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ABSTRACT:

The bloodbrain barrier (BBB) controls and restricts the entry of therapeutic medications because it plays a critical role in protecting the brain from toxins.Nasal medicine administration allows fo r immediate drug delivery into the brain through the nose-to brain pathway.avoiding both the first-pass impact and the blood-brain barrier. Various novel and promising formulation approaches have been explored for drug targeting to the brain by nasal administration. Nanoemulsions have the potential to avoid problems, including low solubility, poor bioavailability, slow onset of action, and enzymatic degradation. The present review highlights research scenarios of nanoemulsions for nose-to-brain delivery for the management of CNS ailments classified on the basis of brain disorders and further identifies the areas that remain unexplored. The significance of the total dose delivered to the target region, biodistribution studies, and long-term toxicity studies have been identified as the key areas of future research.Direct access to the brain through the nasal route is made possible by the maxillary and nasal nerves, which are located in the upper part of the nose cavity.Nanoemulsions are formulatio ns used in the field of nanomedicine.They consist of emulsions (typically, oil in water), which ar e then combined with one or more surfactants and, in the end, cosurfactants that are added in the form of small, highly surface area droplets.Promising formulations for intranasal drug administration that can reach the brain a re nanoemulsions.This review focuses the present situation in literature regarding the use of nanoemulsions for nose-to-brain targeting, with particular attention to recent publications. Nasal nanoemulsions appear to be effective, non-invasive and safe drug delivery systems to achieve brain targeting for the treatment of neurological diseases.

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Keywords*:* Intranasal; Blood brain barrier; Drug delivery; Nanoemulsions ; Brain delivery.

- **INTRODUCTION:**

The term "bloodbrain barrier" refers to the microvasculature of the central nervous system (CNS) , which divides the brain from the rest of thebody.Cerebral artery, capillary, and vernule-level CNS arteries are continuous.fenestrated, and able to control the flow of ions, chemicals, an d other substances between the blood and the brain brFirst of allBecause of its strong barrier func tion, the BBB can protect the central nervous system from external stimuli, viruses, and poisons. The blood artery walls' brain endothelial cells (BECS) and their distinct properties dictate how th e bloodbrain barrier (BBB) performs as a barrier.BECS are polarised cells bound together by gap junctions that effectively control.
Two types of transport systems that are typical of BECS include efflux transporters, which remov e lipophilic poisons by passively diffusing across the cell membrane, and into the brain [1,2].Kno wing the mechanisms governing the blood-
brain barrier in health and how they alter in disease includes highlighting the distinctions that tw o scientists have accurately demonstrated. This knowledge can be extremely helpful in determini ng the most appropriate medical treatments for a variety of neurological disorders.[3,4]Numerou s severe disorders affecting the neurological system, such as neuroinfections,neurodegenerative d isorders include conditions like Parkinson's disease, Alzheimer's disease, multiple sclerosis, prol onged agerelated neurological impairments, cerebral ischemia, and others.According to health da ta, the frequency of CNS infections is extremely high worldwide, and so are medical expenses [5].TheExternal magnetic fields can be used to deliver medication directly to the brain. Other meth ods of local delivery include focused ultrasound, catheter infusions, intra-
cerebroventricular or intra-parenchymal infusions, intracerebral delivery with mini-
pumps, and focused ultrasound approaches.However, considering the need for surgical interventi on, all of these procedures are exceedingly risky and intrusive [6], and many of them are not acce ptable in circumstances involving ongoing or nurtierous therapy.Owing to these reasons, numero us attempts have been made to create strategies for getting active substances where they need to go without utilising the blood-
brain barrier.A strategy for brain targeting includes both the use of non-
traditional administration methods and the development of medication formulations with properti es optimised for the most effective administration through these routes.Intra-
nasal drug delivery is a comfortable, non-
invasive way to deliver medications into the brain by avoiding the blood-brain barrier.18–
12]Such drug delivery system paths have a number of advantages, such as enhanced patent comp liance, superior safety, remarkable ease of administration, rapid beginning of action, and less syst emic exposure [7].

- **NOSE-TO-BRAIN DRUG DELIVERY**:
  Since the olfactory nerve within the nasal mucosa has a direct connection between the bra

in and nose, the nasal route is the most preferable method for administering drugs that tar get the central nervous system.The two main purposes of the nose are smell and breathing .The human olfactory region is currently made up of between 125 and 100% of the nasal cavity's surface area, and it is where the olfactory and trigeminal nerves terminate.The ext ernal world is a conduit for information into the brain.due to the drug's targeting of the tri geminal and olfactory pathways, which can be accomplished by injecting formulations int o the nasal mucosa.[8-10]

- **ADVANTAGES:** [11-13]

a) It is a non invasive method.
b) Does not cause any sort of pain.
c) High level safety.
d) Having Patient compliance.
e) Fast onset of action.
f) Lesser systemic exposure.
g) Avoid the first -pass metabolism.

- **DISADVANTAGES:**[11-13]

a) Lower bioavailability due enzymatic degradation of the drugin the nasal mucosa.

b) High level clearance of the drug.

c) Due to limited surface area of olfactory mucosa small volume of the drug can be instilled.

d) Attaining actual quick cerebrospinal fluid concentration.

- **COMPONENTS OF NANOEMULSION:**

1) Drug
2) Oil phase
3) Surfactant and Cosurfactant
4) Aqueous phase

Oil, surfactant, cosurfactant, and aqueous phase make up the majority of nanoemulsions, which are dispersions that are further micronized by an outside energy source.Low interfa cial tension provides the basis for the creation of nanoemulsions, which can be achieved by adding co-
surfactant.Lowering the interfacial tension results in a nanoemulsion that is thermodynam ically stable.The solubility of the drug and the kind of nanoemulsion (O/W or W/O) deter mine how much lipid component needs to be used in the formulation.When selecting an o il phase to solubilize a medication, solubility is one of the most important factors to take i nto account. The oil with the highest solubility is selected to limit the amount of oil in the

formulation and, consequently, the amount of surfactant due to toxicity concerns.Depending on the length of the chain, oil can be categorised as long-chain, medium-chain, or short-chain triglycerides.Sesame oil, cottonseed oil, soy oil, coconut oil, olive oil, and several others are a few examples of these.The bioavailability of a nanoemulsion can be influenced by the type of oil phase employed in its manufacture. For example, curcumin, when formulated with long- and medium-chain triglycerides, has the maximum bioavailability.Emulsifying agents also improve the kinetic stability of the nanoemulsion while it is being stored, which is necessary for its formulation.The most widely utilised emulsifying agents for the creation of nanoemulsions are surfactants, such as Tween 20, 40, 60, 80, and Span 20, 40, 60, 80.Sodium dodecyl surfactant, polyethylene glycol, poloxamers, and numerous others are among the additional surfactants.Co-surfactants are employed in nanoemulsion stabilisation.Ethanol, propylene glycol, glycerine, polyethylene glycol, and ethylene glycol are a few examples of co-surfactants that can be employed separately or in combination.[14-23]

➢ METHODS OF PREPARATION OF NANOEMULSION:

- **High-Pressure Homogenization-**
  This technique uses a highpressure homogenizer to create nanoemulsion with incredibly small particle sizes (up to Inm).Oil phase can be dispersed into aqueous phase by forcing a mixture via a tiny inlet orifice at extremely high pressure. This causes the oil and water phases to disperse through extremely high turbulence and hydraulic shear.It creates emulsion particles that are tiny and fine.The sole disadvantage of this highly efficient approach of creating nanoemulsion is the need for high energy and high emulsion temperature.[24]

- **Microfludization:**
  It is a mixing technique that makes use of a microfluidizer tool to prepare nanoemulsion. A positive displacement high-pressure pump is used in the microfluidizer to integrate the product into microchannels, or tiny channels.Sub-micron size particle emulsion is produced as a result of the products passing through these microchannels.To create a coarse emulsion, the dispersion of oil and aqueous phases are added to a homogenizer. This coarse emulsion is then added to a microfluidizer to create a stable emulsion.recurring this procedure ofUp to that point, microfluidization is used to get the emulsion particle size that is required.Afterwards, big droplets are removed from this emulsion by filtering it with nitrogen.[25]

- **Spontaneous Emulsification:**
  The method of spontaneous emulsification consists of three main steps:

a) Making a uniform organic mixture of oil, hydrophilic surfactant, and surfactant in a sol vent that is soluble in water.
b) An oil-in-
water emulsion is produced when this organic combination is introduced into the aqueous phase while being stirred magnetically.
c) Evaporating the watermiscible solvent at a lower pressure.[26]

- **Solvent Evaporation Technique:**
  In order to prepare a nanoemulsion, a drug solution must first be prepared and then emuls ified into a different liquid (a non-
  solvent).Drugs precipitate when the solvent from them continues to evaporate.[27]

- **Hydrogel Method:**
  The drug solvent mixture and drug anti-
  solvent are miscible in this approach.This technique can stop crystal formation and Ostwald ripenin g because of the strong shear force. [28]

CHARACTERIZATION OF NANOEMULSION: [29-32]

- **Pseudoternary phase diagram construction:**
  Pseudoternary phase diagrams were used to identify nanoemulsion areas.Water was adde d drop by drop to the mixture of oil and surfactant/co-
  surfactant at specific weight ratios.Phase diagrams were built using distil water as the aqu eous phase.The water titration method was employed to build pseudoternary phase diagra ms due to its ease of use and scalability.Nanoemulsions were created for this study in ord er to identify the specific component system region.

- **Electrical Conductivity:**
  Electrical conductivity (o) can be used to determine the kind of nanoemulsion (O/W or W /O) and the stability of the nanoemulsion (Phase inversion on storage).By inserting a con ductivity electrode into the nanoemulsion formulation and calibrating it with NaCl solutio n, the electrical conductivity of the nanoemulsion was measured using a digital conducto meter.In the event when nanoemulsion formulation
  the O/W type nanoemulsion formulation was indicated by the conductivty.

- **Refractive index:**
  Refractive index (RI), an optical parameter, is used to describe the nanoemulsion's isotrop ic characteristics.Utilising an Abbe type refractrometer, the formulations' refractive indice s were ascertained, and it was noted that the nanoemulsion formulations were isotropic in nature and chemically stable, indicating the absence of drug-excipient interaction.

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- **pH:**
  Tanco digital pH metre was used to measure the pH nanoemulsion at 25 1 °C.
  Before usage, the pH metre was calibrated, and the pH values of each composition were a scertained three times.

- **Globule size or droplet size analysis:**
  Analysis of droplet size or globule size
  using a digital electronic microscope, the globule size of each formulation was examined.

- **Percent drug content:**
  A UVVisible spectrophotometer set to 280 nm was used to measure the drug concentratio n of the samples after 1 mL of the nanoemulsion had been properly diluted with water to make 10 mL.

- **Viscosity determination:**
  The viscosity of the nanoemulsion formulations that were created was assessed using the Brookfield DV-
  I Rheometer (Brookfield Engineering Laboratories, Inc., Middleoro, MA) without the nee d for dilution.The viscosity of the nanoemulsion is measured by placing it immediately be neath a viscometer spindle that rotates at 10 RPM for ten minutes.

- **Zeta potential:**
  Using a clear, disposable zeta cell, the Delsa nano zetasizer was used to assess the nanoe mulsion's zeta-
  potential.Particle diffusion resulting from Brownian motion, which is connected to particl e size, served as the foundation for the theory.After that, built-
  in software uses the Stokes-
  Einstein equation to calculate particle size based on the translational diffusion coefficient. Using the Helmholtz-Smoluchowski equation, built-
  in software translated the electrophoretic mobility (um/s) to zeta potential.zeta cells with modest volumes that were disposable were used for the measurements.The average zeta p otential of each sample was calculated using the mean of three measurements.As a standa rd, latex dispersion with a zeta potential of -50 mV ± 2.5 mV was employed.

- **Ex-vivo diffusion study of nanoemulsion :**
  The freshly removed sheep nasal mucosa, with the exception of the septum portion, was o btained in phosphate buffer (pH 6.4) from the abattoir.The membrane was allowed to accl imatise for fifteen minutes in PBS (pH 6.4).After identifying and separating the nasal me mbrane from the superior nasal conche, the superior nasal membrane was removed and p aced on a Franz diffusion cell.Phosphate buffer (pH 6.4) was used to stabilise the tissue in both compartments, and a magnetic stirrer was used to agitate it for 15 minutes.After 15

minutes, the solution from each compartment was taken out, and the acceptor compartme nt was filled with brand-new phosphate buffer (pH 6.4).
At predefined intervals, samples were extracted and examined from the receptor compart ment.EverybodyA similar volume of diffusion media was used in place of the deleted sa mple.Every investigation was conducted for 6.0 hours, during which every sampling poin t's drug concentration (µg/mL) throughout the sheep's nasal membrane was determined.F or diffusion investigations, the formulations were examined in triplicate, and the mean cu mulative data for the percentage of drug diffused over time were plotted against the passa ge of time.

- **FORMULATION FOR NASAL DRUG DELIVERY TO TARGET BRAIN**: An overview of the body of research on nanoemulsion intended for nose-to-brain aiming demonstrationsIt appears that using intranasal medication replaces oral thera py.Furthermore, if the medication is taken orally in order to reach the brain, this mode of administration may cause problems for a number of the medications listed in Table 1.In v ivo experiments have shown that nasal mucosabased CNS delivery can occasionally resul t in superior parenteral administration as well.

Table no.1: Nanoemulsion formulation prepared for nose to brain drug delivery[33-43]

Author	Drug	Category	Topic	Reference
Kumar et. al	Risperidone	Schizophrenia	Intranasal nanoemulsion based brain targeting drug delivery system of Risperidone.	33
Kumar et. al	Olanzapine	Schizophrenia	Mucoadhesive nanoemulsion- based intranasal drug delivery system of Olanzapine for brain targeting.	34
Yu. et. al	Ergoloid mesylate	Schizophrenia	Preparation of Ergoloid mesylate submicron emulsions for enhansing nasal absorption and reducing nasal ciliotoxicity	35
Jain et. al	Amiloride	Anti- epileptic	AntiepilepticintranasalAm iloride loaded mucoadhesive nanoemulsion:Developme nt and safety assessment	36

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Bahadur et. al	Ziprasidone hydrochloride	Anti-psychotic	Buffered nanoemulsions for nose to brain drug delivery of ziprasidone hydrochloride: preformulation and pharmacodynamic evaluation	37
Mahajan et. al	Saquinavir mesylate	HIV Infections	Nanoemulsion-based intranasal drug delivery system of saquinavir mesylate for brain targeting	38
Pathak. et. al	Nimodopine	Cerebrovascular spasm and semile dementia	Role of mucoadhesive polymer in enhancing delivery of Nimodopine microemulsion to brain via intranasal route	39
Sood et. al	Curcumin	Neurodegenerative disease	Optimization of nanoemulsion for intranasal delivery using design of experiment and it's toxicity assessment	40
Pangeni et.al	Resveratrol	Parkinson's disease	Vitamin-E loaded resveratrol nanoemulsion for brain targeting for the treatment of Parkinson's disease by reducing oxidative stress	41
Nasr et. al	Resveratrol	Age- related neurodegenerative disease	Development of an optimized hyluronic acid-base lipidic nanoemulsion co- encapsulating two polyphenols for nose to brain delivery	42
Yadav et. al	Cyclosporine	Neuro-protective	Comparative distribution and pharmacokinetic analysis of cyclosporine-A in the brain upon intranasal administration in an Oil-in-Water nanoemulsionformulation	43

- **CONCLUSION:**

Nanoemulsion formulations are gaining prominence in the field of nanomedicine.Their c haracteristics, such as their larger surface area and nanodroplet size, make them suitable f or medication delivery from the nose to the brain.The use of mucoadhesive compounds lo wers mucosal clearance.Chitosan has two purposes in firmulation: first, it improves medi cation penetration through the nasal mucosa; second, it functions as a mucoadhesive agen t.As Table 1 illustrates, there are numerous examples in the literature from previous years of using nanoemulsion to target a medication to the brain.Because of the unique features of the drag, nasal medication delivery is preferable to oral drug delivery for CNS drug del ivery.Moreover, endothelial cell merabranes may benefit from the fluidizing effect of surf actant(s) added to nanoemulsions.

A nanoemulsion designed for intranasal delivery seems to have a promising application f or nose-to-brain drug release and CNS directing for the treatment of near-term illnesses.SeveralEfforts must be made to enhance nanoemulsion performance going forward.

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