DRUG DELIVERY TO BRAIN THROUGH NOSE FOR IMPROVED BIOAVAILABILITY

Abstract

Some of the disadvantages of the most popular oral route are inadequate bioavailability and hepatic first pass metabolism, which is why alternative therapies are continuously being explored. Oral administration is recognized for causing medication to dissolve in the stomach before being absorbed into the bloodstream. This can cause a delay in the medication's effects and lower its strength and efficacy. When it comes to brain targeting, few lipophilic medications are accessible to the brain, which limits the therapeutic effect. Drug administration through the nasal mucosa to the brain is a newer method of medication transportation. This approach minimizes dosage requirements, enhances absorption, and concentrates on the first pass effect. After being administered, nasal in-situ gel quickly transforms from a liquid to a gel upon coming into touch with the nasal mucosal region, enabling the medicine to adhere to the nasal region. Because molecular mass up to 500 Da can pass through the nasal epithelium, drugs can accumulate quickly in the brain.

Keywords: Neural pathways, olfactory neural route, trigeminal neural pathway, vascular pathway, nose to brain medication administration, in situ gel.

Authors

Mangesh D. Godbole
Dadasaheb Balpande College of Pharmacy
Besa Nagpur, Maharashtra, India.

Pravin B. Suruse
Abha Gaikwad-Patil College of Pharmacy
Nagpur, Maharashtra, India.

Bhalchandra M. Hardas
Department of Electronics Engineering
Shri Ramdeobaba College of Engineering and Management
Nagpur, Maharashtra, India.

I. INTRODUCTION

The blood-brain barrier (BBB) is composed of astrocytes, which surround the capillary endothelium on the exterior of the brain, paricytes, which are embedded in the capillary basement membrane, and capillary endothelial cells[1]. ATP-binding cassette transporters and P-glycoprotein drive therapeutic drug molecules out of the brain, preventing their buildup[2]. Less lipophilic medicines have lower brain accessibility, delaying the therapeutic effect. These constraints highlight the need for a dosage form that can deliver drug to the brain with adequate concentration to create a pharmacological impact. Drug molecules that insist on entering the brain must be very lipophilic and have a molecular weight of less than 500 Da.

The most likely routes of drug delivery for the central nervous system are carrier-mediated transport and receptor-mediated endocytosis. This is due to the tight confluence of capillaries, which limits the paracellular route of delivery. A drug delivery system must fulfil certain requirements in order to execute these pathways of medicine entrance into the brain. There are several therapies available for brain diseases. If tablets are used for therapy, the patient must take those 2-3 times each day. Patients commonly forget to take prescribed medication due to a tight schedule or mental stress, which is a primary cause of therapeutic failure.

Nasal Drug Delivery, Nasal drug administration is a technique achieves various tasks like brain-targeting, systemic transport, and topical application[3]. Drops, sprays, gels, *in situ* gel, powders, inserts, insufflators, monodose powder inhaler, multidose dry powder system are some modes of nasal medication delivery. By bypassing gastrointestinal and first-pass metabolism, intranasal absorption improves medication effectiveness. Nasal delivery offers quick, non-invasive, safe, and effective form of pharmaceutical administration. It bypasses the liver's first-pass metabolism and enables direct delivery to the brain and spinal cord with minimum systemic exposure. It is an alternative to parenteral administration and improves patient adherence and self-medication. With some limitations like, mucocilliary clearance, uneasiness in administration and unsuitability for high molecular weight it is now emerging as preferred area for the research.

II. VARIOUS TRAILS OF NASAL DRUG DELIVERY SYSTEM

Drugs enter the nasal space via two primary pathways: a major channel called the neuronal pathway and a smaller pathway called systemic circulation. Neural pathways primarily include two channels, namely, olfactory and trigeminal neuronal way for the drug delivery from the nasal mucosa to the brain. Mucocilia found in the vestibular region (frontal section of the nasal cavity) limit the number of foreign particles. Trigeminal sensory neurons and highly vascularised blood vessels are also seen in the breathing region. Trigeminal neurons carry drugs from the nasal cavity to the pons and cerebrum of the brain, with lesser degree to the olfactory and frontal brains. Before entering the nasal canal, a medication molecule first passes through mucociliary clearance in the vestibular region. The medication leaves the body after passing through the respiratory and olfactory portions of the nasal cavity. The olfactory nerve pathway, the trigeminal nerve pathway, the lymphatic/vascular system, and cerebrospinal fluid all transport drugs from the nasal cavity to the brain[4].

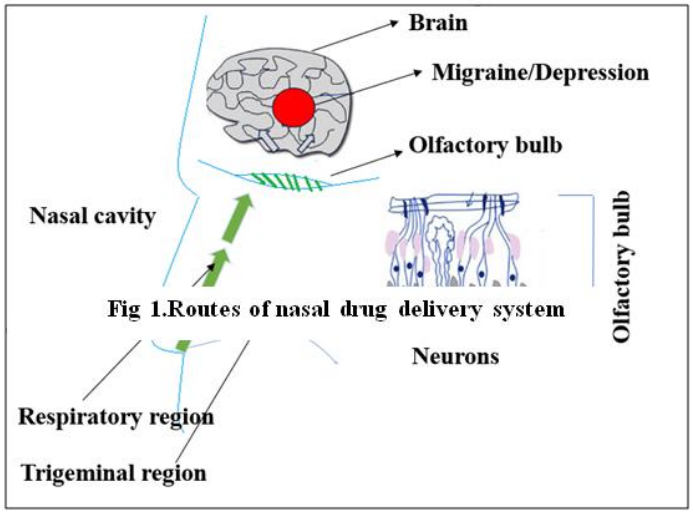

Figure 1: Routes of Nasal Drug Delivery System

1. **Olfactory Neural Pathway:** Olfactory neural pathways primary function is to transport lipophilic medicinal compounds. The rate of transport is determined by the lipophilicity of the molecules. This route is driven by pharmaceuticals with molecular weights ranging from 300 to 500 Da. It increases drug bioavailability without the use of an absorption enhancer, and fluid-phase endocytosis and receptor-mediated endocytosis were seen throughout the sustentacular cells[5].

2. **Trigeminal Neural Pathway:** The trigeminal nerve route is a major neural pathway that ends in the olfactory bulbs and stimulates the respiratory and olfactory epithelium of the nose passages. The trigeminal nerve is divided into three sections: maxillary, ocular, and mandibular, and it transports sensory information from the nasal cavity, mouth, and CNS to the eyelids and corneal nervous system[6].

3. **Vascular Pathway:** The drug is carried from the nasal to the cerebral systemic circulation by absorbing it into the blood capillaries of nasal mucous membrane. The mucosa of the nose receives blood from the carotid arteries, both internal and exterior, as well as branches of the maxillary and facial arteries. The respiratory mucosa is the optimal place because it is larger than the olfactory mucosa, gets blood from the anterior and posterior ethmoidal arteries, which are the smallest arteries in the ocular cavity, and is perfect for drug adsorption into the systemic circulation[7].

III. NASALDRUG DELIVERY TYPES

1. **Nasal Gels:** Nasal gels are liquids or solutions with a high viscosity. Nasal gels have properties such as increased viscosity due to postnasal drip, less impact on taste due to decreased intake, elimination of anterior formulation loss, less irritation due to the use of soothing and emollient excipients, and targeted transport to the mucosa, resulting in improved absorption[5]. The first nasal gel on the market was containing folic acid and B12[8].

2. ***In Situ* Gels:** An *in situ* gel is a product that is present in solution form prior to delivery into the nasal cavity and is transferred into gel form after administration. In recent years,

in-situ gelling formulations have become the primary route of administration, notably in the realm of nasal drug delivery systems. They change from a sol to a gel according to environmental factors such as temperature, pH, magnetic field, and biological factors[9][2]. Gelation is caused by ionic cross-linking or pH fluctuations, and the efficacy of gels is also determined by their rheological qualities, which are critical for holding the gel in place at the application or absorption site[4]. In-situ gel just requires 1-2 drops daily to offer relief, making it more convenient than treatment. This formulation has fewer side effects and provides drug release for a prolonged length of time, which improves patient compliance[10][11][12].

3. **Drops and Sprays:** These are some of the simplest methods of administering drugs through the nose and often used to treat localised conditions. The nostril/nasal drops are administered using squeeze containers or similar devices. Some disadvantages include mucociliary failure, microbial growth, and non-specific loss from the back of the throat or nose[13].

4. **Nasal Powder:** Certain medications are unstable in solution and suspension forms. Such medications can be made more stable by converting them to powder form. Powder formulation is highly stable; there is no preservative. The acceptability of the nostril formulation is dependent on particle size, solubility, nasal irritancy, and aerodynamic properties[13].

5. **Nasal Inserts:** Nasal inserts are bioadhesive and solid in nature, and are used in the long-term delivery of systemic medications through the nose. They absorb nasal mucosa fluid and turn into gel in the passages after delivery, preventing the sense of a foreign body[14].

6. **Insufflations:** Insufflators are the equipment used to give medicine by inhalation. It is made with a syringe or tube containing the psychoactive chemical, as well as a straw or tube. Because of inadequate particle disaggregation, the observed particle size in these systems is typically larger than the particle size of powder particles[9].

7. **Monodose Powder Inhaler:** The monodose device enables dose accuracy and now may be used with freeze-dried powder that lyophilizes rapidly. The numerous parameters, such as the pressure employed in lyophilisation and the apparatus, affect the physical features of freez-dried powder, which in turn affects the particle size and deposition of the powder[15].

8. **Multidose Dry Powder Systems:** Novel techniques for administering numerous dosages of dry powder nasally have been created to improve patient compliance.

9. **Novel Drug Formulations:** Nanoparticles, microspheres, and liposomes are examples of novel formulations for intranasal medication delivery. The use of various mucoadhesive polymers, enzymatic inhibitors, and nasal absorption enhancers enhances nasal cavity stability, membrane penetration, and retention time[16].

IV. EVALUATION OF IN SITU GELS

1. **Clarity:** Clarity is assessed visually in comparison to a black or white backdrop.

2. **Viscosity:** The viscosity of the gel may be measured using several viscometers such as the Brookfield viscometer, cone and plate viscometers with varying spindle and speed[13].

3. **Texture Analysis:** The viscosity, consistency, and cohesiveness of gels are assessed using a texture analyzer, which is also used to demonstrate the solution's syringe ability so that the formulation may be easily injected during the pharmacokinetic research. Gels must have higher adhesiveness ratings in order to sustain close contact with a surface.

4. **pH of Gel:** The pH meter is used to measure the pH. The formulation is placed in a beaker, and a tiny amount of Triethanolamine or NaOH is added to keep the pH of the formulation in the range of 5.5-6.5.

5. **Drug Content:** Generally in a 10 ml volumetric flask, 1ml sample is added and volume is made up to 10 ml with distilled water. The drug content in the sample is determined using UV visible spectroscopy at particular wavelength of drug.

6. **Sol-to-Gel Transition Temperature and Gelling Time:** The *in situ* gel formulation is deposited in a sample tube at low temperature and subsequently heated slowly. The sol-to-gel transition can be defined as the temperature at which the sol meniscus first undergoes phase change. When you tilt the tube, the meniscus should not move, indicating that gel has formed[11].

7. **Gel Strength:** A Rheometer is used to measure this parameter. In a beaker, a certain amount of gel is put. A probe is put into the beaker holding the gel while it is slowly lifted. Changes in the probe's load are studied to determine how far the probe is buried under the gel's surface.

8. **Accelerated Stability Studies:** According to ICH regulations, accelerated stability is performed.

9. ***In vitro* Drug Release Studies:** Drug release experiments using dialysis membrane are carried out for in situ gel formulations utilizing modified Franz diffusion cell. A dialysis membrane divides the donor and receptor compartments. The desired quantity of formulation is deposited in the donor compartment, and the acceptor compartment is filled with the dissolving medium. The diffusion cell is set to revolve at 50 revolutions per minute. The solution is removed and reintroduced with the same volume at the set time interval. The absorbance was measured at a wavelength representing drug max absorption.

Table 1: Available Patents on Intranasal Administration Drug Devices [17]

Type	Patent No.	Year	Assignee	Dosage form
Nasal drug delivery device	9550036 B2	2017	Impel Pharmaceuticals Inc.	Intranasal
Nasal medicine inhaler	359,555	1993-	Nippon Glaxo Limited, Tokyo, Japan	Intranasal
Drug delivery in the nervous system	US 2005/0027110 A1	2003	Gray Cary Ware & Fredenrich LLP USA	Intranasal
Pre-filled nasal drip device	USD610253S1	2020	Daikyo Seiko, Ltd.	Intranasal

V. CONCLUSION

Currently nasal route is become the most preferred route for the research due to its benefits over other routes in delivery of drug. Nasal route overcomes many limitations of oral route. It allows direct delivery of drug into brain assuring required concentration of drug into brain. The various routes through which drug reaches to brain through nose are now known and scientist are working on it for the better brain delivery. The formulations to be given through nasal route are very ease to formulate. In situ gelling formulations, which are made of polymeric materials capable of undergoing a sol-to-gel transition when exposed to biological stimuli, have emerged as innovative drug delivery strategies for nasal medicine administration. The mucoadhesive *in-situ* gelling preparations have been shown to promote medicine absorption by boosting residency in the nasal cavity. If the nanoform of drug is added in to nasal formulation it improves the efficacy of drug to several folds. It can be concluded that nasal drug delivery will be the future route for the direct delivery of drug.

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