



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article


August 2020 Vol.:19, Issue:1

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## Nasal Nanoemulsion: A Novel Approach for Targeting to Brain



IJPPR  
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals



ISSN 2349-7203

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**Submission:** 24 July 2020  
**Accepted:** 30 July 2020  
**Published:** 30 August 2020



HUMAN JOURNALS

[www.ijppr.humanjournals.com](http://www.ijppr.humanjournals.com)

**Keywords:** Brain targeting, Blood-brain barrier, Nasal delivery, Nanoemulsion

### ABSTRACT

For many years scientists are being involved in research for developing an effective and efficient drug delivery system to deliver the drug to the brain. The blood-brain barrier (BBB) acts as an obstacle for many drugs, as a result, it does not allow many effective therapeutic agents for several disorders related to the brain to reach it. The BBB has a key role in protecting the brain from various toxic or harmful substances to reach to the brain and it also acts as a physiological barrier but nose to brain pathway i.e via nasal administration of drugs targets drug directly to the brain by bypassing BBB, avoiding first-pass metabolism of the drug, absorption of the drug by permeable nasal mucosa and safest route for brain targeting. Due to several advantages of nasal delivery of the drug to brain-like non-invasive and easy administration, it becomes a more feasible route. For drugs to show its action an appropriate pathway for the administration of the drug to reach its site of action becomes very important. Nanoemulsion becomes the most promising approach for delivering drugs. Oil, surfactant, co-surfactant, water are primary components of nanoemulsion Therefore it can be used as an alternative to oral administration avoiding drawbacks like poor solubility in aqueous media, poor bioavailability, slow onset of action and degradation by enzymes. This review focuses on Nasal Nanoemulsion for delivering drugs effectively to the brain by bypassing BBB.

## **INTRODUCTION:**

Brain disease is one of most concerning in various platforms like social, economic, and global with about affecting 1.5 billion people around the globe. Despite having several developments in brain and CNS (Central nervous system) disorders various diseases like Parkinson, Alzheimer's, Huntington, Brain tumor, brain stroke, brain cancer, Acquired immunodeficiency syndrome, multiple sclerosis, and some other disorders are now pandemic and lead to suffers many people daily. [1-5]

Around more than 95% of drugs are not able to enter the brain due to the Blood-brain barrier (BBB) which leads to the administration of a very high dose of drugs to attain proper drug concentration in the brain, but it has several severe side effects. Thus, it becomes very important to overcome the Blood-brain barrier for targeting the drug to the brain. Conventional treatment like using radiation and intravenous delivery of chemotherapeutic agents was not successful. There are two approaches by which BBB can overcome the first one is a direct approach that includes an invasive method in which drilling a hole in the cranium to direct the drug to brain tissues. The second approach is the indirect approach which includes non-invasive methods like colloidal drug delivery, micelle, polymeric as well as lipid nanoparticles, liposomes and it was observed that lipid carriers can deliver the drug to the brain more rapidly by traversing BBB.[6-12] Nanoemulsions are lipid-based nanocarrier having a dispersed phase (20nm). Nanoemulsions are widely used for enhancing bioavailability and able to deliver the drug through various routes like oral, nasal, parenteral, transdermal, and ocular. Due to its lipid nature, it has excellent potential to deliver the drug to the brain.[13-22] This review will cover various components and design of nanoemulsion for targeting to brain their applications and prospects.

### **Blood-Brain Barrier**

The BBB is also known as the microvasculature of the central nervous system (CNS) because it isolates the brain from the remaining parts of the body. Bypassing BBB is the first for enhancing the targeting of drugs to the brain. The CNS vessels cannot be fenestrated, and the main function of CNS vessels is to exchange molecules and cells amongst the brain and blood. This strongest BBB capacity to protect CNS from the exogenous invasion of toxins, pathogens, and other agents including drugs also. [23]

The specific properties of the brain that composes the BBB structure are endothelial cells which mainly composed of walls of blood vessels. The endothelial cells of BBB vary from endothelial cells of non-neural tissues as they are polarized and held in together by a tight junction that inhibits the influx of solutes (molecules and ions) and restricts transcytosis and pinocytosis transport system. The endothelial cells have two different types of transport systems first is efflux transporters which eliminates the lipid-soluble toxins which passively diffuse through the cell membrane, for example, p-glycoprotein which plays a major role in drug-resistant tumors and epilepsy and the second one is the influx transporters which carries nutrients to the brain by crossing BBB. BBB is also an active interface that controls the CNS micro-environment for its normal neuronal functions. BBB can communicate with cells of CNS to adapt behavior according to the needs of CNS due to some pathological conditions or due to some disease progression. [24]

Cerebral capillaries remain lined organized through astrocytic end-feet progressions then high-density endothelial cells. Endothelial cells also accompanying astrocytes remain stitched together to arrange tight junctions at edge amongst blood as well as the brain. The following are the tight junctions that have been comprised of transmembrane proteins for example in occludin, claudins as well as a junctional adhesion molecule (JAM). Each transmembrane protein is presently affixed by an additional protein complex that contains zonula occludens protein 1(ZO-1) and their correlated proteins incorporated in endothelial cells. Paracellular transport is facilitated through tight junctions [25]. Membranes of endothelial cells come up with two individual sections, luminal (blood side) and abluminal (brain side). Molecules ought to impede perivascular space enclosed by the plasma membrane of capillary endothelial cells, particularly astrocyte end feet that includes a major section of an endothelial surface (> 90%) toward regulating the permeability of BBB. The elevated electrical resistance of brain capillaries identified to be 1000-2000  $\text{cm}^2$  represents an additional crucial barrier that restricts access of polar as well as ionic substances within the brain [26]. Such a high electrical resistance is assigned to the soaring manifestation of occludin [27]. Even Though choroid plexus shows a most important part in blood CSF barrier to prohibit exogenous materials [28], the blood-CSF barrier may perhaps be believed irrelevant owing to the constrained surface area. Brain disease states frequently interrupt BBB. [29]

### **Nose to brain drug delivery**

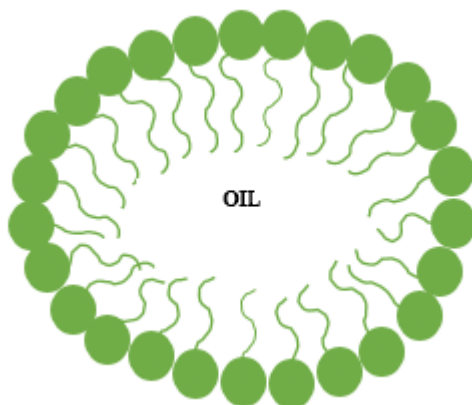
The nasal route for delivering drug which targets CNS is the most preferred route due to olfactory nerve, within nasal mucosa has direct connection among brain and nose. The nose has two major functions respiration as well as olfaction. The human olfactory region is an area where termination of olfactory and trigeminal nerves are presently occupying about 1.25-10% surface area of the nasal cavity. The brain is connected via the outside environment by the means of trigeminal and olfactory pathways just because of this drug targeting, which can be achieved utilizing administering formulations into the nasal mucosa. [30-32]

Brain to nose delivering of the drug has several advantages, such as it is a non-invasive method, does not cause any sort of pain, high level of safety, do not cause any harm, having patient compliance, ease in administering, fast onset of action, lesser systemic exposure, avoid the first-pass metabolism, as a result, nasal dose which is administered is about 2-10 times lesser than the oral dose. The nasal administration of drugs is most promising in comparison to intravenous or oral route. But despite having numerous advantages nasal delivery of drugs has some drawbacks also, such as lower bioavailability due to enzymatic degradation of the drug in the nasal mucosa, high level of clearance of the drug, due to limited surface area of olfactory mucosa small volume of the drug can be instilled. [33-35] Drug preparation on nasal administration arises in connection through mucosa then quickly moved straight into the brain, avoiding BBB, and attaining actual quick cerebrospinal fluid concentrations. Approximate quantity of administered drug gets into systemic circulation by respiratory area then little quantity is wasted to nasal-related lymphoid tissues. [36] According to various literature various types of a nanocarrier are utilized for formulating nasal preparations so to target brain delivery these are polymer or lipid-based nanoparticle but amongst all of them, nanoemulsion having liquid-based dispersed medium is more prominent in the nose to brain delivering of the drug as it is a novel approach to target drug to the brain. [37-39,100,101]

### **Nanoemulsion: A lipid Nanocarrier**

Nanoemulsion is an emerging and best approach for targeting drugs at a specific site. Nanoemulsion may be defined as oil in water emulsion or water in oil having mean droplet size ranging between 50-1000nm due to which it is can also be termed as a sub-micron emulsion (SME) these are kinetically stable, non-equilibrium mixtures containing oil, water,

surfactant, and co-surfactant. Nanoemulsion can easily be formulated into several dosage forms like cream, gel, liquid, foam, spray, and many more and can also be administered through several routes like oral, topical, parenteral, ocular, and nasal. [40-43]

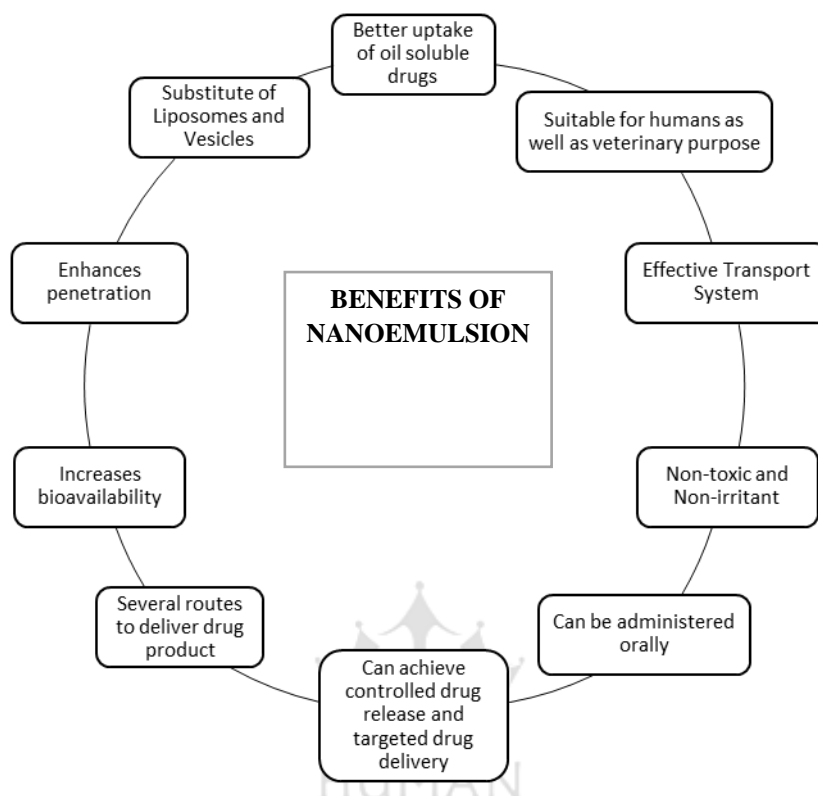


**Figure No. 1: Structure of Nanoemulsion**

Having small droplet size leading to the high surface area in comparison to other formulations and due small droplet size has many advantages like it avoids destabilization processes like creaming, sedimentation, and coalescence. Nanoemulsion can resolve complications like solubility and drug stability. Hydrophobic drugs dissolve in the oil phase of nanoemulsion and further releases drug from this oil phase and come into an aqueous phase which leads to nanoprecipitation. This process results in the occurrence of particles with very high surface area and enhances the dissolution of the drug. But there are certain limitations to this type of method like heat-sensitive drugs for example enzymes, nucleic acid, proteins, and retinoids can be manufactured and due to inadequate use of energy required for the emulsification process of nanoemulsion can limits manufacturing of nanoemulsion. [41-45]

In recent years nanoemulsion has become an area of interest among different fields such as cosmetics, pharmaceuticals, food, personal care, agrochemical, and chemical. Nanoemulsion is regarded as a novel drug delivery system as it acts as a vehicle for carrying drug formulations and it is widely used for targeted drug delivery systems, for controlled release of drugs and has numbers of advantageous properties over conventional emulsion. [45] Nanoemulsions are used to deliver hydrophobic as well as lipophilic drugs which are formulated by utilizing very smaller concentrations of surfactants which are generally recognized as safe (GRAS) for human use by FDA for using it as mucosal and nasal

administration. It enhances the bioavailability of poorly water-soluble drugs due to its smaller droplet size which ensures faster drug solubilization and permeation. It also protects the drug from oxidation and hydrolysis there are several advantages of nanoemulsions some of them are depicted in the below-mentioned figure 2.



**Figure No. 2: Benefits of Nanoemulsion**

### 1. Components of Nanoemulsion

- Drug
- Oil phase
- Surfactant and Co-surfactant
- Aqueous phase

Nanoemulsions are dispersions mainly composed of oil, surfactant, co-surfactant, and aqueous phase which are further micronized by some external energy source. Nanoemulsion is created on the phenomenon of low interfacial tension which can be done by the addition of co-surfactant. By lowering interfacial tension, a thermodynamically stable nanoemulsion is

formed. The solubility of the drug and type of nanoemulsion (O/W or W/O) determines the amount of lipid component that must be used within the formulation. Solubility ability of oil phase is one of the most important factors for selection of oil phase for solubilizing drug and the highest solubility of oil is chosen to reduce the amount of oil in formulation thus reducing the surfactant within formulations due to its toxicity issues.

According to chain length oil can be sub-divided like a long chain, medium-chain, and short-chain triglycerides for example sesame oil, cottonseed oil, soyabean oil, coconut oil, olive oil and many more. The type of oil phase is used for the preparation of nanoemulsion sometimes affects its bioavailability such as Curcumin has the highest bioavailability by formulating it with long and medium-chain triglycerides.

Emulsifying agents are also required for formulating nanoemulsion by enhancing its kinetic stability while storing it. The emulsifying agents that are used are mainly surfactant like Tween 20, 40, 60, 80, Span 20, 40, 60, 80 are most commonly used for the preparation of nanoemulsion. Some of the other surfactants are poloxamers, sodium dodecyl surfactant, polyethylene glycol, and many more. Co-surfactants are used for stabilization of nanoemulsion some of the co-surfactants are ethanol, propylene glycol, glycerine, polyethylene glycol, ethylene glycol as these can be used alone or in combinations. [46-57]

## **2. Preparation methods of Nanoemulsion**

High-pressure equipment can be most effectively used for the preparation of nanoemulsion of a very small particle size range. Some of the most commonly used methods adopted for the preparation of nanoemulsion are high-pressure homogenization and microfluidization methods used for both at the laboratory level as well as at the industry level also. Ultrasonication and In-situ emulsification are other methods by which nanoemulsion can also be suitably prepared. [58]

Consideration while preparing Nanoemulsions are:

- a) A foremost important requirement for preparing nanoemulsion is to choose surfactant very carefully as it is used to get lower interfacial tension among the oil and water phase.
- b) For producing ultra-low interfacial tension appropriate amount of surfactant must be utilized to stabilize nanoemulsion droplets.

- c) The oil and water interface must be flexible for producing nanoemulsion.

### **High-Pressure Homogenization**

This method produces extremely low particle size (up to 1nm) of nanoemulsion by utilizing High-pressure homogenizer. Dispersing oil phase into aqueous phase can be obtained by passing mixture via small inlet orifice at very high pressure which leads to dispersion of oil and water phase through the very high intensity of turbulence and hydraulic shear as a result it produces small fine particles of emulsion. This method of preparing nanoemulsion is of high efficiency but the only drawback is the utilization of high energy and high temperature of emulsion. [58]

### **Microfluidization**

It is a mixing method that is employed for preparing nanoemulsion by using a microfluidizer device. Microfluidizer uses a positive displacement high-pressure pump which incorporates the product into microchannels (small channels). The products flow through these microchannels and results in the production of sub-micron size particle emulsion. The dispersion of oil and aqueous phases are introduced into homogenizer to get coarse emulsion, this coarse emulsion is further introduced into microfluidizer to get a stable emulsion repeatedly this process of Microfluidization is done till then to achieve the desired size of the particle of emulsion. After that this emulsion is filtered by using nitrogen to get rid of large droplets. [59]

### **Spontaneous Emulsification**

Spontaneous emulsification method is involving three major steps:

- a) Preparing a homogenous organic mixture of oil, surfactant in a water-miscible solvent, and a hydrophilic surfactant.
- b) Under magnetic stirring introducing this organic mixture into aqueous phase results in oil in water emulsion.
- c) Under reduced pressure evaporating the water-miscible solvent. [60]



### **Solvent Evaporation Technique**

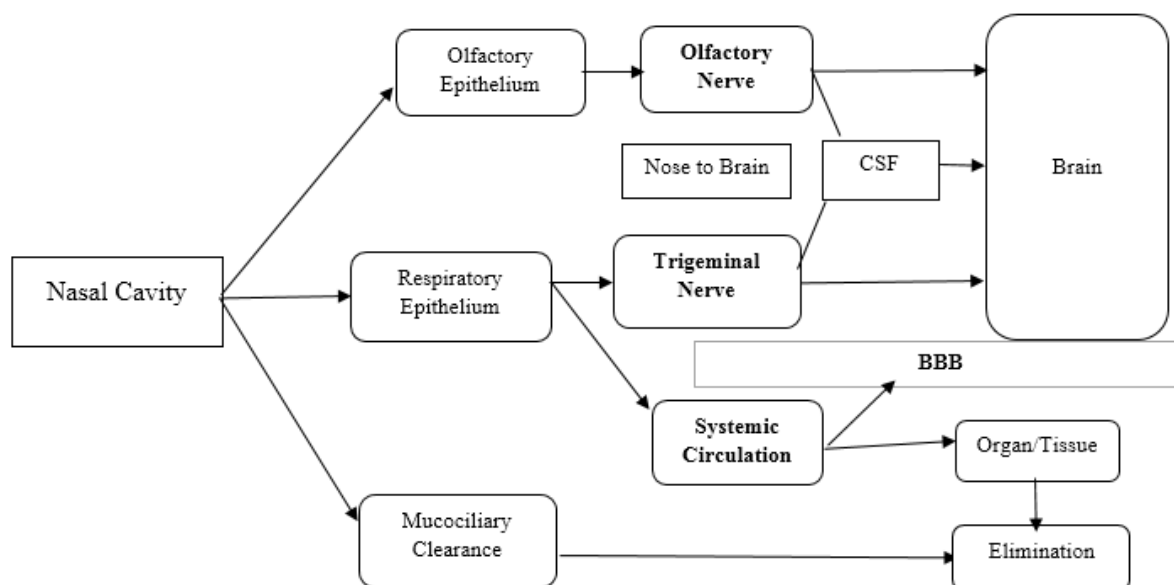
This method of preparing nanoemulsion involves the preparation of a drug solution and emulsifying it into another liquid (non-solvent). Further evaporating solvent from drugs leads to precipitation of drugs. [61]

### **Hydrogel Method**

In this method, the drug solvent mixture is miscible with drug anti-solvent. By this method, Ostwald ripening and crystal growth can be prevented due to the presence of high shear force. [62]

### **Nanoemulsion for Nose to Brain Delivery**

For the systemic delivery of drugs, nasal mucosa is one of the best approaches. Nanoemulsion targeted from nose to brain delivery is an alternative method for oral administration of CNS drugs. Delivering CNS drugs via the nose to the brain is most efficient as compared to parenteral route due to which nose to brain drug delivery method is best adopted safest approach as compared to both oral and parenteral route [63] but there are certain issues related to brain targeted drug delivery like drugs which are hydrophilic in nature and drugs having high molecular weight because of impermeable nature of endothelium as endothelium layer is present in between systemic circulation and barrier amongst blood and brain i.e. BBB. [64] Nose to brain drug-delivering route comprises of major two routes the olfactory and trigeminal nerve pathways. Olfactory nerves begin from the brain and end towards the olfactory neuroepithelium whereas trigeminal nerve begins from the brain and ends towards the respiratory epithelium. The main function of the olfactory area is to analyze and sense any sort of smell and it has three types of cells named olfactory receptor cells, epithelial cells, and receptor cells. The olfactory area has a straight link from nose to the brain by utilizing nanoemulsion preparations of drugs. [65-67]



**Figure No. 3: Nose to Brain drug delivery pathway**

There are some applications of nanoemulsion formulation for brain targeting via the nose, like these can also be used as for the influenza virus vaccine in the form of non-toxic mucosal adjuvant. One of the most important applications of the intranasal drug delivery system is the development of vaccines in the current intranasal route. Due to reduced activity of the enzyme, moderately penetrable epithelium, and higher availability of target sites nasal drug delivery is utilized as a better option of delivering drugs. Nanoemulsion which carries drugs in the nano form protects the drug from mucosa and also prevents direct contact of the drug to the antigen of lymphoid tissue. For treating CNS disorders nanoemulsion for the nose to brain drug delivery techniques is most appropriate due to its efficient results in targeting the drug to the brain but there are certain limitations of this drug delivery method like only limited quantity of drug can be given due to its lower volume in the nasal cavity and on the interaction of drug to mucosa influences drug absorption which further leads to lesser therapeutic efficacy. [68-70]

**Properties which constitute CNS drug for Nasal Nanoemulsion as a better alternative to oral drug administration: [71]**

- Intestinal and first-pass metabolism of the drug (enzymatic degradation).
- Slow onset of action.

- Poor solubility and bioavailability.
- Lower ability to cross the Blood-Brain Barrier.
- Poor absorption.
- Issues related to stability.
- Reduce dose to avoid oral side effects but a high dose is given to overcome BBB.
- Have a bitter or disagreeable taste.

### Formulations for Nasal drug delivery to target brain

An over-all summary of existing literature around Nanoemulsion intended designed for nose-to-brain aiming demonstrations evidently that intranasal usage is a substitute for oral therapy. Moreover, if the drug is managed orally to get to the brain, this sort of administration be capable of current difficulties for several drugs that are reviewed in Table 1. CNS delivery via nasal mucosa at times achieves superior to parenteral administration too, as demonstrated by in vivo tests.

**Table No. 1: Nanoemulsion formulations prepared for Nose to brain drug delivery**

Author	Drug	Category	Topic	Reference
Kumar et. al	Risperidone	Schizophrenia	Intranasal nanoemulsion based brain targeting drug delivery system of risperidone	72
Kumar et. al	Olanzapine	Schizophrenia	Mucoadhesive nanoemulsion-based intranasal drug delivery system of olanzapine for brain targeting	73
Yu et. al	Ergoloid mesylate	Schizophrenia	Preparation of Ergoloid mesylate submicron emulsions for enhancing nasal absorption and reducing nasal ciliotoxicity	74

Jain et. al	Amiloride	Anti-epileptic	Antiepileptic intranasal Amiloride loaded mucoadhesive nanoemulsion: Development and safety assessment	75
Bahadur et. al	Ziprasidone hydrochloride	Anti-psychotic	Buffered nanoemulsion for nose to brain delivery of ziprasidone hydrochloride: Preformulation and pharmacodynamic evaluation.	76
Mahajan et. al	Saquinavir mesylate	HIV infections	Nanoemulsion-based intranasal drug delivery system of saquinavir mesylate for brain targeting	77
Pathak et. al	Nimodipine	Cerebrovascular spasm and senile dementia	Role of mucoadhesive polymers in enhancing delivery of nimodipine microemulsion to brain via intranasal route	78
Sood et. al	Curcumin	Neurodegenerative disease	Optimization of curcumin nanoemulsion for intranasal delivery using design of experiment and its toxicity assessment	79
Pangeni et. al	Resveratrol	Parkinson disease	Vitamin E loaded Resveratrol nanoemulsion for brain targeting for the treatment of Parkinson disease by reducing oxidative stress	80
Nasr et. al	Curcumin/Resveratrol	Age-related neurodegenerative diseases	Development of an optimized hyaluronic acid-based lipidic nanoemulsion co-encapsulating two polyphenols for nose to brain delivery	81
Yadav et. al	Cyclosporine	Neuro-protective	Comparative Biodistribution and Pharmacokinetic Analysis of	82

			Cyclosporine-A in the Brain upon Intranasal or Intravenous Administration in an Oil-in-Water Nanoemulsion Formulation	
Yadav et. al	Anti-TNF $\alpha$ siRNA	Neuroinflammation	Intranasal brain delivery of cationic nanoemulsion encapsulated TNF $\alpha$ siRNA in the prevention of experimental neuroinflammation	83
Parikh et. al	Riluzole	Amyotrophic lateral sclerosis (ALS)	Nanoemulsions for Intranasal Delivery of Riluzole to Improve Brain Bioavailability: Formulation Development and Pharmacokinetic Studies	84
Kumar et. al	Selegilin	Parkinson's disease	Design Expert(®) supported optimization and predictive analysis of selegiline nanoemulsion via the olfactory region with enhanced behavioral performance in Parkinson's disease	85
Ahmad et. al	Thymoquinone	Cerebral Ischemia	Quantification and evaluation of thymoquinone loaded mucoadhesive nanoemulsion for treatment of cerebral ischemia	86
Pandey et. al	Paroxetine	Depression and anxiety	Intranasal delivery of paroxetine nanoemulsion via the olfactory region for the management of depression: Formulation, behavioral and biochemical estimation	87

Boche et. al	Quetiapine	Schizophrenia	Quetiapine Nanoemulsion for Intranasal Drug Delivery: Evaluation of Brain-Targeting Efficiency	88
Abdou et.al	Zolmitriptan	Migraine	Brain targeting efficiency of anti-migraine drug-loaded mucoadhesive intranasal nanoemulsion	89
Ahmed et. al	Aggregation-caused quenching (ACQ) probes	Labeling action	Evidence of nose-to-brain delivery of nanoemulsions: Cargoes but not vehicles	90
Colombo et. al	Kaempferol	Gliomas	Validation of an HPLC-UV method for analysis of Kaempferol-loaded nanoemulsion and its application to in vitro and in vivo tests	91
Colombo et. al	Kaempferol	Gliomas	Kaempferol-loaded mucoadhesive nanoemulsion for intranasal administration reduces glioma growth in vitro	92
Haider et. al	Rivastigmine	Alzheimer disease	Optimization of rivastigmine nanoemulsion for enhanced brain delivery: In-vivo and toxicity evaluation	93
Ahmad et. al	Chloramphenicol	Bacterial meningitis	Quantification and evaluation of thymoquinone loaded mucoadhesive nanoemulsion for treatment of cerebral ischemia	94
Ahmad et. al	Amiloride	Epilepsy	Impact of ultrasonication techniques on the preparation of novel Amiloride-nanoemulsion used for intranasal delivery in	95

			the treatment of epilepsy	
El-Zaafarany et. al	Oxcarbazepine	Epilepsy	Identifying lipidic emulsions for improved oxcarbazepine brain targeting: In vitro and rat in vivo studies	96

### Challenges for the nose to drug delivery

There are numerous limitations for delivering drugs through the nasal route which at last limits it's a success. One of the foremost limitations is drug preparation delivered through nasal route can lead to nasal-mucosa irritation and can also cause toxicity which is due to formulation additive incompatibility with nasal mucosal tissues [97]. Some of the preservatives are also sensitive to the nasal mucosa. Some of the common side effects of incompatibility among drug additives are loss of ciliary layer, loss of epithelial cells, and shrinkage of the mucosal layer. [98]

Mucociliary clearance leads to lesser retention time for drugs and can also cause improper drug absorption. Absorption enhancers cannot be used in this type of formulations. There are certain variations in drug absorption in the brain and spinal cord. [99]

### CONCLUSION:

In the area of Nanomedicine, Nanoemulsion formulations are having their importance. Their properties such as having nanodroplet size with the higher surface area make it appropriate for delivering drugs from nose to brain. For reducing mucosal clearance mucoadhesive additives are employed. Chitosan has two roles while adding it to formulation it enhances penetration of drugs via nasal mucosa and it also acts as a mucoadhesive agent. There are several instances in literature during the past years of nanoemulsion for targeting the drug to the brain as depicted in table 1. For CNS drug delivery nasal drug delivery is a better approach than oral due to different properties of the drug. Furthermore, surfactant(s) introduce in nanoemulsions may perhaps possess a fluidizing impact on endothelial cell membranes defining improved drug permeability as well as benefiting through this process the olfactory and trigeminal routes.

Nanoemulsion meant for intranasal administration appears to have a favorable approach for nose-to-brain drug release and to attain CNS directing for therapy of neuro ailments. Lots Of attempts are necessary to be produced to improve further performance of nanoemulsions.

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