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# A REVIEW ON INTRANASAL NANOEMULSION BASED BRAIN TARGETING DRUG DELIVERY SYSTEM

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**Abstract:**

*The major role of blood–brain barrier (BBB) is to protect the brain from toxic substance. It does not allow therapeutic agents to enter. The nasal administration of drugs via nose-to-brain pathway allows direct drug targeting into the brain and avoids the first-pass effect. Through the nasal route the drug can enter the brain directly. Nasal delivery has become area of interest as it has advantages as ease of administration and non-invasiveness. It avoids hepatic first-pass metabolism and shows efficient absorption across the permeable nasal mucosa which confirms its selection over other traditional routes like parenteral delivery. Thus nasal delivery has many applications for local, direct nose-to-brain and mucosal vaccine delivery systemic. Selecting nanoemulsions for carrying drug is said to be a promising approach. For a drug to show its effect it should have a right route of administration which provides a right channel to reach the target they require to be suitably protected in the biological milieu till they are delivered to the site of action. This review focuses on the current situation in the use of nanoemulsions for targeting the Brain. Nanoemulsions for nasal use appear to be non-invasive and safe for brain targeting in order to treat diseases.*

**Keywords:** *Blood-Brain Barrier, Brain targeting, Nanoemulsion, Nasal.*

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## INTRODUCTION:

The microvasculature of the CNS is said to be as a blood–brain barrier (BBB) as it separates the brain from the remaining part of the body. CNS vessels look after the exchange of molecules and cells between the blood and the brain. The barrier allows the BBB to protect the CNS from external agents. BBB cells can communicate with CNS cells and adapt accordingly [1]. Study of the mechanisms which regulate the BBB during health and their modification during disease includes interdisciplinary studies that several researchers put correctly into evidence and give an important support in finding the required therapeutic treatments [2-3]. When a direct delivery to the brain required the drug can be taken via intra-parenchymal injections, catheter infusions, focused ultrasound approaches or external electromagnetic field-based methodologies, intracranial delivery with mini-pumps. But all such techniques are risky in particular because of the need for surgical intervention and most of them do not suite in cases of multiple or chronic regimens [4]. The nose looks over respiration and olfaction. The human olfactory region where olfactory and trigeminal nerve terminations 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 [5]. There is a direct connection of the olfactory and trigeminal nerves present between the olfactory epithelium and the brain drug targeting is thus possible with the administration of formulations onto nasal mucosa [6-8]. Nose-to-brain drug delivery is been recognized widely as it a non-invasive, painless administration route used to deliver therapeutic agents via BBB into the brain [6,9-12]. These drug administration pathways are characterized by many advantages such as increased patient compliance, high safety and remarkable ease of administration and rapid onset of action as well as minimized systemic exposure. The use of nasal mucosa as a route of drug administration allows drugs to avoid hepatic first-pass metabolism. Various kinds of nanocarriers are used to prepare nasal formulations able to target the brain constituted by polymer-based and lipid-based nanoparticles [13–15]. Amongst the nanocarrier the liquid dispersed systems represented by nanoemulsions (NEs) are attracting more and more interest in nose-to-brain delivery.

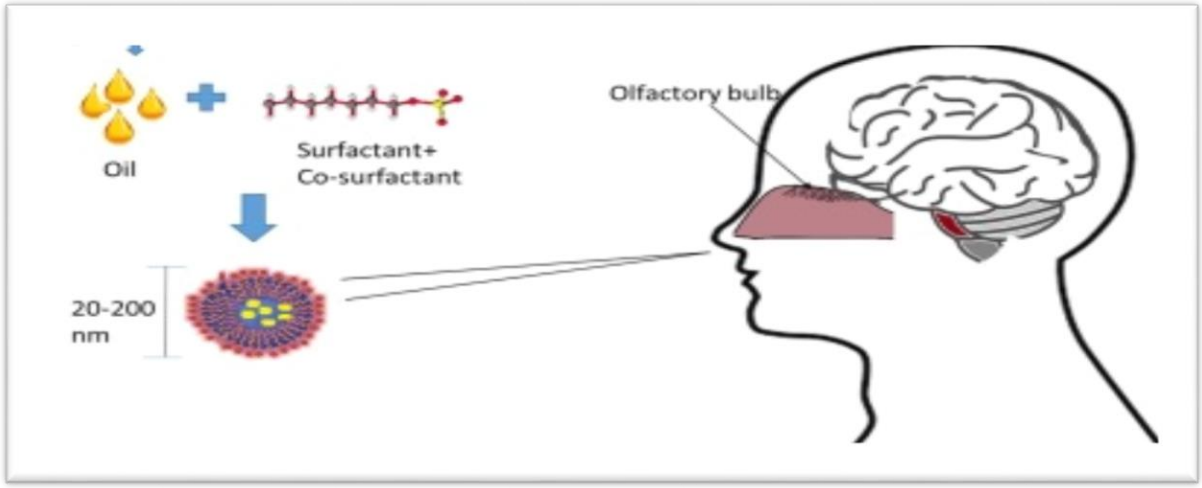


**Figure1: The nose as a route for the administration of drugs**

## NANOEMULSIONS FOR DRUG DELIVERY:

Using nanoemulsions as vehicles for carrying active pharmaceutical ingredients is emerging as a better approach for the targeted delivery. Nanoemulsions with a droplet size of 20-200 nm were developed around 20 years ago. Often referred to as mini submicron, ultrafine or fine dispersed emulsions. Nanoemulsion formulations either involve oil droplets dispersed in aqueous medium (O/W) or the reverse (W/O). They are non equilibrium systems and hence their preparation involves the input of a large amount of either energy or surfactants and in some cases a combination of both. NEs can be formulated into different kinds of dosage forms like liquids, creams, gels, foams, sprays and can be administered by different routes including oral, parenteral and ocul ar in addition to nasal. NEs are characterized by a higher surface area with respect too ther formulations and by along term physical stability because the small droplet size impairs destabilization phenomena like coalescence, creaming and sedimentation [17-18]. Nanoemulsions can solve problems of solubility and drug stability. When a hydrophobic drugs

dissolve in the oily phase is released from the NE and comes in contact with the surrounding aqueous envir onment, precipitation can occur. This estimates formation of particles with an enormously high surface and an improvement of drug dissolution rate. However there are limitations to this method. Firstly it is not suitable for heat sensitive drugs such as retinoids and proteins, nucleic acids, enzymes.

Secondly due to the high-energy requirements and inefficient use of energy (approximately 0.1% of the energy produced is directly used for the emulsification process) this approach is also relatively expensive. Thus low-energy methods are considered advantageous in regard to cost, energy efficiency, simplicity of implementation and can be used for fragile or heat sensitive drugs. However low-energy methods generally require higher surfactant concentrations than high-energy emulsification methods. A recent study by Ostertag and colleagues compared the low-energy phase inversion technique to the high-energy microfluidisation technique and found that small droplets could be produced by both methods however much less surfactant was needed for the high-energy method than the low-energy method with a surfactant to oil ratio required to obtain droplets with diameter smaller than 160 nm of ≥0.1 and ≥0.7 respectively.

Nanoemulsions have become a topic of much interest in recently over a number of different fields including the personal care, cosmetics, agrochemical, chemical, food and pharmaceutical industries. Within the pharmaceutical industry, nanoemulsions are being investigated as a formulation approach suitable for a number of different administration routes such as topical, parenteral, transdermal, ocular, pulmonary, nasal and oral. Even though nanoemulsions are primarily regarded as a vehicle for drug formulation they have received increasing attention for a number of novel applications as delivery systems for the controlled release of 168 drugs the targeted delivery of anti-cancer agents and mucosal vaccination. This interest can be largely attributed to their many unique and favorable properties providing a number of advantages over conventional 170 emulsions [16].

Nanoemulsions are stable kinetically and are thus not much affected by flocculation, coalescence, creaming or sedimentation during storage time. They can be formulated into foams, liquids, creams and sprays and being transparent/translucent can be incorporated into these preparations without loss of clarity. They are used to deliver lipophilic and hydrophilic drugs and are generally considered non-toxic and non-irritant formulations. Nanoemulsions are usually manufactured using reasonably low concentrations of surfactants that are Generally Recognized as Safe (GRAS) for human consumption by the FDA rendering them safe for enteral and mucosal administration. Furthermore nanoemulsions present large surface area and high free energy which ensures faster drug permeation of drug through absorption barriers (intestinal epithelium, skin and mucosal surfaces); as a consequence enhanced bioavailability is obtained particularly of poorly water soluble drugs but also of peptide and proteins. One additional 180 advantage of nanoemulsions is the protection from hydrolysis and oxidation provided by the encapsulation of the drug in the dispersed droplets which also provides taste masking in regard to oral administration.

**Major components of nanoemulsion:**

1. Drug: API (drug acting on CNS disease)
2. Oil: Capmul MCM, Olive Oil, Castor Oil, Soya Bean Oil, Sesame Oil, Isopropyl Myristate, Oleic Acid.
3. Surfactant: Tween 80, Span80, Span20, Tween20, Span60, Poloxamer 407, Poloxamer 188.
4. Co-solvent: Polyethylene Glycol 200, Propylene Glycol 400, Ethanol, Propylene Glycol.
5. Aqueous phase: Water

**Preparation Methods Of Nanoemulsion:**

Various methods are given for the preparing nanoemulsion. NEs preparations are classified into two broadly categories high-energy and low-energy methods. In high-energy methods small droplets includes a mechanical device which forms disruptive forces which in turn causes breaking of oil and water phases in order to produce small oil droplets this process requires high energy. The devices utilized are microfluidic, high pressure homogenizers. On the other hand low-energy methods include phase inversion methods spontaneous emulsification, and solvent displacement method. In the latter method the droplets are constituted when the system undergoes a phase inversion when there are certain changes such as temperature and goes through a low interfacial tension state [15]. The amount of lipid component(s) present depends on the emulsion (5–20% lipidic droplets in cases of O/W emulsion) and on solubility of the drug [15,16].

## GENERAL OVERVIEW OF NEs FOR NOSE-TO-BRAIN DELIVERY:

Nasal mucosa has become a wide spread approach for the administrating systemic drugs. NEs for targeting the brain show that an alternative to oral dose is an intranasal route. In fact if the drug is taken

orally to reach the brain this kind of administration can present problems for some drugs. CNS delivery using the nasal route is seen to be more efficient than parenteral administration also shown by in vivo experiments. Intranasal drug delivery system is said to be a safe route of administration of drugs next to parenteral and oral routes. [17]

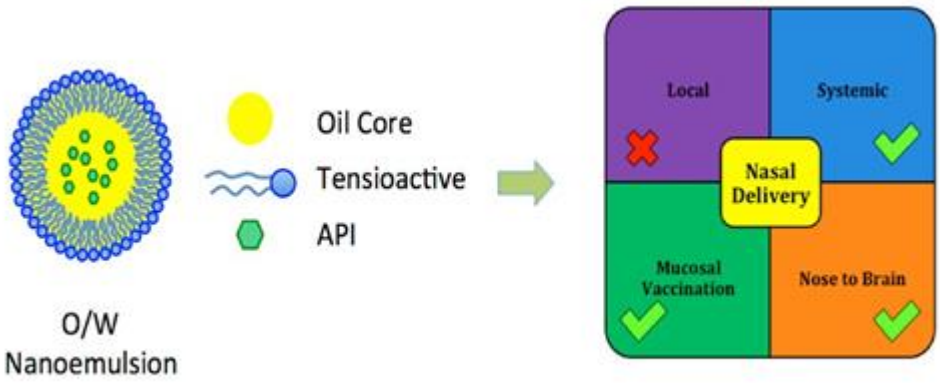


**Figure 2: Nanoemulsion improve efficasy by nasally deliverd drugs**

There are many problems related with targeting drugs to brain especially the hydrophilic ones and those of high molecular weight. This happens because of the impervious nature of the endothelium. Endothelium divides the systemic circulation and barrier present between the blood and brain [19]. This route includes the olfactory or trigeminal nerve systems for transporting exogenous substances. Olfactory or trigeminal nerve systems start from the brain and end in the nasal cavity at the olfactory neuro epithelium or respiratory epithelium respectively. The olfactory region of the nasal cavity is also involved in the detection of smell and comprises of three cell types namely olfactory receptor cells, epithelial (sustentacular) cells and basal cells. Olfactory receptor cells are present in the scattered form among the sustentacular cells of the olfactory epithelium. They originate from the olfactory bulb in the brain. Electron microscopy studies revealed that the olfactory axon of a 2 month old rabbit has a diameter of 200 nm. The olfactory area has a direct link between the nose and brain and by using nanoemulsions of the drugs can be treated. It is particularly more useful compared to oral and parenteral routes among pediatric patients as the former routes may increase the anxiety among them have reviewed the use of nanoparticles for the targeting the drug from nose to brain. They also emphasize for the need for evaluating the toxicity of the nanoparticle delivery system through the nasal route. Nanoemulsions of risperidone for its delivery to the brain via nose have been reported. Several physicochemical factors such as molecular weight, hydrophilicity and degree of ionization affect the transport of drug in solution from nose to brain. It is concluded that the emulsion show better results through the nasal rather than intravenous route [20-22].

These types of emulsions can also be used as a non toxic mucosal adjuvant for influenza vaccine virus. Another application of intranasal drug delivery system in therapeutics is their use in development of vaccines. Immunity is achieved by the administration of mucosal antigen. Currently the first intranasal vaccine has been marketed. The nasal cavity is one of the most efficient sites because of its reduced enzymatic activity, high availability of active sites and its moderately permeable epithelium. Among the possible delivery systems the use of nano based carriers hold a great promise to protect the biomolecule 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 treatment of diseases related to the central nervous system. Limitations in intra nasal delivery systems include interaction of drug with nasal mucosa thereby influencing the nasal drug absorption and also its therapeutic efficacy. Moreover only restricted amounts of drug formulations can be administrated due to the low volume of the nasal cavity [23-25].

**Characteristics that make the central nervous system (CNS) drug a candidate for nasal NE, as an alternative to oral administrations [26]**

- Low capacity to cross the Blood-Brain-Barrier
- Active substrate of intestinal P-glycoprotein
- Problems of stability
- Slow onset of action
- Bitter/unpleasant taste of the drug

Low solubility in water Nano Emulsions of Riluzole a drug approved for amyotrophic lateral sclerosis (ALS) have been recently proposed. ALS is a progressive neuro degenerative disorder belonging t o the group of motor neuron diseases and characterized by the progressive deterioration of upper and lower motor neurons. Rilu zole belongs to BCS class II. It cannot cross the BBB to reach the brain. These nano emulsions were of 24nm and the results had no presence of nasal ciliotoxicity and were stable for three months. Drug brain uptake of riluzole NEs was more compared to oral administration. It was concluded that intranasal administration is a better approach for ALS treatments. [27]

Quetiapine is an antipsychotic drug used for schizophrenia it affects about 1% people in the world. This drug has certain limits in oral therapy. It has low solubility in water and following oral administration shows low bioavailability (5–15%) and a strong first-pass effect.
For such reasons O/W NEs were prepared to target th e drug directly into the brain following nasal administ ration [28]. Tween 80 was used as surfactant. In vivo studies of the nasal administration of NEs of Transcutol P
and propylene glycol showed shorter $T_{max}$ as compared to intravenous administrations as well as higher drug transport efficiency into the brain. Brain distribution studies show that quetiapineis trans ported in the brain after the nasal administration of qu etiapine NEs. It was thus confirmed by that NEs are better option for the brain-targeted delivery of quetiapine. [28]

**Table no. 1 Examples of drugs used in brain targeting by nanoemulsion [29-34]**

| **Drugs** | **Categories** |
|---|---|
| Risperidone | Schizophrenia |
| Olanzapine | Schizophrenia |
| Ergoloid mesylate | Antiaging |
| Amiloride | Antiepileptic |
| Ziprasidone hydrochloride | Antipsychotic |
| Saquinavir mesylate | HIV infections |
| Nimodipine | Cerebrovascular spasm and senile dementia |
| Curcumin | Neurodegenerative diseases |
| Resveratrol | Parkinson's disease |
| Curcumin/Resveratrol | Age-related neurodegenerative diseases |

## FORMULATIONS INTENDED FOR NASAL DELIVERY TO TARGET BRAIN:

Different type of formulations have been developed and studied for naso-mucosal drug delivery to brain including micro or nanoemulsion, nasal gel or thermo responsive nasal gel etc. Some recent reports on nasal emulsion for brain targeted delivery include microemulsion formulation of Rivastigine, Quetiapine [38]. All of the articles reported promising drug absorption via nasal route. Among other intra-nasal delivery platforms gel formulation is very popular in pharmaceutical researchers. Gel formulation can retain on any application site more longer time than solution due to imparted viscosity. For intra nasal application inclusion of Bioadhesive polymer helps to retain the dosage form more pronged period of time onto nasal mucosa. There are some polymers that can be converted to gel form by altering pH or temperature. A delivery system which is solution in normal temperature but converted into gel at elevated temperature can also retain longer onto mucosal epithelium as well as enhances patient

compliance in term of easy administration measurable dosage etc. Such kind of system is termed as in situ gelling drug delivery platform. This dosage form showed efficient brain targeted drug delivery via intra nasal route. But effect of temperature on such type of dosage form is very crucial and needs critical evaluation.

## CHALLENGES OF INTRA NASAL DRUG DELIVERY:

There are several limitations which restrict the success of this route of drug delivery. Irregular drug absorption and less retention time of drug due to mucociliary clearance is major challenge for delivered drug into the nasal cavity. There are modified formulation methods to ensure presence of drug into nasal cavity for longer period of time. Absorption enhancers cannot be used in intra nasal preparation. Also there is variation in absorbed drug amount in different regions of brain and spinal cord [35].

Major limitation is formulation delivered via nasal route may cause naso-mucosal irritation and toxicity due to the potential incompatibility of many formulation additives with nasal mucosal tissue [36]. Some preservatives are sensitive to nasal mucosa like benzalkonium chloride. Loss of epithelial cell, loss of ciliary layer and shrinkage of mucosal layer are common toxic effects that might be incurred by incompatible active or inactive ingredient of formulation [37]. Repeated uses of nasal drops cause such type of adverse effects on nasal mucosal layer. So all the ingredients used in a formulation should be checked for nasomucosal toxicity.

## CONCLUSION:

Nanoemulsions are formulations that are more and more important in the field of nanomedicine. Their features make them suitable for nose-to-brain delivery. Mucoadhesive polymers can be added in their composition to slow down nasal clearance. The presence of chitosan as an additional excipients plays a double role because it is mucoadhesive and has penetration enhancing properties on nasal mucosa. The pathologies are all important and serious if not treated effectively can reduce the quality of life or even lead to death.

The nose-to-brain delivery is often a mode selected as an alternative to oral therapies for the CNS that can present problems usually related to the characteristics of the drug. However as demonstrated by the reported literature intranasal administrations of NEs often lead to better results also with respect to intravenous administrations. These good results can be explained by mechanisms of transcytosis /endocytosis of the nano droplets by the brain endothelial cells. Moreover the surfactant(s) present in the nanoemulsions could have a fluidizing effect on endothelial cell membranes determining enhanced drug permeability and favoring by this mechanism the olfactory and trigeminal pathways.

A nanoemulsion for intra nasal administration seems to be a promising strategy for nose-to-brain drug delivery and to achieve CNS targeting for the treatment of neuro diseases. Many efforts are required to be made to further improve the performances of nanoemulsions. Future perspectives could consider the use of additional excipients.

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## CONFLICT OF INTEREST:

Nil

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