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A SCIENTIFIC REVIEW ON NANOEMULSION FOR TARGETING DRUG DELIVERY SYSTEM

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ABSTRACT: Nanoemulsions have attracted great attention in research, dosage form design, and pharmacotherapy. This is as a result of some attributes peculiar to nanoemulsions such as optical clarity, ease of preparation, thermodynamic stability and increased surface area. Poor water solubility remains the main culprit for the formulation scientist which can be overcome by canonization. Nanoemulsion is a kinetically stable and isotropic system of two immiscible liquids in the submicron size range. Nanoemulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. Many parenteral nutrition and drug emulsions on the market confirm the safe use of NE over the years. Parenteral emulsions loaded with APIs (active pharmaceutical ingredients) are considered as drug delivery systems (DDS). DDS focuses on the regulation of the in-vivo dynamics, such as absorption, distribution, metabolism, and extended bioavailability, thereby improving the effectiveness and the safety of the drugs. Nanoemulsion is the thermodynamically stable isotropic system in which two immiscible liquid (water and oil) are mixed to form a single phase using an appropriate surfactant or its mix with a droplet diameter approximately in the range of 0.5-100 µm. Nanoemulsion droplet sizes fall typically in the range of 20-200 nm and show narrow size distributions. Problems such as creaming, coalescence sedimentation, and flocculation are not a concern for nanoemulsions due to their small droplet size. A comprehensive review is presented to give basic ideas about nanoemulsions, their preparation methods, and stability aspects. In this review, the attention is focused on giving brief regarding nanoemulsion formulation aspect, a method of preparation, characterization techniques with special emphasis on various applications and explains the components required, low and high energy processes involved in the preparation of nanoemulsions. This review sheds light on the current state of nanoemulsions in the delivery of drugs and other bio-actives. The morphology, formulation, characteristics, and characterization of nanoemulsions were also addressed.

Keywords: Nanoemulsion, drug delivery, targeting, and characterization

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INTRODUCTION: An ideal drug delivery system fulfills the objective of maximizing therapeutic effect while minimizing toxicity.

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With the progress in time and advances in science and technology, dosage forms have evolved from simple mixtures and pills to highly sophisticated systems, which are known as novel drug delivery systems [1]. The term 'Nanoemulsion' refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water stabilized by an interfacial film of surfactant molecules. Nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and water phase in

combination with a surfactant. The dispersed phase droplet size is about 5 nm-200 nm and should have very low oil/water interfacial tension. Cosurfactant or cosolvent is used in many cases in addition to the surfactant, the oil phase and the water phase [3]. Nanoemulsions are novel drug delivery systems consisting of emulsified oil and water systems with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm and can exist as oil-in-water (o/w) or water-in-oil (w/o) form, where the core of the particle is either oil or water, respectively. Nanoemulsions are made from pharmaceutical surfactants that are generally regarded as safe (GRAS). The surfactant type and concentration in the aqueous phase are chosen to provide good stability against coalescence. Several types of oils-natural semi-synthetic and synthetic are used in the formulation of nanoemulsions. The capacity of nanoemulsions to dissolve large quantities of low soluble drugs along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal drug delivery vectors [1]. The major advantages of nanoemulsions as drug delivery carriers include increased drug loading, enhanced drug solubility and bioavailability, reduced patient variability, controlled drug release, and protection from enzymatic degradation [2].

A lot of techniques are available for enhancing absorption of poorly water-soluble drugs, like the use of lipid-based systems. Thus enhancement of aqueous solubility in such case is a valuable goal to formulate them into bioavailable dosage forms successfully. A range of novel strategies are currently being developed for efficient delivery of poorly water-soluble drugs, such as the formulation of amorphous solid form, nanoparticles, microemulsions, solid dispersions, melt extrusion, salt formation and formation of water-soluble complexes [4, 5].

Perspective drug delivery systems can be defined as mechanisms to introduce therapeutic agents into the body. Chewing leaves and roots of medical plants and inhalation of soot from the burning of medical substances are examples of drug delivery from the earliest times. However, these primitive approaches of delivering drugs lacked a very basic need in drug delivery; that is, consistency and uniformity (a required drug dose). This led to the development of different drug delivery methods in the later part of the eighteenth and early nineteenth century. Those methods included pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions, suspension, cachets, troches, lozenges, nebulizers, and many other traditional delivery mechanisms. Many of these delivery mechanisms use the drugs derived from plant extracts [6]. As the technological advancements been made the scientists have devised some new formulation approaches. Most of the new chemical entities being invented pose the problem of poor solubility. Nanotechnology and nanoscience are widely seen as having great potential to bring benefits to many areas of research and applications where poor solubility is an issue with API [7, 8].

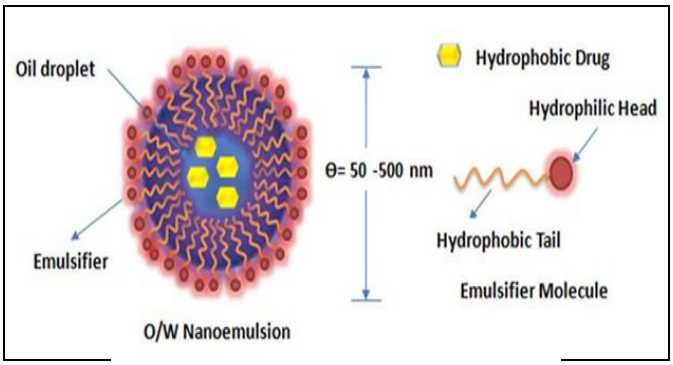

FIG. 1: NANOEMULSION DROPLET

Nanoemulsions are part colloidal dispersions of two immiscible liquids [9]. Although some lyotropic liquid crystalline phases, also known as 'micellar phases,' 'mesophases,' and 'microemulsions,' may appear to be similar to nanoemulsions in composition and nanoscale structure, such phases are quite different. Lyotropic liquid crystals are equilibrium structures comprised of liquids and surfactant, such as lamellar sheets, hexagonally packed columns, and wormlike micellar phases that form spontaneously through thermodynamic self-assembly. By contrast, nanoemulsions do not form spontaneously; an external shear must be applied to rupture larger droplets into smaller ones. Compared to microemulsion phases, relatively little is known about creating and controlling nano-emulsions. This is primarily because extreme shear, well beyond the reach of ordinary mixing devices, must be applied to overcome the effects of surface tension to rupture the droplets into the nanoscale regime [6].

Nanoemulsion droplet sizes fall typically in the range of 20-200 nm and show narrow size distribution [9]. Since, the preparation of the first nanoemulsion in 1940s, it can be of three types such as oil-in-water (O/W), water-in-oil (W/O), and bicontinuous. The transformation between these three types can be achieved by varying the components of the emulsions. Each type of the nanoemulsions serves as a template for preparing polymer latex particles, Nanoporous polymeric solids, *etc*. Apart from this, the nanoemulsions with pharmaceutically accepted ingredients are utilized in the development of drug formulations for oral drug delivery. Phase behavior studies have shown that the size of the droplets is governed by the surfactant phase structure (bicontinuous micro-emulsion or lamellar) at the inversion point induced by either temperature or composition. Studies on Nanoemulsion formation by the phase inversion temperature method have shown a relationship between minimum droplet size and complete solubilization of the oil in a microemulsion bicontinuous phase independently of whether the initial phase equilibrium is single or multiphase [9-12].

Nanoemulsion incorporates a very high concentration of surfactant which is selected from the list of generally regarded as safe agent (GRAS). If they are mixed with oil and other formulating components **Table 1** in an appropriate ratio, one can avoid destabilization process like Oswald ripening [13]. The dispersed phase mainly aqueous phase is practically immiscible with the dispersed medium like oil and lipid. Interfacial tension has been minimized in such systems by film formation around oil droplets by amphiphiles like cosurfactant and surfactant. Mainly oils are selected which are of low carbon chain length, and they can form a stable system with amphiphiles. The concentration of surfactant gears the system towards nano size [13, 14]. Many times high shear rates apply to form nano-sized globules [15]. A system tends to form the nano globules due to shear which governs the movement of amphiphiles to the nano-sized globules [16]. Main components **Table 1** of this system are the same as the components of microemulsion system [17]. Oil or lipid components, Surfactant, Co-surfactant, aqueous phase and additives like consistency binder and permeation enhancer [10, 15, 18-21]. Nanoemulsion can be formulated **Fig. 2** with a variety of technologies like High-pressure homogenization, Ultrasonication, Microfluidization and Titrimetric method [22].

Mainly GRAS (Generally regarded as safe) Nanoemulsion, formulated with oil, surfactant and co-surfactant are nontoxic, nonirritant and approved for human consumption that is "generally recognized as safe" by the FDA 23 **Table 1**.

TABLE 1: FORMULATION INGREDIENTS OF NANOEMULSION [23]

Component	Examples
Oils	Castor oil, Corn oil, Coconut oil, Evening primrose oil, linseed oil, Mineral oil, olive oil, peanut oil
Emulgent	Natural lecithins from plant or animal source, phospholipids, castor oil derivatives, polysorbates, sterylamine
Surfactant	Polysorbate 20, Polysorbate 80, Polyoxy 60, castor oil, Sorbitan monooleate, PEG 300, Caprylic glyceride
Co-Surfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer
Tonicity modifiers	Glycerol, Sorbitol, and xylitol
Additives	Lower alcohol (ethanol), propylene glycol, 1, 3-butylenes glycol, sugars such as butylenes glycol, sugars such as glucose, sucrose, fructose, and maltose
Antioxidants	Ascorbic acid and tocopherol

Formulation Factors that Affect the Stability of Nanoemulsions: Although nanoemulsions enhance the physical as well as chemical stability of drugs, the stability of drug product is one of the problems associated with the development of nanoemulsions [98-99]. Stability studies are performed on nano-emulsions by storing them at refrigerator and room temperatures over some months. The viscosity, refractive index, and droplet size are determined during this period of storage. Insignificant changes in these parameters indicate formulation stability. Accelerated stability studies can also be performed on the nanoemulsions. In this instance, nanoemulsion formulation is kept at accelerated temperatures, and samples withdrawn at regular intervals and analyzed for drug content by a stability indicating assay methods. The amount of drug degraded and remaining in nanoemulsion formulation is determined at each time interval [100]. Stability of nanoemulsion formulation may be enhanced by controlling factors such as type and concentration of surfactant and cosurfactant, type

of oil phase, methods used, process variables and the addition of additives [98-101]. Overall, nanoemulsion formulation may be considered as effective, safe and patient compliance formulation for the delivery of pharmaceuticals. Factors to be considered during preparation of nanoemulsion include the following among others [101]:

a. The prime requirement in nanoemulsion production is that an ultra-low interfacial tension should be attained at the oil-water interface, so surfactants must be carefully chosen.

b. The concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the nanodroplets.

c. The interface must be flexible to promote the formation of the nanoemulsion.

Nanoemulsion can be formulated for delivery of drugs through various routes. Nanoemulsions are well tolerated orally and on the skin and mucous membranes when used to deliver topically active drugs.

Preparation of Nanoemulsion: Nanoemulsions are non-equilibrium systems of structured liquids [24-26], and so their preparation involves the input of a large amount of either energy or surfactants and in some cases a combination of both. As a result, high energy or low energy methods can be used in their formulation [25]. The high-energy method utilizes mechanical devices to create intensely disruptive forces which break up the oil and water phases to form nanosized droplets. This can be achieved with ultrasonicators, microfluidizer, and high-pressure homogenizers [26-28].

Particle size here will depend on the type of instruments employed and their operating conditions like time and temperature along with sample properties and composition [29]. This method allows for greater control of particle size and a large choice of composition, which in turn controls the stability, rheology, and color of the emulsion. Although high-energy emulsification methods yield nanoemulsions with desired properties and have industrial scalability, they may not be suitable for thermolabile drugs such as retinoids and macromolecules, including proteins, enzymes, and nucleic acids.

Nanoemulsion can be prepared by a low energy emulsification method, which has been recently developed according to the phase behavior and properties of the constituents, to promote the formation of ultra-small droplets [30, 31]. These low-energy techniques include self-emulsification, phase transition and phase inversion temperature methods [32]. The low energy method is interesting because it utilizes the stored energy of the system to form small droplets. This emulsification can be brought about by changing the parameters which would affect the hydrophilic-lipophilic balance (HLB) of the system like temperature, composition, *etc*. [33, 34]

TABLE 2: NANOEMULSION PREPARATION METHODS

High energy emulsification method	Low energy emulsification method
Ultrasonification	Phase inversion method
High-pressure homogenization	Solvent Displacement method
Using micro fluidizer	Phase Inversion Composition Method
Using high-pressure homogenizer	

Ultrasonification: The preparation of Nano-emulsion is reported in various research papers which aim to use the ultrasonic sound frequency for the reduction of the droplet size. Another approach is the use of a constant amplitude sonotrode at system pressures more than the ambient value. It is well known that increasing the external pressure increases the cavitations threshold within an ultrasonic field and thus fewer bubbles form. However, increasing the external pressure also increases the collapse pressure of cavitations bubbles. This means that the collapse of the bubbles when cavitation occurs becomes stronger and more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a low-frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to optimum level [35].

Phase Inversion Method: In this method, fine dispersion is obtained by chemical energy resulting from phase transitions produced by the emulsification pathway. The phase transition is produced by varying the composition of the

emulsion and keeping temperature constant or *vice versa*. The phase inversion temperature was first done by it was concluded that an increase in temperature results in the chemical changes of polyoxyethylene surfactants by degradation of the polymer chain with the temperature.

High-Pressure Homogenization: Emulsification using high-pressure homogenizers. Homogenizers may be used in one of two ways:

1. By mixing ingredients in the emulsion and then passing those through the homogenizer to produce the final product and
2. Produce a coarse emulsion first using a different method then passing it through a homogenizer.

The purpose is to decrease droplets size and obtain a greater degree of uniformity and stability. The homogenizers operate at pressures of 1000 to 5000 psi to produce some of the finest dispersions obtainable in an emulsion. The production of small droplets (submicron) requires the application of high energy. Nanoemulsion formation requires input, generally from mechanical devices or the chemical potential of the components. The methods using mechanical energy (high shear stirring, high-pressure homogenizers, and ultrasound generators) are designed as dispersion or high energy emulsification methods [36].

Solvent displacement method: The solvent displacement method for spontaneous fabrication of nanoemulsion has been adopted from the nano-precipitation method used for polymeric nanoparticles. In this method, the oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol and ethyl methyl ketone. The organic phase is poured into an aqueous phase containing a surfactant to yield spontaneous nanoemulsion by rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation [37-40].

Microfludization Method: Microfluidization is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000 psi), which forces the product through the interaction chamber, which consists of small channels called "microchannels." The product flows through the microchannels. The product flows through the microchannels on to an impingement area resulting in very fine particles of sub-micron range.

The two solutions (aqueous phase and oily phase) are combined and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until the desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion [41].

Phase Inversion Composition Method (Self-nanoemulsification Method): This method generates nanoemulsions at room temperature without the use of an organic solvent and heat. Forgirani *et al.,* observed that kinetically stable nanoemulsions with small droplet size (~50 nm) could be generated by the stepwise addition of water into the solution of surfactant in oil, with gentle stirring and at a constant temperature. Although the components used in the investigation above were not of pharmaceutical grade, the investigation opened doors to design pharmaceutically acceptable nanoemulsions using a similar approach. The spontaneous nano-emulsification has been related to the phase transitions during the emulsification process and involves lamellar liquid crystalline phases or D-type bicontinuous microemulsion during process [42].

Using High-Pressure Homogenizer: High-pressure homogenization is the most common method used for the fabrication of nanoemulsions. During high-pressure homogenization, the coarse macroemulsion is passed through a small orifice at an operating pressure in the range of 500 to 5000 psi. During this process, several forces, such as hydraulic shear, intense turbulence, and cavitation, act together to yield nanoemulsions with extremely small droplet size. The resultant product can be re-subjected to high-pressure homogenization until nanoemulsion with the desired droplet size and polydispersity index is obtained [43].

Advantages, Disadvantages and Major Challenges of Nanoemulsions as Drug Delivery Systems:

Advantages: The attraction of nanoemulsions for application in personal care and cosmetics as well as in health care is due to the following advantages. The very small droplet size causes a large reduction in the gravity force, and the Brownian motion may be sufficient for overcoming gravity. This means that no creaming or sedimentation occurs on storage.

1. The small droplet size also prevents any flocculation of the droplets.
2. Weak flocculation is prevented, and this enables the system to remain dispersed with no separation.
3. The small droplets also prevent their coalescence, since these droplets are elastic, Surface fluctuations are prevented.
4. Nanoemulsions are suitable for efficient delivery of active ingredients through the skin. The large surface area of the emulsion system allows rapid penetration of actives.
5. The transparent nature of the system, their fluidity (at reasonable oil concentrations) as well as the absence of any thickeners may give them a pleasant aesthetic character and skin feel.
6. Unlike microemulsions (which require a high surfactant concentration, usually in the region of 20% and higher), nanoemulsions can be prepared using reasonable surfactant concentration. For a 20% O/W nanoemulsion, a surfactant concentration in the region of 5% - 10% may be sufficient. Nanoemulsions are usually formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.
7. The small size of the droplets allows them to deposit uniformly on substrates. Wetting, spreading and penetration may be also enhanced as a result of the low surface tension of the whole system and the low interfacial tension of the O/W droplets.
8. Nanoemulsions can be applied for delivery of fragrants, which may be incorporated in many personal care products. This could also be applied in perfumes, which are desirable to be formulated alcohol-free.
9. Nanoemulsions may be applied as a substitute for liposomes and vesicles (which are much less stable), and it is possible in some cases to build lamellar liquid crystalline phases around the nanoemulsion droplets [44, 45].

Disadvantages: In spite of the above advantages, nanoemulsions have only attracted interest in recent years for the following reasons.

1. Preparation of nanoemulsions requires in many cases special application techniques, such as the use of high-pressure homogenizers as well as ultrasonics. Such equipment (such as the Microfluidiser) became available only in recent years.
2. There is a perception in the personal care and cosmetic industry that nanoemulsions are expensive to produce. Expensive equipment is required as well as the use of high concentrations of emulsifiers.
3. Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and cosurfactants.
4. Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsion systems.
5. Lack of understanding of the interfacial chemistry that is involved in the production of nanoemulsions [44, 45].

Major Challenges: Although nanoemulsions provide great advantages as a delivery system, however, they suffer for some major challenges and limitations which include.

- ✓ The formulation of nanoemulsions is an expensive process due to the size reduction of droplets is very difficult as it required a special kind of instruments and process methods. For example, homogenizer (instrument required for the nanoemulsions formulation) arrangement is an expensive process. More

ever micro-fluidization and ultrasonication (manufacturing process) require a large amount of financial support.

- ✓ One problem associated with nanoemulsion is their stability. Although it is generally accepted that these systems could remain stable even by years, however, due to the small droplet size, it has been reported that the Oswald ripening could damage nano-emulsions, causing their application to be limited. Therefore, in most cases, nano-emulsions are required to be prepared shortly before their use.
- ✓ Use of a large concentration of surfactant and cosurfactant necessary for stabilizing the nanodroplets.
- ✓ Limited solubility capacity for high melting substances.
- ✓ Nanoemulsion stability is influenced by environmental parameters such as temperature and pH.
- ✓ Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and cosurfactants.
- ✓ Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsion systems.
- ✓ Lack of understanding of the interfacial chemistry that is involved in the production of nanoemulsions [46-48].

Applications of Nanoemulsions in Drug Delivery: Nanoemulsions could be and have been applied in various aspects of drug delivery including: cosmetics and transdermal delivery of drug, cancer therapy, vaccine delivery, prophylactic in bio-terrorism attack, non-toxic disinfectant cleaner, cell culture technology, formulations for improved oral delivery of poorly soluble drug, intranasal drug delivery, parenteral drug delivery and pulmonary delivery of drugs.

1. Applications in Cosmetics: Recently, the importance of nanoemulsions has become increasing as good vehicles for the controlled delivery of cosmetics and the optimized dispersion of active ingredients in particular skin layers. Due to their lipophilic interior, nano-emulsions are more suitable for the transport of lipophilic drug than liposomes Similar to liposomes, nanoemulsions support the skin penetration of active ingredients and thus increases their concentration in the skin. Another advantage is the small-sized droplet with its high surface area permits effective delivery of the active to the skin. More ever, nanoemulsions gain increasing interest due to their bioactive effects. This may reduce trans-epidermal water loss (TEWL), suggesting that the barrier function of the skin is strengthened. Nanoemulsions are acceptable in cosmetics because there is no chance of creaming, sedimentation, flocculation or coalescence, which is observed within microemulsions. The incorporation of potentially irritating surfactants can be avoided by using high-energy equipment during the manufacturing process. PEG free nanoemulsions for cosmetics has also been developed, and formulations exhibited good stability [46-48, 49, 50].

2. Antimicrobial Nanoemulsions: Antimicrobial nanoemulsions are o/w droplets that range from 200-600 nm. They are made of oil and water and are stabilized by surfactants and alcohol. The nanoemulsions have a broad spectrum of activity against bacteria like *E. coli*, Salmonella, *S. aureus*; enveloped viruses like HIV, herpes simplex; fungi like candida, dermatophytes, and spores like anthrax. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death.

In the case of spores, additional germination enhancers are added into the emulsion. Once starting of germination takes place, the germinating spores become susceptible to the antimicrobial action of the nanoemulsions. An aspect of the nanoemulsions is their highly selective toxicity to microbes at concentration range that are non-irritating to skin or mucous membrane. The safety range of nano-emulsions is because of the low amount of detergent in each droplet, yet when acting in concert, these droplets have enough energy and surfactant to destabilize targeted microbes without affecting healthy cells.

Nanoemulsions can get a level of topical antimicrobial activity, which can only be previously achieved by systemic antibiotics [46-49].

3. Prophylactic in Bio-Terrorism Attack: Because of their antimicrobial activity, research has begun on use of nanoemulsions as a prophylactic medicated dosage form, a human protective treatment, to prevent the people exposed to bio-attack such as Anthrax and Ebola. The broad-spectrum nanoemulsions were checked on surfaces by the US Army (RestOps) in Dec 1999 for decontamination of Anthrax spore. It was checked again by RestOps in March 2001 as a chemical decontamination agent. This technology has been tested on gangrene and clostridium botulism spores, and can even be used on contaminated wounds to salvage limbs. The nanoemulsions can be formulated into a cream, foam, liquid, and spray to decontaminate a large number of materials, which is marketed as NANOSTAT™ (Nanobio Corp.) [46-49].

4. Nanoemulsions and Vaccine Delivery: A vaccine carrier system using nanoemulsions is currently being researched. This medication delivery system uses nanotechnology to vaccinate against human immunodeficiency virus (HIV). There is recent evidence that HIV can infect the mucosal immune system. Therefore, developing mucosal immunity through the use of nanoemulsions may become very important in the future fight against HIV [46]. The oil-based emulsion is administered in the nose, as opposed to traditional vaccine routes. Research is demonstrating that genital mucosa immunity may be attained with vaccines that are administered into the nasal mucosa [51].

5. Nanoemulsions as Non-Toxic Disinfectant Cleaner: Nanoemulsions have been employed as a disinfectant cleaner. A nontoxic disinfectant cleaner for use in routine markets that include healthcare, travel, food processing, and military applications has been developed by EnviroSystems. They have been found to kill tuberculosis and a large spectrum of viruses, bacteria and fungi within 5 to 10 min without any of the hazards posed by other categories of disinfectants. The disinfectant is not flammable and so safe to store anywhere and to use in unstable conditions. It is non-oxidizing, non-acidic and nonionic. It will not corrode plastic, metals or acrylic, so it makes the product ideal for use on equipment and instruments. It is environmentally safe, so the economic cost and health risks associated with hazardous chemical disposal are removed. The preparation is a broad-spectrum disinfectant cleaner that can be applied to any hard surface, including equipment, walls, fixtures, counters, and floors. One product can now take the place of many other, decreasing product inventories and saving valuable storage space. Chemical disposal costs can be removed, and disinfection and cleaning costs can be reduced. Marketed as EcoTru ™ (EnviroSystems) [46-49].

6. Nanoemulsions in Cell Culture Technology: Cell cultures are used for *in-vitro* assays or to produce biological compounds like antibodies or recombinant proteins. For the optimization of cell growth, the culture medium can be supplemented with a large number of molecules or with blood serum. It has been very difficult to provide the media with oil-soluble substances that are available to the cells, and only a few amounts of the lipophilic compounds could be absorbed by the cells. Nanoemulsions are a new method for the delivery of oil-soluble substances to human cell cultures. The system is based on a nanoemulsion that is stabilized by phospholipids. This nanoemulsions is transparent and can be passed through 0.1 mm filters for sterilization. Nanoemulsions oil droplets are very easily taken up by the cells. The encapsulated oil-soluble substances, therefore, have a high bioavailability to cells in culture. The advantages of using nanoemulsions in cell culture technology include:

- Better uptake of oil-soluble supplements in cell cultures.
- Improve growth and vitality of cultured cells.
- Allows toxicity studies of oil-soluble drugs in cell cultures [52-55].

7. Nanoemulsion Formulations for Improved Oral Delivery of Poorly Soluble Drugs: Nanoemulsions formulation was developed to increase oral bioavailability of hydrophobic drugs. Paclitaxel was selected as a model hydrophobic drug. The o/w nanoemulsions were made with pine nut oil as the internal oil phase, water as the

external phase and egg lecithin as the primary emulsifier. Stearylamine and deoxycholic acid were used to give a positive and negative charge to the emulsions, respectively. The formulated nano-emulsions had a particle size range of 100-120 nm and zeta potential ranging from 34 mV to 245 mV. After oral administration of nanoemulsions, a significantly higher concentration of paclitaxel was observed in the systemic circulation compare to control aqueous solution. The results of this study suggest that Nanoemulsions promise novel formulations which can promote the oral bioavailability of hydrophobic drugs [46-49].

8. Nanoemulsions as a Vehicle for Transdermal Delivery: Drug delivery through the skin to the systemic circulation is convenient for some clinical conditions due to which there has been considerable interest in this area [56, 57]. Drug delivery through the skin to the systemic circulation is convenient for some clinical conditions due to which there has been considerable interest in this area [58, 59]. It offers the advantage of steady state controlled drug delivery over an extended period, with self-administration also being possible, which may not be the case with the parenteral route. The drug input can be eliminated at any time by the patient just by removing the transdermal patch. Their transparent nature and fluidity confer on nanoemulsions a pleasant skin feel. An extra advantage is the total absence of gastrointestinal side effects like irritation and bowel ulcers which are invariably associated with oral delivery.

Transdermal drug products have been developed for some diseases and disorders including cardiovascular conditions, Parkinson's and Alzheimer diseases, anxiety, depression, *etc.* [24] Caffeine has been used for the treatment of different types of cancer by oral delivery. Water-in-oil nanoemulsion formulations of caffeine have been developed for transdermal drug delivery. Comparison of *in-vitro* skin permeation profile between these and aqueous caffeine solutions showed a significant increase in permeability parameters for the nanoemulsion loaded drugs [60]. Use of nanoemulsions in transdermal drug delivery represents an important area of research in drug delivery, which enhances the therapeutic efficacy and also the bioavailability of the drugs without any adverse effects. Many studies have shown that nanoemulsion formulations possess improved transdermal and dermal delivery properties *in-vitro* [61-69], as well as *in-vivo* [70-72]. Nanoemulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions [73, 74] and gels [75, 76].

9. Nanoemulsion in Cancer Therapy and Targeted Drug Delivery: Another interesting application, which is experiencing an active development, is the use of nanoemulsion formulations, for controlled drug delivery and targeting [77]. Because of their submicron size, they can easily be targeted to the tumor area. Although nanoemulsions are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, photosensitizers, neutron capture therapy agents, or diagnostic agents. The development of magnetic nanoemulsions is an innovative approach to cancer therapy. These can deliver photosensitizers like Foscan® to deep tissue layers across the skin thereby inducing hyperthermia for a subsequent free radical generation. This methodology can be used for the treatment of cancer in the form of photodynamic therapy [78].

10. Nanoemulsions and Intranasal Drug Delivery: Intranasal drug delivery system has now been recognized as a reliable route for the administration of drugs next to parenteral and oral routes. Nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic drugs and also appears to be a favorable way to overcome the obstacles for the direct entry of drugs to the target site [79]. This route is also painless, noninvasive and well tolerated. The nasal cavity is one of the most efficient sites because of its reduced enzymatic activity, high availability of immunoreactive sites and its moderately permeable epithelium [80]. There are several problems associated with targeting drugs to the brain, especially the hydrophilic ones and those of high molecular weight. This is because of the impervious nature of the endothelium, which divides the systemic circulation and barrier between the blood and brain [81].

The olfactory region of the nasal mucosa provides a direct connection between the nose and brain, and by the use of nanoemulsions loaded with drugs, conditions such as Alzheimer's disease, migraine, depression, schizophrenia, Parkinson's diseases, meningitis, *etc*. can be treated [82, 83].

Preparation of nanoemulsions containing risperidone for its delivery to the brain *via* nose has been reported [83]. It is inferred that this emulsion is more effective through the nasal rather than the intravenous route. Another application of intranasal drug delivery system in therapeutics is their use in the development of vaccines. The administration of mucosal antigen achieves immunity. Currently, the first intranasal vaccine has been marketed as [84]. Among the possible delivery systems, the use of nano-based carriers holds a great promise to protect the biomolecules, promote nanocarrier interaction with mucosa and to direct antigen to the lymphoid tissues. Therefore the use of nanoemulsions in intranasal drug delivery system is set to bring about significant results in targeting drugs to the brain in the treatment of diseases related to the central nervous system [85].

11. Nanoemulsions and Parenteral Drug Delivery: This is one of the most common and effective routes of drug administration usually adopted for actives with low bioavailability and narrow therapeutic index. Their capacity to dissolve large quantities of hydrophobic, together with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make nanoemulsions ideal vehicles for parenteral transport. Further, the frequency and dosage of injections can be reduced throughout the drug therapy period as these emulsions guarantee the release of drugs in a sustained and controlled mode over long periods. Additionally, the lack of flocculation, sedimentation, and creaming, combined with a large surface area and free energy, offer obvious advantages over emulsions of larger particle size, for this route of administration [24]. Their very large interfacial area positively influences the drug transport and their delivery, along with targeting them to specific sites. Major clinical and pre-clinical trials have hence been carried out with parenteral nanoemulsion-based carriers [86].

Pharmacokinetics and anticancer activity have been studied by loading it in parenteral emulsions prepared by high energy ultrasonication method. Treatment of colon adenocarcinoma in the mouse with this nanoemulsion leads to higher tumor suppression rate compared to plain drug solution treatment concluding that the drug-loaded emulsion could be an effective carrier for its delivery in cancer treatment [87].

12. Nanoemulsions and Pulmonary Drug Delivery: Until now, the submicron emulsion system has not yet been fully exploited for pulmonary drug delivery and very little has been published in this area [88]. Emulsion systems have been introduced as alternative gene transfer vectors to liposomes [89]. Other emulsion studies for gene delivery (non-pulmonary route) have shown that binding of the emulsion/DNA complex was stronger than liposomal carriers [90]. This stable emulsion system delivered ness more efficiently than liposomes [91]. Bivas-Benita *et al.,* [92] reported that cationic submicron emulsions are promising carriers for DNA vaccines to the lung since they can transfect pulmonary epithelial cells, which possibly induce cross-priming of antigen-presenting cells and directly activate dendritic cells, resulting in stimulation of antigen-specific T-cells. Therefore the nebulization of submicron emulsions will be a new and upcoming research area. However, extensive studies are required for the successful formulation of inhalable submicron emulsions due to possible adverse effects of surfactants and oils on lung alveoli function (adverse interactions with lung surfactant.

Patents on Nanoemulsions: Though many of them have not reached the market yet, a good number of patents have been received on nanoemulsion formulations. Probably due to the challenges of industrial-scale production of nanoemulsions, few patents have been transferred into commercial products. Some patents related to nanoemulsions are presented in **Table 3** [93-95].

Commercial Nanoemulsions: In spite of some difficulties, certain nanoemulsion formulations have been translated into commercial products, available in the market for use. Some commercial nanoemulsion formulations are listed in **Table 4** [96].

Nanoemulsion for Phytopharmaceuticals: Phytopharmaceuticals have been formulated into microemulsions. The same cannot be said of nanoemulsions. The literature search showed a few documented phytopharmaceutical microemulsions with different degrees of activity. A new self-micro emulsifying drug delivery system has been successfully developed to improve the solubility and oral absorption of curcumin [97]. Since, it is a function of globule size; these microemulsions could also be transformed to nanoemulsions through appropriate technologies that could cause breakdown of the globules to nano range.

TABLE 3: PATENTS ON NANOEMULSION FORMULATIONS

Patent Name	Assignee	Patent Number
Transparent nanoemulsion less than 100 nm based on fluid non-ionic amphiphilic lipids and use in cosmetics or dermopharmaceuticals	L'Oreal (Paris, FR)	US Patent number: 5,753,241
Nanoemulsions based on sugar fatty ethers and its uses in the cosmetics, dermatological and/ophthalmological fields	L'Oreal (Paris, FR)	US Patent number: 6,689,371
Non-toxic antimicrobial compositions and methods of use.	NanoBio Corporation US	Patent Number:
Method of preventing and treating microbial infections	NanoBio Corporation US	6,559.189 and 6,635,676 Patent Number: 6,506,803
Nanoemulsion of 5-aminolevulinic acid	ASAT AG Applied Science and Technology (Zug, CH)	PCT/EP99/08711
Nanoemulsion of poorly soluble pharmaceutical active ingredients and methods of making the same		WO/2007/103294
Nanoemulsion based on ethylene oxide & propylene oxide block copolymers and its use in the cosmetics, dermatological & ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,464,990
Nanoemulsion based on glycerol fatty esters and its uses in cosmetics, dermatological & ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,541,018
Nanoemulsions based on oxyethylenated or non-oxyethy-lenited sorbitan fatty esters and its uses in cosmetics, dermatological and ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,335,022

TABLE 4: COMMERCIAL NANOEMULSION FORMULATIONS

Drug/Bioactive	Brand name	Manufacture	Indication
Palmitate alprostadil	Liple	Mitsubishi Pharmaceutical, Japan	Vasodilator, platelet inhibitor
Dexamethasone	Limethason	Mitsubishi Pharmaceutical, Japan	Steroid
Propofol	Diprivan	Astra Zaneca	Anaesthetic
Flurbiprofenaxtil	Ropion	Kaken Pharmaceutical, Japan	NSAID
Vitamins A, D, E, K.	vitalipid	Fresenius Kabi Europe	Parenteral nutrition

Future Perspectives: Nanoemulsions are proposed for numerous applications in pharmacy as drug delivery systems because of their capacity to solubilize non-polar active compounds. Future perspectives of nanoemulsion are very promising in different fields of therapeutics or application in the development of cosmetics for hair or skin. One of the versatile applications of nanoemulsions is in the area of drug delivery where they act as efficient carriers for bioactive, facilitating administration by various routes. The advantages and applications of nanoemulsions for oral drug delivery are numerous, where the droplet size is related to their absorption in the gastrointestinal tract. Due to the renewed interest in herbal drug formulation, nanoemulsion may be the ideal delivery platform for these difficult-to-formulate phytopharmaceuticals.

The prospects of nanoemulsions lie in the ingenuity of formulation experts to utilize the advantages of nanoemulsion carriers in overcoming peculiar problems of drug delivery such as absorption, permeation, and stability of both orthodox and herbal drugs. With the advent of new instruments for high-pressure homogenization and the competition between various manufacturers, the cost of production of nanoemulsions will decrease. Fundamental research in the investigation of the role of surfactants in the nanoemulsion production process will lead to optimized emulsifier systems, and more economic use of surfactants will emerge. Nanoemulsions can be manipulated for targeted delivery, and this holds significant promise in the area of oncology for the treatment of tumors and drug delivery to the brain.

CONCLUSION: The importance of design and development of emulsion nanocarrier systems aimed at controlling and improving required bioavailability levels of therapeutic agents cannot be overemphasized. Reducing droplet sizes to the nanoscale leads to some very interesting physical properties, such as optical transparency and unusual elastic behavior. In the world of nanomaterials, nanoemulsions hold great promise as useful dispersions of deformable nanoscale droplets that can have different flow properties and optical properties ranging from opaque to nearly transparent. Moreover, it is very likely that nanoemulsions will play an increasingly important role commercially since they can typically be formulated using significantly less surfactant than is required for nanostructured lyotropic micro-emulsion phases.

The article has highlighted developments in this area. Nanoemulsions offer several advantages for the delivery of drugs and are thus receiving increasing attention as drug carriers for improving the delivery of active pharmaceutical ingredients. They are applicable for almost all routes of delivery and therefore hold promise for different fields, be it cosmetics, therapeutics or biotechnology. This new technology could be developed to overcome the poor absorption of some phytopharmaceuticals and poor miscibility of these compounds with the lipid contents of cell membrane linings.

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