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RESEARCH ARTICLE

NANOEMULSIONS FOR BRAIN DRUG DELIVERY SYSTEMS

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ABSTRACT

Nano – emulsions are quiet an importance nowadays in order to improve the technology of drug administration in various routes of administration. In this study it has been illustrated about the different routes of administration with the evaluation and characterisation. Different routes such as the nose to brain drug delivery system along with transdermal delivery and brain drug delivery system. The effect of surfactant and co- surfactant with its effect in the viscosity and concentration plays an important role in the formulation basis of the nano - emulsions are studied. It also shows the difference in characteristics between the nano-emulsion and micro- emulsion. The effectiveness in the enhancement of the technologies in nano-emulsion also is a great debate which has been studies. This study also illustrates the effect in the viscosity, porosity, zeta potential, kinetic model, invitro in vivo studies, viscosity and surface studies.

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INTRODUCTION

Nano formed emulsions are usually oil in water based constituting of mean diameter about 50-1000nm. Usually the average of the size lies in the range between 50 -100nm. It is also possible to inherit emulsions water in oil type as well. The main constituent if the emulsions are the choice and quantity of the surfactant used in the formulations of the emulsion which was recogonized safe by the "Generally Recognized as Safe" (GRAS) from the FDA policies and conditions. These emulsions are generated from the water-immiscible oil phase under high shear stress or by the method of mechanical extrusion technique. These type of emulsions are called as mini-emulsions or the ultra-fine emulsions or the sub-micron emulsions. By the phase behaviour studies it was showed that the droplet size of the emulsion produced a surfactant structure during the phase of lamellar production at the inversion point induced either by temperature or the composition. The nano-emulsions have a great tendency to dissolve large quantities of hydrophobic that prevent the drugs for further compatibility against from further oxidation and enzymatic action for the parental administration. As a result it gives the advantage of reducing the dose of the drugs and control the release characteristics of the drugs. As a result it leads to lack of sedimentation, flocculation and creaming in combination with large surface area and free energy bound between the drug particles for this route of administration. Due to it consists of large interfacial area of tension it improves the drug transport into the specific site of action and their delivery to the specific sites.

Preparation of Nanoemulsions: They are non-equilibrium systems of structure liquids and hence their preparation involves infusion of large amount of their surfactant level or their energy bound between them. As a result, high energy or low energy results in mechanical forces in order to bind the particles together into 2 different phases of the particles from that of the oil and water phases should be separated from each other so that the drug particles are separately generated in order to render the accurate release characteristics in the site of action. This process is achieved by ultra soni -cation process, micro fluidizer and high pressure homogenizer. The particle size of the particles generated depends upon the instrument used for the generation of the particles with the factors like temperature, pressure, properties and other formulation properties of the chemicals used. This method allows for a greater control of par- ticle size and a large choice of composition, which in turn controls the stability, rheology and colour of the emulsion. Although high-energy emulsification methods yield nanoemulsions with desired properties and have industrial scalability, they may not be suitable for ther- molabile drugs such as retinoids and macromolecules, including proteins, enzymes and nucleic acids.

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It is easily prepared by low energy emulsification method which in turn generates phase transition behaviour and other properties which in turn promotes the formation of small particles that are required for the generation of nano particles in the oil in water type of emulsion. The low energy method is utilised because it has the the capacity to utilise the energy stored from the systems that generate energy for the particle formation nano sized. As a result it produced change in some parameters that has an impact on the hydrophilic lipophilic balance on the system like the temperature, pressure of the rotating speed of the instrument, composition, energy generated during the process etc.

Energy usage as well as generation always plays an important role in the formation of nano particles in oil water emulsion because it forms a thermodynamic non spontaneous generation of the emulsion. As a result it renders energy that is responsible in the formation of macro-emulsion. The presence of surfactant plays an important role in the nano emulsion formation due to lower surface tension property like the PVC, PVA etc.. During emulsification an increase in the interfacial area takes place and this causes a reduction in surface excess. The equilibrium is restored by adsorption of surfactant from the bulk, but this takes time (shorter times occur at higher surfactant activity). Because of the lack or slowness of equilibrium with polymeric surfac- tants, dilatational modulus will not be the same for ex- pansion and compression of the interface .In practice, surfactant mixtures are used and these have pronounced effects on surface tension and dilatational modulus. Some specific surfactant mixtures give lower surface tension values than either of the two individual compo- nents. Polymer-surfactant mixtures may show some syn- ergistic surface activity. Another important role of the emulsifier is to prevent shear-induced coalescence during emulsification. The requirement is that the continuous phase has a significant excess of surfactant. This excess enables new surface area of the nanoscale droplets to be rapidly coated during emulsification, thereby inhibiting shear-induced coales- cence. This excess is generally in the form of surfactant micelles in the continuous phase. These micelles dissoci- ate into monomers that rapidly adsorb onto the surfaces of newly created droplets.

Nanoemulsions and Transdermal Delivery: 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 con- trolled drug delivery over extended period of time, with self -administration also being possible, which may not be the case with parenteral route. The drug input can be eliminated at any time by the patient just by removing the transdermal patch. Their transparent nature and fluidity, confers on nano-emulsions 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 dis- eases and disorders including cardiovascular conditions, Parkinsons' 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 bio actives. The three routes by which drugs can primarily penetrate the skin are through the hair follicles, sweat ducts or directly across stratum comeum, 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 con- trolled. 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 treatment of different types of cancer by oral delivery. Water-in-oil nano emulsion for- mutations of caffeine have been developed for transdermal drug delivery. Comparison of in vitro skin permeation profile between these and aqueous caffeine solutions showed significant increase in permeability parameters for the nano emulsion loaded drugs.

Use of nano emulsions in transdermal drug delivery represents an important area of research in drug delivery, which enhances the therapeutic efficacy and also the bioavailability of the drugs without any adverse effects. 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 bio availability 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 nano emulsion formulations possess improved trans- dermal and dermal delivery properties in vitro, as well as in vivo. Nano emulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels. For these reasons, many efforts have been made to design strategies to bypass the BBB for the delivery of active substances to the target site. The design of a strategy for brain targeting means to use non-conventional administration routes and, in turn, to design drug formulations with properties suitable for optimal delivery through these routes.

The nose is responsible both for respiration and for olfaction. The human olfactory region, where olfactory and trigeminal nerve terminations are present, occupies 2–12.5 cm^2, representing approximately 1.25–10% of the total surface area of the nasal cavity, and it is about 60 μm thick. Olfactory and trigeminal pathways are the only routes by which the brain is connected to the outside environment. Thanks to the direct connection provided by the olfactory and trigeminal nerves present between the olfactory epithelium and the brain, drug targeting can be achieved with the administration of formulations onto nasal mucosa .Therefore, particular attention must be given to studies of the blood–nerve barrier (BNB), which consists of endoneurial microvessels within the nerve fascicle and the investing perineurium. These microvessels are actively involved in the mechanisms that regulate the permeability of the perineurium and endoneurial capillaries, and surely they play an important role in the passage of substances from olfactory and trigeminal pathways into the CNS. Nose-to-brain drug delivery is a painless, non-invasive administration route that can be used to deliver therapeutic agents into the brain by bypassing the BBB. These drug administration pathways are characterized by many advantages such as increased patient compliance, high safety, remarkable ease of administration and rapid onset of action, as well as minimized systemic exposure. Furthermore, the use of nasal mucosa as a route of drug administration permits drugs to avoid hepatic first-pass

metabolism. Consequently, nasal doses are often 2–10 times lower than oral doses. Direct transport of drug to brain through nasal administration is therefore more promising than oral or intravenous routes of administration. However, despite its numerous advantages, nose-to-brain drug delivery can be limited by possible low bioavailability due to enzymatic degradations of sensitive drugs onto the mucosal surface, high clearance and restrictions determined by the anatomy of the nasal cavity (e.g., small volume, limited surface area of the olfactory mucosa, mucociliary clearance, etc.). These problems should be correctly addressed in designing suitable nose-to-brain formulations (Figure 1). Despite these limitations, examples of promising results are present in clinical trials.

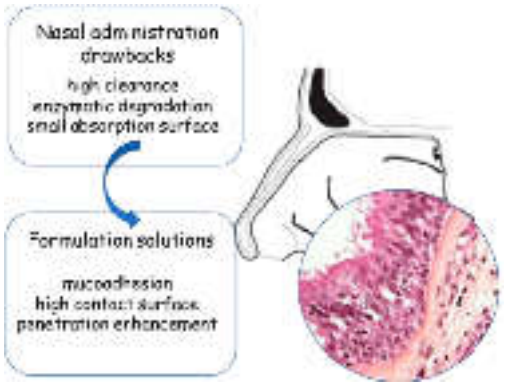

Figure 1. The nose as a route for the administration of drugs

According to the present literature, different kinds of nanocarriers are used to prepare nasal formulations able to target the brain, constituted by polymer-based and lipid-based nanoparticles. Among nanocarriers, the liquid dispersed systems represented by nanoemulsions (NEs) are attracting more and more interest in nose-to-brain delivery. The aim of this review is to define the present situation, according to literature, regarding the use of NEs for the treatment of neurological pathologies through the nose-to-brain route.

General Overview of NEs for Nose-to-Brain Delivery: The easiest classification of NEs designed for nose-to-brain delivery is based on the drug loaded and the therapeutic purpose. As the final target is the brain through the nose, the pharmacological actions regard pathologies of the CNS. In one case, a probe is loaded in the NE to obtain brain imaging. The formulations used in the intranasal administrations of drugs are always, in our knowledge, O/W emulsions. A general overview of the present literature about NEs for nose-to-brain targeting shows clearly that intranasal use is often an alternative to the oral therapy. In fact, if the drug is administered orally to reach the brain, this kind of administration can present problems for some drugs, which are summarized in Table 1. CNS delivery through the nasal mucosa sometimes performs better than parenteral administration as well, as shown by in vivo experiments. One of the first examples in the literature of the use of NEs to reach the brain through the administration onto nasal mucosa is a paper by Kumar et al. in which NEs were utilized to carry risperidone, an antipsychotic drug belonging to the group of benzisoxazole derivatives .This drug is available in trade as oral formulations (tablets and oral solutions) which are characterized by a problem of low bioavailability, mainly owing to the first-pass hepatic metabolism.

Furthermore, the systemic oral administration has many side effects. Risperidone NEs were prepared using Capmul MCM as the oily phase (8%, *w*/*w*) and Tween 80 as a surfactant. Risperidone mucoadhesive NE was prepared adding chitosan (0.50%, *w*/*w*) to NEs and stirring the dispersion for 1 h. In vivo studies were carried out on Swiss albino rats: Drug distribution in the blood and in the brain following intranasal and intravenous administrations of NEs and risperidone solutions were determined using technetium (99mTc) labeling. These studies showed more rapid and larger drug transport into the CNS after the intranasal administration of the mucoadhesive chitosan-containing NEs in comparison with nasal and intravenous NEs and solutions. Analogous results were obtained by the same authors preparing drug-loaded NEs containing olanzapine, a second-generation antipsychotic agent with broad efficacy .According to the authors' opinion, these positive results were related to the enhancing of the nasal retention time due to the presence of chitosan, thus confirming the importance of this polymer as mucoadhesive agent in nasal formulations. An important application of nose-to-brain delivery with NEs was that described by Mahajan et al., who used NEs to carry anti-HIV drugs [28]. It is known that after the initial infection, CNS is the region in which HIV viruses constitute a sort of "anatomic reservoir", and from which they can reactivate the infection. Furthermore, the brain infection from HIV can determine neuro-AIDS, a form of dementia and cognitive impairment. It is clear that improved drug delivery to the CNS will reduce the possibility of underlying persisting infections. Saquinavirmesylate is a protease inhibitor with activity against HIV-Type 1 (HIV-1). However, its bioavailability is low, owing to its low solubility in water. Furthermore, saquinavir permeability through the BBB is poor and is a P-glycoprotein and cytochrome P450 substrate. For all these reasons, nasal O/W NEs containing saquinavirmesylate were prepared by the spontaneous emulsification technique using Capmul MCM, a mono-diglyceride of medium-chain fatty acids (mainly caprylic and caproic). NEs were characterized in terms of drug content, droplet size and zeta potential. Ex vivo permeation studies were carried out using excised fresh sheep nasal mucosa. NEs showed an increase in drug permeation compared to plain drug suspension. Cilia toxicity was low. In vivo biodistribution studies, carried out after nasal administration of 99mTc formulations, showed higher drug concentration in the brain after nasal administration of NE with respect to intravenous administration. Gamma scintigraphy imaging of a rat brain demonstrated increased drug transport to the CNS after NE nasal administration.

NEs have also demonstrated the ability carry active principles of natural origin, and NEs loaded with curcumin led to formulations with interesting potentialities. Curcumin is a phenolic phytochemical achieved from the rhizome of *Curcuma longa* L. The curcumin oral administration in Alzheimer's disease animal models determines the inhibition of Amiloid beta (Aβ) peptide oligomerization and deposition in the brain. Furthermore, curcumin has been found to improve memory and cognitive deficits in rats. However, the efficacy of this drug is limited by its low aqueous solubility, poor absorption from the gastrointestinal tract and rapid metabolism. For these reasons, a study was carried out about the development of curcumin-loaded NEs for intranasal delivery to the CNS. NEs were prepared using the spontaneous nanoemulsification method, adding curcumin to

the oil phase (Capmul MCM). Chitosan was added to obtain mucoadhesive NEs. The goal of the study was to optimize the curcumin NE formulation process using a Box–Behnken design that was constructed using oil, surfactant and co-surfactant concentrations as independent variables. Globule size and zeta potential were studied as responses. The concentrations of oil and surfactant were found to be critical for obtaining the desired globule sizes, whereas the addition of chitosan affected zeta potential of NEs. In vitro cytotoxicity studies were carried out using SK-N-SH cell line, showing that the formulations determined no toxicity. Ex vivo diffusion studies were carried out with Franz diffusion cells: Chitosan-containing NEs showed the highest flux and permeation across the mucosa compared to NEs without chitosan and drug solutions, confirming the importance of chitosan not only as mucoadhesive polymer but also for its penetration enhancing properties.

Nano- emulsions and Drug Targeting: Another interesting application, which is experiencing an active development, is the use of nanoemulsion formula- tions, 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 atten- tion as colloidal carriers for targeted delivery of various anticancer drugs, photosensitizers, neutron capture ther- apy agents, or diagnostic agents. The development of magnetic nanoemulsions is an innovative approach for cancer therapy. These can deliver photosensitizers like Foscan® to deep tissue layers across the skin thereby in- ducing hyperthermia for subsequent free radical genera- tion. This methodology can be used for the treatment of cancer in the form of photodynamic therapy.

Advantages of Nanoemulsions as Drug Delivery Systems: Smaller the droplet size, greater the reduction in the gravitational force hence renders very small droplet size. Small droplet size also prevents from flocculation which helps the dispersion of the medium to be smooth without any hindrance.

- Smaller the size of the droplets, lesser the flocculation it will prevent coalescence and surface flocculations are prevented.
- The increase in surface area of the emulsion system also raise the penetration activity of the actives.
- The emulsion system produced renders a transparent medium with their fluidity and absence of their thickness may give pleasant aesthetic character on the skin.
- Unlike micro-emulsions (which require surfactant concentration on an increased quantity for its formulation basis) nano-emulsions can be prepared with lesser surfactant concentrationin the formulation basis.

Disadvantages of Nano -emulsion Drug Delivery Systems

- Formulation of nano – emulsions may require special application techniques like the high pressure homogenizer and the usage of ultra -sonic as well.
- It was been studied that there is tremendous increase in the production and manufacturing aspects for nano-emulsions to be produced.
- The cost of equipment are also high in the use of emulsifiers.
- Misunderstanding in the knowledge about the mechanism of production of submicron droplets and usage of surfactants and cosurfactants.

Thermodynamic Stability and Surface Characteristics: There is correlation between nano- emulsion and micro-emulsion in which the resemble in their transparency and low viscosity properties. The differences between the two systems are that there is a difference in their kinetic stability whereas on the other hand the system is thermodynamically stable. Nano – emulsions due to their small droplet size it possess higher stability over the process of sedimentation and creaming than macro- emulsions.

Nano -emulsion Droplet Size, Polydispersity and Zeta Potential. Light scattering which is also known as photon correlation spectroscopy was used to analyse fluctuations that were produced during the emission of scattering particles. Nano –emulsion of its droplet- size, poly dispersity could be assessed by the PCS analyser. It is also used to determine the poly dispersion capacity which is used to measure the PSD of the nano - emulsion based on the quality and quantity of homogenicity of the dispersion. PCS renders a z-average of particle diameter. Laser diffraction is another method for measuring the particle size of the nano- emulsion. The suitablePSD is generated by this method is usually volume based and is expressed in the basis of the volume of equivalent spheres ($D_{N\%}$) and weighted mean of the volume distribution. Span = $(D_{90\%} - D_{10\%})/D_{50\%}$ (1)where $D_{N\%}$ (N = 10%, 50%, 90%), means the percentage volume of the nano- sized particles with diameters to $D_{N\%}$ equals to N%. The smaller the span value the narrower will bethe particle size distribution of the nano particles generated during the formulation of the nano- emulsion.

Viscosity Determination: This method is carried out with the help of a viscometer. Surfactant is responsible for the viscosity of the nano- emulsions in the water in oil components of the emulsions and concentrations. As a fact mentioned before in the study the amount of surfactant used lowers the viscosity on the other hand, the presence of co-surfactants increases the interfacial tension between the water and oil phases in the emulsion preparation. Viscosity is a critical factor in the formulation of the nano – emulsions since it has direct impact on the drug release and stability. Water in oil type of emulsions, it has effective and better release of the drug, less greasier than oil in water type of emulsion. They possess better viscosity as well.

***In Vitro* Skin Permeation Studies:** Franz diffusion cell method was used to render the drug release level profile of the formulated nano- emulsion for transdermal drug delivery system. Confocal scanning laser microscopy is used to measure the extent of the skin depth penetrated by the release of the drug content. In vitro – drug release studies can be determined by the donor compartment of the Franz cell as the barrier and monitor the appearance of the encapsulated drug in the recipient medium with PBS of ph 7.4 and the magnetic stirrer at 100rpm n 37 ˚C ± 1 ˚C. *In vivo* release study is also referred to as derma- top pharmacokinetics, which is performed by the administration of the preparation on the animal skin. Blood samples were taken and then withdrawn at intervals which was then centrifuged and the analysis of

the plasma level were determined for the drug release content using HPLC. Results obtained by IV-IVC has an effect on the bio- availability of the drug and the basis of formulation.

Thermodynamic Stability and Surface Characteristics: Though there is some resemblance in the appearance of nano- emulsion as well as micro emulsion having the same transparency and viscosity, the system differs thermodynamically stable or kinetically stable. Nano- emulsion is kinetically stable whereas, on the other hand micro- emulsion is dynamically stable. Nano- emulsions because of the smaller particle size they render higher stability over sedimentation and creaming than that of micro emulsions.

Major Challenges of Nano-emulsion Drug Delivery Systems
The production of nano- emulsions utilises significant amount of energy input and as a result low energy system are integrated for industrial scale as a result these process use higher concentration of surfactants which does not yield a stabled nano - emulsion. Nano- emulsions are produced by using high energy method on the usage of mechanical instruments such as high pressure homogenizers which are expensive, extreme use of energy and hence difficult for service. This shows it is a low translation for the patented nano- emulsion formulation. There is also an absence of understanding the mechanism of the production of sub-micron droplets and the usage of surfactants and co-surfactants in the formulation of nano- emulsion. Finally, there is a drawback for the introduction of the new systems without the full evaluation of it's cost and benefits.

Future Industrial Perspectives: Nano- emulsion has shown and exhibited characteristics to emerge as a novel drug in delivery system. They have been used in the pharmacies and other laboratories due to the ability of showing solubilizing non polar active compounds. The application of various nano emulsions have become a promising demand in various fields of pharmaceutical and therapeutics industry in the development of cosmetics and skin. One of the critical aspect of nano- emulsions is that they act as efficient characters of bio active that render various routes of administration. Their parenteral route of administration has been utilised for the transport of nutritional supplements, controlled delivery system, vaccine delivery system specific targeted drug delivery system. The main feature is that the droplet size is correlated to the absorption in the GIT. In the formulation of nano- emulsions there might be possible limitations but in order to overcome in the pharmaceutical and food industry the production of nano – emulsions. It has provided various strategies in the production and technology basis for those industries that are involved in the production of parenteral and macro emulsions for economic form in a long run.

With the usage of new instruments required during the process of the formulation of nano- emulsions for high shear homogenizer, the cost of production would be reduced. Further analysis and study was done the role of surfactants in the production process that would lead to emulsifier process and new techniques for the usage of nano- emulsions would be used. Nano-emulsions can be moulded in to targeted delivery system and this stands significant in the area of oncology for the treatment of tumours and brain drug delivery system.

Conclusion

From the study we have concluded that the effect of the nano- emulsion in the advancements of the processing formulation mechanism is quiet a big deal. It has been proved that the nano- emulsions have a better viscosity than that of micro- emulsions in order for the drug release in the targeting system. The best way for the route of administration is the nose to brain drug delivery system. The release rate of the drug is enhanced by this method and the method of formulation which showed these are results are oil in water type of emulsion.

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