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A REVIEW ON NOSE TO BRAIN DRUG DELIVERY SYSTEM

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ABSTRACT

The aim of this review is to make easy availability of the information about nasal drug delivery system to the people who are busy in doing the study of nose to brain drug delivery system. The Central nervous system is the main system in human body, and due to BBB, it become a complex system. So many diseases of central nervous system which is very difficult to treat, because of one hurdle and the name is Blood Brain Barrier which is present in brain. BBB blocks the entry of compounds like macromolecules into the brain. For avoiding this problem during the treatment of diseases, the various advanced approaches are used. From that nose to brain delivery system is a good approach for brain targeting. Brain relates to nose through the olfactory route and peripheral circulation. A variety of mental illnesses which include Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, and psychiatric disorders are the big problem on the earth. For reducing this problem, the advanced techniques are used for the treatment of this disease.

KEYWORDS: Nose to brain delivery, blood brain barrier, olfactory and trigeminal nerve.

INTRODUCTION

The mental illness is not easily treated by conventional drug delivery system. And the treatment of the neurodegenerative diseases like schizophrenia, Parkinson's diseases, Alzheimer's diseases, Multiple sclerosis are the challenges in worldwide.

The blood brain barrier present in brain which separate out brain from systemic circulation. The main function of BBB is to protect the brain from toxic or harmful substances.

The BBB is made up of endothelial cells in capillaries and this BBB is prevent and maintain the homeostasis in the brain. It is characterized by low rates of endothelial cells pinocytosis and the intracellular tight junction. And this prevents the entering of 95% molecules in brain.

Oral route is a popular route, but due to BBB the drug cannot given by oral route in treatment of neurodegenerative diseases. The alternative route for oral and parenteral route is Intranasal drug delivery system. Nose to brain delivery is a non-invasive approach of drug delivery which may sidestep the BBB and drug substances direct goes to the CNS.

Nose to brain drug delivery system is used for local as well as systemic effect. For administration of drug by nasal route the many type of formulation is available in market.

The most fashionable examples square measure nasal sprays and nasal drops that the drug is developed as a solution or suspension. different indefinite quantity forms square measure the controlled nasal aerosols and nasal powders. Mostly, liquid nasal spray formulations contain the drug, bioadhesive polymers, surfactants, tension agents and, in some cases, penetration enhancers. Bio adhesive polymers, like metal cellulose usually accustomed increase the viscousness of the formulation so as to stabilize the suspension or to extend the duration within the bodily cavity to switch drug absorption. Surfactants is enclosed within the formulation to solubilize the drug just in case of poor solubility or to extend the wettability. Intranasal administration offers several wise advantages from the purpose of read of patients (non-invasiveness, primarily painless, ease drug delivery and favourable tolerability form)

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. Intranasal administration offers many sensible blessings from the point of view patients (non-invasiveness, basically painless, ease drug delivery and favourable tolerability profile)
2. Speedy drug absorption.
3. Fast onset of action.
4. First – pass metabolism is absent.
5. The bioavailability of larger drug molecules will be improved by means that of absorption enhancer or other approach.
6. Higher nasal bioavailability for smaller drug molecules.
7. Massive nasal tissue layer extent for dose absorption
8. Speedy drug absorption via extremely vascularized mucosa
9. Direct transport into blood circulation and CNS is feasible.
10. Improved convenience and compliance.
11. Self-administration

LIMITATIONS

1. Dose is restricted due to comparatively tiny space offered for the absorption of drug.
2. Time offered for drug absorption is restricted.
3. Pathological condition of nose impairs drug absorption.
4. Absorption extent is a smaller amount when put next to stinker.
5. Nasal irritation
6. Surfactants used as chemical enhancers could disrupt and even dissolve Membrane in high concentration.
7. Not feasible for high molecular weight more than 1kDa
8. Drug permeability may alter due to ciliary movement
9. Drug permeability is limited due to enzymatic inhibition
10. Exact mechanism is not yet clearly known.

The comparison between nasal drug delivery system and oral, parenteral and transdermal drug delivery system

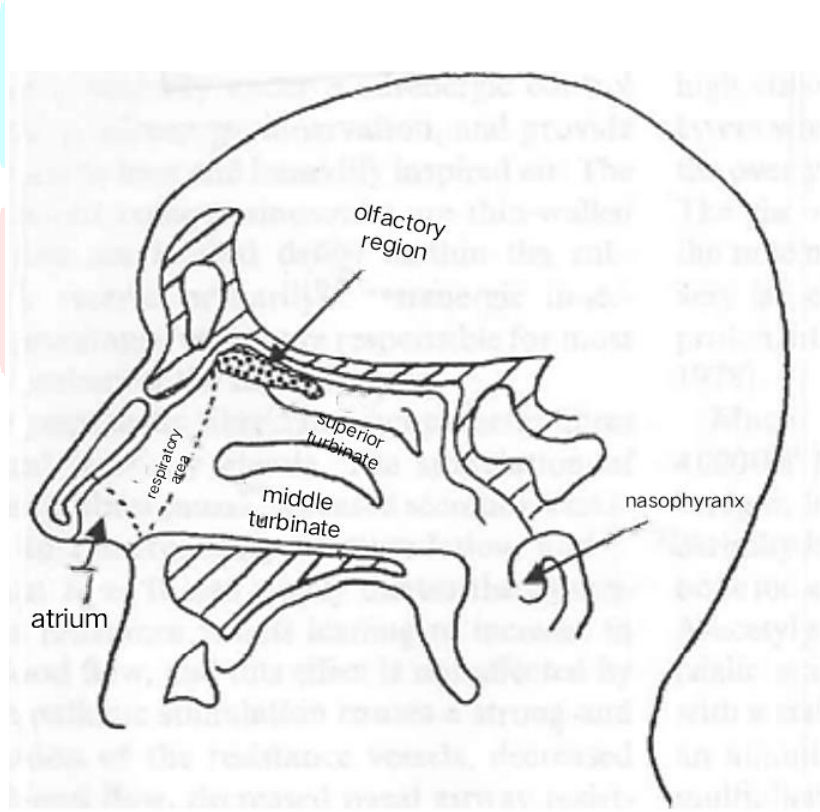
Parameters	**Nasal**	**Oral**	**Parenteral**	**Transdermal**
Targeted delivery	Yes	No	Yes	Yes
Patient compliance	High	High	Low	Low
Pain at the site of administration	No	No	Yes	No
Higher plasma drug level	Yes	No	Yes	Yes
Mucosal irritation	No	Yes	No	Yes
Self-administration	Yes	Yes	No	Yes
Rapid onset	Yes	No	Yes	Yes
Hepatic first pass metabolism	Yes	No	Yes	Yes
Drug degradation	No	High	No	Low
Systemic activity	Yes	No	Yes	Yes

BBB and CSF bypass	Yes	No	No	No

NASAL ANATOMY AND PHYSIOLOGY

Nasal cavity is lined with hair and secretion layer that are concerned in those function catching the particles and pathogens which are inhaled. The total volume of human nasal cavity is 15 to 20 ml and surface area is150 $cm^{2.}$ The nasal halves are carries with it 4 areas and the name are,

1. **Nasal vestibule**
2. **Atrium**
3. **Respiratory area**
4. **Olfactory area**



1. **Nasal vestibule:** During this space of nasal cavity there are nasal hairs additionally known as vibrissae, which filter the inhaled air. Nasal proprioception characteristics are fascinating to afford high resistance against deadly environmental substances however at an equivalent time the absorption of drug becomes terribly troublesome during the region.

2. **Atrium:** atrium is that the intermediate space between nasal vestibule and the respiratory region. its anterior section is recognized by stratified squamous epithelial tissue and also the posterior space by pseudostratified columnar cells presenting microvilli.

3. **Respiratory region:** Respiratory region is split into three sections one is superior, second is middle and last one is inferior turbinate's which are projected from the lateral wall. humidification and temperature regulation of inhaled air is the main function of this specialized structures. In between there are areas and known as passage, that are passageways where airflow is created to assure a depth contact of the inhaled air with the respiratory mucosal surface. nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity which are received by inferior and middle meatus. The nasal respiratory mucosa, thought about foremost vital section for delivering drugs systemically, is recognized by the epithelium, basement membrane and lamina propria. Nasal mucus is indispensable for various physiological functions, such as humidification and warming of the inhaled air, and additionally offers physical and enzymatic protection of the nasal epithelium against several foreign compounds, including medicines The mucin which is present in the nasal mucus layer may trap large molecular weight drugs, such as peptides and proteins.to a lower place of it , there is the lamina propria which is richly supplied with blood vessels as well as many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin an antibody that confer immunological protection against bacteria and virus.

4. **Olfactory region:** The olfactory region is situated in the roof of the nasal cavity and extends a short way down the Septum and lateral wall. In CNS there is one part that is directly exposed to the external environment that is neuroepithelium. the olfactory region is also pseudostratified like respiratory area it also contains specialized olfactory receptor cells important for smell perception.

MECHANISM OF NOSE TO BRAIN DRUG DELIVERY SYSTEM

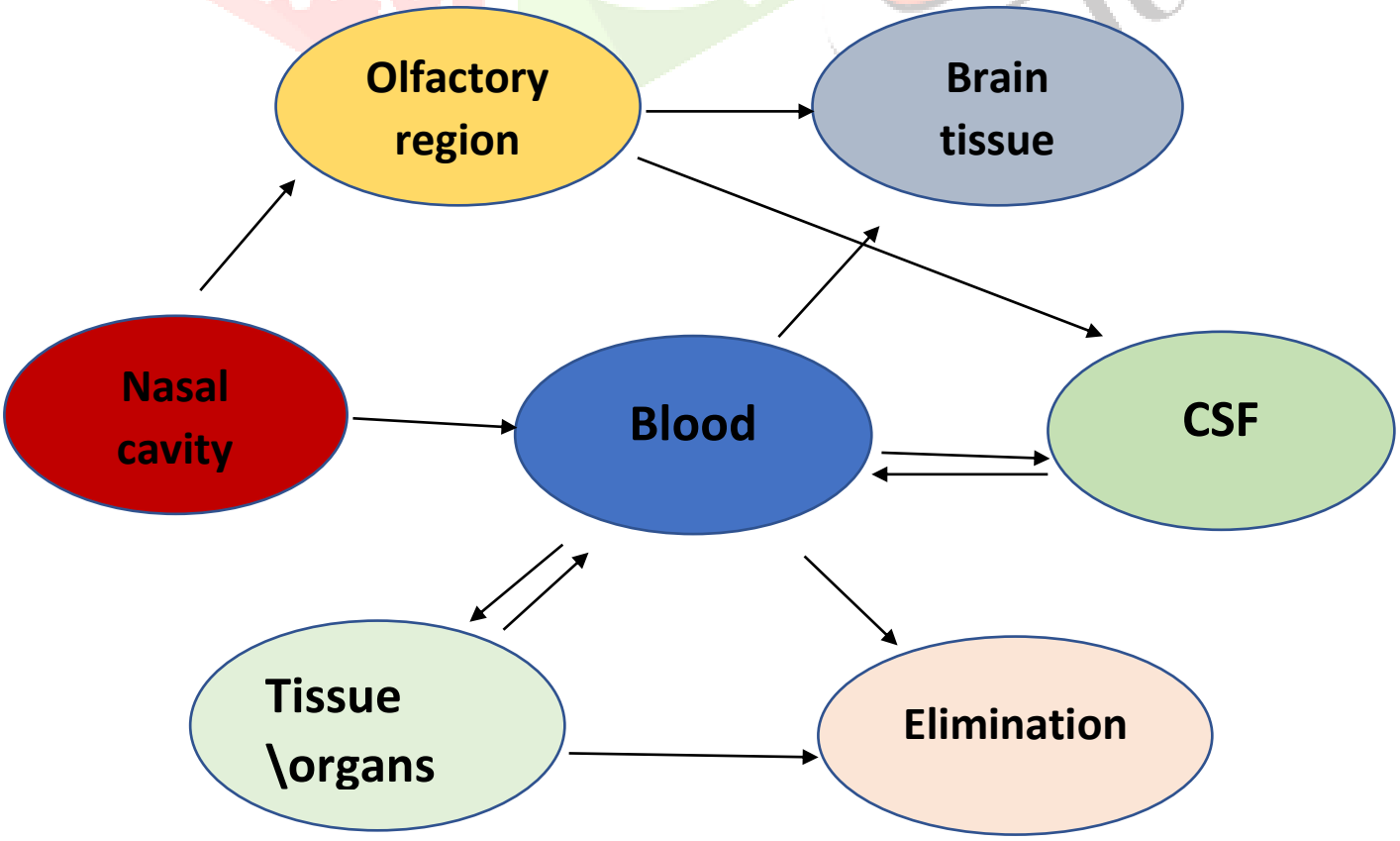
The physical and chemical characteristics of the drug molecules like lipophilicity/hydrophilicity, degree of ionization, and rate of solubilization and mostly molecular weight affect the drug transport through nasal epithelium and this all characteristics interfere in the transepithelial mechanism of passage. There are different drug transportation pathways along the nasal epithelium. There are two main pathways, transcellular and paracellular pathway. In transcellular pathway, the passive diffusion or active transport through the cell or via carriers such as p glycoprotein is included. And for the influx or efflux of anions, organic cations, and peptides the transporters are responsible. And in paracellular pathway, the drug taken through the tight junction of the nasal epithelial cells. These tight junctions ensure the regular transport of drug molecules through the paracellular space but also the mechanical cohesion between the epithelial cell. Generally, paracellular route is for the hydrophilic drugs and transcellular route is for the lipophilic drugs.

The drug transport is affected by molecular weight. Those drugs which have molecular weight below the 300 Da are rapidly absorbed in nasal mucosa and it is not affected by the other physicochemical properties. Those drugs which have molecular weight in between 300Da to 1kDa for this drug some characteristics like lipophilicity is taken into consideration because the lipophilic molecules pass by transcellular and hydrophilic molecules is passes by paracellular pathway. And those drugs which have molecular weight above 1kDa is absorbed very slowly in nasal mucosa.

As compared to molecular weight, the drug ionization is not important, only a fraction of nonionized drug is diffusible and can be easily absorbed in nasal mucosa. Drug diffusion is interfered by drug ionization. In case of small molecules with acidic or basic characteristics, the ionization is controlled by solubilization. And the vehicle used for solubilization having a pH at which the molecules is nonionized and therefore it become a diffusible molecule.

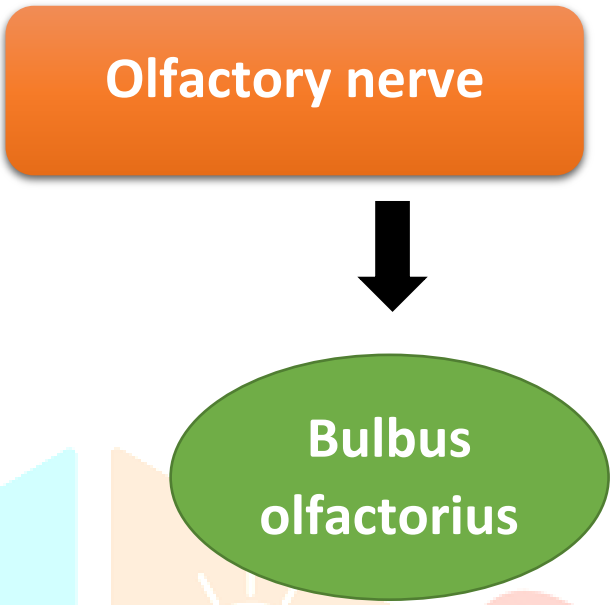
In absorption, drug solubilization is important factor. Because drug in powder or suspension form can have a dissolution time lower than what is needed for mucociliary drainage. Mucus is consisting of water, so mainly hydrophilic drugs are soluble in it. Therefore, dissolution rate is depending on the lipophilicity and degree of ionization.

So, there are two mechanism pathways for nose to brain delivery of drug. One is direct and second is indirect pathway. In direct pathway, drug is going through olfactory nerve and trigeminal nerve and goes into the CNS. In indirect pathway, the drug is going into vasculature and lymphatic system. And after that drug is passes into blood circulation. And crosses the BBB and reaches the brain. For effective transport to the brain, one pr combination of pathway may be used and the formulation, drug properties, delivery devices taken into account during selection of mechanism pathways.



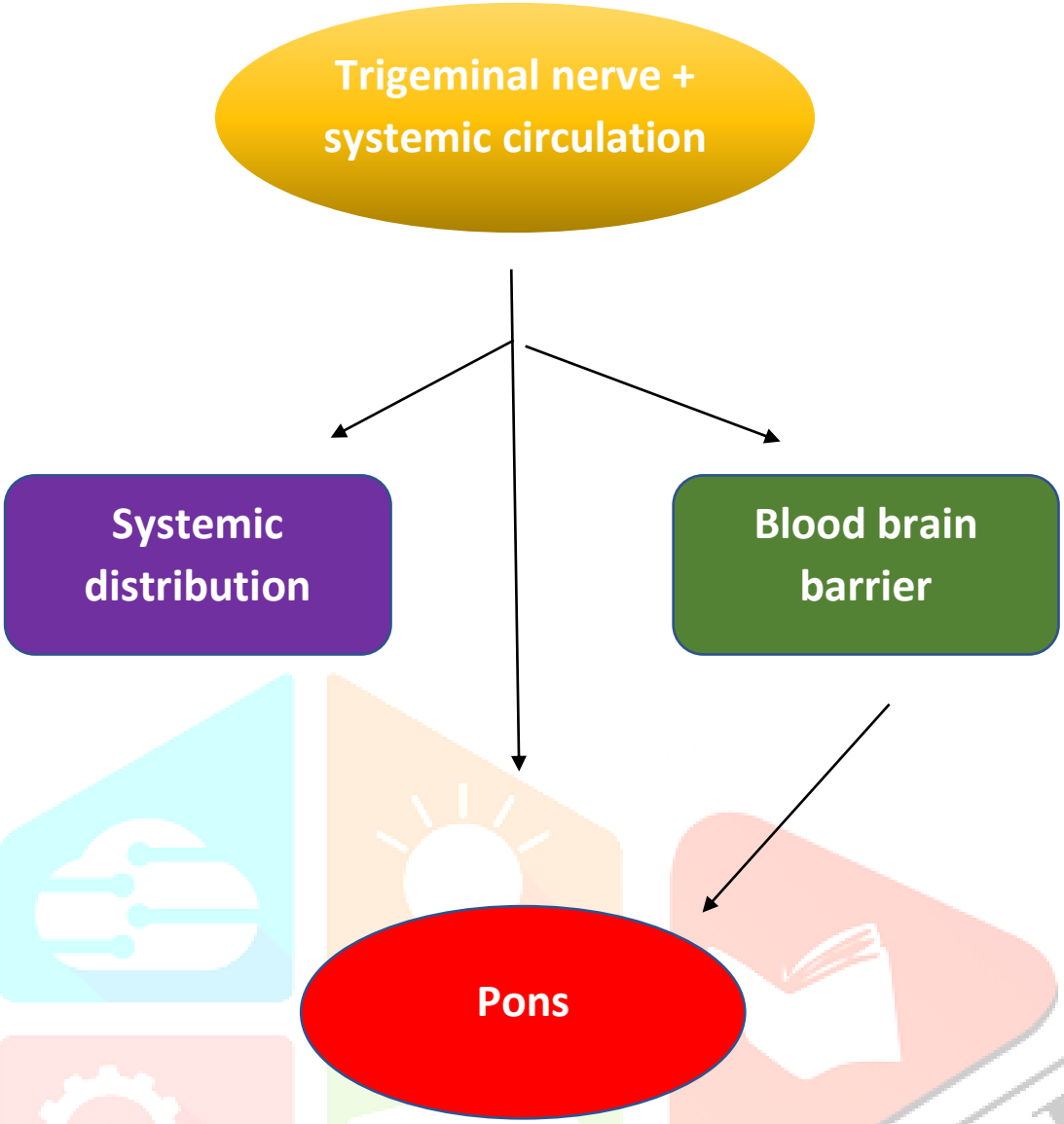
1) Olfactory nerve pathway

In this pathway, the high concentration of drug is transported through the olfactory nerve to the olfactory bulb of the CNS. There is better relationship between the drugs concentration in the olfactory epithelium and that in the olfactory bulb.



2) Trigeminal nerve pathway

The trigeminal nerve boosts the respiratory and olfactory epithelium and reaches the brain. The functions of it is the transmission of sensory information from the nasal and oral cavities, the cornea, and the eyelids to the CNS through the ophthalmic division, the maxillary division, or the mandibular division. A portion of trigeminal nerve enters the brain through the cribriform plate, which is adjacent to the track of olfactory interaction. And due to this it is difficult to know if a drug administration intranasally reaches the olfactory bulb and other regions of the brain by olfactory pr the trigeminal pathway or both.



3) Vascular pathway

the maxillary, facial, and ophthalmic arteries and from the carotid artery provide the blood to the nasal cavity. And this is very vascularized region. The origin of blood supply is different for olfactory epithelium and respiratory epithelium. But they are equally irrigated. Because of high density blood vessels, the respiratory epithelium is more irrigated in comparison of olfactory epithelium. This higher vascularization causes the majority of drug intranasally administered to be absorbed in blood stream preferentially in the respiratory epithelium.

Some disadvantages of drug transportation by systemic circulation are following,

- Drug binding to plasma protein
- Potential peripheral effect
- Drug clearance by hepatic and renal mechanism
- Degradation by plasma protein

4) Pathways involving spinal fluid and lymphatics.

The access of intranasally administered medication to the brain is simplified by the subarachnoid space, that contains humour (CSF), and therefore the perineurial areas, that contain olfactory nerves, in addition because the nasal lymphatics, that square measure essential for CSF drainage. In addition, the perineurial areas and the CSF facilitate the passage of intranasally administered medication on to the central nervous system while not passing through the blood. According to studies, studies, drugs intranasally administered have direct access to the CSF through the nasal cavity, that permits them to reach the brain and be any distributed across the assorted regions of the CNS and spinal region.

EXCIPIENTS USED IN NASAL FORMULATION

1. Mucoadhesive Excipients

The Mucoadhesive polymers are mostly used as excipients in nasal formulation. Some examples of Mucoadhesive polymers are Carbopol, carboxymethylcellulose, polyacrylic acid, chitosan, hypromellose. The mucin is negatively charged and for increasing the interaction the mucoadhesive molecules mostly positively charged. Mostly mucins are bind to the apical surface of epithelial cells. By building connection to these cells bound mucin. These agents prolong the residence of the mucosa. And increases uptake of the drug.

2. Adsorption Enhancers

Examples of adsorption enhancers are laureth-9 sulfate, cyclodextrins, bile salts, fusidate derivates, fatty acids, surfactants, hydrophilic polymers etc. this agent increases absorption and permeation. For poorly water-soluble drugs and for lipophilic drugs the methylated β-cyclodextrins is used mostly for enhancing the absorption. since there is formation of complexes with the drug. Ciliary beat frequency is affected by absorption enhancers which produce reversible effect. The drug which is administered by intranasally have to penetrate the mucus for reach the olfactory mucosa and thus the CNS. Hydrophobic drugs and positively charged drugs mostly interact with mucus. To design drug formulations which penetrate mucus easily, poly(lactid-co-glycolid) acid (PLGA) can be used for nanoparticles.

3. Preservatives

Preservatives are used to formulate nasal preparation because it gives the stability to nasal preparation. There are so many examples of preservatives which shows reversible as well as irreversible effect. From that, as chlorobutol and hydroxybenzoates as well as methylhydroxybenzoates, propylhxdroxybenzoates and chlorobutol shows the reversible cilioinhibition and some examples which shows irreversible effect is chlorocresol, edetate, benzalkonium chloride, phenylmercuric acetate and thiomersal. long-term administration of 0.02% benzalkonium chloride as preservative proved the safety of the drug supplement as it did not cause changes in nasal mucosal morphology. Ciliostatic effect is shown by Phenylmercuric acetate and thiomersal is more than benzalkonium chloride

4. **Surface proteins**

   Surface modified carriers like nanoparticles, have particular ligand for cell surface. The sugar molecules receptor expressed by both olfactory and respiratory epithelium cells, which is identified by lectins for example wheat germ agglutithin. and it can bind specifically and which promote the nasal drug delivery by neural, vascular, olfactory pathway. The clearance of nasal cavity is reduced by comprise efflux from transport protein and absorption into nasal vasculature and which improve the effectiveness of drug delivery.

5. **Enzyme inhibitors**

   Some peptidase and protease inhibitors like bacitracin, boroleucine, amastatin puromycin, and camosta are used to minimize the enzymatic degradation in the nasal epithelium and which increases the drug absorption.

6. **Modulators of tight junction**

   For opening of the tight junction of the epithelial cells, the modulators of tight junction are used. For example, peptides and lipids. And it allows the entry of drug in nasal epithelium. They have been studied in order to verify if they can be used to enhance the absorption of hydrophilic or high molecular weight drugs, although cell toxicity is a consideration.

NASAL FORMULATIONS

1. **Liquid formulation**

   In nasal drug delivery system are typically binary compound loke suspensions, emulsions and sometime it is also in the form of solutions. Humidifying impact is vital for nasal mucous membrane since allergic reactions and irritations are primarily attributed to waterlessness of the secretion's membranes. but some disadvantages are there, from that one is microbial growth. So, for avoiding microbial growth in formulation, the preservatives can be added. But another disadvantage of liquid formulation is because of addition of preservatives. This preservative can produce irritation. Long run use of liquid dosage forms might interfere with nasal mucociliary operation. And one more problem regarding liquid formulation is the liquid formulation can be dripping out after administration.

2. **Nasal powders:** because of bad stability of liquid formulation, the powder is better dosage form than liquid formulation. In case of non-peptide or amide medication, the nasal powder is better dosage form. And there is no need of addition of preservatives. And there is no need of store in low temperature. In comparison of liquid dosage formulation, the patient compliance for nasal powder is more. Residence of the fine-grained drug within nose will be improved. During the preparation of nasal powder some factors are taken into consideration. For example, solubility of the drug, particle size, toxicity like irritation

producing property of drug or excipients. For enhancing the interaction between drug and mucous membrane the polymers are added in powder formulation. These polymers are converted into viscous gel after contacting with fluids within the nasal cavity which leads to weakened rate of mucociliary clearance and prolonged residence of drug within the body. This could improve the drug permeation, increases drug bioavailability and sustain drug unleash from its viscous matrix. The drugs which are water insoluble are prepare in the form of powder and it consist of non-swelling drug carrier which increases bioavailability of deliquescent drug substances. Insufflators are the devices which majorly used for administration of the powders.

3. Nasal gel

Nasal gel is the novel formulation which is semisolid and consist of the drug which mixed with chemical substance matrix. Gels have many benefits including,

i. In liquid formulations irritation is the major disadvantage, but in gel due to soothing effect of excipients the irritation may decrease.

ii. It reduced MMC due to high consistency of gel.

iii. During respiration or sneezing, there is no loss of formulation.

iv. In gel formulation, the interaction between drug and nasal mucosa is more and which increase absorption profile of the drug.

Example. Vitamin B12 was the first nasal gel.

4. Nasal drop

Nasal drops area unit the foremost ancient nasal devices for intranasal administrations of liquids because of their low producing price and skill of most patients to use with simple directions from the community chemist. The special experience needed throughout use of nasal drops because nasal drop devices area unit lack of exactitude within the administered dose and therefore the risk of contamination throughout drug instillation into the nostrils. The administration angle at 90 degrees angle (angle between subject's head and nasal drop device) while ingraining the dose. The head is agitated from side to side after application of drops to the nostrils.

- **Drops delivered with a pipette**

In this type of nasal drops, the number of doses administered depends on actuation a volume of the formulation into a glass pipettes the number of doses administered depends on actuation a volume of the formulation into a glass pipette.

- **Squeeze bottles**

Squeezing bottles are other devices which are used for nasal administration of liquid formulation and exerting local therapeutic effects. squeeze a plastic bottle causes the discharge of air within the bottle from a slender opening. This generates a tiny low spray volume into the frontal region of the anterior naris. the disadvantage of this device is that air is force into the instrumentality following the discharge of the dose which can pull a part of the nasal secretions into the bottle, leading to contamination of the formulation. This device is not use for children because of some disadvantage

like the force applied by the patient during administration affect the droplet size and dose accuracy, resulting in poor control over the delivered dose.

5. **Nasal spray**

Nasal spray is the dosage form which consist of a piston, a chamber, and an actuator.

In contrast nasal drop, nasal sprays generate accurate doses (25–200 µL) per spray due the presence of pumps and actuators. The formulation properties such as thixotropic behaviour, viscosity, and surface tension can affected on Particle size of the generated drops, spray pattern, and dose accuracy are affected by. Other factors like applied force, orifice size, design of the pump, and formulation can all affect the droplet size and plume geometry of the spray. The devices like metered-dose spray pumps or pressurized metered dose inhalers (pMDIs) are used to deliver the doses by nasal spray.

Devices used for nasal spray;

- Metered dose spray pump: in spray pump the generated liquid spray is replaced by air. Preservatives are used to prevent microbial contamination. For avoiding contamination and for preventing irritation caused due to addition of Preservatives, the manufacturers have been prepared very type of spray pattern and it is achieved by doing the changes in designing like movable piston, compressed air to replace the vacuum created by the emitted volume. The main function of pump is to protect the liquid from contamination container from preventing the entry of air. Another one is preservative free system in which the aseptic filtration system is added, through this the air is filtered and contamination of formulation is prevented.
- Nasal pressurized metered dose inhalers: the second device which is used for administration of nasal spray is Nasal pressurized metered dose inhalers. The anterior part of the narrow nasal valve as well as the anterior non ciliated regions of the nasal vestibule are the main sites for drug deposition. For example, beclomethasone dipropionate nasal spray used for treatment for allergic rhinitis.

APPROACHES FOR NASAL DRUG DELIVERY:

1. **Drug delivery from microsphere:**

Microsphere are the type of free-flowing powders which made up of proteins or some time synthetic polymers and these polymers are biodegradable in nature. The range of particle size of microsphere is typically 1- 1000 µm. In polymeric matrix, the drug is dissolved, encapsulated or entrapped. The natural materials like proteins and synthetic materials like polymers are used for preparation of microsphere. There are two types of polymers, one is biodegradable and another one is non-biodegradable polymers. Some example of polymers is chitosan, glycolides.

Example of microsphere containing drug- i) gelatine- chitosan containing microsphere of clonazepam.

ii) DREAM BIG therapy for treatment of treatment of malignant glioma (drug encapsulated aerosolized microsphere as a biodegradable, intelligent glioma therapy.)

2. Drug delivery from colloidal drug carrier system:

Colloidal drug carrier are very small sized carriers used in nasal drug delivery. Various types of colloidal drug carriers are used, for examples, liposomes, nanogels, nano emulsion, and nanoparticles. Nanoparticles are three types like lipid nanoparticles, polymeric nanoparticles, inorganic nanoparticles.

I. Nanoparticles-

for nasal drug delivery, nanoparticles are used for preparation of nasal formulation. The controlled and site-specific delivery of therapeutic agents is possible by using nanoparticles system. The one of the benefits of nanoparticles is the protection of biological and chemical degradation of drug. Nanoparticles may be connected to specific targeting ligands, and due to this release the content of drug at the site of action is possible.

Some useful advantages of nanoparticle regarding to N2B delivery of drug-

- Non toxic
- Bio compatible
- Physical stability
- Compatible to connect to micro molecules like peptides, proteins, and nucleic acid.
- Cost effective manufacturing process and scale up.

Nanoparticles containing formulation provide the controlled drug release profile and due to this patient compliance is increases and also reduces the frequency of drug administration.

There are three points for uptake nanoparticles for nose to brain delivery.

i) Increases the interaction of nanoparticles with mucosa by enhancing the mucoadhesion. This will increase the ability of drug for passing the epithelium and finally reaching the brain.

ii) During the preparation of nanoparticles, the various types of material or excipients are added which reduces the barrier function of tight junction and because of it the drug can easily passes the blood brain barrier.

iii) Last one is the endocytosis of nanoparticles increases and due to this release of content from drug in brain is possible.

There are three types of nanoparticles which included in formulation of nasal formulation, one is lipid nanoparticles, polymeric nanoparticles, and last is inorganic nanoparticles.

Some agents like chitosan, carboxymethylcellulose, hydroxypropyl cellulose are used for preparation of nanoparticles.

The biodegradable polymers like poly lactic acid and poly glycolic acid are used in formulation of intranasal drug delivery. The size of poly glycolic acid can be adjusted. Some plasmid DNA, peptide, proteins or the small drugs can be delivered by using PLGA nanoparticles. The one problem regarding to polymeric

nanoparticles is the contamination of formulation may occur during the production process. And the sterilization process of it is costly.

II. Liposomes

for various routes the liposomes is a novel approach of drug delivery system. by conjugation or cross linking of targeting moiety to the native liposome or by modification of the fabricated liposomal formulation the liposomes, targeting and introduction of therapeutic agents to specific site is possible. Positively charged liposomes have more bio adhesion which increases the residence time in the nasal cavity. And due to this bioavailability is increases. intranasal liposomes containing quercetin decreased anxiety like behaviour and increased spatial memory.

III. Nanoemulsion

Nano emulsion is the oil in water or water in oil dispersion system, which consist of emulsifying agent like surfactant, cosurfactant. It is nanosized dispersion system, which is thermodynamically stable.

The colloidal size ranges from 50-100 nm which is also called as Mini emulsion, nanoemulsion, ultrafine emulsion or the multiple emulsions.

Example of nanoemulsion containing formulation- a risperidone loaded nanoemulsion was developed for brain targeted drug therapy.

IV. Microemulsion

Microemulsion is a stable, clear, isotropic mixture of water, surfactant, oil being frequently is combine with co surfactants. by incorporating of wide range drug molecules, this approach is interested to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicle. There are some benefits of it like easy manufacturing and scale up, thermodynamic stability and it's important to improve the solubilization and bioavailability, spontaneous formation. Microemulsion structure, phase behaviour, factor leading to its thermodynamic stability, factors associated drug release from the formulation is understand by preparing pharmaceutically acceptable dosage form.

3. Drug delivery from microchips

Microchips carrying system is one method developed for the single or multiple drug delivery for brain. Microchips is a device which has some part like pump, valve and which is controlled by electrochemical dissolution.

Example temozolamide containing microchips for brain targeted therapy.

NASAL DELIVERY DEVICES

For direct drug delivery in nasal cavity the Nasal drug delivery devices is versatile tool by using various nasal device. Powder formulation devices and liquid Formulation devices are come under the nasal delivery devices. Liquid formulations have some disadvantages over the powder formulations, so the nasal powder formulations and devices do exist in market, and more are in development.

1. **Powder formulation devices;** The powder nasal devices have more stability than the liquid formulation devices. These devices are more convenient. So many benefits of this devices over the liquid formulation devices. In formulation of nasal powder devices there is no need of addition of preservatives. This device is free from microbial growth. Due to this type of formulation and devices the patient compliances and patient acceptance is increase. the number of proteins, peptides and non-peptide pharmaceutical molecules are prepared in the form of powder formulation and it can deliver by this device easily.

   - **Insufflators:** this device is used for administration of pharmaceutical molecule by inhalation. This device is mainly constructed in the straw or tubes which contains the pharmaceutical molecules. It is a pre-dose powder capsule.

   - **Dry powder inhaler:** a dry powder formulation of an active drug is delivered by this dry powder inhalers for local or systemic effect via the pulmonary route. In dry powder inhalers the propellants are non-polar volatile in nature and the solid drug is dissolved and suspended into it. sometime it dissolved in dry powder inhaler which fluidized after inhalation by patients. These are commonly applied to treat respiratory diseases like asthma, bronchitis, emphysema and also used for the treatment of diabetes mellitus. The capsule is used to held the drug for manual loading. After the loading, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds.

   - **Pressurized Metered-Dose Inhale (PMDI):** The pressurized metered dose inhaler is a nasal device to deliver specific amount of drug to the lungs, this is a short burst aerosolized drug that inhaled the patient PMDI used for treatment of asthma, COPD and other pulmonary disorders.

2. **Liquid nasal devices:** For administration of liquid formulation this type of devices are used. The suspension and emulsion are also delivered by this device. For treatment of chronic nasal disorders, the nasal liquid devices are used.

- **Instillation and rhinyle catheter:** This are a liquid formulation device which is administer the formulation by drop by drop in region of nasal cavity. Catheter dosing is measured by the filling prior to administration. For the experimental studies this type of devices is used.

- **Compressed air nebulizers:** Nebulizers are the liquid formulation device. the drug is delivered to the lung in gases state loaded drug. This is self-explanatory name in which the air is in compressed form. Mostly for treatment of respiratory disease this device is used and it give rapid onset of action and reduces toxicity. This device is not applicable for drug delivering into blood circulation.
- **Squeezed bottle:** They are smooth plastic bottles with simple jet outlet, by pressing the bottle air passes in inside the container is pressed out of the small nozzle, having the optimum volume. the air again passes to inside the bottles After decreasing the pressure, mode of administration can be affected on Dose concentration and deposition of liquid phase delivering via Squeezed bottles. Dose and droplet size of that formulation is affected by pressed application of that container. This is used for delivering the decongestants
- **Metered-dose pump sprays:** The metered dose pump sprays are used for administration of emulsion, solution, suspension nasal hypersensitivity and other nasal disorders can be treated by using this device. It is based on manually operated pump mechanism. local effect such as topical decongestants, antihistamines is given by this device. The part of this containers is the pump, valve and the actuator. Dose of metered dose pump sprays affected by the viscosity and surface tension of that formulations.

EVALUATION OF NASAL DRUG DELIVERY SYSTEM

In pharmaceutical research another objective is o improving the efficiency and effectiveness of active principles, devices and formulation, by improving the link between in vitro test data and in vivo performance. In vitro nasal permeation research Various strategies are used to decide the drug diffusion through nasal mucosa from the formulation. The maximum critical approaches to observe the diffusion profile of the drug are mentioned below

In vitro diffusion studies

The nasal diffusion cell is fabricated withinside the glass. The water-jacketed recipient chamber has a complete potential of 60 ml and a flanged pinnacle of approximately 3 mm; the lid has three opening, each for donor tube chamber sampling, thermometer. The 10 cm lengthy donor chamber tube has an internal diameter of 1.13 cm. From sublayer bony tissues the nasal mucosa of sheep was separated and stoned in distilled water containing few drops at gentamicin injection. After the entire elimination of blood from mucosal surface, is connected to the donor chamber tube. The donor chamber tube is located this kind of manner that it simply touches the diffusion medium in recipient chamber. From recipient chamber 0.5 ml sampler withdraw and transferred to amber coloured ampoules at predetermined intervals. The samples withdrawn are definitely replaced. The appropriate analytical techniques are used for estimation pf samples for drug content. The temperature is maintained at 37°C, throughout the experiment. In vitro one takes a look at confirmed that nearly 95.2% drug was released from the formulation within 2 min

In vivo nasal absorption studies

Animal models for nasal absorption studies. The animal models used for nasal absorption studies can be of two types, first one is whole animal or in vivo model and isolated organ perfusion or ex vivo model. In vivo models are rat model, rabbit model, monkey model, and dog model.

Ex vivo nasal perfusion models

Surgical preparation is that the similar to this is for in vivo rat version. During the perfusion studies, a funnel is located among the nose and reservoir to decreases the loss of the drug solution. In reservoir the drug solution is placed which maintained at 37°C and is circulated through the nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs once more into the reservoir. The drug solution within the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration within the perfusing solution. The drug activity due to stability problems may be lost during experiment. This is especially true for peptide and protein drugs that may undergo proteolysis and aggregation. Rabbit may be used as the animal model for ex vivo nasal perfusion studies. The rabbit is anesthetized with parenteral urethane-acepromazine. A midline incision is made in the neck, and the trachea is cannulated with a polyethylene neonatal endotracheal tube. The esophagus is isolated and ligated. The distal end of the esophagus is closed with suture, and flexible Tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract (that connects the nasal cavity to the mouth) is closed with an adhesive to avoid drainage of drug solution from the nasal cavity. The drug in the isotonic buffer solution is recirculated using a peristaltic pump.

CONCLUSIONS

For treatment of neurological diseases, the nose to brain delivery is good approach for brain targeted drug therapy. For the development of nasal formulation, one has to understand the function of blood brain barrier and the unique structure of respiratory region and the olfactory region of nose. The use of N2B delivery mechanism is beneficial to cross the blood brain barrier over another strategies. Approaches for nasal drug delivery like nanoemulsion is use for nasal formulation which leads to cross blood brain barrier and specific targeting in brain. The specific targeting leads also to a decrease risk of circulatory toxicity. A major advantage of N2B delivery system over the conventional therapy is the patient compliance and decreases the frequency of drug administration. For development of nasal formulation as well as medical delivery devices, there is need for doing the study about some hurdles, and these hurdles have to be cleared.

Target specifically at the site is not achieved by some medical devices. Therefore, more research on advance intranasal N2B delivery and pathway to save and reliable clinical application.

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