Expert Opinion

Physicochemical and physiological considerations for efficient nose-to-brain targeting

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Introduction: Nasal drug delivery that exploits the olfactory and trigeminal neuronal pathways to deliver drugs to the brain is being widely explored by pharmaceutical companies, for the delivery of challenging drugs. Low-molecular-weight and lipophilic drugs are effectively absorbed by the intranasal route for efficacious brain targeting; however, high-molecular-weight and hydrophilic drugs present challenges in intranasal delivery.
Areas covered: The present review critically evaluates the physicochemical properties of drugs and formulation variables that influence brain targeting by the intranasal route. It also encompasses the influence of physiological factors of the nose that can influence absorption and the strategies utilized to increase nasal drug absorption.
Expert opinion: The challenges of drug delivery to the brain can be overcome by chemical and pharmaceutical approaches; current research is focused on developing novel drug delivery systems for both local and systemic actions. Nose-to-brain targeting has vast potential for commercialization, as these systems allow the lowering of doses, by direct targeting of the active molecule that provides easy attainment of the effective concentration at the target site. Consequently, these systems are being explored for the delivery of biologically active molecules, to treat the ailments of the CNS and various proteins, amino acids and hormones.

Keywords: brain targeting, intranasal administration, physicochemical properties, physiological factors, strategies

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1. Introduction

1.1 Nasal drug delivery

Nasal delivery traditionally has been restricted to topically acting substances used to treat common cold and nasal allergies. Recently, however, there has been increased interest in the nasal delivery as an alternative to injections and oral delivery for many systemic drugs and vaccines [1]. The highly vascularized and immunogenic nasal mucosa offers potential advantages in terms of quick action, improved bioavailability and patient compliance [2]. Currently, the route is being employed in the treatment of migraine, smoking cessation, acute pain relief, nocturnal enuresis, osteoporosis and vitamin B_{12} deficiency. Other therapeutic areas that have potential for nasal delivery include cancer therapy, epileptic conditions, psychosis, rheumatoid arthritis, neurodegenerative disease and insulin-dependent diabetes [2-5].

In the last two decades, the number of advances in pharmaceutical technology has resulted in possibilities for large-scale productions of biopharmaceuticals especially proteins and peptides [6]. The inability to administer these drugs by routes other than parenteral injection motivated scientists to explore other possibilities such as pulmonary and nasal administration [7]. Intranasal delivery has been shown to noninvasively deliver drugs from the nose to the brain in minutes along the

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Article highlights.

- Intranasal delivery system is a rapidly expanding field due to an alternative route for oral and parenteral routes and many pharmaceutical products are available in the market.
- Therapeutic agents for central nervous system disease treatment have either low concentration achieved in brain or high dose is required to achieve therapeutic level because of the limitations by blood–brain barrier. Intranasal route for brain targeting is very effective because nasal mucosa has olfactory region through which drug directly delivered to brain.
- Some potential advantages of brain targeting are fast onset of action and low dose will be required to achieve effective concentration of therapeutic agents with improved bioavailability. By direct targeting to the brain and reduced dose of drug, peripheral side effects may be minimized.
- Some considerations that are very important for the selection of drug candidate and formulation for brain targeting by nasal drug delivery system are physicochemical properties of drug and formulation such as molecular weight, partition coefficient, dissociation constant, mucociliary clearance, solubility of drug and solubility.
- Physicochemical factors of formulation such as osmolarity, viscosity, pH and mucosal irritation and dosage form should be considered for nose-to-brain delivery.
- Some peptides and proteins have low bioavailability (1 – 2%) by oral route but bioavailability can be improved (up to 10%) by intranasal delivery.
- Various research reports have suggested approaches that can be used for the targeting of molecules to the brain such as prodrug, absorption enhancer, use of mucoadhesive agents and novel drug delivery system; these approaches give effective and considerable drug delivery.

This box summarizes key points contained in the article.

olfactory and trigeminal nerve pathways, bypassing the blood-brain barrier (BBB). A recent publication by Pires *et al.* reports the exploration of nasally applied drugs for targeting orofacial structures [8].

The nasal route offers a highly permeable epithelial membrane, a relatively large surface area and avoidance of the degradation of the drug in the gastrointestinal tract and liver, making this route effective for drugs that are poorly absorbed orally or have to be given by injection [9]. Intranasal route has been utilized for delivering drugs for systemic action as the drug directly reaches blood after absorption through nasal mucosa. In case of brain, better targeting action can be achieved due to direct movement of drug from the submucosal space of the nose into the cerebrospinal fluid (CSF) compartment of brain [10]. Intranasal delivery is a noninvasive method of bypassing the BBB to deliver the drug substances to the central nervous system (CNS). The highly permeable nasal epithelium allows rapid drug absorption to the brain due to high total blood flow, porous endothelial membrane and large surface area. A wide variety of therapeutic agents (small molecules and macromolecules) can be delivered to the CNS [11] by intranasal drug delivery. Many agents active in the CNS are more effective when given nasally and provide the therapeutic effects in small dose. It neither requires any modification of the therapeutic agent nor has the drug to be coupled with any carrier [12].

2. Nose-to-brain delivery

Intranasal drug delivery for targeting the CNS is a great area of interest because olfactory region of the nasal mucosa has direct connection between nose and brain and can be explored for CNS-acting drugs [13,14]. Improvement in bioavailability of some drugs and therapeutic peptides and proteins has been reported [15-18]. For nose-to-brain delivery, drugs need to permeate the BBB from the circulation. To achieve this, drug or prodrug must be absorbed through active or passive transport to cross the tight junctions of the BBB. Nasally applied drug directly reaches the brain either by direct transport from olfactory region to the brain or from blood to the brain or CSF. The pathways by which nasally administered drugs can reach the CSF, which surrounds brain and brain tissue, are depicted in **Figure 1**.

The olfactory region, next to respiratory region, is the foremost site from where drug can be absorbed directly into the brain by different mechanisms including transcellular, paracellular, olfactory and trigeminal neural pathways. The olfactory region of nasal mucosa contains olfactory cells, which extend up to the cranial cavity [17]. The drug formulation on nasal installation comes in contact with the mucosa and is rapidly transported directly into the brain, skipping the BBB and achieving very rapid CSF levels. Some amount of administered drug reaches systemic circulation by respiratory region and a small amount is lost to the nasal-associated lymphoid tissues [16].

Most of the lipid-soluble molecules can readily enter the blood stream from the nasal mucosa and subsequently reach the CNS by crossing the BBB. But majority of the pharmaceutical drug molecules are hydrophilic, which is a rate-limiting barrier for drug targeting, as highly lipid-soluble drug molecules show easier and better targeting ability due to higher partition coefficient [19]. Hydrophilic agents can also cross nasal mucosa when nasal mucosa breaks down due to local injury. In the recent years, several drugs as well as peptides have been delivered effectively using intranasal route. The delivery of buspirone hydrochloride as mucoadhesive formulation using chitosan and hydroxypropyl-beta-cyclodextrin showed better brain concentration after intranasal administration in mice [20]. Similarly, intranasal mucoadhesive microemulsion of sumatriptan showed better cerebral concentration and reduction in migraine headache. In addition to improvement in targeting, peripheral side effects associated with brain tumor treatment can also be minimized by nasal drug delivery

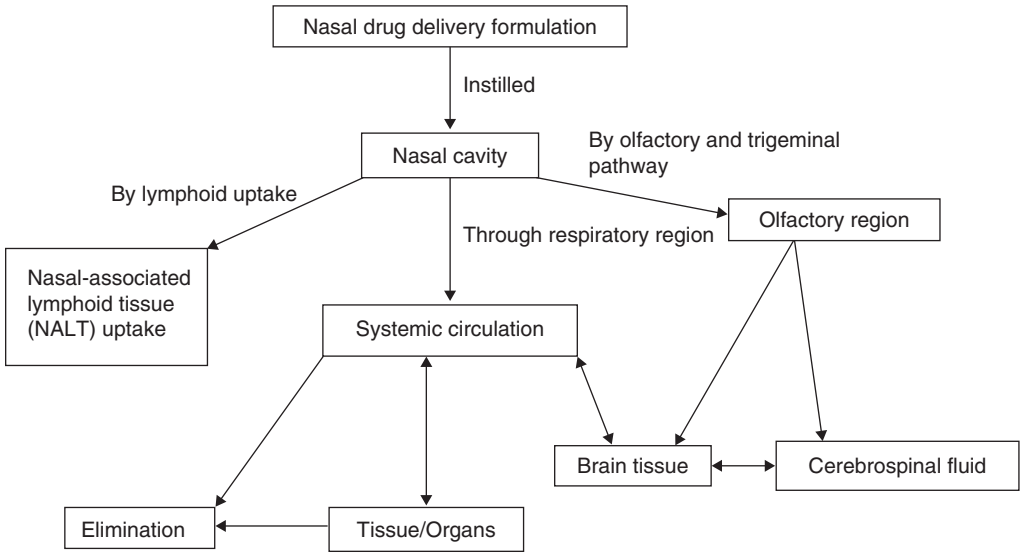

Figure 1. Fate of drug instilled in nasal cavity. The possible pathways by which drugs can reach brain after intranasal drug administration are predominantly either directly by olfactory region or through blood circulation.

system [17]. Various research reports on nose-to-brain delivery describe improvement in bioavailability to the tune of 100% [21] and some research reports have been listed **Table 1**.

3. Advantages of nasal drug delivery system

Nasal drug delivery provides an alternative route for the administration of many pharmaceutical compounds; some of the major advantages are direct transport of absorbed drug into systemic circulation and bypassing first-pass effect of liver and gastrointestinal tract so that dose can be minimized [21,22], lower enzymatic activity when compared with gastrointestinal tract and liver, avoidance of gastrointestinal membrane irritation, reduced risk of overdose and infection, self-medication and ease of convenience that increases patients' compliance [15].

3.1 Limitations

The limitations include the following: compounds of high molecular weight are difficult to be delivered, only limited volume (25 – 200 µl) of formulation can be administered by nasal route [22], mucociliary clearance and ciliary beating can affect the residence time on the nasal mucosa and permeability of drugs, nasal enzymatic barriers, limited understanding of mechanisms and less developed models for experimentation [5].

4. Mechanism of drug absorption

Intranasally administered therapeutics active agents are delivered to CNS by olfactory and trigeminal pathways providing direct connection to the CNS [21]. Direct delivery of therapeutics from nose to brain was initially attributed to the olfactory pathway. More recently, the contribution made by trigeminal pathway by intranasal route to the CNS has also been recognized [2]. The first step in the absorption of drug from the nasal cavity is passage through the mucus. Uncharged, lipophilic and small particles get easily pass through this layer. However, charged, hydrophilic and large particles are more difficult to cross. Mucin being the principal protein in the mucus that has the potential to bind to solutes hinders the diffusion of the drugs. Additionally, structural changes in the mucous layer are possible as a result of environmental changes such as pH and temperature [21]. Subsequent to a drugs passage through the mucus, there are several mechanisms for permeation through nasal mucosa. These include either by paracellular transport via movement between cell and transcytosis by vesicle carrier's pathway or both passively and actively via transcellular or simple diffusion [14]. Several mechanisms such as carrier-mediated transport, transcytosis and transports through intercellular tight junctions have been proposed. The respiratory region is the largest (130 cm^2) part of nasal cavity that contains turbinates, which are responsible for humidification and regulation of temperature of inhaled air. The nasal respiratory mucosa having good permeability is considered as most important section to deliver the systematically acting drugs [8]. Intranasal delivery also provides, more conventionally, an alternative route for systemic delivery of drugs. Some compounds that have poor oral absorption like proteins and peptides can be effectively delivered by intranasal drug delivery. Pharmacokinetic studies have revealed rapid drug action by intranasal administration as compared with conventional drug delivery [15]. However, among all the proposed mechanisms, olfactory and trigeminal pathways have been considered as predominant mechanisms for nose-to-brain delivery of therapeutic agents.

Table 1. Research reports on novel drug delivery systems for brain targeting by intranasal route and their inferences.

S.N	Drug	Delivery system	Result	Ref.
1	Resperidone	Nanoemulsion	Pharmacodynamic and pharmacokinetic studies demonstrated superior delivery of resperidone by nose	[10,13]
2	Buspirone	Mucoadhesive gel	Improvement in bioavailability and high drug targeting efficiency by i.n. when compared with i.v. route	[20]
3	Chlorpromazine	Chitosan/Pectin nasal inserts	On increasing residence time on nasal mucosa, rate of permeation increased and maximum therapeutic level was achieved in the brain	[33]
4	Olanzapine	Nanoemulsion	Higher drug concentration in brain with chitosan as mucoadhesive agent in the formulation, less dose may be required and side effects can be minimized	[35,40]
5	Zolmitriptan	Microemulsion	Pharmacokinetic and pharmacodynamic studies proved an increase in the rate of absorption and bioavailability, and good brain-targeting efficiency	[61]
6	Estradiol	Nanoparticle	Rapid absorption, C_{max} and area under curve were higher and T_{max} was less observed in reference to intravenous	[62]
7	Nimodipine	Microemulsion	AUC of brain/tissue was higher and olfactory uptake of nimodipine was threefolds more in comparison with intravenous route	[63]
8	Carbamazepine	Microemulsion	Mucoadhesive formulation helped in decreasing the dose, frequency of dosing and possibly maximize the therapeutic index	[64]
9	Clonazapine	Microemulsion	Drug concentration in brain was higher at each time point when compared with i.v. administration. Blood–brain ratio of drug was two- to threefold higher as compared with i.v.	[65]
10	Sumatriptan	Microemulsion	Studies demonstrate clinical report that rapid and more extent of amount delivered to CNS by nasal mucosa. No nasal cilio-toxicity is reported on the human nasal mucosa by formulation	[63]

4.1 Transcellular route

The transcellular refers to the transport of drug across the cells that can occur by passive diffusion, carrier-mediated transport and endocytic processes [23]. Basically, transcellular route depends on the magnitude of the lipophilicity of the molecules. Absorption of drug is determined by the magnitude of its partition coefficients and molecular size. However, several investigations have lack of linear correlation between the lipophilicity and permeability, which implies that cell membrane of lipoidal epithelium cannot be a single lipoidal barrier. Transcellular delivery can be categorized into three different processes that are described below.

Transcellular diffusion is most conventional for lipophilic molecules and absorption occurs mainly by this route. Molecular size is an important factor in the determination of drug absorption by passive diffusion and it is reported that when molecular weight of the drug is higher than 1000 Da, absorption sharply decreases. Degree of ionization is also an important property in the determination of amount of drug absorption and consequently the pKa of the drug and pH of the environment are also important considerations for drugs absorbed by this route [24]. This pathway is specially suited for small or large hydrophilic molecules through a tight junction or through the open cleft in the cell membrane. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions of the nasal mucosa. In case of drugs with poor permeability, excipients can be utilized in the formulation to facilitate permeation. For example, chitosan, a natural biopolymer from shellfish, opens the tight junctions between epithelial cells to facilitate drug transport across the nasal mucosa. Second mechanism of carrier-mediated absorption in nasal mucosa was first suggested by Kimura *et al.* They identified P-glycoprotein, organic cation transporters, dopamine transporters and amino acid transporters as the carriers of drugs in the nasal mucosa [25]. These transporters determined absorption and elimination of polarized proteins and peptide drug molecules. Lastly, endocytosis process in nasal mucosa is mostly mediated by M cells [26].

4.2 Paracellular route

This route refers to the transport of the drug between the adjacent epithelial cells by passive diffusion or solvent drag mechanism. Paracellular permeability of the drug through nasal epithelium is same like intestinal epithelial barrier. This route is especially for large or small lipophilic molecules [25]. Polar and charged drugs with molecular weight less than 1000 Da are absorbed by paracellular route. Passive

diffusion of hydrophilic drugs via paracellular routes is driven by concentration gradient across the epithelium and rate of diffusion is controlled by Fick's first law of diffusion [24]. A major limiting aspect of paracellular route is the tight junctional region that is characterized via joining of continuous tight junctional proteins. It is reported that modulation of tight junctional routes is possible by using toxin (e.g., cholera toxin) as an adjuvant in mucosal vaccines or using a tight junction-modulating peptide (e.g., PN 59), or encapsulating drugs in microspheres. For example, insulin encapsulated in aminated gelatin results in loosening of the tight junctions and increases in the absorption of insulin.

5. Factors affecting nasal drug absorption

When drug is administered for systemic effects or for CNS targeting by intranasal route, it is required to pass through mucous layer and epithelial membrane before reaching directly the CNS or blood circulation. On considerations of reported literature, it is evident that the molecular weight and lipophilicity of drugs may have a great impact in the rate and extent of nasal drug absorption. However, other physicochemical properties of the drug and the characteristics of drug formulation must be also considered. These factors can influence bioavailability and transport of drug from nose to brain. The preceding text describes the physicochemical characteristics of drugs and formulations that affect nose-to-brain delivery.

5.1 Physicochemical characteristics of drugs

The influence of physicochemical characteristics of drug molecules on the rate and extent of gastrointestinal absorption is well understood. In the same way, but with some differences, the physicochemical properties of drugs can influence the nasal absorption. Thus, these properties are highly important not only for the choice of the route of drug delivery but also for the selection or development of appropriate drug delivery system.

5.1.1 Molecular weight

Despite many advantages of nasal drug delivery system, molecular weight is a major limiting factor in the absorption of drugs [27]. An inverse relationship has been reported between nasal drug absorption and molecular weight of the drugs [28]. The compounds having molecular weight < 300 Da in solution are quickly and efficiently absorbed across the nasal membrane aqueous channels. Some molecules (e.g., butorphanol) demonstrate 100% bioavailability in comparison with intravenous administration [29]. Difficulties arise with more than 300 Da molecular weight. The nasal absorption of lipophilic drugs bigger than 1000 Da is significantly reduced [27]. However, some drugs such as cyanocobalamin, desmopressin acetate, salmon acetate and nafarelin acetate that have molecular weight in the range of 1000 – 3400 Da are available in the FDA-approved nasal spray dosage form and solutions. Unfortunately, these formulations have a very poor nasal bioavailability of approximately 10%. Drug molecules with a molecular weight more than 1000 Da require specialized drug delivery systems to achieve clinically relevant bioavailability [30]. The therapeutic agents of molecular weights 1000 – 6000 Da achieve good bioavailability with the help of absorption enhancers. Absorption enhancers are basically surfactants, glycols, glycosides and cyclodextrins and most of them exhibit molecular weight-dependent absorption [22]. Peptide and proteins with molecular weight more than 1 kDa have poor bioavailability and require absorption enhancers for its improvement. Bioavailability of macromolecules can be dramatically improved by the use of permeation enhancers [13], tight junction-modulating peptides, lipid and surfactants, cyclodextrins and chelators. Inverse relationships have been observed between the molecular weight and the drug's permeation ability for nasal formulations even in the presence of permeation enhancers. **Table 2** exemplifies the reports of bioavailability determinations of various peptides and proteins administered intranasally with and without permeation enhancers [31,13].

Lipid-soluble substances with molecular weight less than 600 Da may permeate BBB depending on the partition coefficient, but the permeability of lipid-insoluble or charged molecules is limited by their molecular weight(s). The rate and degree of nasal absorption of polar drugs is low and highly dependent on the molecular weight. Several studies demonstrate that the permeation of polar drugs with a molecular weight of less than 300 Da is not considerably influenced by their physicochemical properties. These can mostly permeate through aqueous channels of the membrane [14]. The rate of permeation is highly sensitive to molecular size; if the molecular weight is higher than 300 Da, an inverse relationship exists between rate of absorption and molecular weight, and for some small polar molecules, a bioavailability as low as 10% is suggested. **Figure 2** shows a relationship between molecular weight and absorption of drug through intranasal route [22] and illustrates that on increasing molecular weight, absorption of drug decreases by intranasal delivery [15]. The value goes down to 1 – 2% for large molecules such as proteins and peptides [32].

5.1.2 Lipophilicity

Lipophilicity is also a major physicochemical factor that limits the transport of therapeutics on nasal administration. On increasing lipophilicity of the compounds, the permeation of the compounds normally increases through nasal mucosa. Although the nasal mucosa has some hydrophilic character, it appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Consequently, lipophilic compounds alprenolol and propranolol are well absorbed from the nasal mucosa, in contrast to the hydrophilic drug metoprolol. The lipophilic drugs such as propranolol, progesterone, pentazocine and fentanyl generally demonstrate rapid

Table 2. Comparative data of bioavailability of various peptides and proteins administered intranasally with and without permeation enhancers.

Peptides/Proteins	Molecular weight (Da)	Bioavailability without enhancer	Bioavailability with permeation enhancer
ACTH 4-9	906	10% (rabbit), 15% (rat)	17% (rabbits), 65% (rats)
Salmon calcitonin	3,432	3% (human)	27% (rats)
PTH_{1-34}	4,118	2% (human)	12 – 15% (human)
Insulin	5,808	0.9% (rabbit), 0.3% (rat)	3 – 13% (human)
rhg-CSF	18,800	2% (rat)	8.4% (sheep)

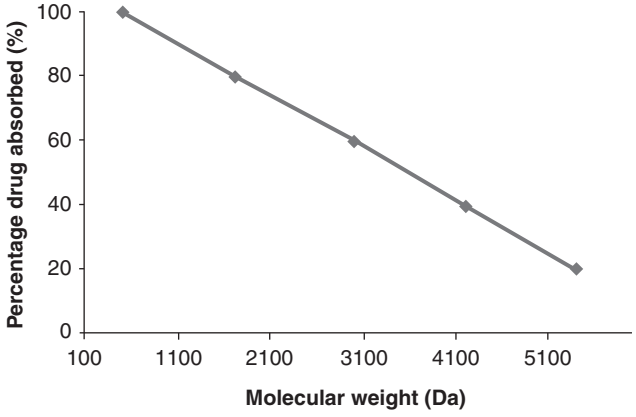

Figure 2. The linear relationship (hypothetical) is depicted between molecular weight and concentration of drug in the brain that is based on the literature reports. An increase in molecular weight of the therapeutic agent results in reduced bioavailability.

and efficient absorption when given nasally, presenting pharmacokinetic profiles similar to those obtained after intravenous administration and bioavailability approximately to 100% [14,16].

In a study, the absorption of lipophilic prodrug of acyclovir administered by nasal route in rats demonstrated higher absorption than acyclovir. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid bilayer of the cell membrane and diffuse into and traverse the cell. A number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinylestradiol have shown to be completely or almost completely absorbed nasally in animal models. A correlation between lipophilicity and nasal drug absorption has been demonstrated with several compounds. Transport of steroids was directly related to their lipophilicity; for example, progesterone and its derivatives showed increased nasal absorption on increasing in lipophilicity of progesterone compounds. The transport of barbiturate increased by 40-folds on increasing the partition coefficient fourfolds [16]. In yet another study, it was concluded that the nasal absorption of a series of quaternary ammonium compounds increased with increasing both molecular weight and lipophilicity, and it was observed that absorption was the highest with the compound of least molecular weight with least lipophilicity and the absorption of highest molecular weight compound with highest lipophilicity was the lowest.

5.1.3 *Dissociation constant*

Nasal absorption depends on the pKa of the drug and on the pH of the absorption site (5.0 – 6.5 for human nasal mucosa). The nasal absorption of weak electrolytes depends on their degree of ionization and the highest absorption occurs for the nonionized species. The nasal absorption of salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption increased with increase in pH and was found to fit well with the theoretical profile, substantial deviations were observed with salicylic acid. It concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid. Similarly, when the absorption of benzoic acid was studied at pH 7.19 at which 99.9% of the drug existed in ionized form, 10% of drug was absorbed indicating that the ionized species also permeates through nasal mucosa [33].

5.1.4 *Partition coefficient*

The nasal membrane is predominantly lipophilic hence drug absorption is expected to diminish with a decrease in lipophilicity. Thus, it is evident that polar drugs are not easily transported across nasal membrane. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of the nasal cavity. In general, the passage across biomembranes is affected not only by lipophilicity/hydrophilicity but also by the amount of drug existing as uncharged species.

In a study where absorption rates versus partition coefficient data were plotted for nasal and rectal drug absorption in rabbits, it was observed that absorption rate increases linearly with increase in partition coefficient. The slope of the nasal plot was higher than rectal, indicating that nasal mucosa is more permeable than rectal route [15]. In another report, different sulfa drugs such as sulfanilic acid, sulfamethizole, sulfisoxazole and sulfisomidine of increasing

partition coefficient (0.012, 0.250, 0.261 and 0.892, respectively) were administered intranasally and the drug concentration in the CSF was measured. There was a linear increase in CSF concentration with increase in partition coefficient of the drug [22]. The quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs was explored by the researchers. The results confirmed the quantitative relationship between the partition coefficient and the nasal absorption constant. Partition coefficient value modified by structural changes such as acyl esterification of L-tyrosine resulted in higher partition coefficient and faster absorption through nasal membrane whereas *N*-acetyl-L-tyrosine esters had partition coefficients and absorption rates similar to the parent compound. Difference in the absorption rate was attributed to the absence of negative charge on the carboxylate moiety rather than higher lipophilicity of the molecule. This concluded that absorption of L-tyrosine is carrier mediated and rate of absorption depends on the concentration and not on the partition coefficient of the drug. However, drugs such as acetylsalicylic acid and benzoic acid showed some permeability across the membrane even in environments where they are expected to exist as the ionized species. Based on these observations, it was concluded that, for polar drugs, partition coefficient is the major factor influencing the permeability through nasal mucosa [15] and a quantitative relationship existed between the partition coefficient and the nasal absorption constant (**Figure 3**) [22,34]. In a study on antipsychotic agents resperidone and olanzapine with partition coefficient values of 3.96 and 2.65 respectively, better brain targeting efficiency have been observed [10,35] that accounted partition coefficient as major factor governing nasal absorption and also other transport pathways for hydrophilic drugs might be of importance.

5.1.5 *Solubility*

Drug solubility is also a major factor in determining rate and extent of absorption of drug in nasal physiological pH. However, very few reports are available regarding the relationship between the solubility of a drug and its absorption via the nasal route. As nasal secretions are more watery in nature, a drug should have an appropriate aqueous solubility for increased dissolution [35]. Commonly, intranasal drugs are administered in the form of molecular dispersion, that is, in solution form. Intranasal volume of administration is relatively low compared with gastrointestinal fluids in oral drug delivery; therefore, drugs having low aqueous solubility and/or requiring high doses may present a problem [36]. When powder formulation is administered into the nasal cavity, dissolution process precedes the absorption process. The drug has to dissolve in the nasal cavity; therefore, the strategies are based on non-dissolving particulate systems for nasal delivery such as nanoparticles or some other novel drug formulations that cannot be transported from nose to brain without prior dissolution [15]. The uptake is size dependent: smaller the size of the molecule, higher the uptake [37]. Therefore, sometimes it is necessary to increase the solubility of drug to deliver therapeutically relevant dose. There are several approaches that may increase solubility of poorly soluble drugs for nasal administration, some of which are use of prodrugs, the salt forms, addition of co-solvent and use of cyclodextrins as solubilizing excipients.

5.2 Physicochemical properties of formulation

Apart from the factors associated with the drug, formulation-related factors should also be considered for proper absorption of the drugs as these may also affect the bioavailability of the drug.

5.2.1 *pH and mucosal irritancy*

The pH of the formulation as well as that of nasal surface can affect a drug's permeation through nasal mucosa. To avoid nasal irritation, the pH of the nasal formulation should be adjusted 4.5 – 6.5 close to nasal mucosa pH. In addition to avoiding irritation, pH also results in obtaining efficient drug permeation and prevents the growth of microorganisms on the surface of nasal mucosa. Pathogenic bacteria can be checked by keeping pH of formulation at slightly acidic side. Lysozyme found in nasal secretions can dissolve certain bacteria and maintain acidic pH [22]. When the pH changes from acidic to alkaline, lysozyme becomes inactivated and microbial infection may be possible. The pH of formulation must be selected in a manner that attends to the stability of the drug as well as favors the existence of the greatest quantity of nonionized drug species. Thus, the pH of nasal mucosa is of significance to avoid nasal irritation, to allow unionized form of drug delivery, to check growth of pathogenic microorganism in nasal membrane and to maintain functionality of the excipients.

5.2.2 *Osmolarity*

The osmolarity of formulations should be between 285 and 310 mOsmol/l for nasal drug delivery to avoid the nasal mucosa irritation, precisely the tonic effects. In a study, the effect of osmolarity on the absorption of secretin in rat was determined as it was observed that absorption reached a maximum when sodium chloride concentration was 0.462 molar and shrinkage of the nasal epithelial mucosa was also observed at this concentration of salt. A higher concentration of sodium chloride not only led to higher bioavailability but also caused nasal membrane toxicity [22]. This was the result of increased permeation of the compound resulting from structural changes. This was confirmed by using sorbitol as an osmoregulatory agent. It was found that permeation of secretin subsequently decreased. Therefore, isotonic solutions with osmolarity of 308 mOsmol/l are preferred for safe and effective drug administration [38].

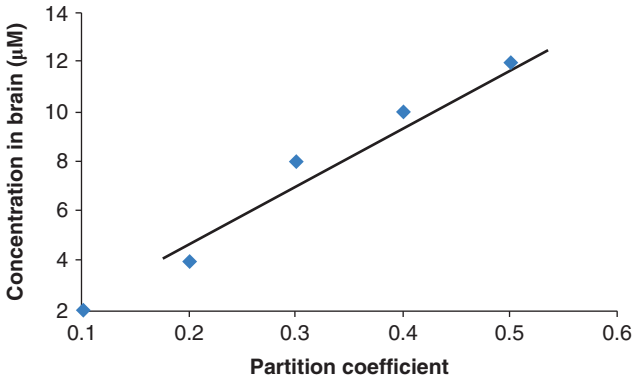

Figure 3. Diagrammatical relationship between partition coefficient and drug concentration in the central nervous system.

5.2.3 *Viscosity*

The viscosity of the formulations intended for nasal drug delivery ensures proper contact time between the drug formulation and the nasal mucosa. An increase in viscosity increases the contact time and thereby increases the time for permeation. However, the viscosity should not be too high because highly viscous formulations interfere with the normal functions such as ciliary beating or mucociliary clearance and thus alter the permeability of drug [22]. It has been considered that higher the viscosity, higher is the residence time and larger therapeutic period. Therefore, formulations are converted as nasal mucoadhesive systems or as gel dosage forms to increase the nasal residence time that will affect the total absorption of drug and improve bioavailability [39].

5.2.4 *Dosage form*

Nasal dosage forms are selected on the basis of physicochemical properties of drug, proposed indications and marketing preferences. Nasal drops are the most convenient and simplest dosage form for nasal drug delivery [39], but the exact quantity of drug is not delivered and often results in overdose and rapid drainage. Solution and suspension sprays are preferred over powder sprays because powder can cause nasal irritation [22]. But powders are preferred when drug is unstable in solution dosage form, and no preservative or antioxidants are required for powders [40]. Presently, gel devices have been developed that provide accurate delivery and fix the drug formulation to nasal mucosa and reduce postnasal drip [8]. A gel enhances the residence time and also diminishes mucociliary clearance and increases nasal drug absorption [40]. In the last few years, some specialized systems such as nanoemulsions, microspheres, liposomes and nasal films have been developed to improve nasal drug delivery. These novel drug delivery systems contain mucoadhesive polymer and improve stability and retention time and increase drug absorption by reversible alteration of nasal membrane structure to increase permeation of drugs from nasal membrane.

5.2.5 *Pharmaceutical excipients*

For nasal drug delivery, excipients are selected on the basis of their functions and should not be toxic to the nasal mucosa, and their concentrations and chemical properties should be considered in the preformulation study. It is required that the blank formulations should be tested for nasal cilio-toxicity [35] at the preformulation stage. Some common excipients used for the nasal formulations are solubilizers (emulsifying and suspending agents), antioxidants, preservatives, humectants and gelling or viscosity modifying agents. Some of them may cause nasal irritation and alter nasal drug absorption [36], therefore, careful choice is mandatory.

5.3 Physiological factors of nose

5.3.1 *Mucociliary clearance*

The combined effect of mucus and cilia are defined as the mucociliary clearance, an important physiological factor in the defense mechanism of the respiratory tract against the inhaled hazardous substances such as pathogens and particles. In normal healthy human, mucociliary clearance is assumed to be 10 mm/min [38], which can be altered by pharmaceutical excipients, by airborne irritation or by nasal diseases. The contact time of drug formulation with absorbing tissue influences the amount of drug that crosses the mucosa. In the nasal cavity, this is influenced by the rate at which the drug is cleared from the absorption site that is decided by mucociliary clearance [41]. Usually nasally administered drug formulations are cleared from the site of deposition within 30 min [42].

5.3.2 *Enzymes*

Although nasally administered drugs avoid first-pass metabolism effects, bioavailability of nasally administered proteins and peptides drugs can be limited because of some drug-metabolizing enzymes present in the nasal mucosa cavity and also on epithelial cells lining the cavity [43]. These enzymes such as epoxide hydroxylase, carboxyl esterase, aldehyde dehydrogenases, glutathione *S*-transferases, cytochrome P-450, UDP-glucoronyltransferase and glutathione transferase have been identified in human nasal mucosa. Cytochrome P450, an isoenzyme present in nasal mucosa, metabolizes some drugs in nasal mucosa such as cocaine, nicotine, alcohols, decongestants and progesterone. However, it is also reported that bioavailability of peptides and proteins is less affected by the nasal administration in comparison with the gastrointestinal tract. Although it is reported that nasally administered peptides have low bioavailability due to degradation of the peptides in the nasal cavity or epithelial cells of nasal mucosa, nevertheless bioavailability of insulin is reported up to 100% in rats [28]. Therefore, nasal route is a better alternative to the oral delivery for enzymatically labile drugs such as insulin and some other drugs whose bioavailability is close to nil by oral route. It is important to consider that various pathophysiological conditions such as common cold, seasonal rhinitis and nasal polyps may influence the

absorption of the drug from the nasal cavity by changing the rate of mucociliary clearance, thereby altering the residence time of the drug formulation in the nasal cavity. However, more thorough investigations are still necessary on this topic [41].

6. Strategies to increase nasal drug absorption

Although nasal drug delivery is efficient for CNS and systemic delivery of wide range of drugs, some drugs exhibit low bioavailability even when administered by intranasal route. [44]. The low bioavailability may be due to the low solubility of drugs, rapid enzymatic degradation in nasal cavity, poor membrane permeability and rapid mucociliary clearance [45]. Several strategies employed to overcome these limitations include prodrug approach, use of enzymatic inhibitors, structural modification, absorption enhancers and mucoadhesive drug delivery systems.

6.1 Prodrug approach

Commonly, the drugs that are administered in the solution undergo dissolution prior to absorption [46]. Lipophilic drugs get easily absorbed through nasal membrane; however, they are poorly water soluble. So the prodrug approach may be utilized to get compounds of higher hydrophilic character that can made as aqueous formulation of lipophilic drugs [47]. It should be also noted that when formulation reaches systemic circulation, prodrug must be converted to the parent drug. L-Dopa is a poorly water-soluble drug, but when administered as prodrug, its solubility is enhanced significantly in comparison with the parent compound favoring its development as aqueous formulation. Similar results were obtained with testosterone, which is a poor water-soluble drug but in the prodrug form with higher lipophilic nature, permeation increases through the membrane. Prodrug approach may be also used to inhibit enzymatic degradation of drugs in nasal mucosa and to render a formulation that has enzymatic stability; for example, L-aspartate–β-ester prodrug of acyclovir was more permeable and more stable toward enzymatic degradation. The prodrug approach is a powerful strategy to increase the bioavailability of peptides drugs by intranasal drug delivery [48].

6.2 Co-solvent

An alternative approach to increases the solubility of the drugs is the use of co-solvent. Mostly used co-solvents in intranasal formulations include glycerol, ethanol, propylene glycol and ethylene glycol, since these are nontoxic, nonirritant to nasal mucosa and pharmaceutical acceptable [48].

6.3 Enzymatic inhibitors

Nasally administered drugs bypass the gastrointestinal tract and hepatic first-pass metabolism, but some metabolic enzymes are also present in the lumen of nasal cavity that can metabolize the drug. Various approaches have been used to avoid enzymatic degradation, and use of proteases and peptidase inhibitors has been recommended. For example, comostate amylase and bestatine are used as aminopeptidase inhibitors and aprotinin as trypsine inhibitor that is involved in the calcitonin degradation. Additionally, amastatin, boroleucin, bacitracin and puromycin have been used to avoid enzymatic degradation of drugs such as leucine, human growth hormone and enkephalin. Furthermore, some enzymatic inhibitors also act as permeation enhancers, for example, disodium ethylene-diamine-tetraacetic acid, an absorption enhancer that reduces enzymatic degradation of beta sheet peptide, which is used for the treatment of Alzheimer's disease [8,41].

6.4 Absorption enhancers

The poor permeability of hydrophilic drugs may be overcome by the use of absorption enhancers that induce reversible modifications of epithelial barrier. The absorption enhancers used in nasal delivery are surfactants (sodium lauryl sulfate, poloxamer, tween and span), bile salts (sodium glycodeoxycholate, sodium taurodeoxycholate), fatty acids (taurodihydrofusidate, oleic acids, lauric acid, caprylic acid and phosphotidylcholine), chelators (EDTA, citric acid, sodium salicylate), peppermint oil and polymers. There are some examples of polymers such as α, β, γ cyclodextrins and methylated cyclodextrins, chitosan and trimethyl chitosan, Carbopol, starch and aminated gelatine [8,48]. These cause changes in the permeability of epithelial layers of nasal mucosa by modifying phospholipids bilayer and also change fluidity or reversible opening of tight junctions between epithelial cells and increase paracellular transport of drugs. The high-molecular-weight polymeric absorption enhancers are not absorbed and minimize systemic toxicity in comparison with low molecular weight. Chitosan interact with protein kinase C and opens tight junctions between epithelial cells and increases paracellular transport of polar drugs. It strongly interacts with nasal mucous layer and increases contact time to overcome mucociliary clearance, hence is widely used in intranasal dosage forms [30]. Cyclodextrins interact with the lipophilic components of biological membranes and increases permeability and absorption of drugs. Although cyclodextrins are widely used for intranasal drug delivery, some local and systemic toxicity has been reported [27]. Novel formulations such as mucoadhesive micro-/nanoemulsions [48], microspheres, nanoparticles [49] containing absorption enhancers have demonstrated better brain–blood ratio.

6.5 Mucoadhesive agents

Mucociliary clearance is a major limitation that it reduces the contact time between formulation and nasal mucosa that can be improved by the use of mucoadhesive agents. Mucoadhesion involves an interaction between mucin and natural or synthetic polymer such as chitosan or cyclodextrin [50].

Mucoadhesive system first absorbs water from mucous layer and gets wet and swollen. The polymer then penetrates into mucus and localizes the formulation in the nasal cavity resulting in enhanced drug concentration gradient across the nasal epithelium [51]. Frequently used mucoadhesive agents include chitosan, alginates and cellulose [52].

6.6 Novel drug formulations for effective brain targeting

Several claims in nasal drug formulations include liposomes, microspheres, nanoemulsions and nanoparticles and their results are very promising. Microspheres based on mucoadhesive polymers have various advantages in nasal drug administration. Much attention has been given to nanotechnology to improve nasal drug administration [53]. Nanoparticles have several advantages due to their small size and penetrate the nasal mucosal membrane by paracellular route [54]. Liposomes offer the advantage of effective encapsulation of small and large molecules with wide range of hydrophilicity and pKa values. They offer enhanced membrane penetration, mucosal membrane disruption, protection of entrapped peptides and protection of entrapped peptides from enzymatic degradation [55,56]. Mucoadhesive dosage forms have demonstrated better brain-targeting efficiency [57,58] when compared with oral and intravenous dosage forms and a cross section of the research reports on novel formulations [59] intended for nose-to-brain targeting is tabulated in **Table 1**.

6.7 Structural modifications

Modification of structure of drug without altering pharmacological activity is also one of the lucrative ways to improve nasal drug absorption. On structural modification of the drug molecule, the physicochemical properties that are commonly modified are molecular weight, molecular size, partition coefficient and solubility, all changes favorable for nasal drug absorption. For example, chemical modification of salmon calcitonin into ecatonin (C–N bond replaced by an S–S bond) showed improved bioavailability when compared with parent compound [60].

7. Conclusion

Considering the potential benefits of intranasal administration and widespread interest in nasal drug delivery, it is expected that novel nasal products will continue to enter the market. Targeting of drugs directly into the CNS with reduced systemic side effects and better therapeutic effects will lead to the triumph of the intranasal products. However, nasal route has some limitations that must be overcome to develop a successful nasal product. Physicochemical properties of drugs, physiological conditions and formulations are most important factors that determine nasal drug absorption. Conclusively, the use of enzymatic inhibitors, absorption enhancers, prodrug, mucoadhesive drug delivery and novel pharmaceutical dosage forms are the most commonly used strategies. The development of drugs for brain targeting to achieve better therapeutic effect with reduced systemic side effects is feasible for CNS-related disorders.

8. Expert opinion

There are many potential benefits that nasal administration has to offer compared with oral or parenteral route. Rapid onset of action, improved bioavailability and avoidance of first-pass metabolism become more important along with better tolerability; these systems have emerged as the more patient-complying system. Attempts for successful delivery of the drugs to the CNS are challenged by various physicochemical properties of the drug(s) and formulation that can be successfully resolved by a pharmaceutical scientist. The physicochemical challenges can be overcome by application of chemical and pharmaceutical approaches including drug derivatization, prodrug designing and novel drug delivery system. The pharmaceutical scientists are focusing on developing novel drug delivery systems as the development of new drug delivery system does not need to undergo a very complicated clinical process and are easy to be launched.

Nasal drug delivery had got immense importance for brain targeting, but it can also be used for local and systemic actions. Nose-to-brain targeting has a vast potential for commercialization as these systems allow lowering of dose to be administered as the direct targeting of the active molecule will provide easy attainment of effective concentration at the site of activity. Consequently, these systems are being explored for delivering the biologically active molecule to treat the ailments of the CNS including migraine, depression, psychosis, epilepsy, neurodegenerative disease (Alzheimer's disease), Parkinson syndrome and brain cancer. In addition to the treatment benefits of CNS disorders, intranasal route also has the potential to deliver various proteins, amino acids and hormones. Increasing number of diabetic patients globally has attracted the researchers to explore the route for insulin delivery that will offer a patient convenient dosage form.

The development of novel drug congeners with better physicochemical properties also has the potential for effective brain targeting. But these derivatives need strong preclinical and clinical backgrounds so that their application can be justified on the basis of the CNS toxicity. Any novel drug molecule having optimized properties that can be utilized for treating the CNS disorders can provide help to the researchers to develop delivery system with a lot ease.

There is considerable clinical pressure to transform successful nasal drug delivery into launched products. Conversely, the market for nasal administration for systemically acting drugs is estimated to be growing at around 33% per annum and 16 – 20 major pharmaceutical companies have active nasal drug delivery programs. The current value of nasal drug market is approximately US$ 10 billons. Among the topmost 20 pharmaceutical companies, 16 have

active nasal drug delivery programs. This implies the recognition and potential of the nasal route for drug delivery; so efforts are required to make this route more efficient and patient friendly.

Declaration of interest

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