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NANOEMULSIONS: A VERSATILE DRUG DELIVERY TOOL

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ABSTRACT: Since last decade, the interdisciplinary research of Nanoemulsions (NEs) have gained great attention in research and drug designing owing to their promising range of applications in the field of pharmaceutics, drug delivery through different route, cosmetics, to name a few. In addition to the small droplet size these non-equilibrium liquid systems have interesting properties including optical clarity, preparatory ease, thermodynamic stability, high bioavailability, resistant to creaming, flocculation, coalescence and sedimentation, low viscosity and increased surface area, among others. Due to these peculiar properties, NEs have become an authentic tool in the drug delivery system. This article pertains to the types of NEs, characterization techniques, different methods of preparation of stable NEs with special emphasis on the various routes by which drug formulated NEs can be administered. Recent advancements of the fascinating applications of NEs in the delivery of the usually hydrophobic drugs and other bio actives/biotechnology, pharmaceutical ingredients are highlighted.

INTRODUCTION: Emulsions (**Fig. 1**) are liquid dispersion in which one fluid (oil) is dispersed in another (water) with which it is immiscible. The emulsions are stabilized by the addition of an appropriate surfactant and co-surfactant [1]. NEs (**Fig. 2**) are kinetically stable, optically clear liquid dispersion of an aqueous phase and an oily phase, blended with a surfactant or co surfactant. The dispersed phase consistently contains small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because of the small droplet size, NEs are transparent [1-2].

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NEs are also known as miniemulsions, sub micrometer emulsions or ultrafine emulsions, [3-5], translucent and milky emulsion [6]. The primary difference between emulsions and NEs is related to the shape and size of the particles of the dispersed phase: droplets are at least an order of magnitude smaller in the case of NEs(10-200 nm) than those of emulsions (1-20 μm)[1].

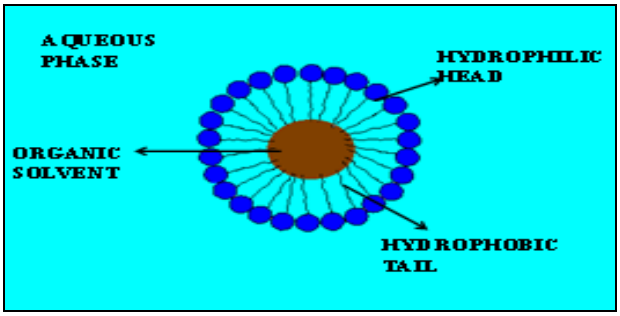

FIG. 1: EMULSION

Secondary difference pertains to their stability and appearance; emulsions are cloudy and unstable, can

undergo creaming or sedimentation, Ostwald ripening, flocculation and coalescence while NEs are clear or translucent and stable [1]. Ostwald ripening or molecular diffusion, which arises from emulsion polydispersity, is widely considered as the main mechanism for NE destabilization (**Fig. 3**).

FIG.2: HOMOGENOUS AND STABLE NEs

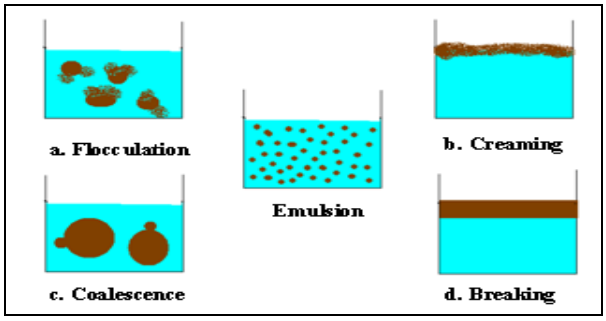

FIG. 3: EMULSION: PHYSICAL INSTABILITY

Even though physically NEs, appears similar to that of a micro-emulsion, in that both the systems are transparent or translucent and of low viscosity, yet there is an elementary difference between micro-emulsions and NEs: micro-emulsions are thermodynamically stable systems while NEs are non-equilibrium, kinetically stable or metastable systems with an ability to separate in to the constituent phases[7-8]. Depending on the composition, three types of NEs are most likely to be formed: [1] (**Fig. 4**)

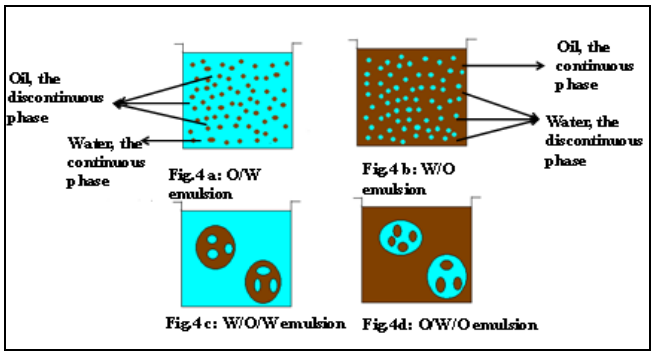

FIG.4: TYPES OF EMULSION

1. **Water-in-oil NEs:** NEs in which discontinuous water droplets are dispersed in the continuous oily phase;

2. **Oil-in-water NEs:** NEs in which discontinuous oil droplets are dispersed in the continuous aqueous phase;

3. **Bi-continuous NEs:** NEs in which micro domains of oil and water are inter-dispersed within the system i.e. O/W/O and W/O/W

In all three types of NEs, the interface is stabilized by the use of appropriate surfactants and/or co-surfactants [1] like

1. Cationic head groups: H-dependent primary, secondary or tertiary amines.

2. Anionic: Anionic surfactants contain anionic functional groups at their head, such as carboxylates, sulfate, phosphate and sulfonate.

3. Zwitterionic surfactants: Zwitterionic (amphoteric) surfactants have both anionic and cationic groups attached to the same molecule. The cationic part is based on primary, secondary or tertiary amines or quaternary ammonium cations. The anionic part can be more variable and include sulfonates.

4. Nonionic surfactant: Many long chain alcohols exhibit some surfactant properties. Prominent among these are the cetyl alcohol, stearyl alcohol, fatty alcohols, and cetostearyl alcohol (consisting predominantly of cetyl and stearyl alcohols) and oleyl alcohol.

The attraction for NEs is due to its applications in various fields such as drug delivery systems, personal care and cosmetics and as reaction media for polymerization. In this review paper we are trying to elaborate the applications of NEs in various fields and its preparation.

Methods of Preparation:

Stability of NEs depends on the method of preparation. The most commonly used methods are:

1. High-pressure homogenizers [4, 9-12]
2. Sonication method [9-11]
3. Emulsion Phase inversion methods (EPI) [9-10,13-15]
4. Micro fluidization [4, 10-11]
5. Hydrogel method [4]
6. Solvent Evaporation technique [4]
7. Low Energy Method [2, 4, 12-13]

High-Pressure Homogenization:
In this method NEs are prepared by applying high pressure over the system containing two liquids i.e. the oil phase and water phase. The pressure is applied with the help of a special instrument known as homogenizer. In this method NE up to size 1 nm can be prepared. The droplet size depends on the no. of homogenization cycles. The higher the homogenization cycles, the smaller is the droplet size obtained. The problems of using this technique are high energy consumption, poor productivity and increase in the temperature of emulsion during processing.

Sonication method:
This is also a good method for the preparation of NEs. This technique makes use of sonicator (**Fig. 5**). The droplet size of emulsion can be reduced with the help of sonicator. The only one disadvantage associated with this method is that, this method is not appropriate for large samples, only small samples of NE can be prepared by this method.

FIG. 5: PROBE SONICATOR USED IN LABORATORY SCALE FOR PREPARATION OF NE

Phase Inversion method:
Emulsions are prepared using the emulsion phase inversion (EPI) method. This method involves titrating an aqueous phase into an organic phase with constant stirring. Initially, an organic phase is prepared by adding the surfactant and oil to the beaker and then mixing using magnetic stirrer (750 rpm). Aqueous phase is then added into the organic phase using a burette. The requisite phase transitions are produced by varying the temperature at constant composition or by varying the composition at constant temperature.

Micro fluidization: In this method of NE preparation, micro fluidizer (**Fig. 6**) is used. This device uses a high-pressure positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called 'micro channels'. The product flows through the micro channels on to an impingement area resulting in very fine particles of sub- micron range.

The two liquids (oily phase and aqueous phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is fed into a micro fluidizer where it is further processed to obtain a stable NE. The coarse emulsion is passed through the interaction chamber micro fluidizer repeatedly until desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform NE.

FIG. 6: MICRO FLUIDIZER

Solvent Evaporation technique:
In this method a water-miscible organic solvent containing lipophilic functional compound is mixed in an aqueous phase containing an emulsifier. The rapid diffusion of the organic solvent in the aqueous phase facilitates the formation of NEs enabling their preparation in one step at low-energy input with high yield of encapsulation. At last, the organic solvent is removed from the nano dispersion under reduced pressure. The use of this technique is limited to water-miscible solvents.

NEs have an advantage over micro-emulsions that they can be prepared at moderate surfactant concentration (in the range 4-8 wt. %) while micro-emulsions requires a high concentration of surfactant for their preparation (usually in the range 10-30 wt. %), [16].

Characteristics of NEs:
NEs are characterized by various techniques such as viscosity determination [1, 4, 9, 11] small-angle neutron scattering (SANS) [17], Transmission Electron Microscopy (TEM) [4, 9, 11-12], Zeta Potential [4, 11-12] Scanning Electron Microscope (SEM) [12] and Dynamic Light Scattering (DLS) [1, 12, 17]. Basedon ongoing studies of these techniques, the following properties of NEs have been visualized.

- NEs have higher surface area and free energy that make them an effective transport system.
- NEs never show the creaming, flocculation, coalescence and sedimentation due to very small droplet size.
- NEs are kinetically stable system and the stability allows self-emulsification of the system.
- NEs do not damage healthy human and animal cells so they are appropriate for human and veterinary therapeutic purposes.
- Due to their small droplet size, NEs can penetrate through the “rough” skin surface and this enhances penetration of actives.
- NE formulation requires low amount of surfactant compared to micro-emulsion.
- It is possible to build lamellar liquid crystalline phases around the NE droplets.
- Dispersibility of NE is very high as compared to micro-emulsion because small droplet size prevents the flocculation of the droplets which makes the system dispersed without separation

Applications of NEs:
Due to their divergent properties such as ease of preparation, small droplet size, optical transparency, thermodynamic stability, higher surface area and high bioavailability, NEs have attracted a great attention in research, drug designing and delivery of various bioactive and pharmaceutical ingredients, cosmetics and in personal care products. Some of these applications are briefly discussed below: NE as drug delivery tool. The most important application of NE is to deliver drug through following route:

a) Transdermal delivery
b) Oral delivery
c) Ocular delivery
d) Parenteral delivery
e) Intranasal delivery
f) Targeted drug delivery
g) In cosmetics

Brief description of the above mentioned route is given below:

Transdermal delivery:
Studies have shown that NEs are efficient transdermal delivery vehicle among several formulations such as polymeric nano-suspension, NE and solid lipid nano-particles[10, 18]. Now a day’s drug delivery through the skin is of great interest because systematic circulation through skin is suitable for a number of clinical conditions[19-20].The drug delivery through the skin is preferred over parenteral route as it tenders the steady state controlled drug delivery and target ability [1] of the drug to the affected area over an ample period of time, as well as self-administration of the drug is also feasible.

The patient can get rid of the drug input at any time simply by removing the transdermal patch. Transdermal delivery has a remarkable advantage over oral delivery gastrointestinal side effects like

irritation and bowel ulcers are absent in transdermal delivery of the drug [21]. Many studies have shown that NE formulations possess improved *in -vivo* [22-25]and *in -vitro* [26-36] transdermal delivery properties. NEs have improved transdermal permeation than gels [37-39] and emulsions [39-41]. The human skin is a good biological barrier and is the largest organ of the body. The epidermis is generally 0.02-0.2 mm, and 50-150µm, thin and is 4% of the total body weight. The main skin barrier to diffusion is the horny skin layer, of stratum corneum. For a long time it was not known that like intra-cutaneous glands and follicles, hydrophilic trans-epidermal 'aqueous pathways' also play a vital role in transport of polar and amphiphilic molecules through skin barrier.

The drug delivery through skin can be enhanced by applying a strong electrical current (electroporation/iontophoresis), mechanical stimulus (e.g. sonoporation /sonophoresis), or thermal stimulus to stratum corneum[10].

The NE formulation of carvedilol has great potential for transdermal drug delivery. Carvedilol has antioxidant property, used for the treatment of hypertension and mild or moderate heart failure. Oral administration of carvedilol is well absorbed from the gastrointestinal tract but because of significant first-pass hepatic metabolism, oral bioavailability decreases to only 23%. So transdermal route is preferred over oral administration [28].

Oral delivery:

Painless administration, high patient compliance makes NE formulated oral drug administration the most convenient and preferred application route [41-42]. Due to some exceptional characteristics like safe, convenient for the patient and self-administration ability, oral administration is superior for chronic drug therapy [43]. Various modified chitosans have been developed and proven to be effective for the oral delivery of peptides, proteins, vaccines and efflux-pump substrates [42, 44]. Lipids of various oily liquids and dispersions are designed to increase bioavailability and solubility of biopharmaceutical drug through oral administration[43]. Palatable lipid NEs(50–200 nm) of primaquine were developed using medium chain triglycerides and stabilized with lecithins and poloxamer. It was found that after oral administration effective antimalarial activity at a 25% reduced dose was achieved with novel primaquine NE as compared with the plain drug solution. High oral bioavailability and higher drug levels at the site of action, liver, increases the therapeutic efficacy of primaquine [45].

Most anticancer drugs such as paclitaxel have very less oral bioavailability (less than 1%). Paclitaxel-loaded PLGA/MMT nano-particles were prepared by emulsion evaporation method. Oral administration of paclitaxel-loaded PLGA/MMT nano-particles may develop strong interactions with the GI tract mucus/epithelial surface. Oral chemotherapy by PLGA/MMT nano-particles is also possible[46].

Ocular Delivery:

The major challenge for pharmaceutical scientists is the effective treatment of ocular diseases due to presence of the ocular barriers especially in posterior ocular segments [47]. Many efforts in ophthalmic drug delivery have been devoted to elongate the contact time of the vehicle at ocular surface, slow down the elimination of the drug, to improved patient compliance, to increase bioavailability and increase its corneal penetration [48].Studies have shown that NEs have the ability to provide sustained release of a drug and higher penetration to the deeper layers of the ocular structure and aqueous humor and hence as compared to conventional system of the drug delivery NE enhances the therapeutic efficacy and pharmacokinetic parameters of the drug [47, 49].

Some of the main advantages of novel emulsion for ocular delivery [47]are:

1. Increases corneal contact time which enhances ocular bioavailability of drug
2. Improves therapeutic performance of the drug over conventional systems.
3. Prevents loss to other ocular sites by providing targeting within the ocular globes.
4. Provides controlled and sustained drug delivery

5. Provide comfort and compliance to the patient
6. Ease of sterilization
7. Circumvent the protective barriers like lacrimation, drainage and diversion of exogenous chemicals into systemic circulation by conjunctiva.
8. Provides better placement of the drug in the eye which prevents its loss to other tissues besides cornea
9. NEs act as penetration enhancers to increase corneal drug delivery [50].

NE containing Indomethacin were formulated using Chitosan, Poloxamer 188, Tripolyphosphate, Poly vinyl alcohol, Tween® 80, Lecithin Soya and Migliol 840 oil. The formulation had the ability to interact and remain associated to the ocular mucosa thus increasing the residence time in the cornea and slow and steady IM elimination during 24 h was achieved [48]. The formulated NE of dorzolamidehydrochloride showed thermodynamic stability, acceptable physicochemical properties, fast onset of drug action, prolonged effect, ability to retain the drug and enhanced drug bioavailability [50].

Parenteral Delivery:

Drug delivery through parenteral route specially intravascular leads to direct access to the bloodstream, rapid onset of drug action and targeting to specific organ and tissue sites [51-52]. The first safe parenteral fat emulsion was developed by Wretlind in 1960s. This leads to the starting of delivery of lipophilic drugs through a new delivery system i.e. parenteral. Other pleasing parenteral carrier systems are the liposome and polymeric nanoparticles made from biodegradable and non-biodegradable polymers.

In the middle of the 1990s, solid lipid nanoparticles (SLN) were formulated. At the turn of the millennium, the lipid drug conjugate (LDC) and nanoparticles nanostructured lipid carriers (NLC) have been introduced [53-54]. Lipid nano-sphere (LNS) of egg lecithin, soybean oil and dexamethasone palmitate was formulated. The studies revealed that LNS had superior efficacy to lipid microsphere as an exogenous parenteral carrier for site-specific drug delivery, effective carrier of drugs for the treatment of various disease such as inflammation, cancer and infection, has higher biocompatibility, is digested by the physiological metabolic pathways of lipids, can be sterilized by filtration with a conventional 0.2µm membrane [55].

Intranasal Delivery:

Because of the various problems of drug administration through oral, ocular, parenteral, and other routes pharmaceutical scientists showed the interest towards intranasal delivery of various drugs. The main aim of intranasal delivery is to optimize drug bioavailability for systemic drugs, and for drugs, which are susceptible to enzymatic degradation such as polypeptides and proteins [56].

Nasal delivery is specially used for immunization, as the nasal epithelium is characterized by relatively low enzymatic activity, high permeability and by the presence of an important number of immune competent cells. Drug delivery through nasal route offer simplified and more cost-effective protocols for vaccination with improved patient compliance. Antigenic molecules can be easily delivered through nasal route by the use of nano-carriers[57]. Many studies have shown that the nano-particle formulated drug can be administrated directly from nose to brain[58-60].

The effectiveness of intranasal delivery of risperidone as an antipsychotic agent was studied in rats and found that significant quantity of risperidone was quickly and effectively delivered to the brain by formulated mucoadhesive NE of risperidone through intranasal administration[58]. Intranasal administration of Nitrendipine (NDP), a potent antihypertensive molecule has higher bioavailability (60.44%) than it's oral administration (10% -20%) [61].

Targeted drug delivery:

The use of nanotechnology in targeted drug delivery is promising [62-66]. NE formulated targeted drug delivery has the capability to increase bio distribution of therapeutic agents to target organs and improve the pharmacokinetics, which will result in improved efficacy [62, 67-70].Camptothecin is

a topoisomerase I inhibitor acting against a broad spectrum of cancers[71]. But due to its insolubility, instability and toxicity, clinical application are limited. To circumvent these delivery problems NEs for camptothecin encapsulation were prepared using liquid per fluorocarbons and coconut oil as the cores of the inner phase, stabilized by phospholipids and/or Pluronic F68 (PF68). The NEs were prepared at high drug loading of ~100% with a mean droplet diameter of 220–420 nm.

NEs formulated camptothecin showed retarded drug release and with a lower oil concentration exhibits cytotoxicity against melanomas and ovarian cancer cells. Confocal laser scanning microscopy confirmed uptake of NE into cells. Hemolysis caused by the interaction between the NEs and erythrocytes was also examined. Formulations with phosphatidylethanolamine as an emulsifier showed less hemolysis than those with phosphatidylcholine. With low oil concentration release of camptothecin from the system to the targeting area can be increased [72].

NE in Cosmetics:

In recent years NEs have attracted considerable attention for the controlled delivery of cosmetics and personal care products[73]. The applications of nanotechnology and nano-materials can be found in many cosmetic products including hair care products, moisturisers, make up, sunscreen, to name a few[74-76]. Lipid nano-particles can make products to appear white instead of yellowish, which is more appealing to consumers[77].

Several cosmetic products are available that use NEs, such as Korres' Red Vine Hair sunscreen (www. korres.com). Several companies supply ready to use emulsifiers for creating stable NEs for cosmetic applications, including nano-gel UV for sun care applications, Nano-cream® from Sinerga (www.sinerga.it) and Nano-Gel from Kemira (www.kerima.com)[78]. A list of products claiming to use nano-materials has been compiled in the report 'Nano-materials, sunscreens and cosmetics: Small ingredients, big risks'[79].

CONCLUSION: The aim of nano-emulsion formulation is improving and controlling the required bioavailability levels of therapeutic agents. Small droplet size of NEs leads to some very engrossing physical properties such as optical clarity, high penetration power and unusual elastic behavior. In the field of nano-materials, nano-emulsion offer numerous advantages for the delivery of drugs, bio actives and diagnostic agents and are able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce variability. NEs are applicable for all route of drug delivery.

Recently NEs are receiving great attention as drug carrier for improving the delivery of neutron capture therapy agents, various anticancer drugs and pharmaceutical ingredients. Thus, by this review a lot of information about NEs, their properties and applications is gathered, though still more research is needed in this field. They seem to be very flexible materials capable of delivering fruitful results in several areas other than drug delivery like cosmetics, biotechnology, nutrition fluids etc.

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