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NANO EMULSION FOR THE BRAIN TARGETING FROM THE INTRANASAL ROUTE: A REVIEW

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ABSTRACT

For delivering the drug in selective and effective amount to brain is very difficult due to various obstacles like BBB. BBB is most important hurdle which blocks uptake of various drug through systemic circulation to brain. The most convenient route to bypass BBB is intranasal route, as it allows only the required therapeutic amount to reach brain. These review covers capacity of nano emulsion given by nasal route to deliver the drug to brain, the pathways and mechanism of direct delivery from nose to brain, countless factors affecting nasal drug absorption, traditional as well as cutting-edge nasal delivery, and different methods for intranasal drug delivery and used devices. These send medication from nose-brain helps to treat various diseases in the brain.

Keywords: Brain, medication targeting, nasal drug delivery, delivery systems, and delivery equipment

INTRODUCTION

Because of BBB, brain is the least accessible organs for drug delivery. Delivery via intranasal, intracerebral, intravascular, and intraventricular routes are some potential methods for getting therapeutic compounds into the brain. Due to potential for efficacy, safety and compliance intranasal administration is seen as a promising method for delivering many medications **[29]**. The biggest portion of nose cavity is covered by

respiratory area of nasal mucosa, which is too a region where most drugs are absorbed into the bloodstream. There are many different channels, including olfactory pathway, systemic pathway and trigeminal neural pathway for medication delivery to brain through intranasal method. Drugs which follow systemic pathway are absorbed through the nasal cavity into general circulation before passing through BBB and entering brain.

The medicine must be capable to pass BBB in enough amounts to reach therapeutic levels in order to target the brain. The barrier is thought to prevent 98% of low molecular mass medications from permeating and 100% of macromolecules, resulting in a considerably reduced CNS bioavailability. For intranasal drug administration to brain, nanotechnology-based delivery devices are currently receiving a lot of attention. Over the past few decades, substantial research has been done on nano-sized drug delivery devices as a closer approach to overcome low bioavailability of numerous pharmaceutical medications. Nano emulsions, liposomes, dendrimers, nanoparticles, microspheres, and carbon-based nano formulations for successful intranasal drug delivery to brain.

The mean droplet size of the heterogeneous dispersion of two non-miscible liquids (O/W or W/O) is from 50 to 1000 nm is referred to as nano emulsion. The typical range of droplet sizes is 100 to 500 nm. There are two different kinds of emulsions: oil-in-water and water-in-oil. Three elements make up the nano emulsion: water, oil, and surfactant. The choice and quantity of surfactant used in the formulations of emulsions, which was acknowledged by the "Generally Recognized as Safe" from the FDA policies and conditions, are the primary components of the emulsions **[30]**. Large amounts of hydrophobic molecules that hinder the medications from being compatible against further oxidation and enzymatic action for parenteral administration can be easily dissolved by the nano-emulsions. As a result, it offers the benefit of lowering the drug dose and controlling the drug's release characteristics. It increases the administration of drugs to specific places and the transfer of drugs into the specific site of action because it has a wide interfacial tension **[31]**.

NANOEMULSION SPRAY FOR NOSE TO BRAIN TARGETING

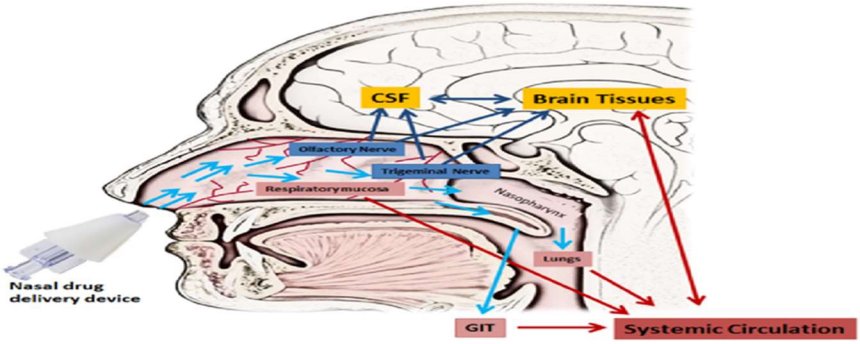

Figure 1: Routes for Nasal Delivery System

MECHANISM OF DRUG ABSORPTION

The demonstration of drugs trans nasal absorption into the brain has been supported by a number of hypothesized mechanisms **[1]**. By the tight intercellular connections or the open clefts of the nasal mucosal epithelial cells, the paracellular/extracellular mechanism is a passive and slowly moving water pathway **[2]**. The paracellular method for nose-brain drug delivery uses 2 extracellular paths, the 1st which crosses olfactory neurons and the 2nd which crosses trigeminal nerve **[3]**. An artery pulsation driven perivascular pump allows the treatment to penetrate other brain regions via simple diffusion after it has reached trigeminal area or olfactory bulb. Regardless of their lipophilicity, drugs with molecular weights larger than 1000 Dalton have been shown to have poor bioavailability **[4]**. The tight connections between the nasal epithelial cells have also been manipulated with substances like chitosan to aid trans nasal drug absorption **[5]**.

The second transcellular/intracellular process involves the transfer of molecules via a lipoidal pathway via either receptor mediated endocytosis or fluid phase endocytosis, passive diffusion **[6]**. Both small and big lipophilic substances are absorbed trans nasally according to this method. As a result, transcellular drug absorption mostly depends on the drug composition lipophilicity, alongside highly lipophilic medicines being predicted to have rapid/complete trans nasal intake. However, the intercellular axonal transport by mechanisms like endocytosis inside olfactory neurons is a sluggish process that takes hours for nasally delivered medicines to get to the olfactory bulb **[7]**.

PATHWAYS FOR DRUG DELIVERY FROM NASAL TO BRAIN

The delivery of desired medicine concentrations to the targeted site is the main goal of various drug delivery mechanisms. The nasal route can deliver variety of therapeutic compounds (macromolecules and micromolecules) to the central nervous

system. Numerous medications have been found to work too quickly and effectively in central nervous system when administered nasally. The various routes for nose to brain administration of drug are described below:

1. **Olfactory Pathway**

It is well acknowledged that the olfactory area, which is present on the upper area of the nasal chamber, may serve as a nose to brain drug administration pathway for the therapy of variety of central nervous system illnesses **[32]**. Medication can cross olfactory epithelium cells by endocytosing by the cell membrane or passively diffusing through the narrow spaces between cells, or they can be carried by neurons. The majority of medicines that are settled on the olfactory area are moved between cells extracellularly **[33]**.

Olfactory neurons play a significant part in the intranasal delivery of medication to brain **[34]**. From the intracellular axonal channel, drugs are delivered to the olfactory bulb and then disseminated throughout the brain **[35]**. Human olfactory axons range in diameter from 0.1 to 0.7 micrometers, suggesting that chemicals with sizes in this range can be administered through this channel with ease **[36]**. Both extracellular and intracellular processes are involved in drug transport through the olfactory pathways. While hydrophilic medications are carried via the paracellular pathway, the majority of lipophilic medications are transferred via passive diffusion. The manner by which medications are absorbed, is significantly affected by their molecular weight and lipophilicity. Drugs with very high lipophilicity are particularly relevant to the transcellular mechanism **[37]**.

2. **Trigeminal Pathway**

Less research has been done on medication transfer from nose to brain through trigeminal pathway. The trigeminal nerve's primary job is to transmit chemosensory and thermos sensory information to the mucosa of the mouth, nasal, and ocular cavities **[38]**. The back part of nasal mucosa, which connects frontal brain and olfactory bulb, is empowered by the trigeminal nerve **[39]**. As a result, one of the potential routes for delivering medications from the nasal chamber to brain is across the trigeminal nerve pathway. For instance, the olfactory and trigeminal pathways were used to deliver an insulin like growth factor 1 solution to brain **[40]**.

3. **Lymphatic Pathway**

From the olfactory area's submucosal region, drugs can be delivered by a number of extracellular pathways, including perivascular, perineural, and lymphatic channels. These extracellular routes connect to olfactory nerves that emerge from the

lamina propria and travel to brain's olfactory bulb **[41]**. As a result, the lymphatic system is the clue for the transfer of medication from nose to brain.

4. Systemic Pathway

The systemic pathway, an indirect transfer method that connects the nose-brain, can be a viable tactic for lipophilic medicines with low molecular mass **[42]**. The medication is subsequently transferred to the blood and absorbed by the vascular sections and lymphatic system of the nasal mucosa's epithelial layer, skipping the presystemic metabolism in the process **[43]**.

TECHNIQUES USED TO PREPARE NANOEMULSION

There are two different ways to make a nanoemulsion:

a) Methods requiring High-energy.
b) Methods requiring Low-energy.

a) Methods requiring High energy:

A lot of high energy techniques are employed in the creation of nanoemulsion **[8]**. Strong disruptive forces are generated using high mechanical energy to break apart large drops in nano-sized drops and create extremely dynamic nanoemulsions. Mechanical tools including high-pressure homogenizers, ultrasonicators and microfluidizers are familiar to produce disruptive forces **[9]**. We can better regulate particle size with a variety of preparation compositions by applying high energy technologies **[10]**.

1. High-pressure homogenization:

Most popular method for creating nanoemulsions is using high-pressure homogenizers. Intensely disruptive forces are produced by high-pressure homogenizers, which result in nanoemulsions with extremely small particle sizes (up to 1 nm) **[11]**. The rough emulsion is then forced under high pressure through a tiny aperture (500 - 5,000 psi). Cavitation, intense roughness and hydraulic shear are only a few of the factors mixed throughout this procedure to produce nanoemulsions with very tiny drop sizes **[12]**. Operating characteristics of the homogenizer, like temperature, energy intensity and time, sample composition & homogenizer type, all affect globlue size of nanoemulsions formed from high-pressure homogenizers. The size of the NE drops reduces as homogenization is intensified.

When biopolymers are utilized as an emulsifier, for example, strong homogenization may produce nanoemulsions with larger particle sizes as a result. Since small-molecule surfactants are more efficient than biopolymers at creating nanoemulsions, they should be utilized as emulsifiers in high-pressure homogenizers **[13]**.

2. Microfluidization:

A tool called a microfluidizer is used in the mixing technique known as microfluidization. Below high pressure (500–20,000 psi) during microfludization, liquids are compelled to travel from the microchannels. Microchannels are typically small channels that enable mixing at the micron level [14]. The water and oil phases of the macroemulsion are combined before being fed through the microfluidizer. Under strong pressure, the macroemulsion is directed via the microchannels and into the interaction chamber. Two streams of fast-moving macroemulsions collide in the interaction chamber. This collision generates impact, cavitation, and shearing forces that result in stable nanoemulsions **[15]**.

In comparison to homogenizers, microfluidizers create narrower and smaller nanoemulsion particle size distributions. Additionally, stable nanoemulsions are created by microfluidizers even at low surfactant concentrations **[16]**.

3. Ultrasonication:

Regarding cleaning and operation, ultrasonication is superior to other high energy technologies **[17]**. Ultrasonic waves produce cavitation forces during ultrasonic emulsifications, which cause the macroemulsion to separate into a nanoemulsion. This technique makes use of ultrasonicators, which are merely an ultrasonic wave-emitting probe. We may adjust ultrasonic energy input and time to get appropriate nanoemulsion stability & particle size. The process of acoustic cavitation is primarily responsible for providing physical shear in ultrasonic emulsification. Cavitation is a phenomenon that results from the pressure changes of the acoustic wave and is characterized by the production, expansion, and subsequent collapse of microbubbles. Nano-sized droplets occur as a result of the extreme turbulence brought on by the collapse of microbubbles **[18]**.

When ultrasonic waves are used to irradiate an oil and water mixture, cavitation forces are created. This extra energy leads to the creation of nanoscale emulsion droplets at the interfaces. Nanoemulsions can be created without surfactants using ultrasonication **[19]**. According to a recent study, the effectiveness of ultrasonic emulsification depends on the duration, power, and type of surfactant used **[20]**.

b) Methods requiring Low energy

Low-energy emulsification techniques use system's inherent chemical energy & only mild shaking to produce nanoemulsions **[21]**. Self-emulsification and phase inversion emulsification are two main low-energy emulsification processes **[22]**.

1. **Phase inversion emulsification method:**

Phase inversion emulsification techniques fall into two categories: TPI techniques, which use PIC, CPI, and PIT techniques, which use EIP. Changes in the surfactant's affinity or spontaneous curvature consequently variations in factors like composition and temperature cause transitional phase inversion [23]. But CPI happens when dispersed phase is constantly introduced, resulting in the aggregated dispersed phase drops that form bicontinuous/lamellar structural phases. Catastrophe refers to a system's behaviour abruptly changing and leading to novel conditions. Rapid phase inversion results from a high rate of coalescence, which occurs so when surfactant is present mainly in the dispersed phase, this is essential for the occurrence of catastrophic phase inversion **[24]**.

2. **Self-nanoemulsification method:**

The self-emulsification approach allows for the creation of nanoemulsion besides from influencing surfactant's natural arc. Turbulence and nanoscale emulsion drops are produced when co-solvent and surfactant molecules quickly diffuse from dispersed phase to continuous phase. The spontaneous emulsification method is another name for the self-emulsification technique. SNEDDS dependents on self-emulsification phenomena & have a lower lipid content, more hydrophilic co-solvent either co-surfactant **[25]**. SNEDDS is an isotropic blend of co-surfactant, surfactant, oil and drug. In the presence of aqueous fluids, this mixture produces a fine and optically transparent O/W nanoemulsion with the help of the mild agitation brought on by the stomach and intestine's digestive motility **[26]**.

The transition of a co-surfactant or hydrophilic co-solvent from the organic phase to the aqueous phase, **[27]** and when there is a brief negative or extremely low interfacial tension, nanoemulsion negative free energy forms, are two most frequently mentioned mechanisms of nanoemulsion formation from SNEDDS. The most well-liked and effective method for delivering hydrophobic medicines with limited bioavailability is SNEDDS **[28]**.

IMPORTANCE OF NANOEMULSION SPRAY

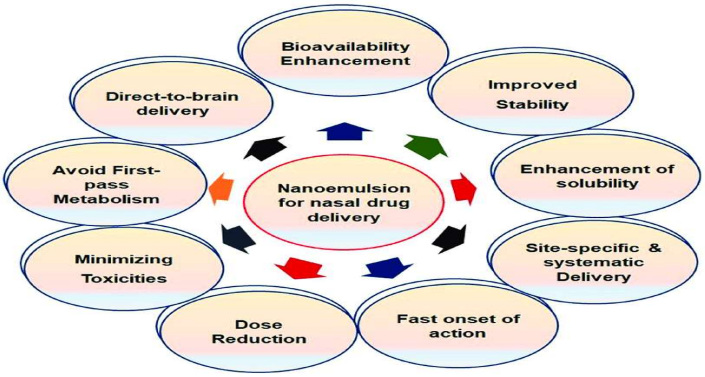

Figure 2: Importance of Nanoemulsion spray

APPLICATION OF NANOEMULSIONS VIA VARIOUS ROUTES

Nanoemulsion are used across variety of pharma sectors, counting personal care and cosmetics, food, healthcare and agrochemicals. They are also used to distribute drugs system in medications and also in the synthesis of new compounds **[44]**.

a) Topical Delivery:

A topical application is one of the biggest advantages for choosing this form of drug delivery over the conventional one decided to avoids hepatic first pass metabolism and permits drug to be targeted to particular areas of the skin or eyes **[45]**.

b) Parenteral Drug Delivery:

Due to the advantage of nanoemulsion, formulations used for the intravenous route must have droplet sizes less than 1 mm. Administering nanoemulsion by parenteral infusion is used for a number of nutritional motives, such as: - Vitamins, carbohydrates, and fats, etc. **[46]**.

c) Intranasal Drug Delivery:

Risperidone nanoemulsion possesses knowledge for delivery to brain. It is implied that this emulsion works even more effectively when used topically rather than intravenously. There are several intranasal vaccines available on the market **[47]**.

d) Pulmonary Drug Delivery:

According to reports, cationic submicron emulsions consist of good delivery system for lung vaccination using DNA because they have Nebulization of submicron emulsions will therefore be a brand-new & emerging field of study, which causes antigen-presenting cells to prepare for cross-presentation and directly activate dendritic cells, stimulating T cells that are specific for the antigen. Nebulization of submicron emulsions will therefore be a brand-new & emerging field of study **[48]**.

e) Oral Drug Delivery System:

In order to transport medications including hormones, steroids, antibiotics, and diuretics,

nanoemulsion is ideal. Primaquine demonstrated efficient anti-malarial action against Plasmodium when coupled with an oral lipid nanoemulsion. Additionally, it decreases the use of medications. Compared to pure medication, primaquine's oral bioavailability by liver was enhanced by lipid nanoemulsion, with at least 45% of the drug being absorbed **[49]**.

f) Ocular Delivery System:

Majority of distribution of drugs to treat of eye disorders occurs topically. In order to enhance absorption, pull off a prolonged release profile, and dissolve poorly soluble medicines, O/W nanoemulsions were investigated for delivery to the eye **[50]**.

g) Transdermal Drug Delivery System:

The drug can easily reach systemic circulation by Nanoemulsion through the skin's pores, where it is further channelized for efficient distribution. These and aqueous caffeine solutions' in vitro skin permeation profiles were compared, and the nanoemulsion-loaded medicines' permeability parameters were increased **[51]**.

h) Cosmetic preparation:

Nanoemulsions are mostly utilized in creams and moisturizers. Because nanoemulsion drop size is so tiny, flocculation and creaming are not frequently seen, leading to extra ethereal and steady goods. Attractive delivery medium in the cosmetics industry **[52]**.

EVALUATION PARAMETERS FOR NANOEMULSION

1. Determination of viscosity:

A crucial factor in the physicochemical characterization of a nanoemulsion is its viscosity. It is a Brookfield viscometer that is most frequently familiar to assess the viscosity of nanoemulsions. Viscosity measurements confirms what kind of emulsion it is-O/W or W/O. Systems with lower viscosity are O/W emulsion, while those with high viscosity are water-in-oil systems [53]. However, the most often used instrument right now is the survismeter, which measures the hydrodynamic volumes, particle sizes, dipole moment, surface tension, contact angle, interfacial tension, and viscosity of nanoemulsions **[54]**.

2. Osmolarity and pH measurements:

To know pH of a nanoemulsion it utilizes a pH meter to measure, and its osmolarity is determined using a microosmometer using the freezing point method. This is done by transferring 100 l of nanoemulsion into a microtube and taking measurements **[55]**.

3. Refractive index:

Refractive index provides information about the transparency and medium properties of nanoemulsion. Refractive index of a medium

is equal to the product of phase speed of the wave in the medium and the reference medium's wave speed. A drop of NES is put on a slide, and its refractive index is compared to that of water, the Abbes type refractometer is familiar to calculate nanoemulsion's refractive index at 250.5°. (1.333). If a nanoemulsion's refractive index is equal to or greater than of water, it is claimed that the nanoemulsion is transparent **[56]**.

4. Percent transmittance:

Using a UV spectrophotometer at certain wavelength and using pure water as a reference, the % transmittance of prepared NE is calculated. A nanoemulsion is considered to be transparent if it's percent transmittance is proven to be greater than 99% **[57]**.

5. Dye solubilization:

An O/W globule can disperse a water-soluble dye that is diffused in the aqueous phase of a water in oil globule. Similar to this, oil-soluble dye is soluble in oily phase of oil in water globule but disperse in water in oil globule **[58]**. If you mix an O/W nanoemulsion with a water-soluble colour, colour will spread equally, but if you use water in oil emulsion, only the scattered phase of the dye will remain. A microscopic study of the emulsion will reveal this **[59]**.

6. Calculating zeta potential:

Zeta potential is a technique for calculating liquid particle surface charges. When predicting dispersion stability, zeta potential is used, and it's worth is resolved by the drug's physicochemical properties, along with those of the polymer, the medium, the existence of ions, and the adsorption of those electrolytes. Malvern Zetasizer equipment is familiar to measure it. Zeta potential is measured by diluting nanoemulsion and extrapolating its value from the electrophoretic potency of oil drops. It is thought that a zeta potential of 30 mV is adequate to guarantee nanoemulsion's physical stability.

7. Particle size & polydispersity index (PDI) determination:

Malvern Zetasizer is familiar to analyze the particle size as well as PDI of NEs by photon correlation spectroscopy, which keeps track of changes in light scattering brought on by the Brownian motion of particles over time. The foundation of PCS is the idea that small particles move at a higher velocity than large particles. The laser beam is warped with the sub-micron particles within the emulsion. Because of particle diffusion, there are abrupt fluctuations in the laser scattering intensity all over a mean value at one predetermined angle, and this depends on particle size. The predicted photoelectron time correlation function's line width distribution histogram

perhaps utilized to calculate the particle size. A weighed quantity of the product is dissolved in double-distilled water to achieve a homogeneous dispersion, which must be utilized right away to calculate the particle size & PDI. A monodisperse system has a PDI of zero, while a polydisperse particle dispersion has a PDI of one **[53]**.

8. Research on drug release *In-vitro*:

On USP dissolution equipment, the in-vitro release rate of a medication is often investigated. Following their introduction within dialysis layer pouches and placement in a beaker with buffer, NE carrying medication similar to 10 m were first mixed with buffer. This experiment is run at 370.5° and 50 rpm for stirring. Periodically, samples are removed, and the same amount of new dissolving medium is then substituted. The absorbance of the mixture is then calculated spectrophotometrically at a certain wavelength after the samples have been appropriately diluted. The absorbance of the sample collected is used to determine the proportion of release of drug at various intervals of time using a calibration curve **[57]**.

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