions are one of strong formulation to mask bitter taste of drug thus preventing nausea thereby improve the patient compliance and directly eliminate the other techniques to mask the bitter taste of drug alone[23], also the nanoemulsions consume a less quantity of surfactants than the colloidal dispersions but the nanoemulsion did not satisfy the commercial criteria and there is a need of still research to do in structural deportment, a suitable tailoring conditions to fabricate to cross commercial barrier or industrial scale to reach consumers. This leads to a wide premise to who have eyeing on this business in the development of nanoemulsions.

Composition of NE

Oil/Lipid Phase

NE consists of usually 5-15% of oil in the case of o/w water NE and many edible oils like olive oil, Rice bran oil, soya bean oil, sunflower oil and sesame oil they are classified as long chain triglycerides and medium chain triglycerides but their selection is also crucial in fabrication of Nanoemulsions because it will impact on the systemic availability of key ingredient.[24] In the recent research suggested that marine oils can also be used as in the fabrication of NE because they have a benefit of bypassing

the intolerance of regular MCT, LCT and safer for cardio vascular patients.[25]

Surfactant/co-surfactant

Surfactants are amphiphilic molecules that stabilize nanoemulsions by reducing interfacial phenomenon and preventing the aggregation of droplets. Because they hold the water and oil with the help of polar and non-polar chain present in the surfactants. Most widely used surfactant is lecithin present in egg yolk or soya bean because it is biodegradable, wide range of safety.[26] Tween 20, 40, 60 and 80 (Polyoxyethylene sorbitan monolaurate), Span 20, 40, 60 and 80 (Sorbitan monolaurate) commonly used due very low irritation potential and belongs to the GRAS,[27] Surfactant and surfactants commix used to decrease the droplet size, stability and may alter the pharmacokinetics and pharmacodynamics of nanoemulsions.[28] Co-surfactants are gives the additional benefit to the nanoemulsions by reducing the interfacial phenomenon to very negative range and ameliorate the stability nano droplet example of co surfactants propylene glycol, polyethylene glycol, ethanol, transcutol IP, glycerine, ethylene glycol and propanol.[29]

Preservatives, Antioxidants

Nanoemulsions are when exposed to air, oxidation may occur due presence of lipids or oil phase leads to rancidity and aesthetic problems hence to arrest the oxidation antioxidants can be employed like ascorbic acid, sodium bisulfite, metabisulfite, thiourea and sodium formaldehyde. Microorganisms are vigorously grown in the aqueous phase and preservatives are mostly applies to the o/w NE.[30] In contrast many research works suggested that preservatives are not required.[31]

Criteria for fabrication of NE

A formulator needs to reach the following criteria for the tailoring the NE for a stable, safe and effective.[32]

1. Drug should have less lipophilicity and coefficient of water/oil partition.
2. The molecular size of drug should possess more than 500 Daltons.
3. The bio available dose of drugs
4. If more oil concentration used stability problems may arise due decrease in the fluidity.
5. Extent of Solubility of drugs in the both aqueous phase and oil phase.

Tailoring methods of NE

To fabricate the NE basic consideration is to achieve the droplet size in the nano meter and formulation stability. There are only two types of techniques to fabricate i.e., High energy and low energy methods.

High energy methods

In this method the application of energy through devices and generated forces is sufficient to rupture the large oil droplets into small with the robustness and reproducible.[33] These methods include a High-pressure homogenizer, Microfluidizer, Ultra-sonication and jet disperser.

High pressure homogenizer

HPH is performed by applying high pressure (50 -500 psi).[33] to the oil phase, aqueous phase and surfactants layer, using a high-pressure homogenizer in a reiterate cycles to achieve nano-emulsions of extremely low droplet size. But there is disadvantages like heat generation, lack of productivity hence thermo labile drugs cannot be used and concentration of oil has to be restricted not more than 20%.[34]

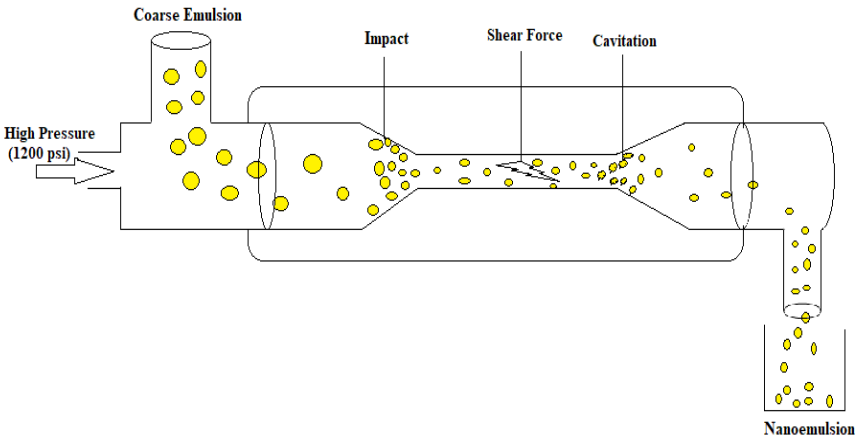

Figure 1: High Pressure Homogenizer

Microfluidization

Concomitantly, emulsion will expose to high shear, impact and attrition in the microfluidizer for reiterate cycles by passing forcefully to interaction chamber comprise of micro channels under high pressure displacement pump (10,000-30,000 psi) till optimal reached size and dispersity. The operational process is laborious and very expensive henceforth pilot scale is challenging.[35]

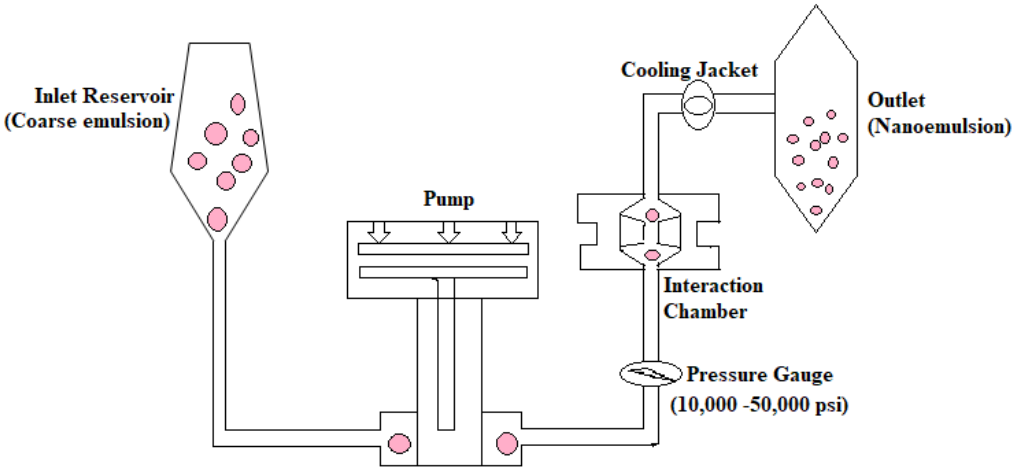

Figure 2: Microfluidizer

Ultrasonication

Ultrasound methods are reliant on high-frequency sound waves (20 kHz and up). And implement to fabricate NE from coarse emulsion with the assistance of generated mechanical force to breakdown big droplets; decreasing droplet size with increasing sonication time and power. It is more viable to implement to pilot scale because consumes less operational requirements and many modified instruments are developed like homogenizer with sonication.[36]

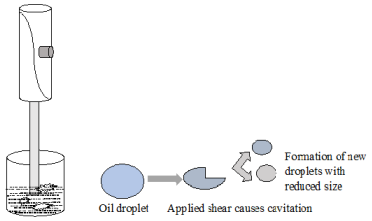

Figure 3: Ultrasonicating coarse emulsion thus cavitation leads generation of Nanoemulsion

Piston Homogenizer

Piston homogenizer works on the principle of colloid mills. An emulsion is rendered to move through a narrow gap i.e., < 10 µm between a fixed stator and a swiftly-moving rotor. Size reduction is due to high shearing, stress and grinding forces created between rotor and stator. Droplet size of emulsion is mainly depending on the size of rotor and stator.[37]

Jet Disperser

Similar to microfluidization but without moving parts, this system is capable of handling extreme pressures of up to 400 MPa.[38] Two jets facing each other stream two distant liquids through the nozzles, allowing them to collide. The generated NE is collected by means of a laminar elongation flow through an orifice plate that controls the energy dispersion. This technique is not as effective as microfluidation, but it is cheaper and more energy efficient.[39]

Low Energy Methods

Nanoemulsions prepared using low-energy emulsification methods have been developed after observing the conglomerative behaviour of oil, surfactants, co-surfactants, aqueous components, hydrophilic lipophilic balance of the oil surfactant mixture used and operating temperature.[40] It includes Spontaneous emulsification, phase inversion temperature and solvent displacement method.

Spontaneous emulsification

This method is very quick and simple because it is mixing of oil phase Surfactant and co-surfactant commix in a right proportion with a very mild agitation and order of mixing of ingredients is

not significant for generation of nanoemulsion.[41] Titration of one phase to another phase determine the type of nanoemulsion but challenge is the selection of ingredients is very crucial and critical for formation of nanoemulsion of desired range.

Phase inversion temperature

This method shapes the nanoemulsions by manipulating changes in the aqueous / oil solubility of surfactants in response to temperature fluctuations. It involves the orderly conversion of a W / O to O / W emulsion or vice versa via a bicontinuous intermediate step. Typically, the oil, water and surfactant mixture are heated past a specified temperature, called PIT (specific for the formulation mixture used) and then rapidly cooled. Phase inversion is due to the temperature fluctuation is low to high and twists the liquid-liquid interface. The nanoemulsions can also generated by diluting composition at constant temperature or vice-versa.[42]

Solvent displacement method

Oil phase is dissolved in volatile organic solvents like ethanol or acetone then mixed to aqueous phase consist of surfactant and co-surfactant blend. Nanoemulsions are formed without energy, as it occurs spontaneously at room temperature.[43] Solvent can also remove by applying negative pressure. The Surfactant type and concentration, viscosity of emulsion is specified parameters that must be maintained to obtain the necessary nanoemulsion.[44]

Nanoemulsion types

Based on the components and relative distribution of the internal phase and the more prevalent continuous phase, nanoemulsions are referred to as biphasic (O / W or W / O) or multiple nanoemulsions (W / O / W). The Volume of Phase Ratio (Φ) determines the comparative volumes of the internal and external phases comprising the nano-emulsion and calculates its number of droplets with stability. Typically, Quantity of which phase is high then that phase is continuous phase. In order to predict the nanoemulsion type developed under given conditions, the interaction of the various components making up the nanoemulsion must be estimated. If the key surfactant is soluble in water, it prefers O / W emulsion and contrarily, if the surfactant is lipid soluble, it prefers W / O emulsification. The polar portion of the emulsifier is generally better for coagulation than for the hydrocarbon portion. There upon emulsions can be interchanged by increasing the volume of phase ratio more than 40%. Based on the principle of scattering of oils determines the type of emulsion if w/o coloured background will be seen contrarily if o/w coloured spots will appear.[45] Whereas for the multiple emulsions like w/o/w difficult to observe scattering due to oil concentration is less.

Figure 4: Types of Nanoemulsion i.e., Oil in water and water in oil emulsions

Theoretical aspect of fabrication of NE

The force of attraction between two liquid phases is negative and interfacial tension created due to that contact point existed between two liquids is called as σ.[46] The energy needed to build an additional interfacial region 'A' between the two liquid phases is σA. Interfacial force is often acting to reduce the interface region. There upon, the interface between two immiscible liquids is like a flat sheet at their point of contact. Commonly in the absence of surfactant blend oil and aqueous phases will be immiscible and oil layer sits on the above water due less density than the water hence the system is thermodynamically equilibrium. After adding surfactants, it will accumulate the contact point created between two immiscible liquids thus interfacial tension will be reduced. Surfactants will be soluble in any of the phase based HLB value but if profoundly soluble in the dispersed phase can significantly reduce the interfacial tension. If the oil-water interface, which is overlayed with surfactants, is pulled near to each other, a thin film of water may remain at the interface. Repulsion of interface will occur due presence of similar and separate charges on the surfactants. The droplets remain spherical with radius ‘a’ at a minimum volume of dispersed phase. The curved interface exerts a pressure on the molecules inside the droplet called Laplace Pressure (p).[47]

$$\text{Laplace pressure (p)} = 2\,\sigma/a$$

Since the radius is inversely proportional to Laplace pressure, macro droplets experience very low Laplace pressure than the micro droplets hence there upon to deform the micro droplets into nano range shear will be apply more than the Laplace pressure (p).[48] Surfactant molecules are present largely in the continuous phase it will overlayed on the newly formed interfacial region so it prevents the droplet aggregation. Viscosity of oil phase and shear rate are the key factors to be considered.

Strategies for maximizing the absorption of lipid soluble drugs

As the novel drug delivery system is getting progress a novel approach came into exist for increasing the solubility of lipophilic drugs and strategies like Formulation of dry powder syrups, nanoparticles, lipid-based formulations, microemulsions, solid dispersion, Hot-melt extrusion, salt forms and formation of complexes soluble in water. The lipid-based formulation is optimized approach for enhancing solubility thereby a bioavailable dose is maximized.

Table 1: List of drug dosage forms under the clinical trials based on lipid-based formulation approach

Brand name/Drug	Type of Formulation	Disease condition/Drug category	Company name/Sponsor name
Curcumin	Nanoemulsion	Atypical ductal breast Hyperplasia	Comprehensive Cancer Center of Wake Forest University
Oxalgin Nanogel®/ Diclofenac sodium	Topical gel	Joint and Muscular pains	Zydus cadila
Restatis®/Cyclosporine	Ophthalmic Nanoemulsion	Chronic Dry eye syndrome	Allergan
CoQ10	Oral Drops	Ataxia oculomotor Apraxia 1	Assistance publique - hopitaux de Paris
Norvir®/ Ritonavir	Capsules	Antiviral	Abbott Laboratories
Estrasorb®/ Estradiol	Topical Emulsion	Hot flashes (vasomotor symptoms in menopause)	Novavax
Oraqix®/ lidocaine and prilocaine	Microemulsion	Local Anaesthetic	Dentsply International

Assessment of Nanoemulsions

Globule size of Nanoemulsions is most crucial parameter because the entire Nanoemulsion concept lies on its size and stability and it was measured by photon correlation spectroscopy, which dissects the variance in light scattering due to Brownian motion of the globules. To investigate the structural deportment of NE More sophisticated techniques such as dynamic light scattering (DLS)[49], X-Ray Scattering,[50] Cryo electron microscopy,[51] is used. The globule volume fraction determines the concentration of globule and its structure by intensity of size distribution and typically used method is DLS.[52]

The droplet Morphology of liquid Nanoemulsions can be measured by X-ray scattering or microscopy techniques like Cryo Transmission electron microscopy or Scanning electron microscopy where the droplets is analysed in frozen hydrated state and it is almost native state so it also reveals special arrangements of droplets.[51]

Zeta potential is used to measurement of static charges around the droplets because droplet agglomeration may occur due to attraction between charges so it is very crucial tool to assess the stability. Many literatures Suggested and reported that range of zeta potential above the ± 30 mV is stable and effective towards some target site or matrix. Through process variables or fabrication composition can altering the zeta potential thereby tackle the stability problems.[53]

The Rheological property of Nanoemulsions can be assessed by measuring Viscosity in various Viscometers. Electro conductivity measurements Decides the type of Nanoemulsions formed.[54]

The stability of nanoemulsions is determined by keeping in stability chamber as per ICH Guidelines is very tedious and it is usually done at the last hence the stability can also assure by conducting Thermodynamic stability studies and it is carried out in 3 steps i.e., Heating cooling cycle (NE were subjected under temperature between 4°C and 45°C not less than 48h), Centrifugation (after passing the heating and cooling cycle NE's centrifuged at 4000-5000 rpm for 30 min), Freeze-thaw Cycle (NE's were subjected to -21°C and 45°C examine for any phase separation by Visually) to ensure the integrity of globules or droplets under different temperatures.[55]

Interfacial Tension is critical parameter to be addressed in emulsions since emulsion are formed only when reducing the interfacial tension and Interfacial tension can be measured by using Spinning-drop apparatus.[56] pH measurement for NE's is needed because drug delivery and drug stability are mainly depending on pH.[57]

Table 2: List of Lipophilic Drugs Fabricated in Nanoemulsions

Drug	Oil Phase	Surfactant	Co-Surfactant	Aqueous phase	Uses
Aceclofenac	Labrafil, Triacetin	Tween-80	Transcutol-P	Water	Permeability enhancement
Indomethacin	Labrafil	Tween-80	Transcutol-HP	Water	Permeability enhancement
Progesterone	Lipoid-E80	Sucrose esters	-	water	Permeability enhancement
Nimesulide	Medium Chain Triglycerides	Polysorbate-80	-	Water	Assessment of Permeability
Amlodipine	Oleic acid	Tween-20	Transcutol-P	Water	Permeability enhancement
Lidocaine	Benzyl alcohol	Tween-80	ethanol	Water	Permeation rate enhancement
Tetracaine	Hexadecane	Synperonic-A7	-	Water	Increase in drug release transdermal
Olmesartan	Clove oil	Tween 20	Poly Ethylene Glycol	Water	Increase in bioavailability
Amphotericin B	Capmul PG8	Labrasol	PEG 400	Water	Permeability enhancement and alternative ROA

Table 3: List of Hydrophilic Drugs Fabricated in Nanoemulsions

Drug	Oil Phase	Surfactant	Co-Surfactant	Aqueous Phase	Uses
Fluconazole	Iso propyl myristate	Lipoid E-80	-	Water	Permeability enhancement
Thiocolchicoside	Linseed oil	Span 80	Transcutol p	Water	Permeability enhancement
Granisetron HCl	Iso propyl myristate	Tween- 85	ethanol	Water	Permeability enhancement
Minoxidil	Iso propyl myristate	Lecithin E- 80	-	Water	Permeability enhancement
5-Aminolaevulinic acid	Soya bean oil	Span 80	α - terpinol	water	Permeability enhancement
Inulin	Olive oil	Tween 80	-	Water	Permeability enhancement

Stability issues in Nanoemulsions

Droplet agglomeration

Destabilization of nanoemulsion is usually caused by droplet agglomeration, which causes globule size increase, meaning that all the unique characteristics assigned to the nanoscale have been lost. Higher aggregation will eventually result in phase segregation that causes permanent damage. Scientific tactic to energetic driving aggregation has been drawn to classical Newtonian mechanics.[58] The Van der Waals force, electrostatic, hydrophobic and steric interactions between the globules in oil Phase are also key considerations for fabricating NE's since it also causes a stability issue.

Ostwald Ripening

Ostwald ripening is phenomenon of growth of droplets eventually leads to increase in the density of oil globules causes separation of phases. But this issue will occur during storage due to less Brownian motion so it can assess periodically like zeta potential guides stability of NE's. Higher the potential value greater the stability.[59] Ostwald ripening can be tackled by selecting an oil which has low solubility in aqueous phase or adding some waxy substances to oil mix by increasing temperature while fabricating but practically it is not possible due to size reduction of globule much more difficult.[60] Nam *et al* shown that oil in water nanoemulsions will be stabilized by using amphiphilic surfactant with copolymers which is soluble in oil phase at high temperature but it will completely coated over the globules when it came to ambient conditions thus it will maintain the interfacial tension constantly in the ultra-negative range and reduce the growth of droplets thereby it prevents Ostwald ripening.[61]

Coalescence

Another element that causes stability issue in nanoemulsion is the droplet coalescence. And this problem is also existed in conventional emulsions leads to sedimentation at bottom, but it is a reversible by gentle shaking along with coalescence Ostwald ripening will intensify the globule growth give rise to separation of phases and it is irreversible. The problem is tackled selecting a surfactant which is more hydrophilic due to hydrated layer is formed around interface.

Nanoemulsions in topical drug delivery

El-Leithy E S *et al*., they worked on the coenzyme Q10 (CoQ10) for improving the solubility and permeability through topical application for anti-aging and anti-wrinkle effect by formulating the nanoemulsions of CoQ10 with minimum concentration of surfactants through constructing the pseudoternary diagrams and characterization of formulation by pH, viscosity measurement, thermodynamic stability studies, TEM, Droplet distribution analysis, *ex-vivo* skin permeation study with permeability coefficient (Kp = 22.14 x 10^{-4} cm^{-2}/h) and carryout *in vivo* anti wrinkle activity on rat model also estimate the amount of coenzyme Q10 was retained In the skin thus enzyme Q10 enhancement the permeability and bioavailability through formulating as nanoemulsion for treating skin aging.[62]

Rachmawati H *et al*., Curcumin nanoemulsions were developed using a self-nanoemulsifying method using an oil phase of glyceryl monooleate, Cremophor RH40 and polyethylene glycol 400 with the mean particle size of droplet, poly dispersity index and zeta potential of 85 ± 1.5 nm, 0.18 ± 0.0 and -5.9 ± 0.3 mV. *Ex-Vivo* skin permeation study was carried out in shed snake of *P. reticulatus* because a very close resembles human skin that to thickness of stratum corneum is very near approximate to shed snake skin. Compatibility of ingredients with curcumin was carried out by Raman spectroscopy, TEM image of nanoemulsion reveal the morphology. Later curcumin nanoemulsion was incorporated in Viscolam T hydrophilic matrix gel. Showed enhanced transdermal availability with high permeability and without degradation and aimed to treat anti inflammation because hydroxyl phenol in curcumin showed anti-inflammatory property hence the nanoemulsion gel is promising transdermal delivery for treatment of analgesia and anti-inflammation.[63]

Duraivel S *et al*. is developed *Moringa oleifera* cream and nanoemulsion because the seed oil is rich in antioxidants that might prevent the oxidative damage of the skin for its anti-aging benefits. By using the *Moringa* seed oil in various ratios, cream and nano emulsion were prepared by ultrasonication with 80% amplitude later stirred using a mechanical stirrer at 16,000 rpm and they are characterised for its physical properties. That the *Moringa oleifera* oil nanoemulsions showed better protective effect compared to conventional emulsion of *Moringa oleifera* and showed an enhancement in the anti- wrinkle efficacy.[64]

Ribeiro R C *et al*. is worked on production and characterization of cosmetic nanoemulsions containing *Opuntia ficus indica* (L) mil extract. NE fabricated by heating the components of oil phase and aqueous phase separately at 75°C then adding an aqueous phase to oil phase homogenising at 11,000 rpm then cooled extracts *Opuntia ficus indica* (L) was added further stirred for 2 min in a mechanical stirrer. Nanoemulsions were characterized by conducting thermodynamic stability studies, Droplet distribution analysis. And the lyophilized extract powder has no occlusive property but it can reduce TEWL Level and anti-aging activity was performed on human volunteers thus confirmed that nanoemulsions can be new vehicle for delivering the herbal or poly herbal drugs to manifestation of many skin disorders.[65]

Hussain A *et al*., They investigated to reduce the side effects of amphotericin B by adopting an alternative route of administration i.e. transdermal drug delivery through nanoscale formulation to show better therapeutic action for systemic fungal infections and they found sustained release of drug compare to conventional drug delivery hence cutaneous absorption of amphotericin B can reduce the side effects like nephrotoxicity.[66]

Nanoemulsions in intranasal drug delivery

Sood S *et al*., They applied design of experiment (DoE) to develop curcumin loaded mucoadhesive nanoemulsions. By constructing a Box–Behnken diagram considering independent variables as concentration of oil phase and surfactant and co-surfactant and dependent variables or responses like globule size and zeta potential. Chitosan is used as mucoadhesive agent and Concentration of oil and surfactant was found to be very critical to give desired globule size whereas addition of chitosan was found to significantly affect zeta potential of developed nanoemulsions. Assessment of nanoemulsions for intranasal activity by carrying out cytotoxicity studies, nasal ciliotoxicity studies, *ex vivo* diffusion studies and they reported highest flux in ship mucosa hence curcumin nanoemulsion can be effectively used in the management of chronic sinusitis. Intra Nasal Nanoemulsions are the potential vehicles for targeting drug to Brain.[67]

Choudhury H *et al*. is developed an intranasal emulsion to targeting the drug to brain by 1% chitosan is used mucoadhesive agent and rotigotine have very low systemic availability due rapid metabolism. Aqueous phase titration was used to fabricating the NE's of having droplet size less than 200 nm and assessed the

NE's with parameters like physico-chemical property, Thermodynamic stability, mucoadhesive strength and *ex-vivo* permeation showed that rotigotine nanoemulsions are substantiate to deliver the drug to brain effectively and in the management of Parkinson's disease there by nanoemulsions are the potential vehicles for the targeted drug delivery.[68]

E. Di Cola, *et al*., fabricated a different nanoemulsions like Vitamin E TPGS, PEG-12 15 hydroxy stearates, as vectors to deliver the drugs through transmucosal route and these nanoemulsion consisting PEGylated surfactants and chitosan and assessed nanoemulsions by scattering techniques like e. dynamic light scattering (DLS), small angle X-ray (SAXS) and neutron scattering (SANS). Thus fabricated nanoemulsions are the potential vehicles for the intranasal drug delivery to target the brain and helps in the management of diseases associated with CNS.[69]

CONCLUSION

This review unwraps the fabrication methods for nanoemulsions with their composition and formulation criteria's there by nanoemulsion is very potential vehicle for delivering the drugs to the site of action with enhancement of bioavailability and patient compliance by without considering the drug lipophilicity and hydrophilicity. Nanoemulsions fabricated by low energy emulsification are stable than the high energy emulsification however nanoemulsions are striving hard to reach in mainstream of market but problems like production cost, stability issues, personnel skill and toxic levels of solvents used in formulations need to be overcome hence still research work on *in vivo* studies need to be conducted to make nanoemulsion fruitful to the patients suffering from many disorders.

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