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A Recent Perspective of Nasal to Brain Drug Delivery System for Alkylating Agent

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ABSTRACT

Brain tumours are one of the most alarming diseases of homosapiens. The presence of the blood-brain barrier is one of the major causes of extreme difficulty in brain tumour treatment, which protects healthy tissue from chemical events. Intranasal drug delivery is one of the fascinating delivery options for brain targeting, as the brain and nasal area are associated with each other via the olfactory route and peripheral circulation. The nasal route is effortlessly attainable for self-administration without the help of health professionals. The main advantage of nasal delivery is the avoidance of first-pass metabolism alkylating agents varies considerably in lipid solubility, membrane transport, pharmacokinetic properties, and clinical application. Nutritional counselling prevents malnutrition in cancer patients. A deep understanding and the study of various factors affecting nasal delivery will overcome the problems associated with nasal drug delivery formulations. This review study focused on the advantages, and disadvantages of the nasal delivery system, various challenges, and solutions for low bioavailability, various nutritional requirements, and a few marketed and investigational drug formulations were also discussed.

INTRODUCTION

For some time, BBB has hindered plausibly fascinating CNS drug candidates due to their poor distribution into the CNS on account of the special connection of the nose and the CNS, the intranasal route can deliver therapeutic agents to the brain by bypassing the BBB. Absorption of Drugs across the olfactory region of the nose offered a unique characteristic and remarkable option to target drugs in the brain. When administered nasally to the rat, some drugs resulted in CSF and olfactory bulb drug levels abruptly higher than those following intravenous administration. Attestations nose-to-brain in transport has been disclosed by many scientists. [1]

Oral drug delivery is the most commendable route for drug administration whensoever systemic effects are indented but oral bioavailability of some compounds has encouraged the search for a more productive route for systemic delivery. [2] Transmucosal route of drug delivery (i.e., the mucosal lining of the nasal, vaginal, rectal, ocular, and oral cavity) peroral administration for systemic administration, the nasal mucosa is the major route of administration to accomplish a rapid and more advanced level of drug absorption. In recent times several medications have been shown to attain finer systemic bioavailability through the nasal route, this is due to the high blood flow, the avoidance of first-pass metabolism, large surface area, porous endothelial membrane, and readily approachable. The various formulations given by the nasal route include nasal spray, nasal powder, nasal gel, etc. thus nasal route is a promising alternative for other drug delivery systems.[3]

Alkylating agents are composed of six major chemical categories nitrogen mustards, alkylsulfonate, ethylenimines, triazines, tetrazines, and nitrosoureas. They all share the common chemical features of forming alkyl radicals, which form covalent linkages with nucleophilic moieties such as the phosphate, sulfhydryl, hydroxyl, carboxyl, amino, and imidazole groups. This radical formation allows them to react with organic compounds such as DNA, RNA, and proteins for cell metabolism and protein synthesis. Alkylating agents aren't cell cycle specific, though they're most destructive to rapidly proliferating tissues and appear to cause cellular death only the cell tries to divide. Alkylating agents vary greatly in lipid solubility, membrane transport, pharmacokinetic properties, and clinical application.[4]

Advantages [5,6]

1. Fast absorption, improved bioavailability, the lower dose
2. Rapid onset of therapeutic action
3. It can be a useful complement product to an existing product.
4. Enhance patient compliance
5. Shortened risk of overdose
6. Non-invasive, ease of acceptance along with self-medication
7. Minimum irritation to the gastrointestinal membrane
8. Accumulation of active compounds in the nasal cavity results in Avoidance of liver first-pass metabolism & metabolism by GIT.
9. Enzymatic breakdown of drug can be overlooked.

Disadvantages [7]

1. Nasal irritation
2. One time the drug administered cannot be withdrawn
3. Absorption surface area is less When compared to GIT
4. The absorption enhancers used to improve nasal drug delivery system may have histological noxious which is not yet evidently authorized.
5. Some therapeutic agents may be sensitive to partial degradation in the nasal mucosa or may cause trouble to the mucosa.
6. Distribution is predicted to decrease with an increased molecular weight of the drug.
7. Concentration attainable in different areas of the brain and spinal cord varies with each agent.
8. The nasal route of delivery is not accessible to all drugs. Absorption of polar drugs and some macromolecules are inadequate due to poor membrane permeability, rapid clearance, and enzymatic degradation into the nasal cavity.

9. We know the effect of the common cold on trans-nasal drug delivery, and it is likely that instilling a drug into a blocked nose or a nose with a surplus of watery rhinorrhoea may eject the medication from the nose.

Various Approaches to Increase Nasal Drug Absorption of Drug [8]

Although the intranasal route is capable of a topic, systemic, and CNS delivery of a wide range of drugs, it cannot be assigned for many others due to their low nasal bioavailability. Summarily, the bioavailability of nasally administered drugs is particularly constricted by low drug solubility, rapid enzymatic degradation in the nasal cavity, poor membrane penetration, and rapid Mucociliary clearance.

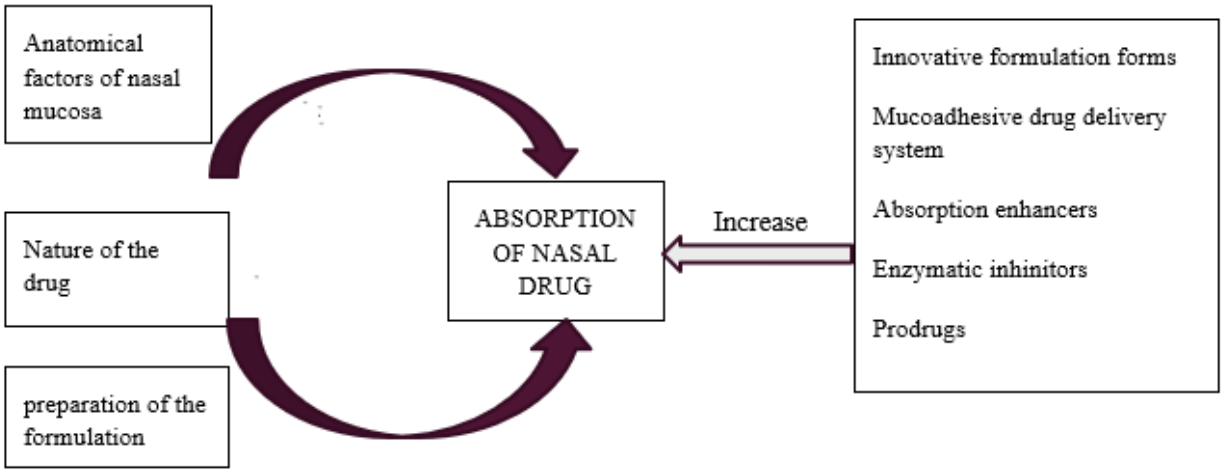

Fig. no.1: Approaches to increase Nasal Drug Absorption

Different Factors Influencing Nasal Drug Absorption [9-12]

a) Drug-related factors:

1. Molecular weight: Most of the small molecular weight drug molecules (up to 300 Da) are easily absorbed and good candidates for the transport of drugs to the brain from the nasal mucosa.

2. Chemical form: It is a very important factor because the alteration of the drug into ester or salt form can alter the absorption.

3. Polymorphism: absorption is very rapid through the nasal route hence the suitable polymorphic form is very important in the development of dosage form it will affect the dissolution rate and solubility of the drug.

4. Solubility & Dissolution Rate: For better absorption of the drug, we should get dissolve. If particles are present, it is somewhat difficult to absorb.

5. Lipophilicity: From the literature, the study revealed when lipophilicity goes on increasing it increases permeation through the nasal mucosa. Lipophilic compounds readily cross biological membranes via the transcellular route.

6. Partition Coefficient and pKa: Decreased partition coefficient of the drug results in a total dose absorbed at the epithelium slightly lower the pH partition theory states that unionized species are absorbed well as compared with ionized ones and it is also the same in the case of nasal absorption.

b) Formulation-related factors:

1. pH Scale: The drug permeation can be affected by the PH of the formulation and the nasal surface area to avoid nasal irritation; the pH of the nasal formulation should be 4.5–6.5.

2. Osmolarity: When osmolarity is not maintained it causes shrinkage of the nasal epithelial mucosa and alters the permeation of drugs.

3. Viscosity: A higher viscosity of formulation increases the time for permeation as well as increases contact time between the drug and nasal mucosa. The high viscosity formulation interferes with the normal function which includes altering the permeability of the drug and mucociliary clearance.

4. Buffer Capacity: When buffer capacity is higher than that nasal epithelium may cause local side effects and also hinder the absorption of drug nasal formulations generally small in volumes ranging from 25-200µL hence nasal secretions alter the PH of the dose.

5. Drug Concentration, Dose & Dose Volume: The performance of the nasal drug delivery system is impacted by the drug concentration, dose, and dose-volume.

c) Physiological factors:

1. Effect of Deposition on Absorption: The anterior portion of the nose provides a large surface area and in the posterior portion of the drug permeability of the drug is generally higher. The anterior portion provides longer residence time while the posterior portion provides shorter residence time.

2. Nasal blood flow: The absorption of the drug will depend on vasoconstriction and the vasodilation of the blood vessels. The nasal mucosa is rich in the vasculature and plays an important role in the thermal regulation and humidification of inhaled air.

3. Effect of Enzymatic Activity: The number of substantial enzymes in the nasal cavity can lead to toxic effects and several enzymes in the nasal cavity can affect the stability of the drug.

4. Effect of Mucociliary Clearance: In the physiological factors mucociliary clearance is one of the most important factors. It removes various delivered particles and trapped substances from the mucus it inversely proportional to the administered dose.

5. Effect of Pathological Condition: The various anatomical and physiological structures of the nasal cavity affect the process of nasal absorption.

Challenges and Possible Solutions, Common Problems Associated with Low Nasal Bioavailability of Drugs [13,14]

PROBLEMS: The various Problems like Poor Physicochemical properties of a drug or the formulation, Enzymatic breakdown, and low permeability through the nasal membrane.

CHALLENGES:

1. Inhibit nasal enzymes
2. Protect drugs from nasal enzymes
3. Reduce drug affinity to nasal enzymes
4. Increase drug permeability and dissolution
5. Modify nasal membrane
6. Enhance drug resistance time in the nasal cavity

7. Improve physicochemical properties of drug or formulation

SOLUTIONS:

1. Use of prodrugs
2. Use of Absorption Enhancers
3. Mucoadhesive Systems
4. Use of Gelling/Viscosity agents
5. Use of Cosolvents
6. Use of Enzymatic Inhibitors
7. Novel Drug Formulation
8. Pharmaceutical Excipients
9. Cyclodextrins

Characteristics Of Different Animal Species Nasal Cavity [15,16]

1. Human: The length of the Nasal cavity is 7.5 cm, the Volume is 20 cm^3, the Surface area is 150 cm^2 and the olfactory area is 10 cm^2.

2. Rat: The length of the Nasal cavity is 2.3cm, the volume is 0.4 cm^3, the surface area is 14 cm^2 and the olfactory area is 7 cm^2.

3. Rabbit: The length of the Nasal cavity is 5.2cm, the volume is 6 cm^3, the surface area is 61 cm^2 and the olfactory area 6 cm^2.

4. Monkey: The length of the Nasal Cavity is 5.3 cm, volume is 8 cm^3, the surface area is 61.6 cm^2 and the olfactory area is still not found.

Distribution of the Nasal Drug Delivery System [17]

The information on the percentage-wise distribution of drug delivery systems, it is disclosed that the major beneficence of oral (58%) drug delivery than that of inhalation (38%) than transdermal (8%), Injectable (3%), ocular (2%) and finally nasal (2%). Nasal routes contribute only 2% to drug delivery, which also inspires researchers to work in this field. The

new researcher can step into this field and can bring a ray of hope to new nasal formulations with greater bioavailability and less toxic effect.

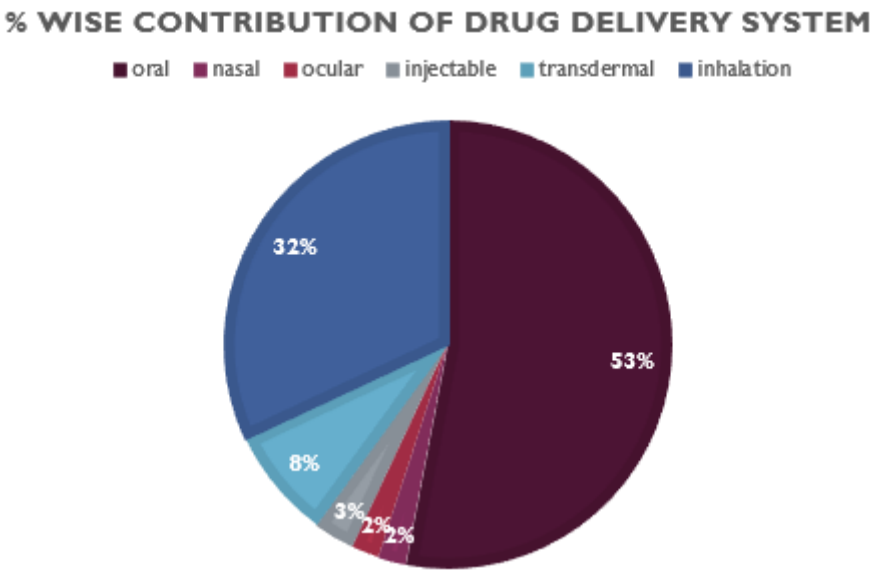

Fig.no.2: Percentage-wise contribution of the Drug Delivery System

Outline of Nasal Formulation [18]

1. In-Situ Nasal Gel: For nasal to brain delivery in situ gels holds great promise by using the Mucoadhesive polymer in the formulation which helps to reduce Mucociliary clearance The various Analytical techniques used for Nasal gel include Particle Size analysis, scanning electron Microscopy, Differential Scanning Calorimetry, Mucoadhesive Property, Viscosity, PH are involved.

2. Nasal Inserts: Nasal Inserts are Novel dosage Forms for prolonged systemic drug delivery Analytical parameters like Scanning electron Microscopy, Differential scanning colourimetry are involved.

3. Micro-Spheres: Microsphere is one of the popular systems for the formulation of nasal products It exerts a direct effect on nasal mucosa resulting in the opening of tight junctions of epithelial cells. Various analytical techniques like particle size analysis, scanning electron microscopy, viscosity, and mucoadhesive property are involved.

4. Micro-particles: Microparticle Drug delivery System includes encapsulation of both water-insoluble and sparingly water-soluble agents and analytical techniques include particle

size analysis, differential scanning colourimetry, mucoadhesive property, and viscosity are involved.

5. Dry powder: Dry powder nasal formulations offer improved drug delivery various analytical methods includes particle size analysis, scanning electron microscopy, mucoadhesive property, and spreadability are involved.

Classification of Alkylating Agent [19]

Class or type of agent	Nonproprietary generic name)	Proprietary (tradename)	Adverse effects	stomatitis	Clinical application
Nitrogen mustard	Chlorambucil Cyclophosphamide Mechlorethamine	Leukeran Cytoxan Mustargen	Myelosuppression,pulmonary fibrosis,hepatotoxicity Immunosuppression, myelosuppression ,alopecia,GI enterotoxicity Myelosuppression,nausea and vomiting, lethargy	0 + 0	Leukaemia, Hodgkin's disease, ovarian cancer Lymphoma,sarcoma, Leukaemia Mycosis fungoides,lymphoma
Alkyl Sulfonate	Busulfan	Myleran	Cataract formation,gynecomastia, hematotoxicity	0	Chronic myelocytic Leukaemia,polycythemia
Ethylenimine Derivative	Thiotepa	Thioplex	Myelosuppression,infertility,nausea And vomiting, hematotoxicity	0	Carcinoma of the breast, ovary, Bladder,rhabdomyosarcoma
Triazine Derivative	Dacarbazine	DTIC	Nausea and vomiting,hepatotoxicity, dermatotoxicity	0	Melanoma,sarcoma, Hodgkin's disease
Tetrazine Derivative	Temozolomide	Temodar	Myelosuppression,GI enterotoxicity	+	Brain tumour,melanoma
Nitrosoureas	Carmustine Lomustine	BiCNU CeeNu	Nephrotoxicity,pulmonary fibrosis, myelosuppression,hepatotoxicity Myelosuppression,nephrotoxicity,pulmonary fibrosis	0 0	Brain tumour,lymphoma,multiple myeloma Lung and brain tumours,melanoma, Hodgkin's disease

Stomatitis: 0, rare; +, occasional; ++, frequent or common

Mathematical Parameters [20]

The mathematical parameters like drug targeting index (DTI), direct transport percentage (DTP %), and drug targeting efficiency (DTE %) as well as their visualization techniques like gamma scintigraphy are used for evaluating the degree of drug targeting to the brain when intranasal administration is often evaluated by DTI which can be described as the ratio of the value of AUC brain/ AUC blood following intranasal administration to that following intravenous administration.

1. Drug targeting efficiency (DTE%) that represents the time average partitioning ratio is calculated as follows

$$DTE\% = \left(\frac{(AUC_{brain}/AUC_{blood})\,i.n.}{(AUC_{brain}/AUC_{blood})\,i.v.} \right) \times 100$$

2. The calculation of Nose-to-Brain direct transport percentage (DTP%) is as follows

$$DTP\% = \left(\frac{B_{i.n.} - B_x}{B_{i.n.}} \right) \times 100$$

B_x is indicate brain Area Under Curve fraction contributed by systemic circulation through the BBB following intranasal administration Where B_x= (B i.v./P i.v.) × Pi.n.

Role of Nutrition in Cancer Patients [21]

Nutrition may be an essential part of health and development. Nutrition includes an essential role in reducing the effects of malnutrition but it is unclear whether the type of nutritional support practice will provide the most effective supply of nutrition. In step with the global cancer analysis fund report, improper diet and lack of physical exertion are responsible for 35% of cancer cases worldwide. Then west WCRF/AICR report (2017) concludes that the consumption of farm foods (Milk) in all probability protects against colorectal cancer. consumption of high fruit and vegetable diet would reduce cancers of the mouth, pharynx, oesophagus, lung, and stomach has stated by a joint report by the world cancer research fund and the American institute of cancer research the assorted varieties of Nutrition Enteral Nutrition, Parenteral Nutrition, Neutropenic diet, Natural Bioactive Compound, Vitamin C rich sources, and Vitamin E rich Sources include.

Overview of Various Marketed Products [22]

Active Ingredient	Formulation	Marketing Status	Half-life
Cyclophosphamide	Capsule	ANDA	3-12 Hrs.
Chlorambucil	Tab. (film coated)	NDA	1.5 Hrs.
Thoi-tepa	I.V., Intravesical	ANDA	1.5-4.1Hrs.
Busulfan	I.V. Infusion	ANDA	2.5 Hrs.
Carmustine	I.V. Infusion	NDA	70 minutes
Lomustine	Cap. (gelatine coated)	NDA	16-48 Hrs.
Temozolomide	Capsule	ANDA	1.8 Hrs.

CONCLUSION

In the field of nasal drug delivery systems, this review may be a shell that emphasizes the current progress in nasal drug delivery systems along with the challenges likewise new hopes and opportunities for the researchers. Advancement is required within the section on brain tumour characterization and BBB research. The most effective drugs for brain tumour treatment are Temozolomide, Procarbazine, Carmustine, and Lomustine. Moderation of these drugs and low side effects of various chemical entities identification with enhanced efficacy and the low side effect is always admirable. Because of the blood-brain barrier and the complexity of the brain typically conventional dosage forms are not fit for treating brain diseases, especially brain tumours.

The era of nasal drug delivery is developing. However, new endeavours are necessary to make this route of delivery more economical and prominent.

Future Prospective of Nasal to Brain Drug Delivery System

Due to the presence of biochemical dynamic barriers such as BBB and blood-cerebrospinal fluid barriers effective non-invasive treatment of neurological disease is often limited to an unconquerable obstacle represented by BBB for a large number of drugs including antineoplastic drugs, antibiotics and different CNS- active drugs. It is crystal clear that crossing BBB and drug delivery to the CNS is an obscured and demanding task and hence requires the close cooperation and common efforts necessary among researchers of scientific areas like biological chemistry, physiology, pharmacology, and pharmaceutical sciences. In comparison to other dosage forms, intranasal delivery systems prove their success in clinical studies of direct nose-to-brain delivery and delivery devices.

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