Nanotechnology comprises technological developments on the nanometer scale, usually 0.1-100 nm. The use of nanotechnology in pharmaceuticals and medicine has grown over the last few years. The pharmaceuticals developed on the basis of nanotechnology are termed as “NANOPHARMACEUTICALS.”

The various nanopharmaceuticals currently being used or in the process of development are:
- Nanoemulsions (NE) (submicron sized emulsions),
- Nanosuspensions (submicron sized suspensions),
- Nanospheres (drug nanoparticles in polymer matrix),
- Nanotubes (sequence of nanoscale C60 atoms arranged in a long thin cylindrical structure),
- Nanoshells (concentric sphere nanoparticles consisting of a dielectric core and a metal shell),
- Nanocapsules (encapsulated drug nanoparticles),
- Lipid nanoparticles (lipid monolayer enclosing a solid lipid core),
- Dendrimers (nanoscale three-dimensional macromolecules of polymer).

Nanoemulsions are submicron sized emulsions that are under extensive investigation as drug carriers for improving the delivery of therapeutic agents. They are by far the most advanced nanoparticle systems for the systemic delivery of biologically active agents for controlled drug delivery and targeting. Nanoemulsions are the thermodynamically stable isotropic system in which two immiscible liquid (water and oil) are mixed to form a single phase by means of an appropriate surfactants or its mix with a droplet diameter approximately in the range of 0.5-100 nm. Nanoemulsion droplet sizes fall typically in the range of 20-200 nm and show narrow size distributions. Nanoemulsion show great promise for the future of cosmetics, diagnostics, drug therapies, and biotechnologies.

In this review, the attention is focused to give brief regarding nanoemulsion formulation aspect, method of preparation, characterization techniques with special emphasis on various applications of nanoemulsion in different areas such as in cancer treatment, in drug targeting, as a mucosal vaccine, as a vehicle for transdermal drug delivery and lipophilic drug, as a self-nanoemulsifying and solid self-nanoemulsifying drug delivery system, etc.

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**Picture:**
Figure 1: Picture of a nanoemulsion (left) and a macro-emulsion right) with droplet diameters of 35 nm and 1 μm, respectively.
by either temperature or composition. Studies on NE 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. Due to their small droplet size NEs possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of NE breakdown. The main application of NEs is the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so-called miniemulsion polymerization method) where NE droplets act as nanoreactors. Another interesting application which is experiencing an active development is the use of NEs as formulations, namely, for controlled drug delivery and targeting. NEs posses various advantages such as its:

- NEs have a much higher surface area and free energy than macro emulsions that make them an effective transport system.
- NEs do not show the problems of inherent creaming, flocculation, coalescence, and sedimentation, which are commonly associated with macroemulsions.
- NEs can be formulated in variety of formulations such as foams, creams, liquids, and sprays.
- NEs are non-toxic and non-irritant, hence can be easily applied to skin and mucous membranes.
- Since NEs are formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.
- NEs do not damage healthy human and animal cells, hence are suitable for human and veterinary therapeutic purposes.

**Formulation aspects for nanoemulsion**

Apart from drug, other formulation additives for NE are shown in Table 1. A typical formulation is given in Table 2.

**Methods of preparation of nanoemulsions**

- **High-pressure homogenization:** This technique makes use of high-pressure homogenizer/piston homogenizer to produce NEs of extremely low particle size (up to 1nm) [Figure 2].
- **Microfluidization:** Microfluidization is a patented mixing technology, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500-20000 psi), which forces the product through the interaction chamber, which consists of small channels called “microchannels.” The product flows through the microchannels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are combined together 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 NE. The coarse emulsion is passed through the interaction chamber of the microfluidizer 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.

Other method used for NE preparation is the phase inversion temperature technique.

**Characterization of nanoemulsion**

Different characterization parameters for NE include transmission electron microscopy, NE droplet size analysis, viscosity determination,

![Figure 2: High-pressure homogenization technique for nanoemulsion preparation](image)

**Table 1: Formulation additive for a nanoemulsion**

<table>
<thead>
<tr>
<th>Components of nanoemulsion formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oils: Castor oil, coconut oil, corn oil, cottonseed oil, evening primrose oil, fish oil, jojoba oil, lard oil, linseed oil, mineral oil, olive oil, peanut oil, PEG-vegetable oil, perflurochemicals, pine nut oil, safflower oil, sesame oil, soybean oil, squalene, sunflower oil, wheatgerm oil</td>
</tr>
<tr>
<td>Emulsifiers: Natural lecithins from plant or animal sources, phospholipids, PEG- phospholipids, poloxamers (e.g. F68), polysorbates, polyethylene castor oil derivatives, polyglycolized glycerides, stearylamine, oleylamine</td>
</tr>
<tr>
<td>Additives: Antioxidants (α-tocopherol, ascorbic acid)</td>
</tr>
<tr>
<td>Tonicity modifiers (glycerol, sorbitol, xylitol)</td>
</tr>
<tr>
<td>pH adjustment agents (NaOH or HCl)</td>
</tr>
<tr>
<td>Preservatives</td>
</tr>
</tbody>
</table>

![Table 2: Examples of a nanoemulsion formulation](image)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Weight (%) mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening primrose oil</td>
<td>Lipid</td>
<td>25.0</td>
</tr>
<tr>
<td>Tocopherol</td>
<td>Antioxidant</td>
<td>5.0</td>
</tr>
<tr>
<td>Lecithin</td>
<td>Emulsifying agent</td>
<td>4.0</td>
</tr>
<tr>
<td>Water</td>
<td>Diluent</td>
<td>ad 100.0</td>
</tr>
</tbody>
</table>
refractive index, in vitro skin permeation studies, skin irritation test, in vivo efficacy study, thermodynamic stability studies, and surface characteristics.

The surface charge of the NE droplets has a marked effect on the stability of the emulsion system and the droplet in vivo disposition and clearance [Figure 3].

The inset [Figure 3] shows microscopy image at a higher magnification. NE droplets were in the size range of 25–40 nm with some particle aggregates in the size range of 100-150 nm.[9]

Applications of nanoemulsions

Use of nanoemulsions in cosmetics

NEs have recently become increasingly important as potential vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers. Due to their lipophilic interior, NEs are more suitable for the transport of lipophilic compounds than liposomes. Similar to liposomes, they support the skin penetration of active ingredients and thus increase their concentration in the skin. Another advantage is the small-sized droplet with its high surface area allowing effective transport of the active to the skin. Furthermore, NEs gain increasing interest due to their own bioactive effects. This may reduce the trans-epidermal water loss (TEWL), indicating that the barrier function of the skin is strengthened. NEs are acceptable in cosmetics because there are no inherent creaming, sedimentation, flocculation, or coalescence that are observed with macroemulsions. The incorporation of potentially irritating surfactants can often be avoided by using high-energy equipment during manufacturing.[10]

New Jersey-based TRI-K Industries and its parent company Kemira have launched a new nano-based gel aimed at enhancing the efficacy of a wide range of skin care products. Kemira NanoGel is said to be a unique NE Carrier system that has been designed around easy formulation, combined with the added benefits brought about by its nanotechnology properties.

NanoGel technology provides a simple process and system to create submicron emulsions from an easy-to-use, oil-in-water concentrate. The formula is particularly suited to minimizing transepidermal water loss, enhanced skin production, and penetration of active ingredient. These characteristics suggest that it would be particularly useful for sun care products as well as moisturizing and anti-aging creams—particular areas where NEs have drawn increasing interest due to their own bioactive effects. This may reduce the trans-epidermal water loss (TEWL), indicating that the barrier function of the skin is strengthened. NEs are acceptable in cosmetics because there are no inherent creaming, sedimentation, flocculation, or coalescence that are observed with macroemulsions. The incorporation of potentially irritating surfactants can often be avoided by using high-energy equipment during manufacturing.[10]


Based on their antimicrobial activity, research has begun on use of NEs as a prophylactic medication, a human protective treatment, to protect people exposed to bio-attack pathogens such as anthrax and ebola. A broad-spectrum NE was tested on surfaces by the US Army (RestOps) in December 1999 for decontamination of anthrax spore surrogates. It was tested again by RestOps in March 2001 as a chemical decontamination agent. All tests were successful.

The technology has been tested on gangrene and Clostridium botulinum spores and can even be used on contaminated wounds to salvage limbs. The NE technology can be formulated into a cream, foam, liquid, or spray to decontaminate a variety of materials marketed as NANOSTAT™ (NanoBio Corp.)

Nanoemulsions as a mucosal vaccines[14]

NEs are being used to deliver either recombinant proteins or inactivated organisms to a mucosal surface to produce an immune response. The first applications, an influenza vaccine and an HIV vaccine, can proceed to clinical trials. The NE causes proteins applied to the mucosal surface to be adjuvanted and it facilitates uptake by antigen-presenting cells. This results in a significant systemic and mucosal immune response that involves the production of specific IgG and IgA antibody as well as cellular immunity. Initial work in influenza has demonstrated that animals can be protected against influenza after just a single mucosal exposure to the virus mixed with the emulsion. Research has also demonstrated that animals exposed to recombinant gp120 in NE on their nasal mucosa develop significant responses to HIV, thus providing a basis to examine the use of this material as an HIV vaccine. Additional research is ongoing to complete the proof of concept in animal trials for other vaccines including Hepatitis B and anthrax. The University of Michigan has exclusively licensed this technology to NanoBio®. Epidemiological and experimental data suggested that both robust neutralizing antibodies and potent cellular responses play important roles in controlling primary HIV-1 infection. In this study, they have investigated the induction of systemic and mucosal immune responses to HIV gp120 monomer immunogen administered intranasally in a novel, oil-in-water NE adjuvant. Mice and guinea pigs intranasally immunized by the application of recombinant HIV gp120
antigen mixed in NE demonstrated robust serum anti-gp120 IgG, as well as bronchial, vaginal, and serum anti-gp120 IgA in mice. The serum of these animals demonstrated antibodies that cross-reacted with heterologous serotypes of gp120 and had significant neutralizing activity against two clade-B laboratory strains of HIV (HIVBaL and HIVSF162) and five primary HIV-1 isolates. The analysis of gp120-specific CTL proliferation, INF-γ induction, and prevalence of anti-gp120 IgG2 subclass antibodies indicated that nasal vaccination in NE also induced systemic, Th1-polarized cellular immune responses. This study suggests that NE should be evaluated as a mucosal adjuvant for multivalent HIV vaccines. Hepatitis B virus infection remains an important global health concern despite the availability of safe and effective prophylactic vaccines. Limitations to these vaccines include requirement for refrigeration and three immunizations thereby restricting use in the developing world. A new nasal hepatitis B vaccine composed of recombinant hepatitis B surface antigen (HBsAg) in a novel NE adjuvant (HBsAg-NE) could be effective with fewer administrations. Comprehensive pre-clinical toxicology evaluation demonstrated that HBsAg-NE vaccine is safe and well tolerated in multiple animal models. Our results suggest that needle-free nasal immunization with HBsAg-NE could be a safe and effective hepatitis B vaccine, or provide an alternative booster administration for the parenteral hepatitis B vaccines. This vaccine induces a Th1 associated cellular immunity and also may provide therapeutic benefit to patients with chronic hepatitis B infection who lack cellular immune responses to adequately control viral replication. Long-term stability of this vaccine formulation at elevated temperatures suggests a direct advantage in the field, since potential excursions from cold chain maintenance could be tolerated without a loss in therapeutic efficacy.

A novel technique for vaccinating against a variety of infectious diseases—using an oil-based emulsion placed in the nose, rather than needles—has proved able to produce a strong immune response against smallpox and HIV in two new studies. The two studies showed that the NE platform is capable of developing vaccines from very diverse materials. The technology is licensed to NanoBio Corp. Researchers have published results from a preliminary test of a NE vaccine’s effectiveness against HIV. The HIV NE vaccine tested in the noses of mice in the study represents a different approach in the way it produces immunity and the type of immunity produced. Vaccines administered in the nose are also able to induce mucosal immunity in the genital mucosa. Evidence is growing that HIV virus can infect the mucosal immune system. Therefore, developing mucosal immunity may be very important for protection against HIV. In the study, the NE HIV vaccine showed that it was able to induce mucosal immunity, cellular immunity, and neutralizing antibody to various isolates of HIV virus. A protein used by the team, gp120, is one of the major binding proteins under study in other HIV vaccine approaches. A patent has been granted and assigned for the NE vaccine technique, which has been exclusively licensed to NanoBio Corp.

Nanoemulsion as non-toxic disinfectant cleaner

A breakthrough nontoxic disinfectant cleaner for use in commercial markets that include healthcare, hospitality, travel, food processing, and military applications has been developed by EnviroSystems, Inc. that kills tuberculosis and a wide spectrum of viruses, bacteria and fungi in 5-10 min without any of the hazards posed by other categories of disinfectants. The product needs no warning labels. It does not irritate eyes and can be absorbed through the skin, inhaled, or swallowed without harmful effects. The disinfectant formulation is made up of nanospheres of oil droplets ≤106 μm that are suspended in water to create a NE requiring only miniscule amounts of the active ingredient, PCMX (parachlorometaxylenol). The nanospheres carry surface charges that efficiently penetrate the surface charges on microorganisms’ membranes—much like breaking through an electric fence. Rather than “drowning” cells, the formulation allows PCMX to target and penetrate cell walls. As a result, PCMX is effective at concentration levels 1-2 orders of magnitude lower than those of other disinfectants; hence, there are no toxic effects on people, animals, or the environment. Other microbial disinfectants require large doses of their respective active ingredients to surround pathogen cell walls, which cause them to disintegrate, fundamentally “drowning” them in the disinfectant solution. The formulation is a broad-spectrum disinfectant cleaner that can be applied to any hard surface, including equipment, counters, walls, fixtures, and floors. One product can now take the place of many reducing product inventories and saving valuable storage space. Chemical disposal costs can be eliminated, and disinfection and cleaning costs can be reduced. It is marketed as a EcoTru ™ (EnviroSystems, Inc.).

Nanoemulsions in cell culture technology

Cell cultures are used for in vitro assays or to produce biological compounds, such as antibodies or recombinant proteins. To optimize cell growth, the culture medium can be supplemented with a number of defined molecules or with blood serum. Up to now, it has been very difficult to supplement the media with oil-soluble substances that are available to the cells, and only small amounts of these lipophilic compounds could be absorbed by the cells. NEs are a new method for the delivery of oil-soluble substances to mammalian cell cultures. The delivery system is based on a NE, which is stabilized by phospholipids. These NEs are transparent and can be passed through 0.1 μm filters for sterilization. NE droplets are easily taken up by the cells. The encapsulated oil-soluble substances therefore have a high bioavailability to cells in culture. The advantages of using NEs in cell culture technology are better uptake of oil-soluble supplements in cell cultures; improve growth and vitality of cultured cells, and allow for toxicity studies of oil-soluble drugs in cell cultures.

Nanoemulsion in cancer therapy and in targeted drug delivery

The effects of the formulation and particle composition of gadolinium (Gd)-containing lipid NE (Gd-nanoLE) on the biodistribution of Gd after its intravenous (IV) injection in D1-179 melanoma-bearing hamsters were evaluated for its application in cancer neutron-capture therapy. Biodistribution data revealed that Brij 700 and HCO-60 prolonged the retention of Gd in the blood and enhanced its accumulation in tumors. Among the core components employed, soybean oil yielded the highest Gd concentration in the blood and tumor, and the lowest in the liver and spleen. When each Gd-nanoLE was IV injected once or twice at a 24-h interval, the Gd concentration in the tumor correlated with the limit required for significantly suppressing tumor growth in neutron-capture therapy. In order to achieve penetration
of Paclitaxel (PCL) into deeper skin layers while minimizing the systemic escape, a NE (NE) was formulated and its in vivo pharmacokinetic performance was evaluated. Further, the same formulation was explored for peroral bioavailability enhancement of PCL. Upon dermal application, the drug was predominantly localized in deeper skin layers, with minimal systemic escape. This has amounted to an absolute bioavailability of 70.62%. Inhibition of P-glycoprotein efflux by D-tocopheryl polyethylene glycol 1000 succinate and labrasol would have contributed to the enhanced peroral bioavailability of PCL. This investigation provides direct evidence on the localization of high-molecular-weight, lipophilic drug, PCL, in dermis. Further, the NE formulation has enhanced the peroral bioavailability significantly to more than 70%. The developed NE formulation was safe and effective for both peroral and dermal delivery of PCL.\[24\]

Camptothecin is a topoisomerase I inhibitor that acts against a broad spectrum of cancers. However, its clinical application is limited by its insolubility, instability, and toxicity. The aim of the present study was to develop acoustically active NEs for camptothecin encapsulation to circumvent these delivery problems. The NEs were prepared using liquid perfluorocarbons and coconut oil as the cores of the inner phase. These NEs were stabilized by phospholipids and/or Pluronic F68 (PF68). The NEs were prepared at high drug loading of approximately 100% with a mean droplet diameter of 220-420 nm. Camptothecin in these systems showed retarded drug release. Camptothecin in NEs with a lower oil concentration exhibited cytotoxicity against melanomas and ovarian cancer cells. Confocal laser scanning microscopy confirmed NE uptake into cells. Using a 1 MHz ultrasound, an increased release of camptothecin from the system with lower oil concentration could be established, illustrating a drug-targeting effect.\[23\]

The scientists have investigated the NE containing risperidone (RSP) to accomplish the delivery of drug to the brain via nose. Risperidone NE (RNE) and mucusadhesive NE (RMNE) were characterized for drug content, pH, percentage transmittance, globule size, and zeta potential. Biodistribution of RNE, RMNE, and risperidone solution (RS) in the brain and blood of Swiss albino rats following intranasal (i.n.) and intravenous (i.v.) administration was examined using optimized technetium-labeled \[99 m Tc-labeled\] RSP formulations. Gamma scintigraphy imaging of rat brain following i.v. and i.n. administrations were performed to ascertain the localization of drug in brain. Higher drug transport efficiency (DTE%) and direct nose to brain drug transport (direct transport percentage, DTP%) for mucusadhesive NEs indicated more effective (DTE%) and direct nose to brain drug transport (direct transport percentage, DTP%) for mucusadhesive NEs indicated more effective transport of RSP amongst the prepared NEs. Studies conclusively demonstrated rapid and larger extent of transport of RSP by RMNE (i.n.) when compared to RS (i.n.), RNE (i.n.), and RNE (i.v.) into the rat brain.\[24\]

The advantages of formulating various lipophilic anti-cancer drugs in submicron O/W emulsion are obvious. The oil phase of the emulsion systems can act as a solubilizer for the lipophilic compound. Therefore, solubility of lipophilic drugs can be significantly enhanced in an emulsion system, leading to smaller administration volumes compared to an aqueous solution. In addition, because lipophilic drugs are incorporated within the innermost oil phase, they are sequestered from direct contact with body fluids and tissues. Lipid emulsions can minimize the pain associated with intravenously administered drugs by exposing the tissues to lower concentrations of the drug or by avoiding a tissue-irritating vehicle. This has been demonstrated with propofol, diazepam, methohexital, clarithromycin, and etomidate.\[34\]

Another study reported the formulation of filter sterilizable emulsion formulation of paclitaxel using α-tocopherol as the oil phase and α-tocopherylpolyethylene glycol-1000 succinate (TGPS) and poloxamer 407 as emulsifiers. The formulation exhibited better efficacy and was more tolerable when studied in B16 melanoma tumor model in mice.\[25\]

Emulsion formulations also show promise in cancer chemotherapy as vehicles for prolonging the drug release after intramuscular and intratumoral injection (W/O systems) and as a means of enhancing the transport of anti-cancer drugs via the lymphatic system.\[26\]

Positively charged NEs systems are expected to interact with negatively charged cell surfaces more efficiently, and this aspect of the positively charged NEs has been explored for possibility of oligonucleotide delivery to cancer cells.\[27-30\] Photodynamic therapy (PDT) of cancer is based on the concept that certain photosensitizers can be localized in the neoplastic tissue, and subsequently, these photosensitizers can be activated with the appropriate wavelength (energy) of light to generate active molecular species such as free radicals and singlet oxygen (O2) that are toxic to cells and tissues.\[31-33\] Various PDT therapies have reported two different vehicles for photosensitizers, a cremophor oil emulsion and DPPC (dipalmitylophosphatidylcholine) liposomal vesicles. The reported pharmacokinetic studies clearly indicate that the former vehicle yields a significantly larger selectivity of tumor targeting, mainly as a consequence of an enhanced accumulation in the malignant lesion. Neutron Capture Therapy (NCT) is a binary radiation therapy modality that brings together two components that work separately and have only minor effects on the cells. The first component is a stable isotope of boron or gadolinium (Gd) that can be concentrated in tumor cells by a suitable delivery vehicle. The second is a beam of low-energy neutrons. Boron or Gd in or adjacent to the tumor cells disintegrates after capturing a neutron, and the high energy heavy charged particles produced through this interaction destroy only the cancer cells in close proximity to it, leaving adjacent normal cells largely unaffected.\[34\] The success of NCT relies on the targeting of boron and Gd-based compounds to the tumor mass and to achieve desirable intracellular concentrations of these agents. At the present time, there are two targets with NCT, namely glioblastoma (malignant brain tumor) and malignant melanoma.

Lu and co-workers developed and evaluated a very low-density lipoprotein (VLDL), resembling phospholipid-submicron emulsion as a carrier system for new cholesterol-based boronated compound, BCH (anti-cancer boron neutron capture therapy compound), for targeted delivery to cancer cells.\[35\] Perfluorochemicals are hydrophobic and are not miscible with water. Perfluorochemicals have to be emulsified for intravenous use. To mimic the natural oxygen carrying cells (RBCs), the droplet size of perfluorocarbon emulsions is maintained in submicron range (median diameter < 0.2 mm). Egg phospholipid has been used as an emulsifier of choice in these formulations. The examples of the commercial perfluorocarbon emulsions are oxygente (Alliance Pharmaceutical Corporation, San Diego, CA, USA), oxyfluorw (Hemagen Inc., St Louis, MO, USA), and fluosol-DA (Alpha Therapeutic Corp., Los Angeles, CA, USA).

The perfluorochemical NEs (PFCE) have opened interesting opportunities in cancer therapy. It is suggested that fluorocarbon emulsions might find a role in photodynamic therapy, both as carriers for sensitizing dyes and to maintain tissue oxygenation in hypoxic regions of solid tumors. The high solubility of oxygen in fluorocarbon emulsions maintains solution oxygen tension, optimizing photo-oxygenative damage. The hydrophobic anti-cancer
drugs can be delivered to the tumor mass by dissolving them in a hydrophobic core of the emulsion. Furthermore, PFCE can be used as an adjuvant to radiation therapy and/or chemotherapy in the treatment of solid tumors.\[36,37\] The preclinical studies have shown very positive effects with single dose and fractionated radiation in several rodent solid tumor models. Many widely used anticancer drugs, including anti-tumor alkylating agents and doxorubicin, have shown improved response by PFCE coadministration.\[38\] Also, local application of toxic doses of PFCE resulted in the necrosis of cancer cells. This is especially promising in the treatment of cancers of the head and neck regions that are currently difficult to treat.\[39\]

**Nanoemulsion in the treatment of various other disease conditions**

Pharmos’ (US-based company) has developed the nanoemulsion topical diclofenac cream as a potential treatment for osteoarthritis (OA) pain. OA is a painful condition affecting more than 30 million people in the USA and is the most frequent cause of physical disability among adults, mainly elderly. Topical diclofenac is also being considered as treatment for soft tissue injuries, sprains, and strains. It is estimated that 20% of OA patients are not receiving treatment, mainly due to gastrointestinal side effects of oral NSAIDs and cardiovascular risk of COX-2 inhibitors. A topical NSAID offering adequate pain relief targeted to the site of injury with an improved safety profile could become a treatment alternative for these patients. In the USA, there are no approved topical NSAIDs for the treatment of OA. Pharmos’ NE technology consists of an efficient solvent-free topical vehicle based and drug entrapment in stable, submicron particles of oil-in-water emulsions with a mean droplet size between 100 and 200 nm that are uniformly dispersed in an aqueous phase. One of the unique characteristics of the NE technology is the relatively high percentage of total particle volume occupied by the internal hydrophobic oil core of the droplets. This provides high solubilization capacity for lipophilic compounds compared to other lipid vehicles such as liposomes. Viscosity-imparting agents are used for nanoemulsion thickening to produce creams with the desired semisolid consistency for application to the skin. The skin penetrative properties of the solvent-free NE delivery technology and its low irritancy make this novel topical vehicle very promising to achieve increased transcutaneous drug penetration of lipophilic drugs in comparison to conventional formulations.

The preclinical studies have shown very positive effects with single dose and fractionated radiation in several rodent solid tumor models. Many widely used anticancer drugs, including anti-tumor alkylating agents and doxorubicin, have shown improved response by PFCE coadministration.\[38\] Also, local application of toxic doses of PFCE resulted in the necrosis of cancer cells. This is especially promising in the treatment of cancers of the head and neck regions that are currently difficult to treat.\[39\]

**Nanoemulsion formulations for improved oral delivery of poorly soluble drugs**

NE formulations were developed to enhance oral bioavailability of hydrophobic drugs. Paclitaxel was selected as a model hydrophobic drug. The oil-in-water (o/w) NEs were made with pine nut oil as the solvent-free NE delivery technology and its low irritancy make this novel topical vehicle very promising to achieve increased transcutaneous drug penetration of lipophilic drugs in comparison to conventional formulations. The preclinical studies have shown very positive effects with single dose and fractionated radiation in several rodent solid tumor models. Many widely used anticancer drugs, including anti-tumor alkylating agents and doxorubicin, have shown improved response by PFCE coadministration.\[38\] Also, local application of toxic doses of PFCE resulted in the necrosis of cancer cells. This is especially promising in the treatment of cancers of the head and neck regions that are currently difficult to treat.\[39\]
internal oil phase, egg lecithin as the primary emulsifier, and water as the external phase. Stearylamine and deoxycholic acid were used to impart positive and negative charge to the emulsions, respectively. The formulated NEs had a particle size range of 90-120 nm and zeta potential ranging from +34 mV to −45 mV. Following oral administration, a significantly higher concentration of paclitaxel was observed in the systemic circulation when administered in the NE relative to control aqueous solution. The results of this study suggest that NEs are promising novel formulations that can enhance the oral bioavailability of hydrophobic drugs.  

Coenzyme Q10 (CoQ10), also known as ubiquinone, is used for energy production within cells and acts as an anti-oxidant. Since CoQ10 is highly lipophilic, the topical and oral bioavailability is very low. Several attempts have been made to improve absorption. Latest technical developments reveal that encapsulation of CoQ10 in NEs results in a significantly enhanced bioavailability. The application of CoQ10 has been further improved by the development of novel CoQ10 double NEs containing tocopherol and CoQ10 in individual nanodroplets. In addition, the CoQ10 concentration in these NEs could be increased by the development of a supersaturated CoQ10 NE.  

**Nanoemulsions as a vehicle for transdermal delivery**

From *in vitro* and *in vivo* data, it was concluded that the developed NEs have great potential for transdermal drug delivery of aceclofenac. The NEs of the system containing ketoprofen evidenced a high degree of stability. Ketoprofen-loaded NEs enhanced the *in vitro* permeation rate through mouse skins as compared to the control.  

The study was developed to evaluate the potential of NEs for increasing the solubility and the *in vitro* transdermal delivery of carvedilol. The prepared NEs were subjected to physical stability tests. Transdermal permeation of carvedilol through rat abdominal skin was determined with the Keshary-Chien diffusion cell. Significant increase ($P < 0.05$) in the steady state flux ($J_{ss}$) and permeability coefficient ($K_p$) was observed in NE formulations as compared to control or drug-loaded neat components. The irritation studies suggested that the optimized NE was a non-irritant transdermal delivery system.  

Celecoxib, a selective cyclo-oxygenase-2 inhibitor, has been recommended orally for the treatment of arthritis and osteoarthritis. Long-term oral administration of celecoxib produces serious gastrointestinal side effects. Skin permeation mechanism of celecoxib from NE was evaluated by FTIR spectral analysis, DSC thermogram, activation energy measurement, and histopathological examination. The optimized NE was subjected to pharmacokinetic (bioavailability) studies on Wistar male rats. Photomicrograph of a skin sample showed the disruption of lipid bilayers as distinct voids and empty spaces were visible in the epidermal region. The absorption of celecoxib through transdermally applied NE and NE gel resulted in 3.30- and 2.97-fold increase in bioavailability as compared to oral capsule formulation. Results of skin permeation mechanism and pharmacokinetic studies indicated that the NEs can be successfully used as potential vehicles for enhancement of skin permeation and bioavailability of poorly soluble drugs.

**Self-nanoemulsifying drug delivery systems**


The research project was done to develop a self-nanoemulsifying drug delivery system (SNEDDS) for non-invasive delivery of protein drugs. An experimental design was adopted to develop SNEDDS. Fluorescent-labeled beta-lactamase (FITC-BLM), a model protein, was loaded into SNEDDS through the solid dispersion technique. The experimental design provided 720 compositions of different oil, surfactant, and co-surfactant at various ratios, of which 33 SNEDDS prototypes were obtained. A SNEDDS was developed to load FITC-BLM into the oil phase that can spontaneously form O/W NE upon the addition of water. Fluorescently labeled BLM (FITC-BLM), a model protein, formulated into 16 SNEDDS preparations through a solid dispersion technique were studied for transport across monolayer. All the SNEDDS NEs resulted in higher transport rate than the free solution. The transport rate by SNEDDS depends on the SNEDDS composition. The SNEDDS significantly increased the transport of FITC-BLM across MDCK monolayer *in vitro*. SNEDDS may be a potential effective delivery system for non-invasive protein drug delivery. The oral absorption of BLM in rats when delivered by such a SNEDDS was investigated and showed significantly enhance in the oral bioavailability of BLM. So the SNEDDS has a great potential for oral protein delivery.

**Solid self-nanoemulsifying delivery systems as a platform technology for formulation of poorly soluble drugs**

New drug discovery programs produce molecules with poor physico-chemical properties, making delivery of these molecules at the right proportion into the body, a big challenge to the formulation scientist. The various options available to overcome the hurdle include solvent precipitation, micronisation/nanonziation using high-pressure homogenization or jet milling, salt formation, use of microspheres, solid dispersions, cogrinding, complexation, and many others. Self-nanoemulsifying systems (SNES) form one of the most popular and commercially viable approaches for delivery of poorly soluble drugs exhibiting dissolution rate limited absorption, especially those belonging to the Biopharmaceutics Classification System II/IV. SNES are essentially an isotropic blend of oils, surfactants, and/or cosolvents that emulsify spontaneously to produce oil in water NE when introduced into aqueous phase under gentle agitation. Conventional SNES consist of liquid forms filled in hard or soft gelatin capsules, which are least preferred due to leaching and leakage phenomenon, interaction with capsule shell components, handling difficulties, machinability, and stability problems. Solidification of these liquid systems to yield solid self-nanoemulsifying systems (SSNES) offer a possible solution to the mentioned complications, and that is why these systems have attracted wide attention.

**Patented nanoemulsions**

Some important patents related to NEs:
3. Patent name: NE based on ethylene oxide and propylene oxide
Table 3: Commercial nanoemulsion (sub-micron emulsion) formulations[9]

<table>
<thead>
<tr>
<th>Drug therapeutic</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Propofol</td>
<td>Diprivan</td>
<td>Astra Zeneca Pharmaceutical, Japan</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Dipiv transports</td>
<td>Limethason</td>
<td>Mitsubishi</td>
<td>Steroid</td>
</tr>
<tr>
<td>Palmitate</td>
<td>Liple</td>
<td>Mitsubishi</td>
<td>Vasodilator</td>
</tr>
<tr>
<td>Alprostadil</td>
<td>Kaken</td>
<td>Pharmaceutical, Japan</td>
<td>Platelet inhibitor</td>
</tr>
<tr>
<td>Flurbiprofen axetil</td>
<td>Ropion</td>
<td>Pharmaceuticals, Japan</td>
<td>Nonsteroidal analogue</td>
</tr>
<tr>
<td>Vitamins A, D, E, K</td>
<td>Vitalipid</td>
<td>Fresenius Kabi, Europe</td>
<td>Parenteral nutrition</td>
</tr>
</tbody>
</table>


Some commercially available NE formulations are shown in Table 3.

Conclusion

NE formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents. Traditionally, NEs have been used in clinics for more than four decades as total parenteral nutrition fluids. Several other products for drug delivery applications such as Diprivan®, Liple®, and Ropion® have also reached the marketplace. Although NEs 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, neuron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumor area. Moreover, the possibility of surface functionalization with a targeting moiety has opened new avenues for targeted delivery of drugs, genes, photosensitizers, and other molecules to the tumor area. Research with perfluoroclohe NEs has shown promising results for the treatment of cancer in conjugation with other treatment modalities and targeted delivery to the neovasculature. It is expected that further research and development work will be carried out in the near future for clinical realization of these targeted delivery vehicles.

References


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