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Review Article

Intranasal Nanoemulsion for Brain Targeting: A Review

SWARUPA NARAYAN SHIRKE, JAMEEL AHMED S MULLA*

Department of Pharmaceutics, Shree Santkrupa College of Pharmacy Ghogaon, Karad, Dist- Satara, Maharashtra-415111, India.

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ABSTRACT

Intranasal administration has demonstrated the ability to cross the blood-brain barrier (BBB) and deliver medications to the central nervous system (CNS) more quickly and extensively than other common routes. Although the mechanism of drug transport from the nose to the brain is not entirely known, it is thought that numerous neural pathways including the olfactory and trigeminal, are involved. Comprehensive research is being done on intranasal nanoemulsion (NE) for brain targeting. Formulations from the area of nanomedicine include nanoemulsions. They are made up of emulsions, which are typically oil in water (sizes between 100 and 300 nm or less), stabilised by one or more surfactants, and subsequently co-surfactants, and delivered as small droplets with a large surface area. To slow down rapid nasal clearance, a mucoadhesive polymer, like chitosan, might be added to the formulation. Nasal nanoemulsions have the potential to be a reliable, non-invasive, and safe drug delivery method for the treatment of CNS diseases as they can target specific areas of the brain. The present developments of intranasal nanoemulsion are the main subject of this review, with a focus on the current difficulties that could serve to guide the direction of future research.

INTRODUCTION

The central nervous system's (CNS) microvasculature has the unique ability to operate as a biological barrier, safely regulating the transport of any molecule in the brain. These continuous non-fenestrated blood capillaries are known as blood brain barrier (BBB), which separates the brain from the rest of the body physically [1]. Atdistinct layers of the human brain, the BBB and cerebrospinal fluid (CSF) protect the brain from numerous external threats, such as toxins or infections, and maintain its unique physiological nature [2].

Recently discovered approaches for treating brain problems have been categorised as either invasive or non-invasive. Invasive techniques include temporarily disrupting the BBB to facilitate drug entrance into the CNS, as well as direct drug delivery by intraventricular or intracerebral administration [3]. Exogenous elements are reported to be delivered directly from the nose to the brain via the olfactory and trigeminal nerve pathways, bypassing the BBB [4-6].

Author for Correspondence:
Email: jameelahmed5@rediffmail.com

The olfactory region of the nasal cavity can be used to deliver medications to the central nervous system by acting as a link between the nose and the brain [7]. Olfactory region has a direct connection to the CNS due to the presence of olfactory receptors, neurons, and its axon send in the olfactory bulb. The only area of the body where the CNS is in contact with the external environment is the olfactory region [8]. The active moieties can be taken directly into the brain from the olfactory area via the olfactory and trigeminal nerve routes [9].

Intranasal administration for targeted delivery to the brain can be beneficial and can help to overcome the drawbacks of other administration routes [10]. Following intranasal administration, it is seen that the drug is delivered to the brain in greater quantity and more rapidly [11, 12]. There has recently been a lot of interest in researching the intranasal route for drug transport to the brain via the olfactory mucosa, though some results are contradictory in this regard [13-16]. Successful intra nasal drug delivery to the brain has been reported by researchers using a variety of nanoparticle, nanoemulsion (NE), liposome, and microsphere [17].

The ability of NE formulation to protect the enclosed drug from biological and/or chemical degradation and extracellular transport makes nose-to-brain drug administration more effective [18]. NEs are substantially absorbed by intranasal administration due to their lipophilic nature and small globule sizes, which result in increased uptake by the nasal mucosa [12]. Due to its ease of solubilizing hydrophobic drugs, ability to lessen severe side effects, and ease of modification into next-generation smart nanomaterials, NEs have enormous potential as effective nanomedicines [19-24].

Nose Anatomy

The nasal septum divides the nasal cavity into two sections along its middle. The two cavities open to the facial side through the anterior nasal apertures and to the rhinopharynx via the posterior nasal apertures [9]. The three anatomically separate regions, the vestibular, the respiratory, or the olfactory in each nostril following intranasal delivery. Each nasal cavity's anterior portion contains the vestibular region, which has a total surface area of about 0.6 cm^2. Also, nasal valve is located in vestibular region. The respiratory region is the largest, measuring around 130 cm^2 in total surface area possesses the highest level of vascularity and is primarily in charge of facilitating systemic drug absorption over nasal mucosa [25]. The olfactory area is crucial in the transfer of drugs to the CNS. Olfactory cells are present in the human olfactory mucosa, which is on the nasal cavity's roof.

Possible Nasal Transportation Pathways to the Brain

1. Olfactory Neuronal Pathways

This is thought to be one of the main routes via which drugs are absorbed into the brain intra nasally. Olfactory neurons are dispersed throughout the basal cells, microvillar cells, and supporting cells (sustentacular cells) in the olfactory region at the roof of the nasal cavity, where olfactory neural pathways originate [25]. To reach the olfactory neurons, the drug delivery must pass via the olfactory epithelium [26]. Three mechanisms, including passive diffusion, paracellular mobility, and neuronal cell endocytosis, control the drug's transmembrane transport. Passive diffusion is mostly used for the transportation of lipophilic drugs, whereas paracellular movement is used for the transportation of hydrophilic drugs [17]. These mechanisms are greatly impacted by a drug's molecule's lipophilicity and molecular weight [27].

2. Trigeminal Nerve Pathways

Trigeminal nerve serves as an important target for CNS drug delivery because it innervates the respiratory region and enters the CNS through the pons [28, 29]. Additionally, a trigeminal nerve branch terminates in the olfactory bulbs [30]. On one end, it innervates the nasal olfactory epithelium, while on the other it enters the brain through two separate sites: near to the pons and cerebrum of the brain, as well as, to a lesser extent, the frontal brain and olfactory bulb [31]. The ophthalmic, maxillary, or mandibular divisions of the trigeminal nerve carry sensory information from the nasal cavity, oral cavity, eyelids, and cornea to the CNS [25].

Researchers found evidence that the olfactory and trigeminal pathways can transfer insulin-like growth factor-I to the CNS when administered intranasally [32]. The data from the previous authors showed that a significant amount of insulin-like-growth factor-I was transported via trigeminal pathways, even if it was difficult to distinguish the degree of drug transport to the brain between olfactory and/or trigeminal pathways [33].

3. Cerebrospinal Fluid and Lymphatic Pathways

Olfactory nerves enclosed in the perineurial space provide a connection between the nasal lymphatic system and the CSF of the subarachnoid space of the brain [34]. Researchers have identified a relationship between the CSF-lymphatic channels of drug transport from the nose to the brain even though no specific investigation has been conducted on these pathways [34]. The nasal lymphatic system and cervical lymph node were shown to be reached by radioactively labelled tracer that was introduced into the CSF through pathways connected to olfactory nerves [35]. These channels are likely capable of carrying drugs administered into the nasal cavity to the CSF and perivascular region for distribution to the other parts of the brain [17]. Drugs' lipophilicity, molecular weight, and level of ionisation all affect how they are transported and distributed in the CSF [36]. The distribution improves as lipophilicity increases. It is experimentally difficult to understand the individual contribution of different pathways to drug transport from the nose to the brain. However, several radio-labeled tracer studies may help to understand the drug delivery pathways from the nose to the brain [17].

Nanoemulsion

NEs are oil-in-water (O/W) or water-in-oil (W/O) dispersions of two immiscible liquids stabilized with the proper surfactant(s), with a mean droplet diameter of approximately 100 nm, although in the literature upper size limits up to 300 nm have been reported [37-39]. Due to the small droplet size of NEs, destabilizing events including coalescence, creaming, and sedimentation are hindered, and as a result, NEs are characterized by a greater surface area compared to other formulations and by long-term physical stability [40].

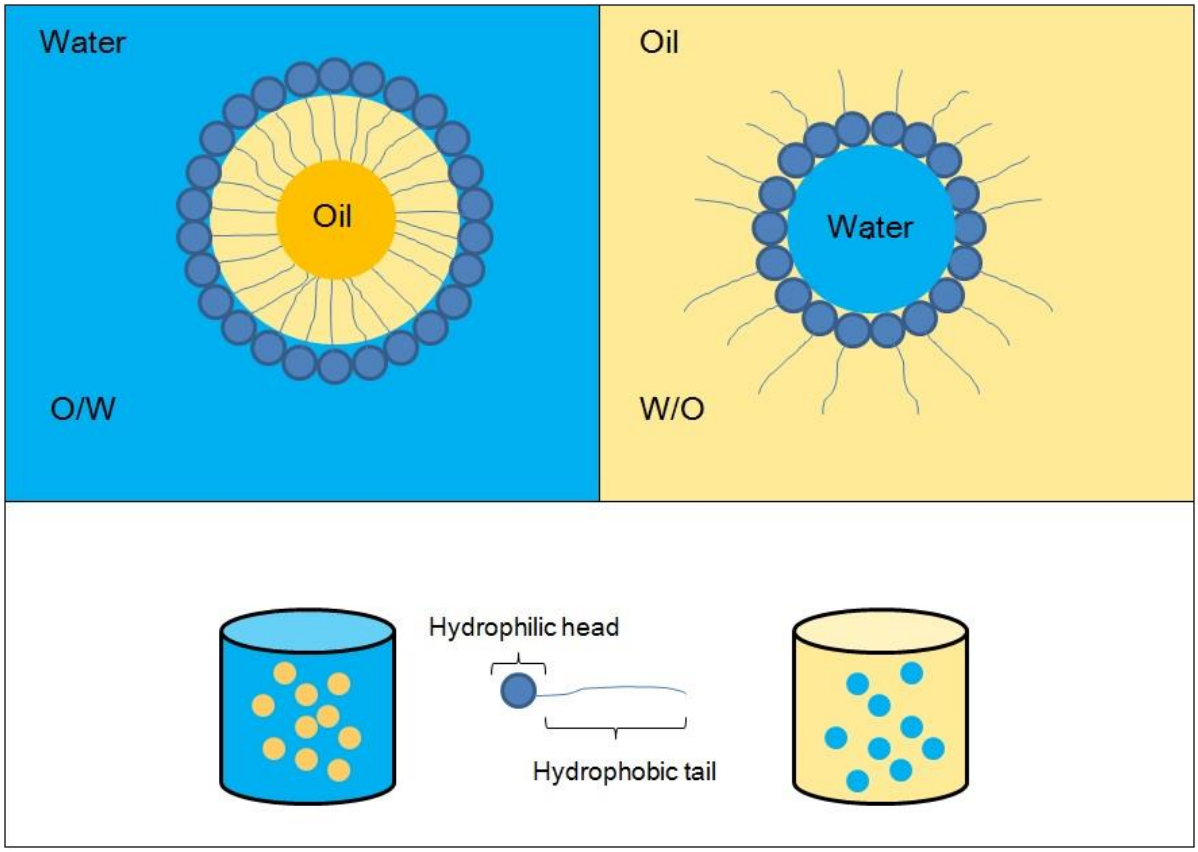

Figure 1: Oil-in-water and water-in-oil emulsions. Nanoemulsions are disequilibrated systems of oil-in-water (O/W) or water-in-oil (W/O) emulsions.

1. Components of Nanoemulsion

1.1. Oil

The size of NE globules typically increases as oil concentration in the formulation rises [41]. The drug's ability to permeate the nasomucosa is decreased by larger globules. In order to effectively dissolve the drug, the ideal quantity of oil is chosen. It is possible for the oil to facilitate drug permeation through the nasal mucosa when employed as a permeation enhancer.

1.2. Surfactant

The essential ingredient in NE, surfactants aid to lower surface tension, prevent the coalescence of globules, and prevent phase separation. A surfactant should be able to dissolve a large enough amount of the drug to exhibit improved drug loading. Surfactant influences both the globule size and stability of the NE. As a result, it significantly affects the drug's ability to permeate the nasomucosa. Evidence suggests that a higher surfactant ratio reduces globule size. The degree of nasomucosal penetration increases with decreasing globule size [17, 42].

1.3. Co-surfactant

In NE, single chain surfactants predominate, which might not significantly reduce interfacial tension [43]. Therefore, co-surfactants are used in NE to support surfactant in lowering surface tension and controlling interfacial phenomena [44]. Similar to surfactant co-surfactant concentration increases improve drug permeability by reducing globule size [43].

2. Preparation Methods of Nanoemulsion

NEs can be made using a variety of methods that can be divided into two categories: High-energy method and low-energy method.

A. High-energy Method

In the case of high-energy methods, such as ultrasonication and high pressure homogenization, the formation of the small droplets involves a mechanical device that generates disruptive forces breaking up the oil and water phases to produce the droplets, a process that uses a lot of energy. High pressure homogenizers, ultrasounds, and microfluidic devices are used [40, 45].

1. High Pressure Homogenization Method

1.1 Microfluidizer

To reduce size, a microfluidizer simultaneously uses hydraulic shear, impact, attrition, impingement, severe turbulence, and cavitation. It uses a high-pressure displacement pump (between 500 and 50,000 psi) to drive feed material through a chamber with microchannels to create very small droplets. Typically, a coarse emulsion is cycled through a microfluidizer several times (up to 100 times), until the appropriate size and dispersity is achieved. The impaction energy produced by the collision of droplets dissipates as heat and necessitates cooling [46]. The Weber number, a dimensionless number used in fluid mechanics that analyses fluid flow patterns and correlates homogenization effectiveness with the ratio of viscosities in the dispersed and continuous phases, can be a useful starting point for determining the overall effectiveness of high pressure homogenization [47]. The biggest benefit of this highly scalable process is that the source material itself causes the reduction, therefore there is no contamination of the feedstock [46].

1.2 Piston Gap Homogenizer

On the same basis as colloid mills, piston gap homogenizers operate. Between a stationary stator and a fast rotating rotor, a narrow gap (less than 10μm in dimension) is created that allows a coarse emulsion to pass through. High shear, stress, and grinding forces produced between the rotor and stator cause size reduction [48]. The upper ceiling of droplet size can be determined by setting the dissipation gap to the necessary size, which implies that a yield won't be produced until the emulsion is ground down to a size that is equal to or smaller than the gap between the rotor and stator [46].

2. Ultrasonication

Due to the high acoustic energy applied to the oil phase by ultrasound, this method is frequently used in NE research and results in finely dispersed NEs [49]. The ultrasound probe oscillates while producing amplified sound waves that cause fast cavitation bubbles. The acoustic energy pulls and rips the dispersed phase, precisely shearing it into droplets [50, 51]. The results of an analysis of the operating parameters show that as the sonication time and input power are increased, the droplet size decreases [52]. The functionality of the probes in an ultrasonicator is influenced by the range of possible dimensions. For working on lower volume batches, typically narrower probes are preferred [46]. Although ultrasonication can create well-dispersed NEs, the process is not scalable because to the high heat output, the difficulty of using ultrasounds with viscous solutions, and the short working distance of the probe head [53, 54].

B. Low-energy Method

The low-energy techniques use particular physicochemical processes to form small droplets without using a lot of energy, such as phase inversion temperature and emulsion inversion points. The droplets are formed in the low-energy methods when the system experiences a phase inversion in response to changes, such as those in composition or temperature, and then moves through a low interfacial tension state [55].

1. Phase Inversion Method

The phase inversion temperature method entails combining two immiscible phases with a surfactant at a high temperature to produce a W/O emulsion that, when cooled, inverts to produce an O/W emulsion [56-58]. The phase inversion approach is based on the phases that change during emulsification. These phase transitions, which are caused by modifications in the surfactant's spontaneous curvature, can be produced either at constant composition or temperature by altering the system's composition using the emulsion inversion point (EIP) approach [59]. The hydrophilic-lipophilic balance of the surfactant, the concentration of the surfactant, the water-to-oil ratio, and the difference between the ambient temperature and the phase transition temperature all contribute to stabilizing this process [53].

2. Spontaneous Emulsification

By using this technique, NEs can be developed at room temperature without the need for any specialised tools. To create O/W NEs, water is gradually added to an oil and surfactant solution

while maintaining a steady temperature and gently stirring. Interfacial tension, interfacial and bulk viscosity, phase transition area, surfactant structure, and surfactant concentration are the primary determinants of the spontaneity of the emulsification process [60]. The main drawbacks of this approach are the solvent's presence and the small amount of the oil phase [61-63].

3. Solvent Displacement Method

This technique involves adding the organic phase, which contains the oil dissolved in a solvent like ethanol or acetone, to the aqueous phase, which contains the surfactants, to create NEs at room temperature. Emulsification happens spontaneously when organic solvent diffuses, and it can later be eliminated via vacuum evaporation. To prepare small droplets, a lot of solvent must be added to the oil [64, 65].

3. Mucoadhesive Intranasal Nanoemulsion

The developed formulation can be bioadhered to the application site via interfacial forces, allowing retention for an extended period of time. This is accomplished by modifying the NE system with mucoadhesive components. Increased retention at the application area causes the drug to be incorporated to be absorbed for longer [66]. Reduced mucociliary clearance was clearly visible in the posterior part of the nasal cavity with the addition of 0.5% chitosan to help the NE adhere to mucous membranes. According to this study, the NE made with chitosan travels directly from the nose to the brain [67]. Extending residence periods at the olfactory epithelium was successfully accomplished by mucoadhesive compounds including pectin and chitosan, which were examined by Charlton et al [68, 69].

Table 1: Examples of nanoemulsion-based approaches for brain targeting through intranasal drug delivery

Drug	Therapy for	NE preparation method	Characterization Parameters	Ref.
Amiloride	Antiepileptic	High pressure homogenization	DS= 89.36±11.18 nm PDI= 0.231±0.018 ZP= −9.83±0.12 mV	[70]
Zolmitriptan	Migraine	Ultra probe sonicator	DS= 54.63±3.24nm PDI= 0.17±0.01 ZP= −0.086±0.014 mV	[54]
Kaempferol	Neuroprotective and anti-tumor	High pressure homogenization	DS= 170.4±4.1 nm PDI= 0.155±0.015 ZP= −18.71±1.72	[71]
Cyclosporine-A	Neuroprotective	Ultra sonication	DS= 158.47±3.02 nm ZP= −30 mV	[72]
Resveratrol	Parkinson's disease	Spontaneous emulsification	DS= 176.3±3.5 nm PDI= 0.17±0.03 ZP= 18.5±1.77 mV	[73]
Selegiline	Parkinson's disease	High pressure homogeniser	DS= 61.43±4.10 nm PDI= 0.203±0.005 ZP= −34.00±0.17 mV	[74]
Ziprasidone hydrochloride	Antipsychotic	Spontaneous emulsification	DS= 145.24±4.75 nm PDI= 0.186±0.40 ZP= −30.2±3.21 mV	[75]
Quetiapine	Antipsychotic	Ultra probe sonicator	DS= 144±0.5 nm	[76]

Abbreviations: DS= droplet size, PDI= polydispersity index, ZP= zeta potential.

4. Evaluation Parameters of Nanoemulsion

4.1. Droplet Size

The diffusion method is used to measure the droplet size analysis of NE utilising the light-scattering, particle size analyser counter, LS 230. Additionally, it was assessed via correlation spectroscopy, which examines variations in light scattering brought on by Brownian motion [77].

4.2. Polydispersity

It shows the uniformity of droplet size in the NE. The uniformity of droplet size in a NE will decrease as polydispersity increases. It can be characterised as the standard deviation to mean droplet size ratio. A spectrophotometer is used to measure it [77].

4.3. Zeta Potential

Zeta PALS is a device used to measure zeta potential. It is utilised to determine the charge on a droplet's surface in a NE [78].

4.4. Transmission Electron Microscopy (TEM)

On a carbon-coated grid, a droplet of the NE is applied, and it quickly absorbs there. Then the stain is applied using an aqueous solution of a heavy metal salt. The material is thereafter allowed to dry before being examined by a TEM at room temperature [79].

4.5. Viscosity Determination

A Brookfield-type rotational viscometer is used to measure the viscosity of NE at various temperatures and shear rates [77].

4.6. Refractive Index

An Abbe's refractrometer was used to calculate the NE formulation's refractive index [80].

4.7. Drug Content

Preweighed NE is extracted by dissolving in a suitable solvent, and the extract is then tested against a drug reference solution using a spectrophotometer or HPLC [81].

4.8. Percentage Transmittance

A UV-visible spectrophotometer is used to determine the NE's percentage transmittance [77].

4.9. Thermodynamic Stability Study

The sample was kept at normal temperature (25˚C) and at refrigerator temperature (4˚C) for stability experiments on optimized NEs. Three months were spent doing these studies. During storage, the droplet size, viscosity, and refractive index were measured using the techniques mentioned above. Three different batches of formulations were put into glass vials and stored at accelerated temperatures of 30˚C, 40˚C, 50˚C, and 60˚C while being exposed to ambient humidity. The samples were taken out at regular intervals of 0, 1, 2, and 3 months, and the drug content was determined using an HPLC method that indicates stability. Zero time samples were used as controls. To ensure that the excipients employed in the formulations did not interact, samples of pure oil, pure surfactant and cosurfactant were run separately. Calculations were made to determine how much of the drug was present and how much had been degraded over time. The graphical method was used to establish the order of degradation. At each temperature, the degradation rate constant (K) was calculated. To assess the shelf life of the improved NEs formulation, an Arrhenius plot was created between log K and 1/T. By extrapolating the value of 25˚C from the Arrhenius plot, the degradation rate constant at 25˚C (K25) was found. The shelf life (T0.9) for each formulation was determined by using the formula [80, 82].

Current Challenges and Future Prospects

The existence of BBB frequently limits effective noninvasive treatment of CNS disorders [83]. It is becoming more and more obvious that crossing the BBB and delivering drugs to the CNS is a difficult task that calls for close cooperation and group efforts from researchers in a number of fields, including pharmaceutical sciences, biological chemistry, physiology, and pharmacology [84].

While intranasal NEs may be a potential method for delivering drugs directly to the brain, the effectiveness of this route depends on a variety of factors [7]. Effective transport to the olfactory region of the nares, prolonged retention duration over the nasal mucosal surface, and a reduction in drug metabolism in the nasal cavity are the main criteria that influence the efficacy of delivery by this route [85].

The crucial criterion for an efficient pharmaceutical action is the total drug dose delivered at the site of the drug action. The biodistribution of the drug throughout the brain and how that relates to an appropriate dose may be an expanding topic of research because the brain is a dynamic organ [86]. To better understand drug delivery to the brain, comprehensive computer models are required to describe aspects like drug release and the transfer of drug molecules across the mucus layer. These models are also needed to aid in the planning, carrying out, and analysis of current and upcoming experimental studies [87-89].

The potential advantages of intranasal NE, there is no doubt that this direct nose to brain drug delivery system would have a promising future in the pharmaceutical industry and would definitely result in the introduction of numerous commercial products to the pharmaceutical market in the near future.

CONCLUSION

The BBB must be bypassed for medications to enter the CNS, making neurological disorders

difficult to treat at the moment. To get around this issue, several solutions have been put forth. For brain targeting, intranasal delivery is a feasible and non-invasive method. The direct nose to brain drug delivery system is one possible tactic for overcoming the BBB's challenges. Certain parts of the brain may be directly accessible through the olfactory and trigeminal routes that would not otherwise be possible. Optimization of these routes is still necessary.

In the field of nanomedicine, NE formulations are becoming increasingly significant. They are suitable for nose-to-brain administration due to their features (high surface area nanodroplets). With the use of industrial techniques like high-pressure homogenization and ultrasonication, they are easily produced on a larger scale.
To slow down mucociliary clearance, mucoadhesive polymers could be added to the NE. Mucoadhesion is enhanced by the inclusion of chitosan as an extra excipient. As seen by Table 1, there are numerous instances of current NE-loaded drugs with various therapeutic objectives in brain diseases in the literature. By improving nasal permeability, NE enhance nasal absorption and achieve great therapeutic efficacy.

The future of NE-based intranasal brain-targeted drug delivery appears bright, but more fundamental research is required.

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