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Biomedical Application of Nanoemulsion- A Features Review

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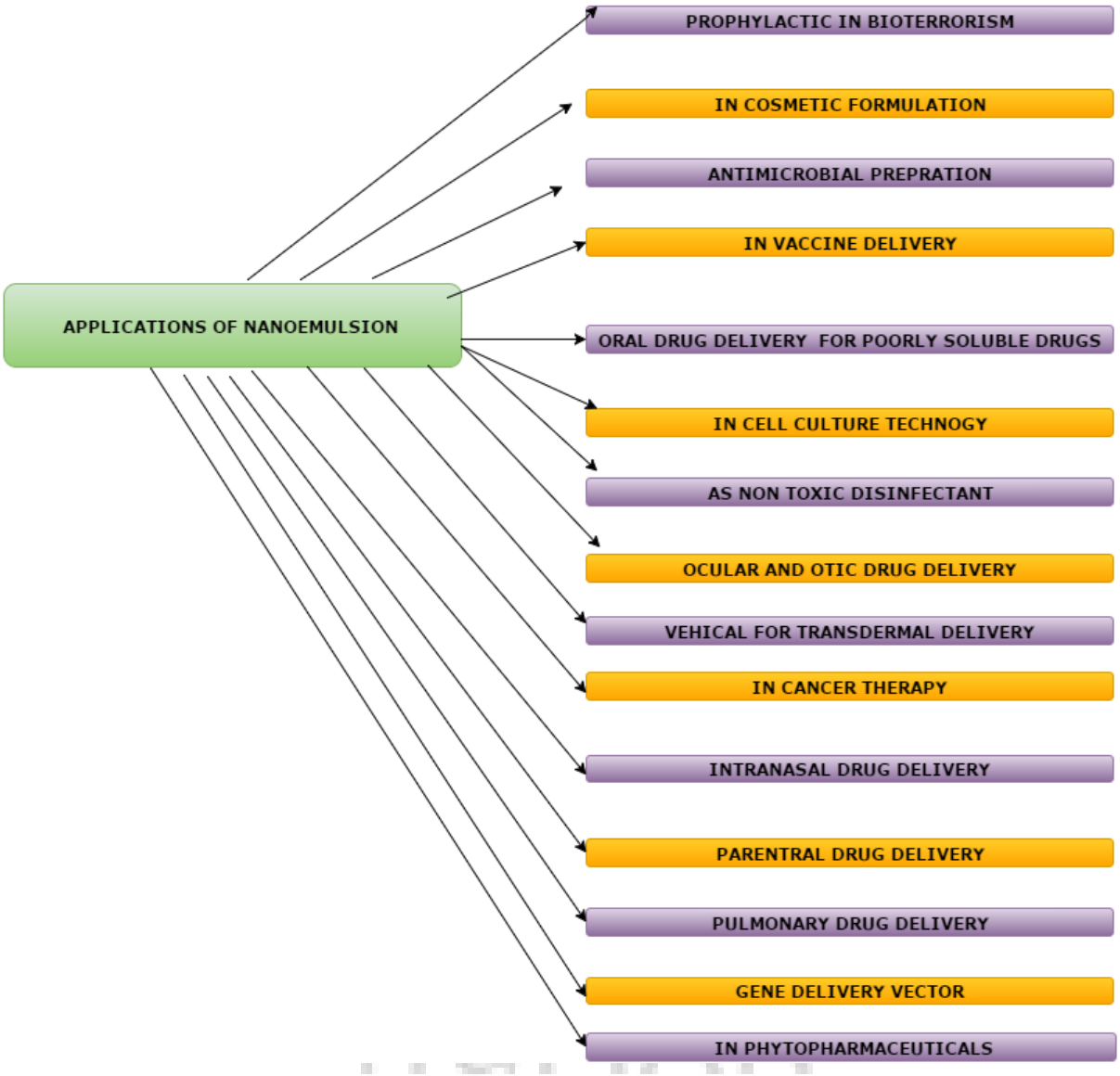
ABSTRACT

The proficiency of any therapeutic agent is highly reliant on the extent of the drug reaches the systemic circulation by voyage number of barriers, smaller the particle size of drug maximum the absorption of any therapeutic agent. The attractiveness of nanotechnology is majorly due to the smallest particle size at the nanoscale. The Nanoemulsion is the latent outcome of nanotechnology. In this review, we have discussed in detail all the application of this nanoformulation, as nanoemulsion will solve the various problems that current therapeutic agents fronting and has been open new prospects to formulate Nanoemulsions with various therapeutic agents with heightened efficiency along with some other applications.

1. INTRODUCTION

The delivery of therapeutics in a cell-specific manner is a highly promising application of nanotechnology. Delivery vehicles composed of smart materials having tunable physical and biological properties will improve current therapeutic strategies by encapsulating toxic agents thereby limiting off-target interactions; improving the bioavailability of poorly soluble drugs imparting tissue or cell specificity and improving or enabling intracellular delivery.[27]Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and co-surfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy. Nanoemulsions are based on low interfacial tension. This is achieved by adding a co-surfactant, which leads to spontaneous formation of a thermodynamically stable nanoemulsion. The term 'Nanoemulsions' is often used to designate emulsions with the internal phase droplets smaller than 1000 nm. The nanoemulsions are also referred as mini emulsions, ultrafine emulsions and submicron emulsions. Phase behavior studies have shown that the size of the droplets is governed by the surfactant phase structure (bicontinuous microemulsion 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 solubilisation 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, nanoemulsions possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of Nanoemulsion breakdown.[28]The major difference between emulsion and nanoemulsion even though emulsion are kinetically stable but thermodynamically unstable, emulsion are cloudy and nanoemulsion is very clear in physical appearance.[1]

Nanoemulsions could be and have been used as effective drug delivery system vaccine delivery, prophylactic in bioterrorism attack, non-toxic disinfectant cleaner, cell culture technology, formulations for improved oral delivery of poorly soluble drug, ocular and optic drug delivery, intranasal drug delivery, parenteral drug delivery cosmetics and transdermal delivery of drug, cancer therapy and pulmonary drug delivery.



1. Prophylactic agent to fight against bioterrorismattack[24]

The nanoemulsion containing antimicrobial agents has proven prophylactic activity to fight with a bioterrorism attack. 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 we rechecked 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.

2. In cosmetic formulations[21]

The cosmetic formulation mainly faced problem of poor absorption of drugs through skin layers. With the help of nanotechnology and nanoemulsion, this problem can be resolve and absorption of cosmetic in skin is get stimulated due smaller droplet size. Recently the importance of nanoemulsions has become increasing as good vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers. Due to their lipophilic interior, nanoemulsions are more suitable for the transport of lipophilic drug than liposomes similar to liposomes, nanoemulsions supportthe 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 permit effective delivery of the active to the skin. More ever, nanoemulsions gain increasing interest due to their own bioactive effects. This may reduce the 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 manufacturing process PEG free nanoemulsions for cosmetics has also been developed and formulations exhibited good stability**.**

3. Antimicrobial preparation[21]

Antimicrobial drugs can be incorporated in nanoemulsion 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 antimicrobial 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*. The nanoemulsions particles are thermodynamically driven to fuse with lipid-containing organisms. This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen. 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 nanoemulsions 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.

4 Nanoemulsions in vaccines delivery[22]

The nanoemulsion can be used as effective vaccine delivery system to deliver attenuated viruses. 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. The oil-based emulsion is admin Nanoemulsions advances in Formulation, Characterization, and applications in Drug Delivery inserted in the nose, as opposed to traditional vaccine routes. Recent researches results indicate that genital mucosa immunity may be attained with vaccines that are administered to the nasal mucosa. Nanoemulsions are being used to transport inactivated organisms to a mucosal surface to produce an immune response. The first applications as a vaccine, influenza vaccine, and an HIV vaccine can proceed to clinical trials. The nanoemulsion causes proteins applied to the mucosal surface to be adjuvant and it helps uptake by antigen presenting cells. This results in the significant systemic and mucosal immune response due to that the production of specific IgG and IgA antibody as well as cellular immunity. Work in influenza has shown that animals can be prevented against influenza after a single mucosal exposure to the virus mixed with the nanoemulsions. Research has also shown that animals exposed to recombinant gp120 in nanoemulsions on their nasal mucosa create significant responses to HIV, thus giving a basis to use this material as an HIV vaccine. Additional research has been ongoing to complete the proof of concept in animal trials for other vaccines including *Anthrax* and *Hepatitis B.*

5. Nanoemulsion formulations for improved oral delivery of poorly soluble drugs[21]

Nanoemulsions formulation can be used 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 the primary emulsifier. Stearylamine and deoxycholic acid were used to give positive and negative charge to the emulsions, respectively. The formulated nanoemulsions 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 are promising novel formulations which can promote the oral bioavailability of hydrophobic drugs.

6. Nanoemulsions in cell culture technology[23]

Cell cultures are used for *in vitro* assays or to produce biological compounds like antibodies or recombinant proteins. For 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 anew 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 nanoemulsion 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 includes:

• 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.

7. Nanoemulsions as non-toxic disinfectant cleaner[24]

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 product requires no warning labels. It does not irritate eyes and can be absorbed through the skin, inhaled or swallowed with harmless effects. The disinfectant formulation is made up of Nanospheres of oil droplets less than 100 μm which are suspended in water to produce nanoemulsions requiring only small amounts of the active ingredient, parachlorometaxylenol. The Nanospheres have surface charges that efficiently penetrate the surface charges on microorganisms' membranes like breaking through an electric fence. Rather than 'drowning' cells, the formulation allowsparachlorometaxylenol to target and penetrate cell walls. So parachlorometaxylenol is applicable at concentration ranges I-2 times lower than those of other disinfectants, so there are no toxic effects on human, animals or the environment.

8. Nanoemulsions in ocular and otic drug delivery[30]

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. It is a common knowledge that the application of eye drops as conventional ophthalmic delivery systems results in poor bioavailability and therapeutic response because of lachrymal secretion and nasolacrimal drainage in the eye. Most of the drug is drained away from the precorneal area in few minutes. As a result, frequent instillation of concentrated solutions is needed to achieve the desired therapeutic effects but, by the tear drainage, the main part of the administered drug is transported via the nasolacrimal duct to the gastric intestinal tract where it may be absorbed, sometimes causing side effects. In order to increase the effectiveness of the drug, a dosage form should be chosen which increases the contact time of the drug in the eye. This may then increase the bioavailability, reduce systemic absorption, and reduce the need for frequent administration leading to improved patient compliance. Nanoemulsions could be employed to overcome some of these problems. Dilutable nanoemulsions are potent drug

delivery vehicles for ophthalmic use due to their numerous advantages as sustained effect and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor. Formulated the antiglaucoma drug dorzolamide hydrochloride as ocular nanoemulsion of high therapeutic efficacy and prolonged effect. These nanoemulsions showed acceptable physicochemical properties and exhibited slow drug release. Draize rabbit eye irritation test and histological examination were carried out for those preparations exhibiting superior properties and revealed that they were nonirritant. Biological evaluation of dorzolamidehydrochloride nanoemulsions on normotensive albino rabbits indicated that these product shade higher therapeutic efficacy, faster onset of action, and prolonged effect relative to either drug solution or the market product. It was concluded from the study that formulation of dorzolamide hydrochloride in a nanoemulsion form offered a more intensive treatment of glaucoma, a decrease in the number of applications per day, and a better patient compliance compared to conventional eye drops.

9. Nanoemulsions as a vehicle for transdermal delivery[30]

Drug delivery through the skin to the systemic circulation is convenient for a number of clinical conditions due to which there has been a considerable interest in this area. It offers the advantage of steady state controlled drug delivery over an extended period of time, 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 fluidityconfers 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 a number of diseases and disorders including cardiovascular conditions, Parkinson's, and Alzheimer diseases, anxiety, depression, etc. However, the fundamental disadvantage which limits the use of this mode of administration is the barrier imposed by the skin for effective penetration of the bioactive. The three routes by which drugs can primarily penetrate the skin are the hair follicles, sweat ducts or directly across stratum corneum, which restricts their absorption to a large extent and limits their bioavailability. For improved drug pharmacokinetics and targeting, the primary skin barriers need to be overcome. Also, the locally applied drug redistribution through cutaneous blood and lymph vessel system needs to be controlled. Nano-sized emulsions are able

to easily penetrate the pores of the skin and reach the systemic circulation thus getting channelized for effective delivery. 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. Use of nanoemulsions in transdermal drug delivery represent an important area of research in drug delivery, which enhances the therapeutic efficacy and also the bioavailability of the drugs without any adverse effects. It is also regarded as a promising technique with many advantages including high storage stability, low preparation cost, thermodynamic stability, absence of organic solvents, and good production feasibility. They have also made the plasma concentration profiles and bioavailability of drugs reproducible. These systems are being used currently to provide dermal and surface effects, and for deeper skin penetration. Many studies have shown that nanoemulsion formulations possess improved transdermal and dermal delivery properties *in vitro* as well as *in vivo.* Nanoemulsion shaves improved transdermal permeation of many drugs over the conventional topical formulation such as emulsions and gels. Barakat *et al* prepared nanoemulsions by the spontaneous emulsification method for transdermal delivery of indomethacin. A significant increase in the permeability parameter such as steady-state flux, permeability coefficient, and enhancement ratio was observed in nanoemulsion formulations compared with the conventional indomethacin gel. The anti-inflammatory effects of nanoemulsion formulations showed a significant increase in percent inhibition value after 4 hours when compared with conventional indomethacin gel on carrageenan-induced paw edema in rats. Significant increase in permeability parameters was observed in nanoemulsion formulations ($P< 0.05$). The steady-state flux and permeability coefficient for optimized nanoemulsion formulation (were found to be 22.61±3.45 µg/ cm^2/hand 0.22 x 10−2 ± 0.0003 cm/h, respectively), which were significant compared with conventional indomethacin gel ($P< 0.001$). Enhancement ratio was found to be 8.939 in optimized formulation compared with indomethacin gel. These results suggested that nanoemulsions can be used as potential vehicles for improved transdermal delivery of indomethacin as an approach to eliminate the side effect of the oral dose. Singh*et al* developed nanoemulsion formulation for transdermal delivery of carvedilol toenhance the water solubility as well as the bioavailability of the drug. O/W nanoemulsions were prepared by the spontaneous emulsification method. Post application

plasma carvedilol was increased 6.41 fold to the marketed dosage form. The study suggested that nanoemulsion significantly enhanced bioavailability of transdermally applied carvedilol and eliminated the first pass metabolism. Sajid *et al* prepared betamethasone valerate nanoemulsions by aqueous phase titration method, using Sefsol, Tween 20, Transcutol P, and distilled water as the oil phase, surfactant, cosurfactant and aqueous phase, respectively and evaluated them based on the induction of contact dermatitis in rats using a dispersion of nickel sulfate in solid baseline at 5%, carrageenan induce inflammation and their irritation study. The optimized nanoemulsion was converted into hydrogel using Carbopol 934. Drug deposition in the skin was found to be 58.46μg/cm^2. *In vivo,* anti-inflammatory activity indicated 84.2% and 45.05% inhibition of inflammation in case of developed nanoemulsion gel and marketed cream, respectively. The irritation score was found to be 1.83 which indicates that the optimized nanoemulsion did not cause any irritation. Results of nickel-induced dermatitis demonstrate that the nanoemulsion formulation gel did not appear to stimulate an inflammatory or immune response using the contact dermatitis model. Zhou *et al.* carried out a study to establish a lecithin nanoemulsion without any synthetic surfactant as a topical delivery vehicle and to evaluate its topical delivery potential. Experimental results demonstrated that an increasing concentration of soybean lecithin and glycerol resulted in a smaller size lecithin nanoemulsion droplet and increasing viscosity, respectively. Lecithin nanoemulsion, incorporated into o/w cream, improved the skin hydration capacity of the cream significantly with about 2.5-fold increase when the concentration of lecithin nanoemulsion reached 10%. Lecithin nanoemulsion was also demonstrated to improve the penetrability of Nile red dye into the dermis layer, when an o/w cream, incorporated with Nile-red-loaded lecithin Nanoemulsion, applied on the abdominal skin of rat *in vivo*. Specifically, the arbitrary unit of fluorescence in the dermis layer that had received the cream with a Nile red-loaded lecithin nanoemulsion was about 9.9-fold higher than the cream with a Nilered-loaded general emulsion. These observations suggest that lecithin nanoemulsion could be used as a promising topical delivery vehicle for lipophilic compounds. Modi *et al* investigated the potential of a nanoemulsion formulation for topical delivery of aceclofenac. The *in vitro* skin permeation profile of optimized formulations was compared with that of aceclofenac conventional gel and nanoemulsion gel. A significant increase in permeability parameters such as steady-state flux, permeability coefficient and enhancement ratio was observed in optimized nanoemulsion formulation consisting of 2% w/w of aceclofenac, 10% w/w of Labrafac, 45%

w/w surfactant mixture (Cremophor® EL: Ethanol), and 43% w/w of distilled water. The anti-inflammatory effects of formulation showed a significant. Increased percent inhibition value after 24 hours when compared with aceclofenac conventional gel and nanoemulsion gel on carrageenan-induced paw edema in rats. These results suggested that nanoemulsions are potential vehicles for improved transdermal delivery of aceclofenac. Batoota *et al* investigated the potential of nanoemulsion formulations for transdermal delivery of celecoxib. The *in vitro* skin permeation profile of optimized formulations was compared with celecoxib gel and nanoemulsion gel. Significant increase in the steady state flux, permeability coefficient and enhancement ratio was observed in nanoemulsion formulations (p <0.05). The highest value of these permeability parameters was obtained in the formulation that consisted of 2% (w/w) of celecoxib, 10% (w/w) of oil phase (Sefsol 218 and Triacetin), 50% (w/w) of surfactant mixture (Tween-80 and Transcutol-P) and 40% (w/w) water. The anti-inflammatory effects of the formulation showed a significant increase (p < 0.05) in inhibition after 24 hours compared to celecoxib gel and nanoemulsion gel on carrageenan-induced paw edema in rats. These results suggested that nanoemulsions are potential vehicles for improved transdermal delivery of celecoxib. Harwansh *et al* evaluated an isotropic and thermodynamically stable nanoemulsion formulation for transdermal delivery of glycyrrhizin, with minimum surfactant and co-surfactant concentrations that could improve its solubility, permeation enhancement, and stability. A significant increase in permeability parameters such as steady-state flux and permeability coefficient was observed in the optimized nanoemulsion formulation, which consisted of 1% w/w of mono ammonium glycyrrhizinate, 32.4% Span 80, 3.7% Brij 35, 10% isopropyl alcohol,46.5% soyabean oil and 6.4% distilled water. No obvious skin irritation was observed for thestudied nanoemulsion formulation or the gel. The results indicated that nanoemulsions are promising vehicles for transdermal delivery of glycyrrhizin through human cadaver skin, without the use of additional permeation enhancers, because excipients of nanoemulsions act as permeation enhancers' themselves. Inayat *et al.* developed a potential of nanoemulsion formulation for transdermal delivery of tamoxifene citrate for breast cancer. Transdermal permeation of tamoxifene citrate through rat skin was determined by Keshary-Chien diffusion cell. A significant increase in permeability parameter such as steady–state flux was observed in optimized nanoemulsion formulation, which consists of 5% w/w of the drug, 4.12% w/w of the oil phase, 37.15% w/w of surfactant (mix) and 58.73% w/w of distilled water. It possessed a

mean globule size of 68 nm. Transmission electron microscopy demonstrated spherical particle morphology and DSC and FTIR study revealed the compatibility among the ingredient. These results proposed that the prepared system could be promising to improve the transdermal efficacy of the tamoxifen citrate. Shakeel *et al* investigated the potential of a nanoemulsion formulation for transdermal delivery of aceclofenac. Transdermal permeation of aceclofenac through rat abdominal skin was determined by Franz diffusion cell. The *in vitro s*kin permeation profile of optimized formulations was compared with that of aceclofenac conventional gel and nanoemulsion gel. A significant increase in permeability parameters such as steady-state flux, permeability coefficient, and enhancement ratio was observed in optimized nanoemulsion formulation, which consisted of 2% w/w of aceclofenac, 10% w/w of Labrafil R, 5% w/w of Triacetin R, 35.33% w/w of Tween 80 R, 17.66% w/w of Transcutol PR, and 32% w/w of distilled water. The anti-inflammatory effects of optimized formulation showed a significant increase in percent inhibition value after 24 hours when compared with aceclofenac conventional gel and nanoemulsion gel on carrageenan-induced paw edema in rats. These results suggested that nanoemulsions are potential vehicles for improved transdermal delivery of aceclofenac. Shakeel *et al* presented an overview of the efforts that have been made in the last decade by various researchers in exploring new types of nanoemulsion-based drug delivery system for dermal and transdermal delivery of many hydrophobic compounds. This area of research would be very advantageous for formulation scientists in order to develop some nanoemulsion- based formulations for their commercial exploitation and clinical applications. Moreover, Harwanshet al reviewed efforts made by various researchers in the delivery of phytopharmaceuticals using nanoemulsions.

10. Nanoemulsion in cancer therapy and in targeted drug delivery[26]

Another interesting application, which is experiencing an active development, is the use of nanoemulsion formulations, for controlled drug delivery and targeting. 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, photosensitizes, neutron capture therapy agents, or diagnostic agents. The development of magnetic nanoemulsions is an innovative approach for cancer therapy. These

candeliverphotosensitizers 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.

11 Nanoemulsions and intranasal drug delivery[30]

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. This route is also painless, non-invasive 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. 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. 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. Preparation of nanoemulsions containing risperidone for its delivery to the brain via nose has been reported. It is inferred that this emulsion is more effective through the nasal rather than an intravenous route. Another application of intranasal drug delivery system in therapeutics is their use in the development of vaccines. Immunity is achieved by the administration of mucosal antigen. Currently, the first intranasal vaccine has been marketed. 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. Bhanushali *et al* developed intranasal nanoemulsion and gel formulations for rizatriptan benzoate for prolonged action. Various mucoadhesive agents were tried out to form thermo-triggered mucoadhesive nanoemulsions. Mucoadhesive gel formulation ofrizatriptan were prepared using different ratios of HPMC and Carbopol 980. Comparative evaluation of intranasal nanoemulsions and intranasal mucoadhesive

gels indicated that greater brain-targeting could be achieved with nanoemulsions. Other drugs which have been formulated for nasal deliveries are insulin and testosterone

12. Nanoemulsions and parenteral drug delivery[11]

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 the purpose of 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 of time. 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. 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 hence have been carried out with parenteral nanoemulsion-based carriers. The advances in these novel drug delivery systems have been reviewed by Patel and Patel. Nanoemulsions loaded with thalidomide have been synthesized where a dose as low as 25 mg leadsto plasma concentrations which can be therapeutic. However, a significant decrease in the drug content of the nanoemulsion was observed at 0.01% drug formulation after two months storage which could be overcome by the addition of polysorbate 80. Chlorambucil, a lipophilic anticancer agent has been used against breast and ovarian cancer. Its 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 solutiontreatment, concluding that the drug loaded emulsion could be an effective carrier for itsdelivery in cancer treatment. Carbamazepine, a widely used anticonvulsant drug had noparenteral treatment available for patients due to its poor water solubility. Kelmann *et al.* have developed a nanoemulsion for its intravenous delivery, which showed favorable *in vitro* release kinetics. Parenteral nanoemulsion formulations of the following drugs have been documented as well: diazepam, propofol, dexamethasone, etomidate, flurbiprofen and prostaglandin E1. The high lipophilicity of diazepam (an anxiolytic and

sedative) makes the use of solvents (such as propylene glycol phenyl carbinol and ethanol) for the dissolution of the drug in conventional aqueous preparations (Valium® and Stesolid®) necessary, leading to pain and thrombophlebitison the patient during the injection. The development of a nanoemulsion, commercially available under the name of Diazemuls® (Kabi-Pharmacia) allows for the reduction of these adverse effects, keeping stages of distribution and elimination similar to Valium®. However, higher doses of Diazemuls® are necessary to obtain the same effect as Valium® since this leads to a higher free fraction of plasma diazepam [167,168]. The solution for intravenous administration of etomidate (hypnotic short) due to stability problems, its composition contains 35% propylene glycol (Hypnomidate®). Due to the presence of high osmolarity of the solvent, the administration is associated with various adverse effects such as hemolysis, thrombosis, thrombophlebitis, and pain at the site of application. A nanoemulsion containing 2 mg/ml Lipofundin® etomidate in medium triglyceride named Lipuro-etomidate® (B. Braun) was developed. The emulsion allowed the reduction of the hemolytic and venous sequelae, besides the pain at the time of application. The pharmacokinetics and pharmacodynamics of propofol (anesthetic) are complex. It has an initial rapid distribution of about 2-3 minutes, with high variability between patients and reduced concentrations to subtherapeutic levels within minutes. However, due to its high lipophilicity, it has a high volume of distribution and its complete elimination from the body can take days. Due to the occurrence of anaphylactic effects associated with Cremophor EL, present in the original formulation of propofol nanoemulsion as vehicle for this drug containing composition in soybean oil, glycerol, egg yolk lecithin and disodium edentate, this vehicle helped to reduce the volume of distribution of the drug, accelerating their processes of clearance by the responsible agencies. This formulation also allowed the use of minimal effective dose need to produce the needed therapeutic effect, allowing a rapid onset and recovery from anesthesia, when compared to a non-lipid (ethanol) solution, thereby generating greater security administration, due to the lower continuous accumulation of the drug, and eliminating the need for constant adjustment of the dose. This product was approved in 1989 in the United States, under the name of Diprivan® 1 or 2% (AstraZeneca / APP Pharmaceuticals). In Brazil, the product is available as Lipuro 1% (B. Braun) and Diprivan® 1 and 2% (AstraZeneca), besides the generic 1% (Eurofarma Labs). The various generic formulations currently available are constituted by an additional factor of variability in response between individuals in the induction of anesthesia, apart from the

pharmacokinetic characteristics of the drug itself and the differences in lipoprotein profile of each patient, due to the high binding of propofol to low density lipoprotein and albumin. Due to related pain at the injection site and increased triglyceride levels after administration for long periods, some changes in the formulation of Diprivan® adverse effects have been proposed, including some already being marketed as Propofol® Lipuro (B. Braun) as oil core which contains a mixture of oils. The addition of more oil to the formulation allowed the reduction of pain on injection due to increased incorporation of the drug in the oily core and the lower amount of free propofol phase theexternal aqueous emulsion. Alternative formulations have been developed, for example, the incorporation of higher concentrations of propofol (6%) in the nanoemulsion, or the development of a propofol prodrug in solution (Aquavan®).Furthermore, despite the excellent anti-inflammatory activity of dexamethasone, the clinical use of corticosteroids is limited by numerous side effects. To circumvent these drawbacks, lipophilic prodrugs in the body that are gradually hydrolyzed to the active metabolite can be used (thus presenting prolonged anti-inflammatory effect). The advantage is the use of lower doses than those used in conventional water soluble form (dexamethasone phosphate), reducing the risks of adverse effects. Considering that nanoemulsions are picked up by inflammatory cells of the mononuclear phagocytic system, nanoemulsions were used as a vehicle for the lipophilic prodrug of dexamethasone (palmitate), which is commercially available as Limethason® (Green Cross Co. /Mitsubishi Tanabe Pharma Co.). Limethason® showed excellent results in the treatment of rheumatoid arthritis, West syndrome, inflammatory diseases, and other autoimmune diseases. While the solution of dexamethasone phosphateis rapidly distributed in water-rich tissues, such as muscles, the nanoemulsion is accumulated mainly in tissues inflamed organs such as liver and spleen. The bio distribution profile is different even if the elimination pattern is similar between the two. Limethason® removes over 80% of the phagocytic activity of macrophages at a concentration of 0.03 mg/mL. Flurbiprofen (non-steroidal anti-inflammatory oral use), a lipophilic drug, is used to treat rheumatoid arthritis and other inflammatory diseases associated or not with cancer. Thenon-availability of oral and/or various gastrointestinal effects caused by this drug often require the use of the parenteral route. Considering the severe local irritation caused by the sodium salt of flurbiprofen, it was developed as a prodrug of flurbiprofen (cefuroxime) and because of the lipophilicity of the latter especially in soybean oil, it was incorporated in nanoemulsions for parenteral use (Ropion®, Kaken Pharmaceuticals Co.,

Lipfen®, Green Cross Co.), and is commercially available in the Japanese market since 1992. Administration of Ropion® resulted in an increase in area under the concentration-time curve and reduced clearance when compared to the solution. The incorporation of the drug into nanoemulsions containing unsterilized ethyloleate, lecithin and modified egg yolk led to a lower drug accumulation in organs such as the liver and spleen due to the lower uptake by the mononuclear phagocyte system. Prostaglandin E1, which is synthesized in several places of the body, is responsible for various physiological effects such as vasodilatation, lowering of blood pressure, angiogenesis, and inhibition of platelet aggregation. When administered for the treatment of various diseases, it has a short half-life; high doses are needed, leading to numerous adverse effects such as hypotension, diarrhea, local irritation, and pain. In this context, nanoemulsions were made commercially available in 1975, PGE1 complexed to cyclodextrins and, in 1985, prostaglandin E1 incorporated in lipid nanoemulsions (Liple®, Mitsubishi Tanabe Pharma Corporation, Palux®, Taisho Pharmaceutical) Lipid formulations are used to treat cardiovascular diseases because they accumulate in the walls of injured vessels, transporting the drug to the site of vascular injury and to protect it from rapid inactivation by the lungs .

13. Nanoemulsions and pulmonary drug delivery[31]

The lung is an attractive target for drug delivery due to non-invasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a huge surface area for local drug action and systemic absorption of drug. Colloidal carriers (i.e., nanocarrier systems) in pulmonary drug delivery offer many advantages such as the potential to achieve relatively uniform distribution of drug dose among the alveoli, achievement of improved solubility of the drug from its own aqueous solubility, a sustained drug release which consequently reduces dosing frequency, improves patient compliance, decreases incidence of side effects, and the potential of drug internalization by cells. 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. Bivas-Benita *et al.* reported that cationic submicron emulsions are promising carriers for deoxyribonucleic acid vaccines to the lung since they are able to 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. Thereforethenebulization 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). A novel pressurized aerosol system has been devised for the pulmonary delivery of salbutamol using lecithin-stabilized microemulsions formulated in trichlorotrifluoroethane.

14. Nanoemulsions as gene delivery vector[23]

Emulsion systems have been introduced as alternative gene transfer vectors to liposomes. Other emulsion studies for gene delivery (non-pulmonary route) have shown that binding of the emulsion/DNA complex was stronger than liposomal carriers. This stable emulsion Nanoemulsions — Advances in Formulation, Characterization and Applications in Drug Delivery system delivered genes more efficiently than liposomes. Silva *et al* evaluated factors that influence DNA compaction in cationic lipid nanoemulsions [cationic nanoemulsions containing stearylamine (a cationic lipid that presents a primary amine group when in solution, is able to compact genetic material by electrostatic interactions, and in dispersed systems such as nanoemulsions this lipid anchors on the oil/water interface conferring a positive charge to them. The influence of the stearylamine incorporation phase (water or oil), time of complexation, and different incubation temperatures were studied. The complexation rate was assessed by electrophoresis migration on agarose gel 0.7%, and nanoemulsion and lipoplex characterization was done by dynamic light scattering (DLS). The results demonstrate that the best DNA compaction process occurs after 120 min of complexation, at low temperature (4 ±1 °C), and after incorporation of the cationic lipid into the aqueous phase. Although the zeta potential of lipoplexes was lower than the results found for basic nanoemulsions, the granulometry did not change. Moreover, it was demonstrated that lipoplexes are suitable vehicles for gene delivery.

15. Nanoemulsions for phytopharmaceuticals[22]

Recently, considerable attention has been focused on the development of novel drug delivery systems for herbal drugs. However some limitations of plant bioactive like instability in highly acidic pH and liver metabolism led to drug levels below therapeutic concentration in the blood resulting in less or no therapeutic effect. Hence, encapsulation of plant extracts or its bioactive would minimize their degradation or presystemic metabolism, and serious side effects due to

accumulation of drugs to the non-targeted areas and improves the ease of administration in the peadiatric and geriatric patients. Lipid nanoemulsions containing oil from medicinal plants or hydrophobic drugs have been shown to improve drug solubility, reduce side effects of various potent drugs, increase the bioavailability of drugs, and to prolong the pharmacological effects in comparison to conventional formulations such as conventional emulsions. Formulation of nanoemulsions containing phytoactives has been reported. The effect of nanoemulsion on intestinal absorption of colchicine was demonstrated *in vivo*. Colchicine nanoemulsion was prepared with isopropyl myristate, eugenol, Tween 80, ethanol and water, with eugenol being the oil phase in the formulation. Result obtained indicated that the intestinal absorption of colchicine was significantly enhanced by the nanoemulsion formulation. Genistein has been shown to possess anticancer activities in different experimental systems, yet the same effects could not be translated in the clinical setting due to its poor bioavailability. Researcher have tried various nano approaches including incorporation of genistein into topical nanoemulsion formulations composed of egg lecithin, medium chain triglycerides or octyldodecanol and water by spontaneous emulsification with improved activity. Oil in water nanoemulsion formulation has also demonstrated increased anti-inflammatory activity of curcumin.

2. 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.

3. CONCLUSION

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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