PHARMACEUTICAL NANOEMULSIONS AN ARDENT CARRIER FOR DRUG DELIVERY

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<th>ARTICLE INFO</th>
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30/11/2013 | Nanoemulsions have attracted great attention in pharmaceutical research and dosage form design. This is as a result of the various features peculiar to nanoemulsion such as ease of preparation, optical clarity, thermodynamic stability and increased surface area. Nanoemulsion having average droplet size in between 100-500 nm serves as a vehicle for the delivery of active pharmaceutical agents as well as other bioactives. They are designed to overcome the problems associated with conventional drug delivery system such as low bioavailability and noncompliance. The significance of designing and developing emulsion as a nanocarrier system aimed to control and/or improves required bioavailability levels of therapeutic agents. Nanoemulsions have been used as a carrier for various drug delivery system viz. topical, transdermal, gene delivery, intranasal, parenteral, pulmonary etc. Nanoemulsions as a carrier offer various advantages in drug delivery system. Aim of this article is to shed light on the use of the nanoemulsion in various types of drug delivery system and future prospective of nanoemulsion as a carrier. |

Keywords
Nanoemulsion, preparation, Drug delivery system.

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INTRODUCTION

An emulsion is generally described as a heterogeneous system composed of two immiscible liquids [1]. Nanoemulsions are oil-in-water (o/w) emulsion with mean droplet diameter ranging from 50 to 1000 nm. Usually the average droplet size is between 100 and 500 nm. The particle can exist as oil-in-water and water-in-oil forms, where the core of the particle is either oil or water, respectively [2]. They are transparent or translucent with a bluish coloration. It is worth saying that, while the distinction between a nanoemulsion and an emulsion, in term of their size, is rather arbitrary, nanoemulsion because of their small droplet size, cause a large reduction in gravity force; therefore, Brownian motion may be sufficient to possess a higher stability against sedimentation or creaming than an emulsion [1].

Nanoemulsions are made from surfactant approved for human consumption and common food substances those are “Generally Recognized as Safe” (GRAS) by the FDA. These emulsions are easily produced in large quantities by mixing a water immiscible oil phase with an aqueous phase under high shear stress or mechanical extrusion process that is available worldwide [2]. The capacity of nanoemulsion to dissolve large quantities of hydrophobic, along with their mutual compatibility and ability to protect the drug from hydrolysis and enzymatic degradation makes them ideal vehicle for the purpose of parenteral transport. Further, the frequency and dosage of injection can be reduced throughout the drug therapy period as these emulsions guarantee the release of drug in a sustained and controlled mode over long periods of time. Additionally, the lack of flocculation, sedimentation and creaming, combined with a large surface area and free energy, offer obvious advantage over emulsions of larger particle size, for this route of administration. Their very large interfacial area positively influences the drug transport and their delivery, along with targeting them to specific sites [3, 4].

When we go on comparing the nanoemulsion with microemulsion there is essential difference between these two systems. Nanoemulsion is, at best, kinetically stable or metastable, while a microemulsion is thermodynamically stable [5]. Besides, nanoemulsions are two-phase system where the dispersed phase droplet size has been made in the nanometre size range, the microemulsion, and micellar systems are single phase systems. As a consequence, many of nanoemulsions reported in the literature do not possess long term stability. They may experience Ostwald ripening or coalescence instabilities that could be controlled by modifying oily phase solubility, surfactant quantity and molecular weight [1, 6].

One main advantage of a nanoemulsion over a microemulsion is that it requires a lower surfactant concentration for its formation. When comparing this surfactant concentration with the 20% surfactant typically needed to prepare a microemulsion containing a compatible amount of oil, one should realize that the droplet size of a microemulsion thus produced would typically be equivalent to 10 nm. One additional advantage associated with nanoemulsion is that unlike microemulsion, they can be diluted with water without changing the droplet size distribution [7].

Nanoemulsion, as a consequence of their relatively high kinetic stability, low viscosity and transparency, are very attractive for a range of industrial application, including the pharmaceutical field where they have been explored as drug delivery system. Although nanoemulsion are chiefly seen as vehicle for administering insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, genes, photosensitizers, or diagnostic agents. Various researches has been carried out with perflurochemical nanoemulsion which has shown good results for imaging and treatment of cancer in conjunction with other treatment by targeted delivery to the neovasculature [8].

Nanoemulsion composition consists of oil phase, surfactant or emulsifiers, active pharmaceutical agent and additives. Most commonly used oil phases are natural or synthetic lipids, fatty acids, oil such as medium or long chain triglycerides or perfluorochemicals. Emulsifiers and co-emulsifiers used include either natural or modified lecithins, poly ethylene oxide (PEO) containing block copolymers, PEG-conjugated castor oil derivatives (Cremophore EL), glycerides and positively charged lipids. Other pharmaceutical additives such as pH adjusting agents, antioxidants, flavours, and preservative may also be included in the final formulation if required [8].

Preparation of Nanoemulsions

Nanoemulsions are thermodynamically unstable and require considerable mechanical energy for their preparation. The mechanical energy required can be supplied by various means such as in form of high pressure homogenizer, Microfluidizer or an ultrasonic generator [9]. Particle size of the nanoemulsion will depend upon the type of instruments used and their operating conditions like time and temperature along with sample properties and composition [10].

High energy methods cannot be used for such molecules which are thermolabile in nature such as retinoids and macromolecules including proteins, enzymes and nucleic acids and if there is a limited access to their respective expensive equipments. In such cases low energy emulsification methods may be used. Bouchemal et al. prepared nanoemulsions by injecting oil phase solution in a water miscible organic solvent, e.g. alcohols into an aqueous phase under magnetic stirring [9].

Nanoemulsion may be prepared by low-energy emulsification methods depending upon the phase behaviour and properties of the constituents to promote the formation of ultra small droplets [11, 12]. These low energy methods include self-emulsification, phase transition and phase inversion temperature methods [13]. The low energy methods are very useful because it utilizes the stored energy of the system to form small droplets. The emulsification can be brought about by varying the parameter which would affect the hydrophilic lipophilic balance (HLB) of the system like temperature, composition, etc. [14, 15]. Diffusion of organic solvent into the external aqueous phase leads to the formation of nanodroplets. Fernandez et al. used the method of phase inversion temperature for polyoxyethylene type non-ionic surfactant [7]. When emulsion temperature was increased over phase inversion point it leads to transformation of oil swollen droplets (o/w emulsion) into water swollen droplets (w/o emulsion). The system crosses a point of zero curvature and minimal interfacial tension promoting the formation of finely dispersed nanoemulsion.
The production of nanoemulsion costs more energy than that required to produce macroemulsions. Surfactants are added in the formulation so as to reduce the surface tension between oil and water. Non-ionic surfactant lower surface tension more when compared with polymeric surfactant such as poly vinyl alcohol (PVA). Nanoemulsion are generally characterized for their particle size and surface properties (surface electrostatic charge and morphology). Size of nanoemulsion droplets determines their behaviour both in vitro and in vivo. This can be measured using spectroscopic method viz. light scattering, counting (e.g. microscopy such as electron microscopy) or separation method (e.g. analytical ultracentrifugation). Surface charge of the nanoemulsion droplets has marked effect on the stability of the emulsion system and the droplets in vivo disposition and clearance. Surface charge of the emulsion droplets were conventionally expressed in term of zeta potential, which is measured using Zetasizer or the Zeta Plus instrument. Nanoemulsion droplets are results of interfacial phenomenon brought out by surface active agents and their zeta potential is dependent on the extent of ionization of these surface active agents and counter-ion concentration. According to DLVO electrostatic theory for the stability of the colloid there must be balance between the attractive van der walls forces and the electrical repulsion because of the net surface charge. If zeta potential falls below a certain level, the emulsion droplet tends to aggregate as a result of attractive forces. On the other hand a high zeta potential (either positive or negative), typically more than 30 mV maintains a stable system [8, 16].

**METHODS OF PREPARATION OF NANOEMULSIONS**

**High Pressure Homogenization**

This technique makes use of high-pressure homogenizer /piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1nm). Method is performed by applying a high pressure over the system having oil phase, aqueous phase and surfactant or co-surfactant. Homogenizer is used for applying the high pressure (fig.1). There are some problems associated with homogenizer such as poor productivity, component deterioration and generation of much heat. This method is only applicable for oil in water (o/w) liquid nanoemulsion having less than 20% of oil phase and cream nanoemulsion of high viscosity or hardness with a mean droplet diameter lower than 200 nm cannot be prepared [17].

![Fig. 1- High pressure homogenization](image)

**Microfluidization**

This is patented mixing technology, which makes use of device called microfluidizer. This device uses a high-pressure positive displacement pump (500-20,000 psi), which forces the product into the interaction chamber, consisting of small channels called “microchannels”. The product flows through the microchannels on to an impingement area resulting in very fine particle of submicron range. The two solutions (aqueous phase and oily phase) are mixed together and processed in an inline homogenizer to yield a coarse emulsion [2]. The prepared coarse emulsion is introduced into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is continuously passed into the interaction chamber of the microfluidizer until the desired particle size is obtained. The prepared emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in uniform nanoemulsion.

**Phase Inversion Temperature Technique**

Preparation of nanoemulsion by phase inversion temperature technique may be of two types: transitional inversion induced by changing factors which affect the HLB of the system, e.g. temperature and/or electrolyte concentration, and catastrophic inversion, which can be initiated by changing the HLB number of the surfactant at constant temperature using surfactant mixtures [16]. Phase inversion temperature method (fig. 2) is based upon the principle of temperature –dependent solubility of non-ionic surfactant viz. polyethoxylated surfactants, to modify their affinities for water and oil as a function of temperature. It has been
observed that polyethoxylated surfactant tend to become lipophilic on heating due to dehydration of polyoxyethylene groups. In this method oil, water and non-ionic surfactants are mixed together at room temperature. This mixture comprises o/w micro emulsions having excess oil along with surfactant. When this macro emulsion is heated gradually, the polyethoxylated surfactant becomes lipophilic and as temperature increases the surfactant gets completely solubilized in the oily phase and the initial o/w emulsion undergoes phase inversion to w/o emulsion. As this method involves heating of the component it may be difficult to incorporate thermolabile drugs, such as tretinoin and peptides without affecting their stability.

![Fig. 2- Phase inversion temperature technique](image)

**Solvent Displacement Method**

This method is mainly used for polymeric nanoparticles. This method involves mixing of oily phase in water-miscible organic solvents, such as acetone, ethanol and ethyl methyl ketone. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous nanoemulsion by rapid diffusion of organic solvent. Then the organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation.

The main advantage of this technique is that nanoemulsion can be formed at room temperature and require simple stirring for fabrication. This technique is mainly used for fabricating nanoemulsion for parenteral use. The major drawback of this method is use of organic solvents, such as acetone, which requires additional input for their removal from nanoemulsion. Additionally in this method high ratio of solvent to oil is required to obtain nanoemulsion with a desirable droplet size. Solvent displacement method has been shown in the fig. 3.

![Fig.3- Solvent displacement method](image)

**Self-Nanoemulsification Method**

This method is of great importance as it generates nanoemulsion at room temperature without use of any organic solvent and heat. Using this method kinetically stable nanoemulsion with small droplet size can be prepared by the step wise addition of water into
solution of surfactant in oil, with gentle stirring and at constant temperature. Nanoemulsion obtained by this method are not thermodynamically stable, however they might have high kinetic and long term colloidal stability. Method has been illustrated in fig. 4.

Advantages of Nanoemulsion as drug delivery system
The nanoemulsions are widely used as a carrier for drug delivery due to the following advantages [16, 18-20]:
1) Small droplet size of nanoemulsion causes a large reduction in the gravity force and Brownian motion is sufficient to overcome gravitational force. So there will be no creaming or sedimentation on storage.
2) Due to small droplet size there is less chances of coalescence.
3) The small droplet size also prevents any flocculation of the droplets.
4) Nanoemulsions are suitable for efficient delivery of active ingredient through the skin. Due to large surface area of emulsion rapid penetration of drug occurs.
5) As nanoemulsion is transparent in nature and free from any thickeners they give pleasant aesthetic character and skin feel.
6) As compared to microemulsion, nanoemulsion requires relatively low concentration of surfactant.
7) Nanoemulsions are usually formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.
8) Due to their small size they can be uniformly deposited on substrates.
9) Nanoemulsion can be used for delivery of fragrant, which may be incorporated in many personal care products.
10) Nanoemulsion can be used to increase the bioavailability of poor water soluble drugs by developing oil in water type of nanoemulsion.
11) Nanoemulsion formulation becomes stable alternative for liposome and vesicle type of delivery system.

Disadvantages of Nanoemulsion as drug delivery system
Although nanoemulsion have all the above advantages, but they also have certain limitations as follows [16, 18-20]:
1) The manufacturing of nanoemulsion formulation is an expensive process because size reduction of droplet is very difficult as it required a special kind of instruments. For example; ultasonicator, microfluidizer and homogeniser.
2) Ostwald ripening is the instability problem associated with nanoemulsion.
3) Personal care and cosmetic industry thinks that nanoemulsions are expensive to produce, as it requires special equipment and high concentration of emulsifier.
4) Less availability and comparatively high cost of oils, surfactant and co-surfactant required for manufacturing of nanoemulsion.

Application of Nanoemulsion in topical and transdermal drug delivery system
Drug delivery through the skin to the systemic circulation is convenient for number of clinical conditions and because of this there is a considerable interest in this area [21, 22]. Nanoemulsions have been formulated for broad variety of topical and transdermal application in field of cosmetic, drug and gene delivery. It offers the advantage of steady state controlled drug delivery over extended period of time, with self administration also being possible which may not be possible by parenteral route. Input of drug can be eliminated any time by the patient just by removing the transdermal patch. Additional advantages associated with nanoemulsion are the total absence of gastrointestinal side effects like irritation and bowel ulcers. The three routes by which drug can primarily penetrate the skin are through the hair follicles, sweat ducts or directly across stratum corneum, which restrict their absorption to a large extent and limits their bioavailability. For improving the pharmacokinetics and targeting, the primary skin barriers need to be overcome.
Nano sized emulsions are able to easily penetrate the pores of the skin and reach the systemic circulation thus getting channelized for effective delivery [23]. The previously reported publications considering topical and transdermal application of nanoemulsion are categorised into cosmetic, drug and gene delivery section. A list of commercially available nanoemulsion formulation has been given in the table 1.

Table 1: Commercial nanoemulsion formulations [2]

<table>
<thead>
<tr>
<th>Drug/active molecule</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Therapeutic Indication</th>
</tr>
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<tbody>
<tr>
<td>Dexamethasone</td>
<td>Limethason</td>
<td>Mitsubishi Pharmaceuticals, Japan</td>
<td>Steroid</td>
</tr>
<tr>
<td>Propofol</td>
<td>Diprivan</td>
<td>Astra Zenaca</td>
<td>Anaesthetic</td>
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<tr>
<td>Propofol</td>
<td>Troypofol</td>
<td>Troikaa</td>
<td>Anaesthetic</td>
</tr>
<tr>
<td>Alprostadil palmitate</td>
<td>Liple</td>
<td>Mitsubishi Pharmaceuticals, Japan</td>
<td>Vasodilator, platelet inhibitor</td>
</tr>
<tr>
<td>Flurbiprofen axetil</td>
<td>Ropion</td>
<td>Kaken Pharmaceuticals, Japan</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Vitamin A, D, E and K</td>
<td>Vitalipid</td>
<td>Fresenius Kabi, Europe</td>
<td>Parenteral nutrition</td>
</tr>
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Cosmetic applications

Nanoemulsions have attracted considerable attention for application in personal hair products. They have great value in skin care because of their good sensorial properties and their biophysical properties especially hydrating power [24]. Yilmaz and Borcher have reported the effect of lipid content and charge of nanoemulsion on skin hydration, elasticity and erythema [25, 26]. A comparison between positively charged nanoemulsions with stratum corneum lipids (PNSC), positively charged nanoemulsion without stratum corneum lipid (PN) and negatively charged nanoemulsion with stratum corneum lipids (NNSC) were carried out in 14 healthy female subjects. The formulations were prepared by high-pressure homogenization followed by addition of carbopol 940 as thicker to improve the viscosity of the nanoemulsion. It was observed that the formulations were stable, as there was no significant change of the mean droplet size and viscosity due to the presence of the co-surfactants phytosphingosine (PS) and myristic acid providing zeta potential value of +35±4 mV for PNSC cream, +38±5 mV for PN creams and and - 43±5 mV for NNSC creams. Due to high zeta potential there is strong repulsion of the nanoparticles which prevent them from aggregation, flocculation and coalescence. PNSC cream was compared to Physiogel® cream with similar compositions regarding the content of ceramides. Level of skin humidity and elasticity were determined for both formulations using Corneometer® 825 and Cutometer® SEM 575. When PNSC cream were compared to PN, all values of PNSC creams were significantly higher than those of PN creams, indicates the requirement of SC lipids in order to prolong the effect on skin properties and to improve the barrier function of skin by leading to an increase of skin humidity and thus an increase in skin elasticity.

All value of PNSC creams were significantly higher than that of NNSC creams, indicating that inducing the positive charge was essential for enhanced efficacy on skin humidity and elasticity. It was concluded from the results that, PNSC was significantly more effective in increasing skin hydration and elasticity than PN and NNSC indicating that phytosphingosine inducing the positive charge, SC lipids and ceramides 3B are essential for the enhanced effect on skin hydration and viscoelasticity. In another study, Zhou and coworkers developed lecithin nanoemulsion having droplet sizes below 100 nm and with improved skin hydration capacity when incorporated into o/w cream by 2.5 times of general emulsion [27].

Drug and gene delivery

Nanoemulsions are widely used in the field of topical and transdermal drug and gene delivery, there are several studies based on enhancement of skin permeation and extended release of hydrophilic and lipophilic drugs, application of nanoemulsion for topical gene delivery, and photodynamic therapy.

Enhancement of skin permeation

Wu et al. [28] described topical transport method of hydrophilic compound using w/o nanoemulsion containing sorbitan monoooleate (Span 80), polyoxyethylene 20 sorbitan monoooleate (Tween 80), olive oil and water. Nanoemulsions were prepared and tested for their ability to facilitate transport of model hydrophilic solute, inulin, across hairless and hairy mouse skin and hairy rat skin following topical in vitro application. It was observed that the permeation profile of inulin incorporated in water-in-oil nanoemulsion
through hairy rat and hairless and hairy mouse skin are similar. Results indicate that the transport of inulin from nanoemulsion has been independent of animal skin characteristics such as stratum corneum thickness and follicle type. Along with this they have found that the rate and extent of inulin transport across hairy mouse skin were highly dependent on the hydrophilic-lipophilic balance of the surfactant mixture in the nanoemulsion. Nanoemulsions which are prepared using mixture of surfactant having low HLB value exhibited significantly higher rate and extent of transport. Authors concluded from the study that water-in-oil nanoemulsion prepared with a lipid phase whose HLB is compatible with normal sebum would efficiently facilitate skin transport of large hydrophilic molecules dissolved in the aqueous core and such transport is expected via transfollicular pathway.

Mou et al. [29] have developed a hydrogel thickened nanoemulsion system for topical delivery of lipophilic drugs such as camphor, menthol and methyl salicylate. Nanoemulsion was prepared using high pressure homogenization followed by dispersion into carbomer 940 based gel matrix which had no significant influence on droplet size. The formulation containing 5% drug, soy lecithin, Tween 80, Poloxamer 407 and propylene glycol, had spherical shape, small diameter (50-60 nm) and high permeation rate. The high permeation rate of the formulation had been attributed to several factors. First and most important factor was considered to be high concentration (5%) of the drugs which results in high concentration gradient and it can act as drug reservoirs where drug is released from the inner phase to the outer phase and then further onto the skin. Additionally due to the small droplet diameter, the oily droplets might embed into the stratum corneum and the drug molecules can directly be delivered from oily droplets into the stratum corneum without a transfer via hydrophilic phase of nanoemulsion.

There are various classes of drugs which are considered for nanoemulsion formulations with enhanced topical and transdermal delivery such as steroids, non-steroidal anti-inflammatory and cytotoxic drugs.

A) Steroids
Holler et al. [30] studied the influence of negative (sucrose laureate), non-ionic (polysorbate 80) and the cationic surfactant (phytosphingosine) on physicochemical behaviour of O/w nanoemulsion and skin permeation of model drugs (fludrocortisone acetate and flumethasone pivalate). The nanoemulsions were prepared by mixing the separately prepared aqueous and oily phases. The aqueous phase prepared by heating the sucrose laureate or polysorbate 80 and distilled water together up to 50 °C under slight mixing. The oily phase was prepared by dissolving phytosphingosine in the oil containing PCL-lipid, Lipoid S75, tocopherol and model drug (1%). The two phases were mixed and pre-homogenized at 2500 rpm. Then raw formulation was high pressure homogenized for 12 cycles at 600 bars until mean size of 100-200 nm was obtained. The nanoemulsion containing sucrose laureate and polysorbate 80 showed a uniform particle size over the whole pH range, whereas nanoemulsion containing phytosphingosine exhibited that particle size increases dramatically up to 1200 nm at pH 8.0. The positively charged nanoemulsion containing phytosphingosine were able to more efficiently fludrocortisone acetate and flumethasone pivalate into the skin than the negatively charged ones and also promote the penetration of drug through skin. It was concluded by the author that the degree of skin binding is probably more important with the positively charged particles than with the negatively one as it is known that the skin is negatively charged at neutral pH. Klang et al. [31, 32] described the enhanced stability and skin permeation of lecithin and sucrose stearate based nanoemulsion of progesterone by cyclodextrins. Enhancement was more pronounced for gamma cyclodextrins and lecithin based nanoemulsions. In other studies stecova and co-workers [33] developed topical nanoparticles system (NLC, SLN and nanoemulsion) to improve skin permeation of cyproterone acetate. The highest penetration enhancement as observed for SLN formulation.

2. Non-steroidal anti-inflammatory agents
Kuo et al. [34] investigated bioavailability and anti-inflammatory effect of Microfluidizer based nanoemulsions containing alpha, delta or gamma tocopherol compared to their respective nanoemulsions. The antioxidants nanoemulsion formulations containing phosphatidyl choline and soybean oil in tween 80 and water, had mean size in range of 42-56 nm. It was observed that formulation exhibits a significant anti-inflammatory effect in croton oil induced inflammation in CD-1 mouse that were associated with decreased araurical thickness and production of 1L-1α and TNF-α. Nanoemulsion increases blood concentration of delta and gamma tocopherol 2.2-2.4 fold of nanosuspension formulations, while the effect was not significant for alpha tocopherol. A similar nanoemulsion was developed for the delivery of aspirin [35]. The nanoemulsion having mean particle size of 90 nm, showed two fold increases in the anti-inflammatory activity of aspirin in a CD-1 mouse model of induced inflammation.

Baboota et al. investigated the potential of nanoemulsion for transdermal delivery of celecoxib. They described that the steady state flux and permeability coefficient increases significantly by use of nanoemulsion as compared to the gel formulation. Additionally the anti-inflammatory effects were higher on carrageenan-induced paw edema in rats [36]. Sakeena et al. developed nanoemulsion of palm oil esters by spontaneous emulsification method for delivery of ketoprofen in carrageenan-induced rat hind paw edema. The nanoemulsion demonstrated a significant drug release through methyl acetate membrane in-vitro and a comparable efficacy as compared with Fastun® gel in-vivo [37-39]. In another study, Kim et al. prepared nanoemulsion of ketoprofen with an acceptable stability and high skin permeation rate [40].

Wang et al. [41] developed different o/w nanoemulsions of 1% curcumin, a natural polyphenolic phytochemical. Objective of their work was to compare two methods of nanoemulsion (o/w) preparation, high speed (24000 rpm) and high-pressure homogenization (1500 bar) using medium chain triacylglycerols as oil and Tween 20 as emulsifier. They obtained mean droplet size of 618.6 nm and 79.5 nm for high speed homogenization and high pressure homogenization respectively. It was concluded from the study that there is enhancement in the anti-inflammatory activity of curcumin. Approximately there was two fold increase in the anti-inflammatory effect of curcumin for 12-O-tetradecanoylphorbol-13-acetate (TPA) - induced edema of mouse ear by high pressure homogenizer compared to high speed homogenizer. Such anti-inflammatory activity was achieved by the drug permeation enhancement when the emulsion droplet size was reduced below 100 nm.
Cytotoxic agents

Tagne et al [42] developed nanoemulsion of dacarbazine, which is highly lipid soluble cytotoxic drug and used it for topical application in xenograft nude mice model of human melanoma cell line. The nanoemulsion having mean particle size of 131 nm, demonstrated decreased negative charges which associated with better skin bilayer permeability. There was tenfold greater reduction in the tumor size as compared with the drug suspension. Along with that, during drug cessation period (12 weeks), the nanoemulsion showed fivefold greater efficacy in preventing tumor growth. Kakumenu et al. [43] also showed in-vivo efficacy of dacarbazine nanoemulsion in an epithelial carcinoma xenograft mouse model in comparison with dacarbazine suspension after topical administration. This could be attributed to the reduced particle size (111 nm versus 6000 nm), the reduced zeta potential (-3.2 versus -89.1 mV), and the greater drug dispersibility and stability.

Application of Nanoemulsion in other drug delivery System

Along with the transdermal and topical drug delivery system nanoemulsions are also having various application in the other drug delivery system.

Intranasal drug delivery system

Intranasal drug delivery system is known to be a reliable route of administration of drugs next to parenteral and oral routes. Nasal mucosa has emerged as a therapeutically viable channel for administration of systemic drugs and also appears to be a favourable way to overcome the obstacle for the direct entry of drugs to the target site [44]. This route offers the various advantages over other route viz. painless delivery, non invasive and well tolerated. The olfactory region of nasal mucosa provides a direct connection between the nose and the brain, and by the use of nanoemulsion loaded with the drugs, conditions such as Alzheimer’s disease, migraine, depression, schizophrenia, Parkinson’s disease, meningitis etc. can be treated successfully [45, 46].

Nanoemulsion containing risperidone for its delivery to the brain has been reported [46]. It is inferred that this emulsion is more effective through nasal rather than intravenous route. Some intranasal vaccines are also available in the market [47]. Use of nanoemulsion in nasal drug delivery system is set to bring about significant results in targeting drugs to the brain in treatment of disease related to the central nervous system [48].

Parenteral drug delivery system

Parenteral route is the one of the most common and effective routes of drug administration commonly used for actives with low bioavailability and narrow therapeutic index. Parenteral route offers several advantages like frequency and dosing of injection can be reduced throughout the drug therapy period as these emulsion guarantee the release of drugs in a sustained and controlled mode over long periods of time. Additionally, the lack of flocculation, sedimentation and creaming, combined with a large surface area and free energy, offers obvious advantages over emulsions of larger particle size, for this route of administration [23].

Araujo et al [49] developed Nanoemulsion containing thalidomide where a dose as low as 25 mg leads to plasma concentration which can be therapeutic. However it was observed that there is significant decrease in drug content after two month storage which could be overcome by the addition of polysorbate 80. Chlorambucil a lipophilic anticancer agent is also used as a parenteral nanoemulsion for the treatment of breast and ovarian cancer. Carbamazepine, a well known anticonvulsant drug had no parenteral treatment available for patient due to its poor solubility. Kelmann et al [50] developed a nanoemulsion for intravenous delivery of carbamazepine, which showed good in vitro release kinetics.

Pulmonary drug delivery system

Till date submicron emulsion has not been fully exploited for pulmonary drug delivery system and only some work has been published in this area [51]. Bivas-Benita et al [52] developed a cationic submicron emulsion and reported that it can be used as a promising carrier for DNA vaccines to the lung since they are able to transflect pulmonary epithelial cells, which in turn induces cross priming of antigen-presenting cells and directly activate dendritic cells, resulting in stimulation of antigen-specific T- cells. Therefore nebulisation of submicron emulsions will be a new and upcoming research area.

Major challenges of Nanoemulsion drug delivery system

Production of nanoemulsion requires significant energy input and although low energy methods exist, they are not for the industrial scale manufacture, low energy methods usually requires high concentration of surfactants and generally do not yield stable nanoemulsion. So the high energy methods are the widely used for the production of nanoemulsion on industrial scale which utilises mechanical devices such as high pressure homogenizers which are very costly, requires high energy and difficult to service. This challenges accounts for the low translation of nanoemulsion formulation into commercial products. Another challenge in the development of nanoemulsion is the lack of understanding of the mechanism of production of submicron droplet and the role of surfactant and co-surfactant. A list of patent granted to various pharmaceutical and biotechnological companies has been included in the table 2.
Table 2: Patents on nanoemulsions [52-54]

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<tr>
<th>Patent Claim</th>
<th>Assignee</th>
<th>Patent Number</th>
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<tr>
<td>Transparent nanoemulsion less than 100 nm based on fluid non-ionic</td>
<td>L’Oreal (Paris, FR)</td>
<td>US Patent number: 5,753,241</td>
</tr>
<tr>
<td>amphiphilic lipids and use in cosmetics or in dermopharmaceuticals</td>
<td></td>
<td></td>
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<tr>
<td>Method of preventing and treating microbial infections</td>
<td>NanoBio Corporation US</td>
<td>Patent Number: 6,506,803</td>
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<td>Nanoemulsions based on sugar fatty ethers and its uses in the cosmetics,</td>
<td>L’Oreal (Paris, FR)</td>
<td>US Patent number: 6,689,371</td>
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<td>L’Oreal (Paris, FR)</td>
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<td>Non-toxic antimicrobial compositions and methods of use</td>
<td>NanoBio Corporation US</td>
<td>Patent Number: 6,559.189 and</td>
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<td>6,635,676</td>
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<td>Nanoemulsion of 5-aminolevulinic acid</td>
<td>ASAT AG Applied Science and</td>
<td>PCT/EP99/08711</td>
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<td>Technology (Zug, CH)</td>
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<td>Nanoemulsions based on oxyethylenated or non-oxyethy- lenated sorbitan</td>
<td>L’Oreal (Paris, FR)</td>
<td>Patent Number: 6,335,022</td>
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<td>fatty esters and its uses in cosmetics, der- matological and ophthalmological fields</td>
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<tr>
<td>Nanoemulsion based on glycerol fatty esters and its uses in cosmetics,</td>
<td>L’Oreal (Paris, FR)</td>
<td>Patent Number: 6,541,018</td>
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<td>dermatological &amp; ophthalmological fields</td>
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**CONCLUSION AND FUTURE INDUSTRIAL PERSPECTIVES**

Nanoemulsion formulation offers several advantages for topical delivery of cosmetic and pharmaceutical agents including controlled droplet size, lower concentration of surfactant and ability to efficiently dissolve and stabilize lipophilic drug. Future perspective of nanoemulsion is very promising in different field of therapeutics or development of various topical formulations. One of the versatile applications of the nanoemulsion is in the area of drug delivery where they act as efficient carrier for bioactives, facilitating administration by various routes.

In the production of nanoemulsion there are some limitations, but pharmaceutical and food industries have to adjust their technologies to accommodate nanoemulsion production. Considering the features of the nanoemulsion it offer to formulation scientist in many fields, retooling of production facilities of industries originally involved in the production of parenteral and macro emulsion will lead to a lot of economic hand-out on the long run. This is because the effect of the difficulty in preparation and the high energy input that may be involved in the production of nanoemulsions may just be felt on short run. With the introduction of new instrument for the high pressure homogenization and the competition between various manufacturers, the cost of production of nanoemulsion will decrease. Nano emulsions can be manipulated for targeted delivery and this hold significant promise in the area f oncology for treatment of tumors and drug delivery to the brain. Also in the world of nanomaterials, nanoemulsion holds great assurance as useful dispersion of deformable nanoscale droplet that can have different flow properties and optical properties ranging from opaque to nearly transparent. They are applicable for almost all routes of delivery and therefore hold promise for different fields, be in cosmetics, therapeutics or biotechnology.

**REFERENCES**


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