Permeability issues in nasal drug delivery

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The nasal route is one of the most permeable and highly vascularized site for drug administration ensuring rapid absorption and onset of therapeutic action. It has been potentially explored as an alternative route for drugs with poor bioavailability and for the delivery of biosensitive and high molecular weight (MW) compounds such as proteins, peptides, steroids, vaccines, and so on. This review discusses the major factors affecting the permeability of drugs or biomolecules through the nasal mucosa, including biological, formulation and device-related factors. This information could potentially help to achieve desired plasma concentrations of drugs without compromising or altering the normal physiology of the nasal cavity.

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▼ Nasal drug delivery has generated widespread interest among the scientific community as an alternative route for the administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism [1]. This can be attributed to the high vascularity and the permeability of the nasal mucosa, which aids the drug in bypassing the aforementioned processes of degradation. The enhanced permeability from nasal mucosa was demonstrated by Hussain *et al.* when they achieved plasma concentrations of propanolol comparable with those of intravenous concentrations [2]. Various factors that synergistically enhance the permeation of nasally administered drugs are: the relatively large surface area because of the presence of a large number of microvilli, a porous endothelial membrane and a highly vascularized epithelium [3].

The main barriers for drug permeation are the enzymes present in nasal cavity and the nasal mucosal lining [4]. Despite this, a large number of drugs ranging from proteins and peptides to hormones and vaccines are delivered through the nasal cavity. Oxytocin [5], buserelin [6], desmopressin [7], calcitonin [8,9], insulin [10], luteinizing hormone releasing hormone [6], growth hormone [11] and adrenocorticotrophic hormone [12] are some of the peptides that have been successfully administered through the nasal route. Apart from these, steroids (corticosteroids, estradiol, progesterone, testosterone, and so on) [13,14], antihypertensives (nifedipine, nitroglycerine, propranolol, hydralazine, and so on), analgesics (buprenorphine), antibiotics and antivirals [15] have been shown to produce considerable systemic effects when administered via the nasal cavity. The feasibility of the nasal route for administering vaccines against plague, diphtheria tetanus [16], influenza [17], cholera [18], and HIV [19] has already been tested for inducing both mucosal and systemic immune response against the carried antigen. Various novel concepts such as synthetic biomimetic SMBVs (supramolecular biovectors) have proven, in preclinical and clinical studies, to be suitable candidates for the delivery of nasal vaccines. Further, drugs like levodopa [20], cephalexin [21] and insulin-like growth factor-1 [22] given via nasal administration have shown a marked improvement in neurological functions of the brain. This provides ample proof of the fact that drugs can be directly delivered to the CNS via the nasal route [23]. However, like other routes, nasal delivery also has its limitations, which have restricted its use to the delivery of only a few drug molecules. A relative evaluation of advantages and limitations is depicted in Table 1. It is a known fact that the permeability of drugs is not only affected by the intrinsic characteristics of the route of delivery but also by the characteristics of the dosage form delivered through that route. This is demonstrated by the novel nasal drug delivery systems (microspheres [12], liposomes [14],

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Table 1. An evaluation of potential advantages and limitations of nasal delivery

Advantages	Limitations
Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation	Volume that can be delivered into nasal cavity is restricted to 25–200 μl
Avoids degradation of drug resulting from hepatic first pass metabolism	High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa)
Results in rapid absorption and onset of effect	Adversely affected by pathological conditions
Results in higher bioavailability thus uses lower doses of drug	Large interspecies variability is observed in this route
Easily accessible, non-invasive route	Normal defence mechanisms like mucocillary clearance and ciliary beating affects the permeability of drug
Self-medication is possible through this route	Enzymatic barrier to permeability of drugs
Direct transport into systemic circulation and CNS is possible	Irritation of nasal mucosa by drugs
Offers lower risk of overdose	Limited understanding of mechanisms and less developed models at this stage
Does not have any complex formulation requirement	

proliposomes [24], niosomes [25] and films [26]), which show an enhanced permeability compared with conventional dosage forms (solutions, suspensions, sprays, snuffs, emulsions and ointments [27,28]). The reason, which can be cited for the aforementioned observations, is the intimate and prolonged contact allowed by the novel drug delivery systems between the drug and mucus membrane. Behl *et al.* conducted a detailed survey of drugs delivered through the nasal cavity. He also enlisted 46 investigational nasal products [29].

Functional features of nasal cavity and permeability

Nasal vasculature is richly supplied with blood to fulfil the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The cavity has a relatively large surface area (approximately ~150–160 cm^2) because of the presence of ~400 microvilli per cell and the total volume of nasal secretions is ~15 ml per day under normal physiological conditions. Together all of these factors account for the large and rapid permeability of drugs through the nasal mucosa.

Mechanism of permeation

A drug administered through the nasal cavity can permeate either passively by the paracellular pathway or both passively and actively via the transcellular pathway. This basically depends on the lipophilicity of the compound. Apart from the passive transport pathways, carrier mediated transport, transcytosis and transport through intercellular tight junctions are other possible pathways for a drug to permeate across the nasal mucosa. Lang *et al.* mathematically expressed the effective permeability coefficient P_{eff} under steady state conditions across excised mucosa, as equation 1:

$$P_{eff} = (dc/dt)_{ss}\, V/ (A\, C_D) \qquad \text{[Eqn 1]}$$

Where $(dc/dt)_{ss}$ is the time-dependent change of concentration in the steady state, A is permeation area, V is the volume of the receiver compartment and C_D is the initial concentration in donor compartment [30]. Fluorophore-labelled markers and drugs, in combination with sophisticated microscopy techniques such as confocal laser scanning microscopy have been used in visualizing the permeation pathways.

Factors affecting the nasal permeability of drugs

The factors affecting permeability of drug through the nasal mucosa can broadly be classified into three categories as shown in Box 1.

Biological factors

Although efforts are being made to skillfully modify and explore the structural features and mechanisms of nasal mucosa to increase permeability, this is not advisable because of anticipated alterations in the normal physiology of the nasal cavity, especially during chronic application. These alterations could cause unintended adverse effects and result in pathological implications.

Structural features

The nasal cavity can anatomically be segregated into five different regions: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx as shown in Figure 1. The structural features of the regions that are responsible for the permeability of the nasal cavity are listed in

Box 1. Variable factors affecting the permeability of drugs through the nasal mucosa

Biological

Structural features

Biochemical changes

Physiological factors
- Blood supply and neuronal regulation
- Nasal secretions
- Nasal cycle
- pH of the nasal cavity
- Mucociliary clearance and ciliary beat frequency

Pathological conditions

Environmental factors
- Temperature
- Humidity

Formulation

Physicochemical properties of drug
- Molecular weight
- Size
- Solubility
- Lipophilicity
- pK_a and partition coefficient

Physicochemical properties of formulation
- pH and mucosal irritancy
- Osmolarity
- Viscosity/Density
- Drug distribution
- Area of nasal membrane exposed
- Area of solution applied
- Dosage form

Device related

Particle size of the droplet/powder

Site and pattern of disposition

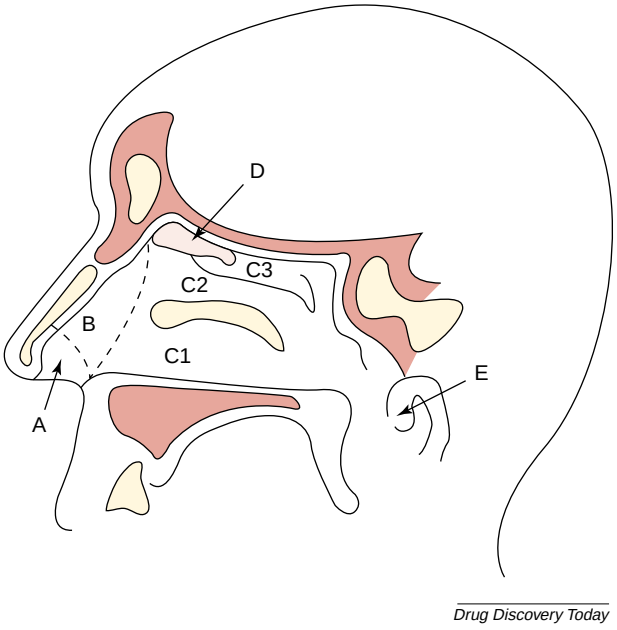

Figure 1. Schematic of a saggital section of the nasal cavity showing the nasal vestible (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E). Reproduced, with permission from ref. [4].

Table 2. Each of the two nasal cavities is limited by the septal wall and dominated by three tubinates: inferior (C1), middle (C2) and superior (C4) tubinate [31], which are mainly responsible for heating and humidification of the cavity [4]. The respiratory region is richly supplied with blood, has a large surface area, and receives the maximum amount of nasal secretions, rendering it most suitable for the permeation of compounds. These factors and the type of cells, density and number of cells present in that region influences the permeability. Different types of cells constitute nasal epithelium, as shown in Figure 2. The presence of microvilli on cells greatly increases the area available for permeation of drugs. Ultrastructural studies have shown fragmentation and discontinuity of tight junctions around filled goblet cells and this discontinuity could be of relevance to the absorption of aerosol drugs deposited on the airway epithelium [32,33]. A large number of absorption enhancers used in combination with drugs increase the permeation of compounds by either increasing the membrane fluidity, decreasing viscosity of the mucosal layer, inhibiting proteolytic enzymes, disrupting the tight junctions, increasing the paracellular or transcellular transport, increasing the blood flow, dissociating protein aggregation, or initiating the pore formation, or they act by a combination of these factors. Apart from this, mucoadhesive dosage forms have also shown to increase the permeation of compounds. It is beyond the scope of this review to give a description of all the approaches that are used to increase nasal permeation.

Biochemical changes

Nasal mucus acts as an enzymatic barrier to the delivery of drugs because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa [34,35] and result in creation of a pseudo-first-pass effect, which hampers the absorption of drugs. The nasal P450-dependent monoxygenase system has been implicated in nasal metabolism of nasal decongestants, alcohols, nicotine and cocaine [36]. Similarly, protease and peptidase were found

Table 2. Structural features of different sections of nasal cavity and their relative impact on permeability

Region	Structural features	Permeability
Nasal vestibule	Nasal hairs (vibrissae) Epithelial cells are stratified, squamous and keratinized Sebaceous glands present	Least permeable because of presence of keratinized cells
Atrium	Transepithelial region Stratified squamous cells present anteriorly and pseudostratified cells with microvilli present posteriorly Narrowest region of nasal cavity	Less permeable as it has small surface area and stratified cells are present anteriorly
Respiratory region (Inferior turbinate Middle turbinate Superior turbinate)	Pseudostratified ciliated columnar cells with microvilli (300 per cell), large surface area Receives maximum nasal secretions because of presence of seromucus glands, nasolacrimal duct and goblet cells Richly supplied with blood for heating and humidification of inspired air, presence of paranasal sinuses	Most permeable region because of large surface area and rich vasculature.
Olfactory region	Specialized ciliated olfactory nerve cells for smell perception Receives ophthalmic and maxillary divisions of trigeminal nerve Direct access to cerebrospinal fluid	Direct access to cerebrospinal fluid
Nasopharynx	Upper part contains ciliated cells and lower part contains squamous epithelium	Receives nasal cavity drainage

to be responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin [37]. In spite of these hurdles, the nasal route is still considered to be superior to the oral route. Various approaches have been used to overcome these degradations. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin [38,39], which have been reported to improve the absorption of LHRH peptides [40], leucin–enkephalin [41] and human growth hormones [42]. Boroleucin has also been found to remarkably enhance the nasal absorption of leucin–enkephalin [41].

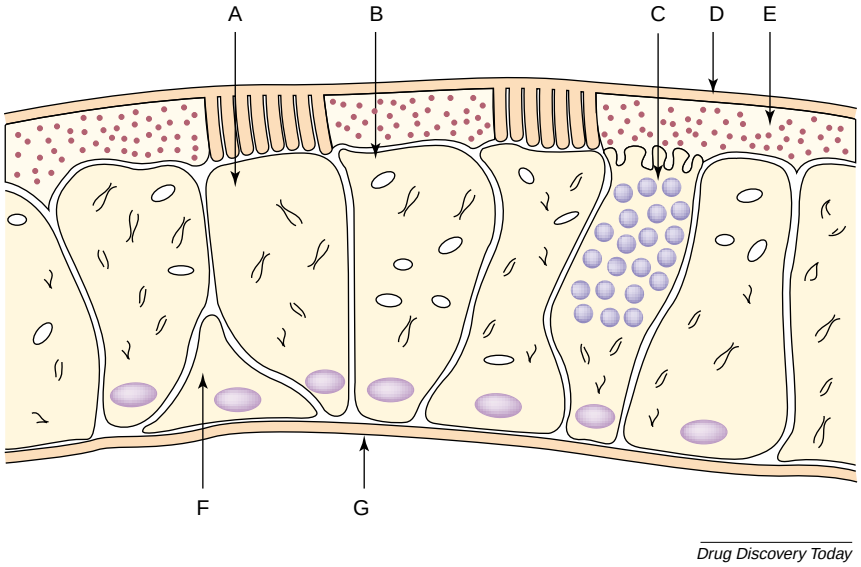

Figure 2. Cell types of the nasal epithelium showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G). Reproduced, with permission, from ref. [4].

Apart from using enzyme inhibitors, efforts arare foussed on designing prodrugs to increase the stability and permeation of compounds. Prodrugs commonly used for nasal drug delivery include esters of steroids (e.g. beclomethasone dipropionate monohydrate), charged prodrugs (e.g. sodium salt of cromoglycic acid), and prodrugs of some peptides and amino acids (e.g. desmopressin acetate and L-tyrosine) [15,43].

Physiological factors

Blood supply and neuronal regulation

The presence of venous sinusoids and arteriovenous anastomosis gives the nasal mucosa the distinction of being a highly permeable site. Nasal cycles of congestion (increased blood supply resulting from parasympathetic stimulation [44,45]) and relaxation (decreased

supply resulting from sympathetic stimulation [45,46]) regulate the rise and fall in the amounts of drug permeated, respectively [47,48]. In a study conducted using dogs anaesthetized with pentobarbitone, electrical stimulation of the parasympathetic nerve fibres innervating the nasal mucosa, evoked frequency dependent increases in both nasal arterial blood flow and nasal secretion. Based on the above observations, we can conclude that the increased permeability of a compound [49] results from parasympathetic stimulation.

Nasal secretions Anterior serous and seromucus glands are responsible for the production of nasal secretions. Approximately 1.5–2 l ml of mucus is produced daily [50]. The mucus layer probably exists as a double layer (5 μm thick) consisting of periciliary sol phase in which the cilia beat and a superficial blanket of gel is moved forwards by the tip of the cilia.

The permeability of drug through the nasal mucosa is affected by:

- Viscosity of nasal secretion. It is reported that if the sol layer of mucus is too thin, the viscous surface layer will inhibit the ciliary beating, and if the sol layer is too thick, mucociliary clearance is impaired because contact with cilia is lost. Impairment or modification of mucociliary clearance affects permeation of the drug by altering the time of contact of drug and mucosa [51].
- Solubility of drug in nasal secretions: a drug needs to be solubilized before it permeates. in addition to almost 90% water [52], nasal secretions contain mucin (2%), salts (1%), proteins (1%; mainly albumin, immunoglobulins, lysozyme, lactoferrin, and so on) and lipids [53]. Thus, a drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions. As in the case of levodopa, the use of water-soluble prodrugs of L-dopa via the nasal route has been shown to increase absorption [20].
- Diurnal variation: circardian rhythms also affect nasal secretions. Various studies revealed that the secretion and clearance rates are reduced at night thus altering the permeation of drug. In such cases chronokinetics will dictate the pattern and rate of permeation [54,55].
- pH of nasal cavity: it varies between 5.5–6.5 in adults and 5.0–7.0 in infants. A greater drug permeation is usually achieved at a nasal pH that is lower than the drug's pK_a because under such conditions the penetrant molecules exist as unionized species [43]. A change in the pH of mucus can affect the ionization and thus increase or decrease the permeation of drug, depending on the nature of the drug. Because the pH of the nasal cavity can alter the pH of the formulation and vice-versa, the ideal pH of a formulation should be within 4.5–6.5 and if possible the formulation should also have buffering capacity.

Mucociliary clearance (MCC) and ciliary beating

These are normal defence mechanisms of the nasal cavity that clear mucus as well as substances adhering to the nasal mucosa (bacteria, allergens, and so on) and drain them into the nasopharynx for eventual discharge into the gastrointestinal tract. Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min [56] by MCC. Reduced MCC increases the time of contact between a drug and the mucus membrane and subsequently enhances drug permeation; whereas, increased MCC decreases drug permeation [57]. Some drugs, hormonal changes of the body, pathological conditions, environmental conditions and formulation factors (especially rheology [58]) are reported to affect the MCC and in turn exert significant influence on drug permeability [3].

Pathological conditions

Diseases such as the common cold, rhinitis, atropic rhinitis and nasal polyposis are usually associated with mucociliary dysfunctioning, hypo or hypersecretions, and irritation of the nasal mucosa, which can influence drug permeation. Merkes *et al.* recently screened and later classified drugs as cilio0friendly or cilio-inhibitory and thus provided a valuable tool in the design of safe nasal drugs [59].

Environmental conditions

Temperatures in the range of 24°C cause a moderate reduction in the rate of MCC whereas on the whole it has been seen that a linear increase in ciliary beat frequency occurs with increase in temperature [60].

Formulation factors

A nasal formulation is usually composed of drug, vehicle, and excipients.

Physicochemical properties of drug

MW and size MW and lipophilicity or hydrophilicity act together to determine drug permeation. A large number of therapeutic agents, peptides and proteins in particular, have shown that for compounds >1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5% [61]. In the case of lipophilic compounds, a direct relationship exists between the MW and drug permeation whereas water-soluble compounds depict an inverse relationship. Based on the reports by Fisher *et al.* [62], McMartin *et al.* [63], Ryszka *et al.* [64], and Yamamto *et al.* [65], it can be

concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug, which will mostly permeate through aqueous channels of the membrane. By contrast, the rate of permeation is highly sensitive to molecular size for compounds with MW >300 Da.

Solubility Drug solubility is a major factor in determining absorption of drug through biological membranes. 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 appropriate aqueous solubility for increased dissolution

Lipophilicity On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. In a study conducted to characterize the barrier properties of mucosal membranes, it was found that the nasal mucosa had the highest *in vitro* transport both of the model hydrophilic compound, mannitol, and the model lipophilic compound, progesterone. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes [66]. In one study on intranasally administered corticosteroids, a high degree of lipophilicity diminished the water solubility of corticosteroids in the nasal mucosa and, therefore, the amount of drug swept away by mucociliary clearance increased considerably [13]. However, excess hydrophilicity is also known to decrease the systemic bioavailability of many drugs [67]. Prodrugs such as testosterone 17 β-*N*,*N*-dimethylglycinate hydrochloride have been synthesized to overcome the poor solubility problem [68].

Partition coefficient and pK_a As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same holds true in the case of nasal absorption. Jiang *et al.* (1997) conducted a study to find out the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The results showed that a quantitative relationship existed between the partition coefficient and the nasal absorption constant [69]. Various studies indicate that drug concentrations in the cerebrospinal fluid (CSF) rise with an increase in lipophilicity or the partition coefficient of the drugs [70]. The nasal absorption of weak electrolytes such as salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile, substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid [71]. Similarly, when the absorption of benzoic acid was studied at pH 7.19 (99.9% of the drug existed in ionized form) it was found that >10% of drug was absorbed indicating that the ionized species also permeates through nasal mucosa [43]. Based on all of these observations, the authors discounted partition coefficients as a major factor governing nasal absorption and supported that other transport pathways for hydrophilic drugs might be of importance.

Physicochemical properties of the formulation

pH and mucosal irritancy The pH of the formulation, as well as that of nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 [72]. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.

Osmolarity Ohwaki *et al.* studied the effect of osmolarity on the absorption of secretin in rats and found that absorption reached a maximum at a sodium chloride concentration of 0.462 M [73], because shrinkage of the nasal epithelial mucosa was observed at this salt concentration [74]. This results in increased permeation of the compound resulting from structural changes and was further confirmed when sorbitol was used as an osmoregulatory agent. The authors found that permeation of secretin subsequently decreased [75] and, therefore, isotonic solutions are usually preferred for administration.

Viscosity A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

Drug distribution

Area of nasal mucus membrane exposed In a study conducted using 40 mg progesterone ointment, absorption was compared between applications to one nostril with application to both nostrils. Increased bioavailability was observed when ointment was applied in both the nostrils [76] concluding that as the area of mucus membrane exposed increases, it should result in increased permeation.

Volume of solution applied The volume that can be delivered to the nasal cavity is restricted to 0.05–0.15 ml. Different approaches have been explored to use this volume effectively including the use of solubilizers [6], gelling, or viscofying agents [77]. The use of solubilizer increases the aqueous solubility of insoluble compounds and can even

promote the nasal absorption of the drug. Gelling agents decrease the drainage and result in an increase in the retention time of the drug in contact with mucus membranes.

Dosage form Nasal drops are the simplest and most convenient dosage form but the exact amount that can be delivered cannot be easily quantified and often results in overdose [78]. Moreover, rapid nasal drainage is a problem with drops. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation [79]. Recently, metered-dose gel devices have been developed that accurately deliver drug. Gels reduce the postnasal drip and anterior leakage, and localize the formulation in mucosa [80]. A limited amount of work has been reported on the use of emulsions [25] and ointments [81] as nasal formulations. Specialized systems such as lipid emulsions [82], microspheres (using chitosan, carbopol 934P and lactose [83]), liposomes, proliposomes, films and niosomes have been developed for nasal delivery as already discussed. These offer a better chance of permeation for the drugs as they provide an intimate and prolonged contact between the drug and the mucosal membrane. Promising results using these novel delivery systems have been reported for gentamicin [84], fluorescein 5′-isothiocyanate (FITC)–dextran [83] and insulin [85].

Device related factor

Different types of device are used to deliver formulations to nasal cavity [86]. Shape and size of the device affects:

Particle size of the droplet or powder The particle size of the droplet produced depends on the shape and size of the device used. If the particle size produced is <10 μm, then particles will be deposited in the upper respiratory tract, whereas if particle size is <0.5 μm then it will be exhaled. Particles or droplets with size between 5–7 μm will be retained in the nasal cavity and subsequently permeated [61].

Site and pattern of deposition The site and pattern of deposition is affected by formulation composition, the physical form of the formulation (liquid, viscous, semi-solid, solid), the device used, the design of actuators and adapters, and administration technique [87]. The permeability of the site at which the formulation is deposited and the area of nasal cavity exposed affects the absorption of drugs [88]. Retention of the drug in the nasal cavity is also dictated by the above factors.

Challenges ahead

For a drug to be successfully administered through the nasal cavity, it has to overcome the challenges posed by the enzymatic barrier of the nasal mucosa, the physical barrier of nasal epithelium, mucociliary clearance and the mucus layer itself before reaching the systemic circulation. From the formulation scientist's perspective, a better understanding of permeation pathways is required so that a correlation can be established between the physicochemical properties of the drug and formulation with that of permeation rate. This will not only aid in the optimal design of formulation for delivery through the nasal route but will also cut down the experimental efforts involved. Further, extensive research for alternatives at the molecular level is required to increase the permeation of drugs through the nasal mucosa without compromising normal function. The era of nasal drug delivery has started but efforts need to be done to make it more popular and efficient.

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