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NANOEMULSION: A SNAPSHOT ON DEVELOPMENT, CHARACTERIZATION, APPLICATIONS, PATENTS AND CLINICAL TRIALS

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ABSTRACT: Nanoemulsionis a special case of emulsion. It is nano-sized emulsion used as a carrier. It has the ability to deliver the drug to the target site. It is a good vehicle for the controlled delivery of the drug. It is prepared by the high energy and low energy emulsification method. Emulsifier plays an important role in stabilizing the nanoemulsion. It is anisotropic and thermo-dynamically stable system of oil, water and surfactant-co-surfactant (S_{mix}) in an appropriate proportion. Nano-emulsion has a droplet size in between 20-200 nm. NE has the ability to encapsulate both the lipophilic and hydrophilic drug in o/w and w/o systems, respectively. Hence, improved solubility, as well as enhanced bio-availability of the drug, can be achieved through nanoemulsion. For stabilizing o/w and w/o type NE, both hydrophilic and lipophilic surfactants are used at once. The present review article is highlighted on various aspects of formulation-development, patents, and clinical trials of NE and its wider application to the different area.

INTRODUCTION: Emulsions are biphasic liquid dosage forms in which one phase is dispersed into another phase with the help of an emulsifying agent. The globule size of the emulsion ranges between 0.1 to 100 µm and having an opalescent appearance. The emulsion is thermodynamically unstable, in which oil and water phase back to separate in due course of time [1-3]. In the case of a special class of emulsion, nanoemulsion (NE) that appears translucent in colour due to their individual size and controlled stability against sedimentation or creaming and having tiny droplet size (o/w and w/o) of 20-200 nm that may vary based on the components and method of preparation used. It contains oil, water, and S_{mix}.

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Emulsifier (surfactant and cosurfactant: S_{mix}) plays an important role in stabilizing nanoemulsion. NE is a thermodynamically, kinetically stable, and isotropic system [4-6]. The structure has represented in **Fig. 1**. Nanoemulsion is a novel drug delivery system (NDDS) that has emerged as a powerful strategy to deliver drugs to the body.

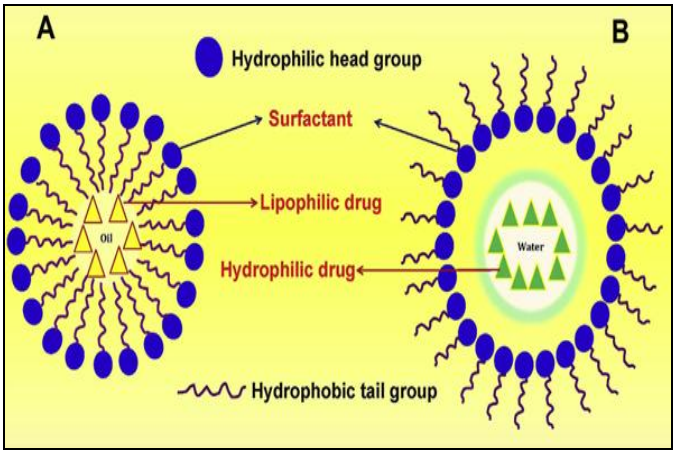

FIG. 1: STRUCTURE OF NANOEMULSION (A) OIL IN WATER TYPE EMULSION (O/W) AND (B) WATER IN OIL TYPE OF EMULSION (W/O). (IMAGE REPRODUCED WITH PERMISSION FROM HARWANSH *ET AL.*, 2019)

NDDS has the capacity to target drug molecules at the specific site of the body and also has the potential to maintain a desire concentration over treatment time under therapeutic index [7, 8]. NE, when taken orally, get dispersed into fine droplets by self-nano emulsification in the gastric environment with GI motility. NE can encapsulate the drug molecule either in oil or in the water phase and thus improve the drug profile such as solubility, permeability, stability, and bioavailability [9-13].

This property contributes to the use of NE in the pharmaceuticals, nutraceutical, and cosmetic industries for improved health. In addition, several plant-based bioactive and extract such as curcumin, neem oil, barbarian, citronella oil *etc*., had been delivered with NE as a carrier system [14-17]. Chaudhary *et al.*, 2014 reported that there was an enhanced oral bioavailability of paclitaxel with NE due to its nanosized droplet as compared to pure [18]. The various applications of NE have been represented in **Fig. 2**.

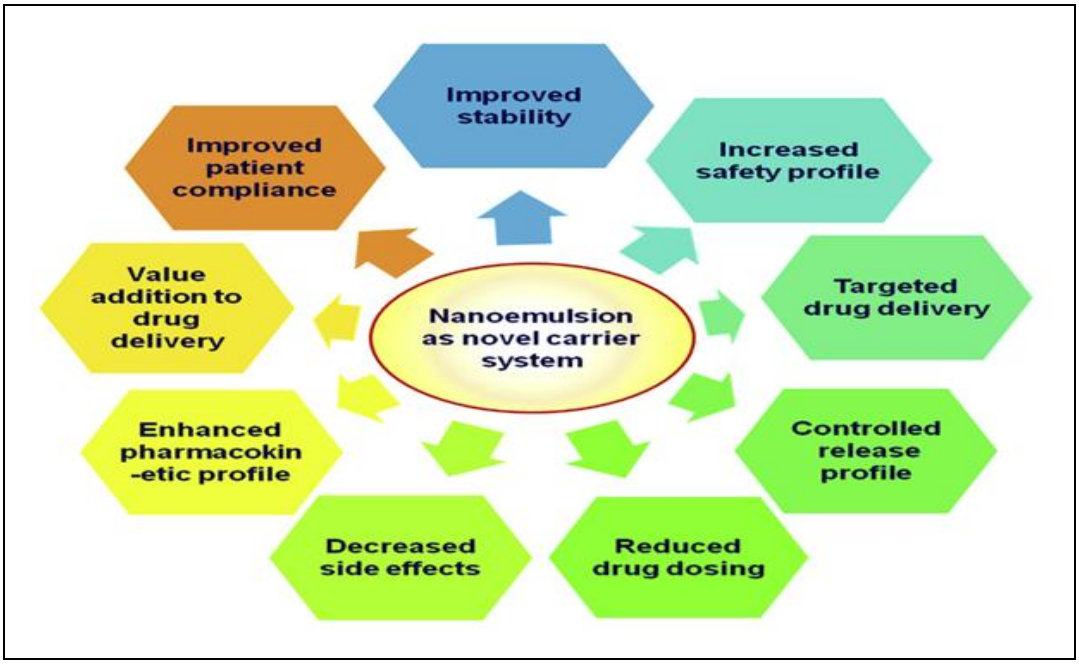

FIG. 2: THE VARIOUS ADVANTAGES OFFER BY NANOEMULSION. (IMAGE REPRODUCED WITH PERMISSION FROM HARWANSH *ET AL.*, 2019)

NE can be simply assembled through the stirring of oil, $S_{mix,}$ and water employing either low or high energy levels of emulsification methods. NE increases the solubility of poorly soluble and solves low bioavailability problems, therefore consider as a promising novel carrier for delivery of drugs in an effective manner. The present review focused on the formulation, characterization, and applications of NE [19].

Formulation Aspects of Nanoemulsion: It can be formulated by blending oil, water, and S_{mix} in the right portion. Surfactant (polysorbate 20, polysorbate 80 *etc.*), cosurfactant (ethyl alcohol, glycerol, poloxamer, polyene glycol, polyethylene glycol 300 (PEG 300) and PEG 400 *etc.*), tonicity modifiers (glycerine, glucitol, xilitol), emulgent (polysorbates, egg yolk, castor oil, sterylamine, natural lecithins), additives (ethyl alcohol, 1, 2-dihydroxypropane,1,3-butylene glycol sugars like-butylene glycol, sucrose), antioxidants (ascorbic acid, tocopherol), oils (captex-200, captex- 8000, witpsol, myritol-318, isopropyl myristate, coconut oil, corn oil, linseed oil, mineral oil, jojoba oil, sunflower oil *etc.*) are used for the development of NE. Penetration enhancers such as isopropyl myristate, limonene, oleic acid, capryol 90, tween 80, poloxamer 124 and 188, PEG MW>400, gelucire 44/14, 50/13, softigen 701, 767, cremophore RH 40etc are also used in the NE formulation development [20-22].

There are various types of formulations, such as foams, creams, liquids, and sprays. Drug solubility studyaids to select the best oil and surfactant for the success of the NE. Some examples of marketed NE were given in **Table** 1.

TABLE 1: EXAMPLES OF MARKETED NANOEMULSION

Drug	Indication	Trade name	Company
Alprostadil palmitate	Vasodilator, platelet inhibitor	Liple	Mitsubishi Pharmaceutical
Vitamins A,D,E,K	Parenteral nutrition	Vitalipid	Fresenius Kabi
Propofol	Anesthetic	Diprivan	Astra Zeneca
Flubiprofenaxetil	NSAID	Ropion	Kaken Pharmaceutical
Dexamethasone palmitate	Steroid	Limethason	Mitsubishi Pharmaceutical

High Energy Emulsification: NE is the imbalance system that cannot be formed automatically that's why it needs a mechanical force to form them. It was generally prepared by high-energy methods.

The various method employing high energy includes ultrasonication, high-pressure homo-genization, high-shear stirring and micro fluidization [23].

A. Ultrasonication: It is one of the high-energy methods that generate ultrasonic waves. Highly intensive ultrasound gives the power required to disperse a liquid phase (dispersed phase) in small droplets in the continuous phase.

It also supplies the formation and slump of tiny bubbles one by one because of the pressure variation of a sole sound wave. In this, the probe emits ultrasonic waves (20 kHz) [24, 25].

B. Gaulin Homogenizers: This is also the best technique for the development of NE. It also provides high pressure. In this method, the NE is vigor to pass through in a tiny orifice with a pressure of 500 to 5000 psi resulting in very little droplet-sized NE.

The stability of droplet size in NE is specified by PDI. Higher PDI means less stability of droplet size in NE [26, 27].

C. Micro Fluidization: This method is used for mixing, and it also provides high pressure to form NE. It uses a reciprocating positive displacement pump (500 to 20000 psi). These pumps provide a force to pass the product, which consists of mini-channels, and products pass by these channels, resulting in extremely fine particles [28, 29].

D. High-shear Stirring: This method was also used to achieve uniformity and very little droplet-sized NE. This method is extremely efficient for the fabrication of NE. This method has various advantages like-rapid, cheap, and applied for extensive production [30].

Low Energy Emulsification: NE can also be achieved by this method which also generates small and uniform droplets. In this small droplet under phase, inversion system are formed in low interfacial tension, and it requires less energy density. This method includes phase inversion technique, solvent diffusion technique, phase separation composition technique [31].

A. Phase Inversion Temperature: It is 2 types-transitional inversion and catastrophic inversion. In a transitional inversion, changing of the surfactant distribution over the phases occurred. It affects the hydrophilic-lipophilic balance. Catastrophic shows the variation of the viscosity and increases the volume fraction of the dispersed phase. In this method, the temperature is a major factor for developing o/w or w/o type NEs. When non-ionic surfactants are mixed with oil and aqueous phase at a certain concentration, it produced o/w type NE but upon heating, this o/w type emulsion can be converted into the w/o type emulsion [32].

B. Solvent Evaporation: In this method, evaporation of the solvent takes place, and it is performed at low or at atmospheric pressure. Distillation, open-dish evaporation, rotatory evaporators are used to remove the solvent from the solution. It is the most effective method and widely used in the pharmaceutical industry. In this solution, of a drug is developed and emulsified into another liquid (non-solvent of a drug). After the solvent evaporates drug gets precipitated in this drug solution mixable with anti-solvent drug [33, 34].

C. Phase Inversion Composition: In this procedure, dispersion takes place. At the high temperature, the size of the droplets of the emulsion decreases, and the formation of NE take place. In this technique, highly stable nanoemulsion are produced. This process leads to the development of an extremely finely dispersed droplet in a continuous phase. It can be induced by changing the number of the HLB scale of the

surfactant at a constant temperature using the mixture of surfactant [35, 36].

Characterization of Nanoemulsion:

Morphology: The morphological characteristics of the nanoemulsion can done by the use of Transmission electron microscopy (TEM) and scanning electron microscopy (SEM). The liquid nature of nanoemulsion makes TEM a more useful tool for studying morphological characteristics. The samples are prepared by negative staining with phosphotungstic acid (1%) or uranyl acetate (2 %) over the copper grid and imaging with TEM at a suitable voltage. In addition, the structure and behaviour of the nanoemulsion can be elucidated with sophisticated techniques like cryo-electron microscopy, x-ray, neutron scattering, and atomic force microscopy [37, 38].

Particle Size and Polydispersity Index (PDI): The quality, stability, uniformity, and dispersibility of nanoemulsion can be assessed by the measurement of its, mean particle diameter (Z-averages), Particle size distribution and poly-dispersity index (PDI).

The photon correlation spectroscopy (PCS) is employed to analyze the particle size and PDI of nanoemulsion. The instrument employed is Malvern Zetasizer. The instrument monitors the scattering of light due to the Brownian motion of globules as a function of time. PCS gives z-average particle diameter. The value of PDI ranges from 0 to 1, 0 indicating a monodisperse system and 1 represents polydisperse particle dispersion [39].

Zeta Potential: The surface charge on the emulsion globules can be measured as a function of zeta potential with the help of a zeta sizer. It represents the electrical properties of the nanoemulsion.

The samples are paced in a zeta cuvette and the charge is measured in terms of mV which can have a negative or positive value. If the value is from -5 mV to5 mV then the emulsion indicates fast aggregation, -20 mV to 20 mV indicates short-term stable emulsion, and a reading of -30 mV to 30 mV or more represents the stable emulsions [40, 41].

Viscosity and Conductivity: The information of the nanoemulsion at the macroscopic level is given by viscosity and conductivity. The measurement of viscosity indicates the presence of rod or worm-like micelles, while the conductivity measurements detect oil-continuous or water continuous phase in the nanoemulsion [42].

Stability and pH Analysis: Stability is an important aspect of the nanoemulsion. The stability can be assured by visualization with the naked eye for the occurrence of the sign of instability like cracking, creaming, coalescences and sedimentation. Similarly, pH is also a key characteristic as dermatological preparations are applied to the skin. The pH of the nanoemulsion can be measured with the help of a pH meter or pH pens [43].

Applications of Nanoemulsion:

Application in Cosmetics: Nanoemulsion is used as a carrier, so they deliver the drug to the targeted site, so it is a good vehicle for prolonged release of cosmetics. Nanoemulsion is acceptable for the transport of hydrophobic drugs. They enhance the concentration in the skin.

In the case of nanoemulsion there are no possibilities of creaming, sedimentation, flocculation or coalescence because of its acceptability in cosmetics. But this is mostly observed in the case of micro-emulsions. They also reduce the transepidermal water loss [44-46].

Nanoemulsion in Vaccine Delivery: Nano-techniques like nanoemulsion are being utilized for the delivery of vaccines against viral infections like human immunodeficiency virus (HIV). It causes acquired immune deficiency syndrome and interferes with the body's ability (immune system) to fight against infection. These viruses may also infect the mucosal immune system. The viruses can be transferred by contact with infected blood, semen or vaginal fluid. HIV can contaminate a mucosal immune system.

So, nanoemulsion is extremely essential in the upcoming fight against HIV. Nanoemulsion is used to transport the recombinant protein or inactivated organism to a mucosal surface to generate an immune response. It can be administered through the intranasal route. An influenza vaccine and Human immunodeficiency virus vaccine can move forward to clinical trial [47, 48].

Anti-microbial Nanoemulsion: Nanoemulsion has all round action in opposite to bacteria (*Escherichia coli*, salmonellosis, *Staphylococcus aureus*), wrapped viruses (HIV, Herpes labialis), Fungi (candidiasis, tinea) and spores (anthrax). The antimicrobial nanoemulsion are o/w globules that range from (200-600 nm) and made of oil and H_2O and stabilized by alcohol & surfactants [15].

Nanoemulsion as Non-toxic Disinfectant Cleaner: Disinfectant cleaner is an o/w type NE, prepared with the help of certain ingredients, parachlorometaaxylenol. There is no requirement of a warning label for this product as it does not irritate the eyes.

It is non-ionic, non-acidic, and non-oxidizing in nature. This cleaner can be applied to any hard surface like walls, equipment, floors, hospital, healthcare, travel, food processing, *etc.* It is environmentally safe in use.

Nanoemulsion in Cell Culture: Nanoemulsion has been employed in cell culture techniques for delivering poorly soluble drugs (hydrophobic substance) into cells. Nanoemulsion globules (o/w) are easily taken up by the cells.

This technology is used for *in-vitro* assays or to generate organic compounds like recombinant proteins. It is favorable for lipophilic components. By this technique, better uptake of oil-soluble additives can be increased in cell cultures which improves the growth of cells [49].

Nanoemulsion against Pathogens: Medicated nanoemulsion are used as a prophylactic treatment approach to protect people from epidemic pathogens such as Ebola, hepatitis, anthrax, gangrene, and Clostridium botulism spores. It is also used on infective wounds [50].

Nanoemulsion as a Transdermal Drug Delivery System (TDDS): The poorly soluble compound can be delivered into the skin through nanoemulsion. In TDDS the drug is distributed from the dermis and reaches systematic circulation.

NE can transport the drug into the bloodstream by diffusing via different layers of skin through the pore, sweat ducts, hair follicle, and stratum corneum. By the use of this vehicle in TDDS drugs, bio-availability increases and enhances the therapeutic efficacy [51].

Nanoemulsion as a Vehicle for Ocular Delivery: Poor bioavailability of drugs from the ocular dosage form is mainly due to tear production. With the tear, there is a loss of drugs.

So, in this case, nanoemulsion is one of the best drug delivery carriers and increases the residence time. There is a various ophthalmic vehicle like suspensions, ointments, gels, *etc.* which increases the residence time and give the effective result [52, 53].

In Chemotherapy and in Targeted Drug Delivery: Nano-emulsion is used as a medium which is very effective and increases the rate of drug release after intramuscular and intra-union injection of w/o system. Magnetic nanoemulsion is a new or innovative approach for cancer therapy, which may be due to nano-sized, effortlessly targeted to the target site.

Gene Delivery Vector: NE is an effective carrier for gene transfer rather than liposomes. Emulsion systems arise to be an alternative gene transfer vector to liposomes.

This system is more suitable than the liposomes have shown the strongest binding of the DNA complex/emulsion than liposomal [54].

Topical Delivery: Nanoemulsion is a good vehicle and has broad-spectrum activity against bacteria. Topical delivery has 2 advantages, first-avoidance of first-pass metabolism and second-target ability of the drug to the affected area of the skin or eyes. For example, acne problem in which sebum oil production increases that cause acne on the skin.

The oil phase in the nanoemulsion can enhance the permeation of active ingredients due to its hydrophobic nature. Nanoemulsion is used in the treatment of acne.

Because of the small droplet size of the NE, transportation of the drug can be easily through hair follicles. Thus, NE can act as a penetration enhancer as well [51, 55]. Different applications of nanoemulsion were depicted in **Table 2.**

TABLE 2: NANOEMULSION AS A NOVEL VEHICLE FOR DRUG DELIVERY

Drugs	Category	Route	Characterization	Excipients	Biological properties	Conclusion	References
Eplerenone	Mineral corticoid receptor antagonist	Oral	Drug content-96.12% to 100.15%, Carr's index-16.02-19.37%, angle of repose-27.61%-32.41%, Zeta potential-25.2-35.7 mv	Cellulose Starch Lactose Silicon powder	After oral administration and reach to the dissolution, EPL is rapidly absorbed from the GIT and achieve maximum plasma concentration within 1.5-2h. It is extensively metabolized in the liver (less than 5% of a dose is excreted in urine). The hepatic first-pass metabolism of the EPL is 12.6% & 27.1%.	EPL-NE liquisolid mixture is a promising dosage form and compression characteristics that increase the release rate, drug absorption and allows the drug to escape liver degradation, with an increase in bioavailability.	Khamer Ahmed, *et.al* [19]
Tenoxicam	Anti-inflammatory	Topical	Zeta potential-13.6±5-31.6±5, Drug content-98.95-99.91%, droplet size-33.5-58.29nm	Ethyl oleate, carbopol 970, tween 80, trietanolamine, propylene glycol.	It is an anti-inflammatory agent with analgesic and antipyretic properties and control acute pain. It inhibits the prostaglandin synthesis.	Out of 6 formulations, F2 formulation which having a better drug release due to the smallest droplet size and of the oil globules.	Sharma P, *et al* [56]
Nabumetone	Nonsteroidal anti-inflammatory	Topical	Ex-vivo drug release-86.32%, In-vitro-84.35%	Tween 80, PEG 600	An NSAID that decreases prostaglandin synthesis.	The drug was incorporated in castor oil with tween80 and PEG 600 to form good Nanoemulsion by homogenization method.	Chaudhari PM *et al.*[57]
Itraconazole	Antifungal	Oral	Drug content-28.23-40.83, *in-vitro*-85.71-84.15%	Capryol 90	Antifungal agent.NE itraconazole that leads to higher dissolution rate and improved bioavailability.	Itraconazol Nanoemulsion was prepared by solvent displacement method which increases dissolution rate and improved bioavailability.	Suyal J, *et al.*[58]
Propranolol	Antihypertensive & antiarrhythmic	Topical	PDI<0.4, ZP-(-20mv)	Ethanol	Antihypertensive &antiarrhythmic, it gives good stability after encapsulation in Nanoemulsion's.	PPN was successfully encapsulated in NE'S & provides good stability for PPN.	da Silva Marques TZ *et al.* [59]
Febuxostat	Xanthine oxidase inhibitor	Oral	FTIR-4000-400cm^{-1}, Melting point-238-239 °C, ZP-(-29.1v), Drug content-100%	Tween 80, Span 80, isopropyl myristate	Poorly soluble and highly permeable.	Febuxostat NE for solubility enhancement was successfully prepared by high speed homogenization.	Kanke PK, *et al.* [60]

Patented Nanoemulsions: Apart from various research and patents on nanoemulsion, a few products are available commercially based on nanoemulsion. It may be due to challenges of commercial scale production, although some of them have been transferred at industrial scale and available commercially. Some important patents related to nanoemulsion are given in Table 3.

TABLE 3: SOME PATENTS ON NANOEMULSION FOR PHARMACEUTICAL APPLICATIONS [61]

Title	Applicant	Publication number with date
Cosmetic composition containing retinol stabilized by porous polymer beads and nanoemulsion	Act Co Ltd	US 20130095157A1 (18-04-2013)
Cosmetic pigment composition containing gold or silver nanoparticles	Korea Research Institute of Bioscience and Biotechnology	US 20090022765A1 (22-01-2009)
Nanoemulsion and cosmetic product compounded there with	Ands Corporation	JP 2008127327A (05-06-2008)
Aqueous photoprotective compositions comprising hydrophilic metal oxide nano pigments and a vinylpyrrolidone homopolymer	L'Oreal SA	EP1768749B1 (15-10-2008)
Skin whitening methods and compositions based on zeolite–active oxygen donor complexes	BIODERM Research	US20070166339A1 (19-07-2007)
Healthy collagen cosmetic	Iwamoto Shigemi	JP 2005206567A (04-08-2005)
Zeolite based UV absorbing and sunscreen compositions	Gupta Shyam K	US20050276761A1 (15-12-2005)
Nanoemulsion comprising metabolites of ginseng saponin and a skincare composition for anti-aging containing the same	Pacific Corp	EP 1327434A1 (16-07-2003)

Clinical Trial of Nanoemulsions: The national institutes of health (NIH), U.S. (https://www.cancer.gov/) provides most clinical trials of the drugs. A detail of the clinical trial of the nanoemulsion formulation has been given in **Table 4**.

TABLE 4: NANOEMULSION BASED CLINICAL TRIALS FOR VARIOUS PHARMACEUTICAL APPLICATIONS (HTTPS://CLINICALTRIALS.GOV/)

S. no.	Tile of trial	Status	Conditions	Interventions	Phase	NCT number
1	Photodynamic therapy for lentigo maligna using 5-aminolevulinic acid nanoemulsion as a light sensitizing cream	Completed	*Lentigo maligna*	5-Aminolevulinic acid nanoemulsion	Phase IV	NCT02685592
2	Clobetasol propionate ophthalmic nanoemulsion 0.05% for the treatment of inflammation and pain associated with cataract surgery (CLOSE-1)	Not yet recruiting	Cataract	Drug: Clobetasol propionate Drug: Vehicle	Phase III	NCT04246801
3	Clobetasol propionate ophthalmic nanoemulsion 0.05% for the treatment of inflammation and pain associated with cataract surgery (CLOSE-2)	Not yet recruiting	Cataract	Drug: Clobetasol propionate Drug: Vehicle	Phase III	NCT04249076
4	Transdermal testosterone nanoemulsion in women libido	Unknown	Menopause	Drug: Testosterone Drug: Placebo	Phase II	NCT02445716
5	Proof-of concept study of topical 3%-diclofenac-nano-emulsion cream for knee OA Pain	Completed	Osteoarthritis of the knee	Drug: 3%-Diclofenac-nano-emulsion cream Drug: Placebo cream	Phase II	NCT00484120
6	Study of brimonidine tartrate nanoemulsion eye drop solution in the treatment of dry eye disease (DED)	Recruiting	Dry eye	Drug: Brimonidine tartrate Drug: Placebos	Phase III	NCT03785340
7	Study of brimonidine tartrate nanoemulsion eye drops in patients with ocular graft-vs-host disease (oGVHD)	Recruiting	Graft versus host disease Ocular surface disease oGVHD	Drug: Brimonidine tartrate Drug: Placebos	Phase III	NCT03591874
8	Use of lipid emulsion or nanoemulsion of propofol on children undergoing ambulatory invasive procedures	Withdrawn	Leukemia	Drug: Propofol	Phase II Phase III	NCT01326078
9	Effect of methotrexate carried by a lipid nanoemulsion on left ventricular remodelling after	Recruiting	Myocardial infarction, anterior wall Myocardial	Drug: Methotrexate Drug: Placebo Drug: Folic Acid	Phase II Phase III	NCT03516903

	STEMI		remodelling, ventricular			
10	Superficial basal cell cancer's photodynamic therapy: comparing three photosensitizers: HAL and BF-200 ALA Versus MAL	Active, not recruiting	Neoplasms, basal cell Carcinoma, basal cell Photochemotherapy Photosensitizing agents	Drug: Hexylamino levulinate (HAL) cream Drug: Aminolaevulinic (ALA) Acid Nano Emulsion Drug: Methylamino levulinate (MAL) cream	Phase I Phase II	NCT02367547
11	Pilot study of curcumin for women with obesity and high risk for breast cancer	Completed	Atypical ductal breast hyperplasia BRCA1 gene mutation BRCA2 gene mutation	Dietary supplement: Curcumin Other: Biomarker analysis, assessment of dietary intake and daily log	Not applicable	NCT01975363
12	A safety and immunogenicity of intranasal nanoemulsion adjuvanted recombinant anthrax vaccine in healthy adults	Recruiting	Anthrax	Biological: BW-1010: 50 µg - sprayer - IN Biological: BW-1010: 50 µg - pipette - IN Biological: BW-1010: 100 µg - sprayer - IN	Phase I	NCT04148118
13	Cholesterol metabolism and lipid transfer in diabetes	Completed	Type 2 diabetes mellitus	Plasma kinetic study	-	NCT01010035
14	Curcumin in reducing joint pain in breast cancer survivors with aromatase inhibitor-induced joint disease	Recruiting	Breast cancer joint pain	Dietary supplement: Curcumin Other: Placebo Other: Nanoemulsion Other: Quality-of-life assessment Behavioural: Questionnaire	Not applicable	NCT03865992
15	Clinical assessment of voriconazole self-nano emulsifying drug delivery system intermediate gel	Completed	Tinea versicolor	Drug: Voriconazole gel once daily Drug: Voriconazole gel twice daily Drug: Placebo	Phase II	NCT04110860
16	Clinical assessment of itraconazole self-nanoemulsifying drug delivery system intermediate gel	Completed	Tinea versicolor	Drug: Itraconazole gel once daily Drug: Itraconazole gel twice daily Drug: Placebo	Phase II	NCT04110834
17	Low density lipoprotein (LDL) cholesterol metabolism in impaired glucose tolerance	Completed	Impaired glucose tolerance	Other: Plasma kinetic study	-	NCT01020578
18	Daylight-PDT for AKs: comparing two photosensitizers (BF-200 ALA and MAL)	Completed	Multiple actinic keratoses	Drug: BF-200 ALA cream Drug: MAL cream	Phase IV	NCT01893203
19	Evaluation of safety and efficacy of BF-200 ALA for the treatment of actinic keratosis with photodynamic therapy	Completed	Actinic keratosis	Drug: BF-200 ALA Drug: MAL Cream Drug: Vehicle	Phase III	NCT02799069
20	Study of efficacy and tolerability of SYSTANE complete in patients with dry eye disease	Completed	Dry eye disease	Other: Propylene glycol-based eye drops	Not applicable	NCT03492541
21	NB-001 treatment of recurrent *Herpes labialis*	Unknown	*Herpes labialis*	Drug: NB-001 (0.3%) Drug: Placebo	Phase III	NCT01695187
22	Efficacy and safety study of tjcs for treatment of moderate to severe dry eye syndromes	Completed	Dry eye syndromes	Drug: CYPORIN N EYE DROPS 0.05% (TJCS eye drop) Drug: Restasis	Phase III	NCT02461719
23	Safety and efficacy study for the field-directed treatment of actinic keratosis (AK) with photodynamic therapy (PDT)	Completed	Actinic keratosis	Drug: BF-200 ALA gel Drug: Placebo to BF-200 ALA gel Procedure: Photodynamic therapy with BF-RhodoLED	Phase III	NCT01966120
24	Pharmacokinetic study on three formulations of coenzyme Q10 with different carriers	Recruiting	Healthy	Dietary supplement: MaxSimil® fish oil + CoQ10 Dietary supplement: Rice bran oil + CoQ10 Dietary supplement: CoQ10 as powder form	Not applicable	NCT04035525

25	Evolution of albumin on AOA1 patients supplemented with coenzyme Q10	Completed	Ataxia-oculomotor Apraxia 1	Dietary supplement: CoQ10 Other: Sanomit Placebo	Phase III	NCT02333305

Major Challenges of Nanoemulsion as a Drug Delivery System: While this system has great merits of a delivery system, yet they tolerate some major challenges, which include:

- The formulation which is used for nanoemulsion is extremely expensive like; in case of size reduction, we need some special apparatus and procedures. Such as homogenizer (uniformizer). Besides this, ultrasonication and micro fluidization need a large amount of financial support.
- A large concentration of the surfactant requires.
- The biggest problem related to nanoemulsion is its stability.
- Nanoemulsion stability is affected by environmental factors like temperature and pH.

CONCLUSION: Nanoemulsion is the best delivery system in comparison to microemulsion. The major issue with drugs is poor solubility, bioavailability, and stability problem. The therapeutic efficacy of drugs depends on the effective level of the delivery system. Hence, nanoemulsion is a novel drug delivery system, having the capability to increase the drug solubility by uptake in o/w or w/o core. It can enhance the absorption of drug molecules through biological membranes if it is delivered through oral (GIT) and topical (skin) route or others. NE can enhance patient compliance through minimizes of dose-related side effects of drugs and their dosing frequency. It is widely used in the pharmaceutical system. It has various advantages for the delivery of drugs, biological as well as diagnostic purposes.

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