Universidade de Lisboa

Faculdade de Farmácia

Drug Absorption through the Nasal Mucosa:

Current Challenges

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Monografia orientada pelo Professor Doutor Luís Filipe Baptista Pleno Gouveia, Professor Auxiliar

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Embora a via de administração oral continue a ser a via de administração preferencial para fármacos com ação sistémica, a baixa biodisponibilidade oral de alguns compostos e as características da cavidade nasal proporcionam o processo de desenvolvimento de novos fármacos para administração nasal. A administração intranasal apresenta várias vantagens, tais como: ser uma via não invasiva e conveniente para auto-administração ou para cuidadores, ausência de efeito de primeira passagem pelo fígado, início de ação quase imediato e aumento da biodisponibilidade do fármaco.

Apesar do potencial da via de administração nasal, o muco e a barreira epitelial, a *clearance* mucociliar e a atividade enzimática representam algumas das suas limitações. Algumas das abordagens mais comuns para promover a absorção nasal incluem: a inibição da *clearance* mucociliar com mucoadesivos; aumento de absorção com intensificadores de absorção; alteração das propriedades físico-químicas da substância ativa usando pró-fármacos ou outras estratégias; inibição do metabolismo com inibidores enzimáticos; otimização da formulação com micro / nanopartículas; design e otimização de dispositivos de administração; utilização de tecidos ex-vivo e métodos de cultura de células *in vitro* para triagem e melhoria da absorção nasal de fármacos.

Para obter autorização de introdução no mercado dos medicamentos para absorção nasal, as entidades reguladoras exigem vários dados e resultados para fins de controlo de qualidade, que são compilados num dossier organizado pela indústria farmacêutica durante o processo de desenvolvimento. Um número considerável de fármacos e várias inovações para administração intranasal foram desenvolvidos e são descritos nesta monografia, bem como suas indicações.

Palavras-chave: administração intranasal; mucosa nasal; absorção nasal; regulação de medicamentos intranasais

Abstract

Although the oral route remains the most popular route for systemic drug administration, low oral bioavailability of some compounds and the characteristics of the nasal encourage the developing process of new products for nasal drug delivery. The intranasal administration presents advantages, such as: being a noninvasive and convenient route for self-administration or for caregivers, the absence of hepatic first-pass metabolism, the quick onset of action and the improvement of drug availability.

Despite the potential of the nasal route, the mucus and epithelial barrier, mucociliary clearance and enzymatic activity represent some of the limitations. Common approaches in order to improve the nasal absorption include: mucociliary clearance inhibition using mucoadhesives; absorption enhancement with absorption enhancers; active ingredient physicochemical properties modification using prodrugs and other strategies; metabolism inhibition with enzyme inhibitors; formulation optimization with micro-/nano-particles; delivery devices design and optimization; utilization of ex vivo tissue and in vitro cell culture methods for screening and improving nasal drug absorption.

In order to have a successful approval and marketing of nasal delivery drugs, authorities will require a lot of data for quality control purposes that is compiled in a regulatory dossier organized by the pharmaceutical company during the development process. A considerable number of products and several innovations for intranasal administration have been developed and are described in this review, as well as its indications.

Keywords: nasal mucosa; intranasal administration, nasal absorption; nasal drug regulation

Abbreviations

API – Active Pharmaceutical Ingredient

AR – Allergic Rhinitis

CDs – Cyclodextrins

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

EMA – European Medicines Agency

FDA – U.S. Food and Drug Administration

ICH – The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

MW – Molecular weight

NALT – Nasal-Associated Lymphoid Tissue

P-gp – P-glycoproteins

Table of Contents

List of Figures

List of Tables

1. Introduction

Although the oral route remains the most popular route for systemic drug administration, low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery. For that reason and considering the understanding of the advantages and characteristics of the nasal cavity, over the last years intranasal route has been progressively considered for drug delivery through the developing process of new drugs or improving the therapeutic profile of existing products (1).

There are many factors for the suitability of the nasal mucosa for drug delivery: being a noninvasive and convenient route for self-administration or for care-givers (2), the absence of hepatic first-pass metabolism, the quick onset of action and the improvement of drug availability (3,4). Many studies have showed encouraging results with intranasal drug route (5–7). Nevertheless, there are some limitations such as: histological toxicity, possible nasal irritation and local side effects (3).

The administration of drugs through the nasal mucosa can achieve different results: local, systemic, or central nervous system (CNS) delivery; and reach different goals: treat symptoms, such as migraines (8), control diseases, like the possible administration of intranasal insulin for diabetic patients (9), or even prevent diseases with the administration of vaccines (10).

Decongestants for nasal cold symptoms or antihistamines and corticosteroids for rhinitis are examples of intranasally administered drugs for local delivery. Since topically administrated drugs are effective with low doses, the intranasal administration of these drugs has a weak potential for systemic adverse effects as opposed to oral therapy. Moreover, the intranasal administration provides a potential alternative route for systemic drug delivery, considering that intranasal absorption avoids the first-pass effect and degradation of drugs in the gastrointestinal tract that we see in oral administration, and is essentially painless compared to the most parenteral administrations (11).

Intranasal transport is also an attractive strategy for brain targeted therapeutic agents delivery from the nasal cavity, involving the olfactory and trigeminal nerves in the olfactory region of the nasal cavity, thereby bypassing the blood-brain barrier (12,13).

Furthermore, intranasal vaccination provides a promising non-invasive alternative to intramuscular administration of vaccines. The nasal mucosa is continuously exposed to microbes and for that reason is extremely immune competent. Due to the presence of the nasal-associated lymphoid tissue (NALT), intranasal vaccination promotes antibody formation and activation of circulating immune cells, that elicits mucosal and systemic immunity. Also, it has been reported that the nasal mucosa can induce cross-protection against variant strains,

such as influenza viruses, which may contribute to the development of so-called “universal vaccines” (2).

2. Objectives

This monograph contemplates an overview of intranasal administration of drugs; clarifies the development process and simplify the regulatory requirements for marketing authorization. Also, this review explains what the current challenges for nasal products and their future perspectives is.

3. Methods

Several browsers for scientific publications were used: PubMed (pubmed.ncbi.nlm.nih.gov) generously provided by the National Library of Medicine (NLM), ScienceDirect (www.sciencedirect.com) managed by Elsevier, and Google Scholar (scholar.google.com). The research was done entirely in English and key terms such as the following were used: intranasal administration; nasal mucosa; absorption through nasal mucosa; nasal drug delivery devices; and so on.

In addition, some guidelines and documents needed for this review were obtained from websites of important health entities, such as European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA) and The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

4. The Nose

The nose is a complex multifunctional organ of the respiratory system. The major functions comprehend filtering, heating and humidifying the inhaled air and olfaction (11).

4.1. Nasal anatomy

Anatomically, the nose terminates anteriorly in two nostrils and connects posteriorly to the nasopharynx. It's separated into two cavities by the nasal septum, which is made from bone and cartilage, and these are divided in three different regions as you can see in Figure 1: the vestibule, the olfactory region and the respiratory region (14).

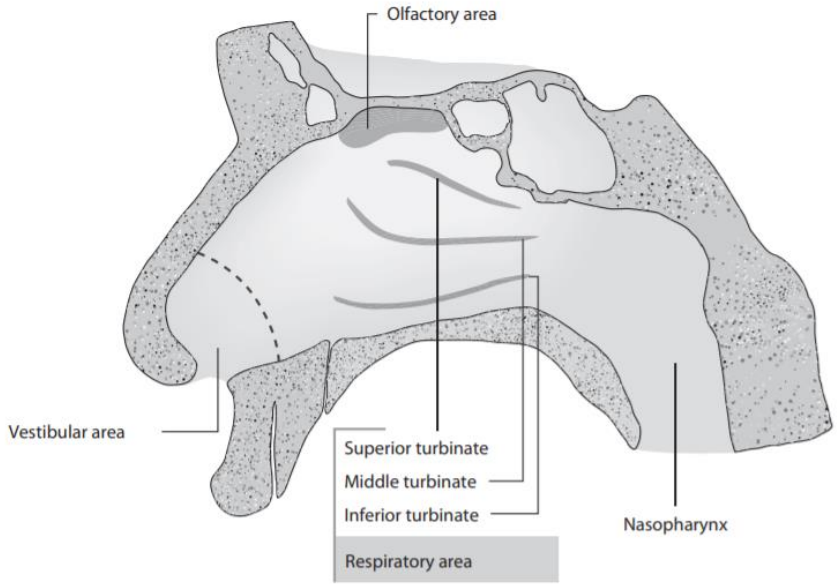


Figure 1 - The Nasal Anatomy (11).

The vestibule is located close to the nostrils and has short stiff hairs that retains large particles from inhaled air; has stratified squamous and keratinized epithelial cells and low vascularization. The olfactory region covers about 10% of the total surface of the nasal cavity and comprises smell receptors and million endings of the olfactory nerve; this area enables olfactory perception and is highly vascularized. The respiratory region is also high vascularized and contains three turbinates that produce turbulent airflow, which ensures better contact between inhaled air and mucosal surface (11,14,15). The nasal mucus is produced by goblet cells and removed via mucociliary clearance, and plays huge part in moisturizing the nasal epithelium and dissolving odorants to assist olfactory transduction responses (15,16). Since

its rich vascularization, the mucosa in olfactory and respiratory zones can provide an efficient absorption of drugs (11).

4.2. Absorption across the nasal epithelium

4.2.1. Barriers

In order to achieve a successful drug absorption, the active pharmaceutical ingredient (API or drug) primarily has to reach the absorbing barrier. In the nasal cavity, the molecules need to be deposited on the epithelial membrane and be absorbed before being cleared or degraded. Moreover, controlling API release profile through barriers, being the mucus layer, the epithelial layer and the capillary endothelium, may be advantageous (17).

a. Mucus layer

The first barrier for drug absorption is the mucus layer. The molecules need to be dissolved or trespass the mucus layer before clearance by mucociliary activity or degradation due to enzymatic activity (17).

b. Epithelial layer

After the mucus layer, drug must cross the epithelial membrane. It is composed by pseudostratified columnar cells connected with tight junctions (17). Each API has a specific route of absorption across the epithelial cell membrane, explained ahead.

c. Capillary endothelium

The last barrier that drug find in other to complete the absorption into the blood, is the capillary endothelium is essential. This barrier is essential for systemically targeting APIs (17).

4.2.2. Routes of absorption

As mentioned before, the absorption of drugs in the nasal cavity happens preferentially in the respiratory, but also in the olfactory region (18). In the epithelial cell membrane in these areas, drugs can cross the nasal mucosa by two main pathways: transcellular (across the cell membrane) and paracellular (between the cells) (19). The route of absorption used by APIs depends on its physicochemical properties, as demonstrated in Figure 2.

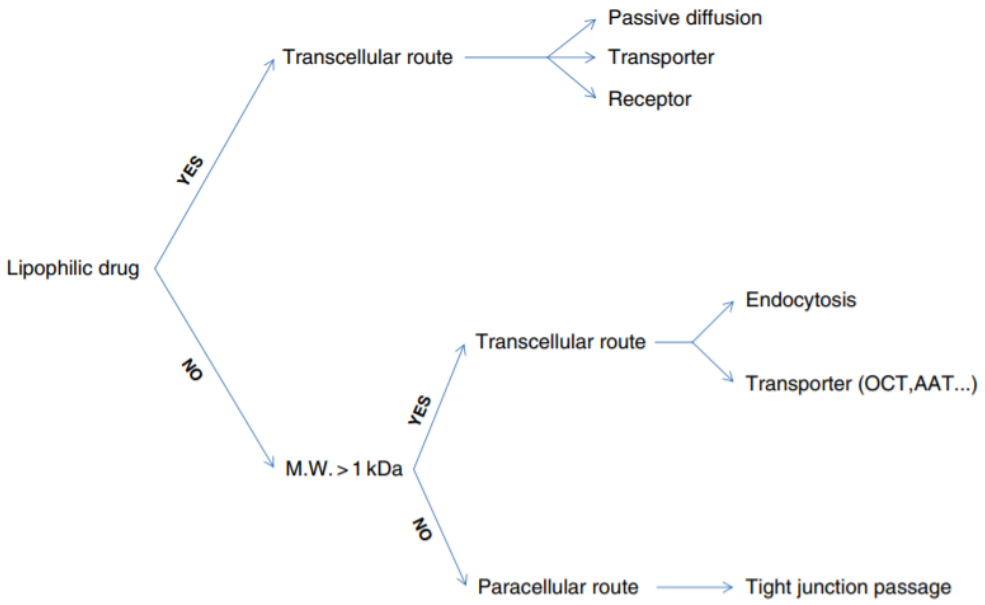


Figure 2 - Mechanisms involved in drug absorption across respiratory epithelium (20).

Lipophilic molecules are generally transported via the transcellular pathway, that includes receptor-, carrier-, and vesicle-mediated routes. Polar drugs are believe to follow paracellular pathways, generally crossing the epithelium via gaps between cells; however, some of the polar drugs, particularly large molecular weight (MW) peptides and proteins, exhibit limited permeability in nasal mucosa and, for that reason, follows the transcellular route (13).

5. Development of Nasal Delivery Drugs

Three main components are to be considered in the design of a new nasal product: the drug, the delivery carrier and the administration device (21). These factors are demonstrated in Figure 3.

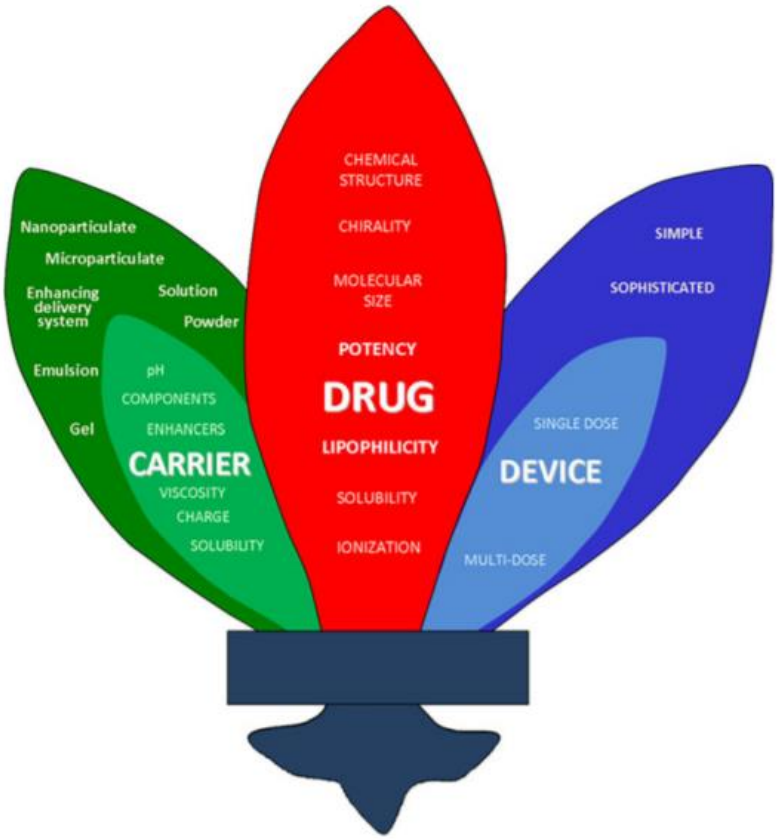


Figure 3 - Three-lobe fleur-de-lys presentation of the main factors in the development of a new nasal product (22).

5.1. Components of drug product

The application for a new nasal drug product should include the quantitative composition of the unit formula of the drug, specifying the name and amount of each API and excipient contained in the formulation. For the final formulation, the concentration of the components should be express, which means the amount per unit, as well as amount per container or per spray (23).

5.1.1. Active Pharmaceutical Ingredient

The drug substance physicochemical and biological properties should be identified during the development of a nasal product. This identification is required because such properties

can influence the performance of the drug product and its manufacturability. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These could be interrelated and might need to be considered in combination. To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted (24). These studies will be discussed in Chapter 6.

5.1.2. Excipients

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not. The compatibility of excipients with other excipients, the ability to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated (24). Identical to studies for API, these studies will be discussed in Chapter 6.

5.2. Pharmaceutical product development

Pharmaceutical product development is a vital task which is directly dependent on its therapeutic objectives: if it is intended for local delivery or systemic delivery and if it is for single or repetitive administration. The ability to achieve the therapeutic objectives will determine whether the development of a nasal delivery system is appropriate (25).

5.2.1. Formulation

Several important morphological and physiological constraints on nasal drug delivery should be kept in mind when formulating new nasal products (22). Almost all drugs for intranasal administration are liquid preparations and just some drugs are used as powders formulations (26).

Liquid preparations are mainly based on aqueous formulations, which is very useful because allergic and chronic diseases are usually connected with crusts and drying of mucous membranes (27). However, suspensions and emulsions can also be delivered for nasal administration. In liquid formulations, preservatives are typically required in order to maintain

microbiological stability, but they could cause irritation (28). For formulations that includes peptides and proteins, limited stability may represent a challenge (10).

Powder formulations are less frequently used compared to liquid formulations. However, they have advantages that makes them potential candidates for nasal delivery (29). Powder preparations have more stability so the use of preservatives may not be required, this forms prevent microbial contamination, and since the powder particles are not easily dissolved, the contact between the drug and the nasal mucosa are prolonged (27–29). Formulation-wise, powders denote a simpler composition in excipients (if any), allowing for the administration of larger drug doses and also facilitate the formulation of poorly water-soluble compounds (30). In a study in humans comparing different formulations of desmopressin, a nasal powder was superior to a commercial nasal liquid spray and also to a sublingual tablet with respect to both bioavailability and patient's compliance (31).

In order to achieve a successful intranasal product, properties like potency, lipophilicity, and water solubility are required (22). In addition, there are many factors that influences an efficient absorption throw nasal mucosa: particle size of the API; pH of the nasal mucosa; osmolarity; viscosity; residence time in the nasal cavity; penetration enhancers. And finally, the product should have no unpleasant smell and should not be irritating or influence the sense of smell (2).

5.2.2. Manufacturing

It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Process development studies should provide the basis for process improvement, process validation, continuous process verification, if applicable, and any process control requirements. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification asked in regulatory for marketing approval (24). The regulatory for marketing approval is discussed and clarified in chapter 6.

The manufacturing process development should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality. In order to provide flexibility for future process improvement, when describing the development of the manufacturing process, it is useful to describe measurement systems that allow monitoring of critical attributes or process end-points, collect process

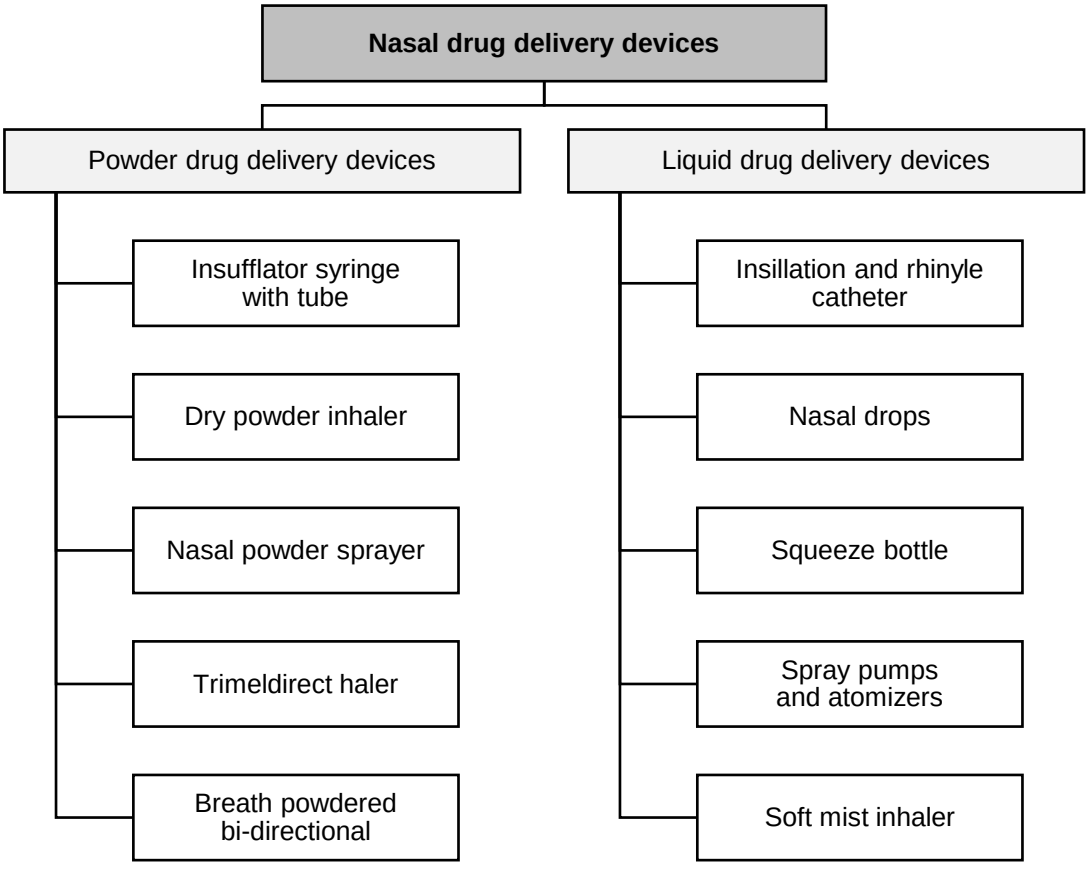
monitoring data during the development and describe the process control strategies that provide process adjustment capabilities to ensure control of all critical attributes (24).

5.2.3. Nasal drug delivery devices

The choose of the appropriate system delivery for the drug formulation is one of the first steps in approaching the development of an intranasal drug administration project. This decision is strongly governed by the type of formulation envisaged for delivery. The classification of nasal drug delivery devices is illustrated in Table 1 (2).

Once the type of system has been selected, some basic compatibility investigation or studies in order to avoid any obvious incompatibilities between the components, the proposed API and any known excipients is required (2), as well as guarantee the protection from moisture and light (24). Moreover, stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing, as well as any secondary packaging and container label (32).

Table 1 - Classification of nasal drug delivery devices. Adapted (14) .



5.3. Pharmacokinetic

The four pharmacokinetic steps that influence the fate of drugs in the body are absorption, distribution, metabolism and elimination. The specific, valuable features of intranasal administration are mainly related to the drug absorption step and a drug's physicochemical properties are key determinants of its ability to cross the nasal mucosa efficiently and thus providing adequate bioavailability for achieving the desired systemic effects, in terms of both intensity and onset of action (20).

Although the absorption and permeability of many drugs, especially peptides and proteins, through the nasal mucosa are higher than those through other mucosae (33), a few studies have compared the respective pharmacokinetic profiles for oral or parenteral versus intranasal administration of a given compound, which concluded the low bioavailability of intranasal administration compared to others administration routes (34–38).

The intranasal route has also some distinctive characteristics during the pharmacokinetic phase that follows absorption, that is distribution. After absorption, drugs pass through the jugular veins, the superior vena cava, the right heart, the lungs and the left heart before reaching the arterial blood flow that irrigates the various organs. The latter are able to extract a proportion of the active principle and release the rest into the venous circulation. This explains the arterial vs. venous differences observed in the blood concentrations of various administered intranasally molecules, such as nicotine and fentanyl (39–41).

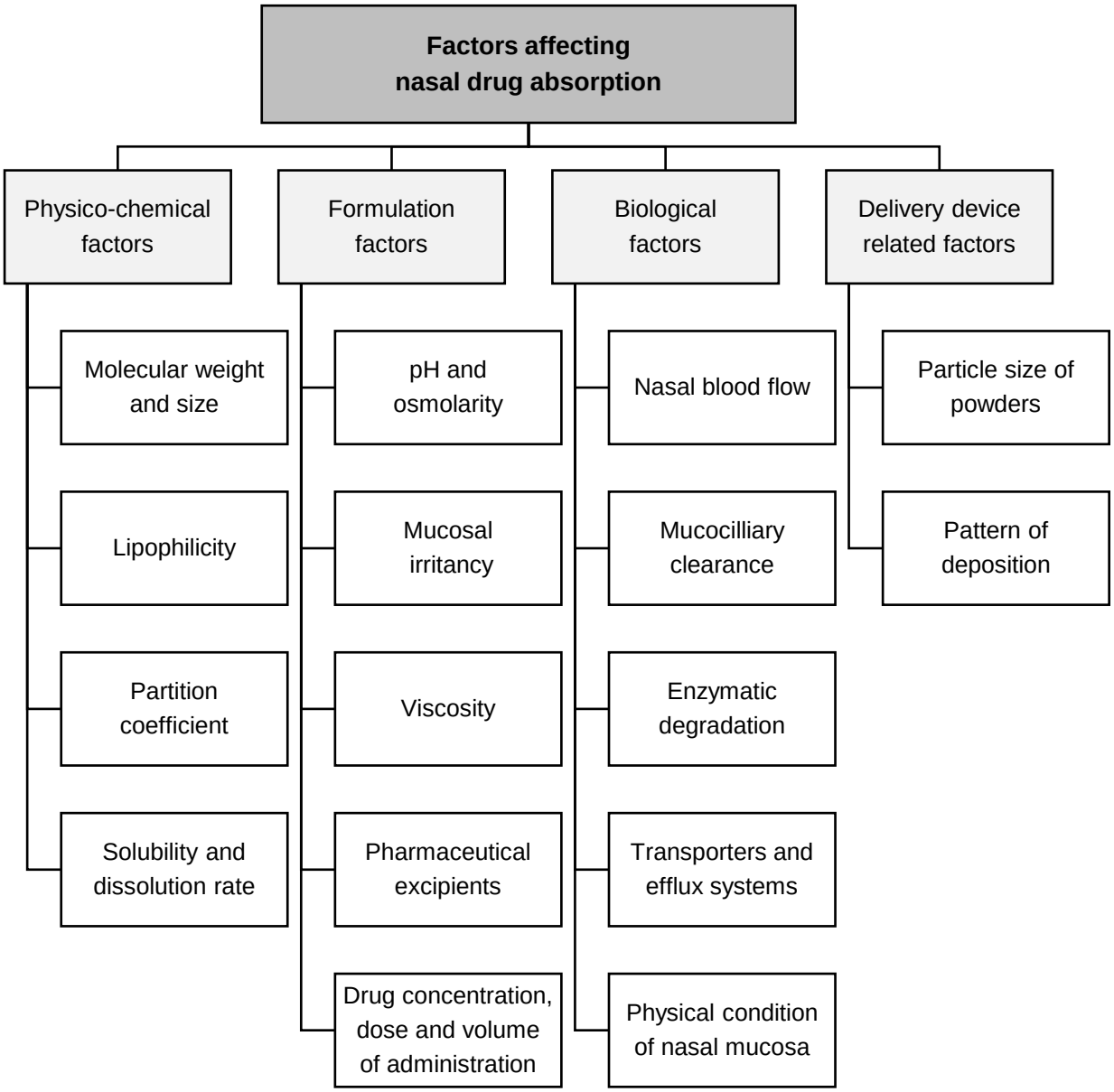
However, before a drug enters the systemic circulation, some intranasal elimination mechanisms come into play. In addition to purely physical phenomena (such as sneezing or anterior or posterior run-off), local degradation of the active principle can occur duo to a lot of factors explained ahead (20).

In conclusion, the unusual aspects of the pharmacokinetics of intranasally administered drugs are mainly due to physiological causes and the molecules' physicochemical properties, which lead to the observed variations in absorption (20). Comprehending the factors that can affect drug deposition, retention and absorption are essential to successfully design nasal formulations in order to achieve better outcomes (25).

5.3.1. Sources of variability in intranasal absorption

In order to be absorbed, nasally administered drugs must overcome physiological, physicochemical and mechanical barriers (15). Apart from these, numerous of physiological, anatomical, and pathological conditions must be considered (25). Absorption and permeability of drugs across nasal mucosa is affected by various factors as illustrated in Table 2.

Table 2 – Factors affecting absorption and permeability of drugs across nasal mucosa. Adapted (42).



5.3.1.1. Physico-chemical factors

a. Molecular weight and size

The nose is a very effective filter. Therefore, the size of the nasal product effects the retention in the nasal cavity. Particles greater than 150 µl run out of the nasal cavity immediately and particles smaller than 10 µm passes directly to the lungs. For that reason, most spray pumps should generate an aerosol with a mean particle size from 40-100 µm in order to deposit the drug well in the nasal cavity (2). Drugs having an MW of less than 300 Da have no major impact on drug permeation through the nasal tract as they will easily permeate

through aqueous channels of the membrane. But, for compounds having an MW above 300 Da, the rate of permeation through the nasal tract is significantly affected (43). To exemplify the importance of size on the nasal drug delivery, *Pardeshi et al.* (42) compared the delivery of dopamine, a small molecule, to that of nerve growth factor, a relatively small secreted protein (MW=26,500 15 Da), and observed that brain concentrations were fivefold higher for dopamine than the protein when dosed at the same concentration (44).

b. Lipophilicity

Lipophilicity refers to the ability of a compound to dissolve in fats, oils, lipids, and nonpolar solvents such as hexane or toluene (45). Biological membrane permeability of a drug is mainly influenced by its lipophilicity. Usually, low-MW lipophilic drugs are well absorbed across the nasal epithelium, whereas peptides and proteins, that is larger hydrophilic drugs, have substantially lower bioavailability (46).

c. Partition coefficient

The partition coefficient is defined as the ratio of delivery compounds distributed between the organic phase and aqueous phase under equilibrium in a delivery system (47). Various studies indicate that drug concentrations in cerebrospinal fluid increases with an increase in lipophilicity or partition coefficient of drugs, concluding partition coefficient as a major factor governing nasal drug absorption. It was observed that a quantitative relationship exists between partition coefficient and nasal drug absorption (42).

d. Solubility and dissolution rate

Drug solubility is a major factor in the process of absorption of the molecules through biological membranes. Even though the relationship between the solubility of a drug and its absorption through the nasal mucosa isn't very reported, as nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution (48). Drug dissolution is another rate-limiting step in nasal absorption, as nasal absorption will only take place after the drug's dissolution. Thus, for nasal powder and suspension dosage forms, the dissolution rate is an important parameter. After nasal administration, if drug dissolution is slow, then the particles will be cleared from the airway with a subsequent reduction in bioavailability (43).

5.3.1.2. Formulation factors

a. pH and osmolarity

The nasal absorption and permeation of the drug are often affected by the pKa value and pH of the formulation as well, and hence this pH factor needs to be acknowledged and selected in the range between 4.5 and 6.5 (43). The pH can affect the stability of the product so this characteristic also needs to be considered during the development process (2).

Osmolality is milliosmoles of solutes per one kilogram (or liter) of water of solution (plasma) and is calculated by osmolarity divided to plasma water (49). Even though, more often isotonic formulations are administered in the nasal cavity to increase the permeation of the membrane due to structural changes in the drug, isotonic solutions also inhibit ciliary activity (43). Moreover, some marketed products have osmolality in the range 300-700mOsmol/K which agrees with many studies that reports that hypotonic nasal spray formulations improve drug permeability through the nasal mucosa (2).

b. Mucosal irritancy

Many factors can promote mucosal irritancy, which leads into low absorption of drugs. Long periods of intranasal administration or pH lower than 3 and higher than 10 of the formulation may provoke mucosal irritation in the nasal cavity (43).

c. Viscosity

Viscosity describes the capacity to respond to deforming forces by flowing (50). The increasing of the solution viscosity may prolong the therapeutic effect of nasal spray preparations (51), but highly viscous formulations may alter the regular functions such as mucociliary clearance and/or ciliary beat frequency, for example, nasal delivery of insulin, metoprolol, and acyclovir (43).

d. Pharmaceutical excipients

During the development of a new drug, several types of excipients may be required. These include solvents and co-solvents to keep the API in the dissolved or suspended state, as well as preservatives for non-sterile products. The excipients accepted for use are in the FDA inactive ingredient guide for nasal products. (2).

e. Drug distribution

Prevention of pulmonary deposition of nasally administered spray formulations is paramount to ensure residency within the nasal cavity (52). Nasal deposition of a drug depends upon the aerosol velocity from the spray device, the velocity of the inhaled airstream and the particle size (53). The drug, when administrated by a nasal spray, is deposited mostly into the anterior region of the nasal cavity. Afterwards, the surface tension of the droplets and the mucociliary clearance will distribute the liquid layer within the nasal cavity. Since the nasal mucus layer is continuously renewed, the nasal residence time of the drug depends on how fast it dissolves within the mucus layer and penetrates into the mucosa (2).

f. Drug concentration, dose and volume of administration

The concentration of drug, the dose and the dosage volume play a vital role in the performance of the nasal delivery. Where concentration is considered, higher concentrations leads to higher absorption. The dose should have a upper limit of 25 mg/dose and dose volume should range between 0,05 and 0,15 ml/dose (43). The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior run off. The unit volume administered is also important because it appears that the administration of a single volume of 100 µL leads to deposition over a greater surface area than that obtained with the administration of two 50 µL volumes (20).

5.3.1.3. Biological factors

a. Nasal blood flow

Nasal blood flow is a key factor in maintaining a concentration gradient at the absorption site, which in turn is essential for promoting drug diffusion. Vasoconstrictor or vasodilator drugs influence the nasal blood flow and thus induce variability in the absorption of compounds at this site (20).

b. Mucocilliary clearance

The first barrier that a pharmacological agent will encounter upon intranasal administration is the mucus layer covering the olfactory and respiratory mucosa. Mucus is a complex mixture secreted by the goblet cells in the mucosa, and consists out of 95% water, 2% mucin, 1% salt, 1% albumin, lysozymes, lactoferrin, immunoglobulins, and lipids (12). The nasal mucociliary clearance determines the nasal residence of the drug, fundamental to drug absorption (54). Mucociliary clearance is the combined action of mucus layer and cilia (55) and is regulated by several factors such as temperature, intracellular calcium, age, exercise, sleep, common environmental pollutants, tobacco smoke, some diseases like asthma, etc. (43). The decreased of the mucociliary clearance rate leads to prolonged contact time of the drug at the absorption site, which enlarged the absorption (56).

c. Enzymatic degradation

The nasal membrane is a thin layer of epithelium sandwiched between mucous membrane on the top and a basement membrane underneath. Goblet cells, seromucous glands and transudates from plasma are responsible for much of the secretion into the nasal cavity. Thus, nasal fluid represents an enzymatic barrier to the intranasal absorption of drugs. The enzymatic activity of nasal fluid and its effect on the in-situ degradation of drugs, particularly peptides, play an important role in further evaluation of the nasal cavity as a site for systemic absorption (57).

d. Transporters and efflux systems

P-glycoproteins (P-gp) are glycosylated membrane proteins present in the epithelial cells and are found in the human nasal respiratory mucosa (43). The role of P-gp with respect to clinically significant restriction of nasally administered drugs has not been demonstrated. However, it is important to mention that P-gp is regionally expressed within the nose, with higher expression in the olfactory mucosa and over-expression in certain forms of chronic inflammation, which could impact drug delivery (15).

e. Physical condition of nasal mucosa

Several diseases and lifestyles can change de characteristics of the mucociliary transport. Some diseases, such as the common cold, rhinitis and nasal polyposis, can influence the drug

absorption as a result of mucociliary dysfunction, hypo or hypersecretions, and irritation of the nasal mucosa (48). Another environmental factors that can influence the IN absorption is cigarette smoke (in both active and passive smokers) (20). Even though mucociliary clearance is altered in smokers, due to the lower number of cilia and alterations in the mucus's rheological properties, this change does not appear to have a major impact on the permeability of the nasal (58).

5.3.1.4. Delivery device related factors

a. Particle size of powders

As discussed before, the particle size and molecular weight of the nasal product particles can determinates the absorption of the administrated drug. In solution administered as a nasal spray, the aerodynamic diameter of the particles emitted by the spray device must be greater than or equal to 10 μm, in order to ensure impaction of the particles on the nasal mucosae and to prevent them from being drawn into the lower airways by inspiratory flow (20).

b. Pattern of deposition

Nasal deposition of a drug depends upon the aerosol velocity from the spray device, the velocity of the inhaled airstream and the particle size. High velocity of the inhaled drug and high particle size favor intranasal deposition (53). Furthermore, the spray administration and plume angles are key determinants of optimal drug delivery. The combination of an administration angle of 30° and a plume angle of 30° led to deposition primarily in the anterior region of the nose, with a deposition efficiency close to 90% (20).

5.3.2. Optimizing the pharmacokinetics

The absorption through nasal mucosa can be improved by several complementary strategies (20,59). Common approaches include: mucociliary clearance inhibition using mucoadhesives; absorption enhancement with absorption enhancers; active ingredient physicochemical properties modification using prodrugs and other strategies; metabolism inhibition with enzyme inhibitors; formulation optimization with micro-/nano-particles; delivery devices design and optimization; utilization of ex vivo tissue and in vitro cell culture methods for screening and improving nasal drug absorption (15). However, some of these strategies

can have toxicity potential related such as the capability to cause severe morphological alterations, significant membrane damage in the epithelium, and inhibition of mucociliary transport (13).

The choice of a absorption enhancer should considered the follow characteristics: the enhancer should be pharmacologically inert at the concentrations used; it should be relatively inexpensive and readily available; the enhancer should be a potent absorption promoter therefore requiring only small amounts to be used; it should be nonirritating, nontoxic and nonallergenic; it should be compatible with the API and the excipients; if the enhancer has any effect on the nasal mucosa, it should be completely reversible; it should be able to remain in contact with the nasal mucosa long enough to achieve a maximal effect; the enhancer should not have any offensive odor or taste (60).

5.3.2.1. Chemical enhancers

a. Bile salts and surfactants

Surfactants are solubilizing excipients widely used in nasal formulations. Anionic, non-ionic synthetic surfactants and bile salts have been extensively studied to enhance transepithelial permeability for different marker molecules, peptides and drugs (8). Bile salts are the most widely used surfactants for nasal absorption optimization. At relatively low concentrations, 10–20 mmol, they improve the absorption throw the nasal mucosa (60). *McMartin et al.* concluded that the most probable route of membrane transport of peptides and proteins is through intercellular junctions and that the surface-active adjuvants which increase absorption may do so by temporarily converting hydrophobic contacts between junctional proteins into hydrophilic pore-type pathways (61).

b. Cyclodextrins

Cyclodextrins (CD) are natural cyclic oligosaccharides derived from starch and used as excipients in marketed pharmaceutical products as complexing agents (8). CDs form inclusion complexes with the molecules of drugs that can fit into the lipophilic cavities of the CD molecules. These inclusion complexes are formed without forming any covalent bonds. The physicochemical properties of drugs can be altered substantially by forming such complexes. The complexes can be formed by different methods including coprecipitation, slurry and paste complexation, damp mixing, heating, extrusion and dry mixing (60).

5.3.2.2. Promoters of nasal absorption

a. Nanoparticulate systems

The use of nanosuspensions of drugs encapsulated in polymeric carriers is a popular method for many routes of administration. In intranasal delivery, these carriers provide enhanced absorption, mucoadhesion and increased stability (59). It has been shown in the literature that the application of drug loaded nanoparticles to the nasal cavity can increase the amount of drug that reaches the CNS directly from the nasal cavity via the olfactory tissue or the trigeminal nerves (62).

b. Liposomes

The intranasal administration of large molecules such as peptides is still a scientific challenge from a formulation development standpoint (60). *Aramaki et al.* studied the activation and mucosal immune response following nasal administration of liposomes in mice. They found that bovine serum albumin-specific serum IgG and IgA levels were significantly elevated when BSA-associated liposomes were administered intranasally twice at 4-week intervals (63).

c. Mucoadhesives

Mucoadhesives have been used to improve local and systemic delivery of therapeutic compounds (64). The process of mucoadhesion following nasal administration relates to the interaction between the mucoadhesive polymer and the mucus secreted by the sub-mucosal glands. The sequential events that occur during the mucoadhesion include the proper wetting and swelling of the polymer, and intimate contact between the polymer and the nasal mucosa. Then, the swelled mucoadhesive polymer penetrates into the tissue crevices followed by the interpenetration between the polymer chains and protein chains of the mucus (65).

d. Chitosan

Chitosan is an N-deacetylated product of the polysaccharide chitin, and shows interesting properties, such as biocompatibility, biodegradability, and low local and systemic toxicity (66). Bioadhesive polymer formulations, such as chitosan G210, increase considerably the residence time on the olfactory region of the nasal cavity and potentially increase the absorption of drugs into the CNS via the olfactory pathway (67).

e. Tight junction modulators

A tight junction modulator peptide, PN159, has been described and shows a dose-dependent reduction of transepithelial electrical resistance with a rapid onset, quick recovery of the barrier functions on removal and good cell viability and low cytotoxicity. PN159 can be a safe and potent TJ modulator to enhance drug delivery by nasal and gastrointestinal routes of administration. (8).

5.3.2.3. Drug stability improvers

a. Enzyme inhibitors

Proteolytic enzyme inhibitors prevent the hydrolysis of peptide and protein drugs and, thus, improve the stability of drugs at the absorption site. However, enzyme inhibitors themselves cannot facilitate the penetration of drugs across the nasal epithelium and, therefore, are generally complemented with another absorption-enhancing strategy (9).

b. Prodrugs

Prodrugs are compounds that have to undergo biotransformation in the body before they can exert their pharmacological action. They can be used to improve the stability and permeability of API that do not have the initially desired absorption properties. Hydrophilic groups can be added to improve the aqueous solubility of very lipophilic molecules (20).

This method has been used to facilitate the intranasal absorption of peptides, like desmopressin acetate, and corticosteroids, such as beclomethasone dipropionate (68), and can also protect the molecules against degradation enzymes and efflux proteins, as has been observed with esterified forms of acyclovir (69).

5.3.2.4. Toxicity of nasal formulations containing enhancers

Strategies for identifying the toxic potential of intranasal formulations have been reviewed, with special reference to studies supporting clinical trials. Even though *Quadir et al.* has pointed out that in vitro data do not always correlate well with in vivo data (70), clinical signs of nasal irritation in rats, including struggling, sneezing, salivation, head shaking and nose rubbing, were seen in studies of less than 90 days duration conducted by *Lilly Research Laboratories*

for an intranasal protein penetration enhancer formulation. In these studies, histological signs of nasal irritation were seen, including inflammation of septal and turbinate mucosal surfaces, epithelial and submucosal infiltration of inflammatory cells, purulent exudates and mucosal hyperplasia (19).

6. Regulatory

In order to have a successful approval and marketing of nasal delivery drugs, authorities will require a lot of data for quality control purposes. During the development of nasal drug products process, the industry has to construct a regulatory dossier that has to follow strict regulatory issued by FDA in the USA and EMA in Europe. (2).

In this dossier, a summary should be provided with the description of the development of the formulation, including identification of those attributes that are critical to the quality of the drug product. The summary should also take into consideration the choice of drug product components, such as the properties of the drug substance, excipients and the container closure system, but also the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug products. A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided (24).

Specification reference to analytical procedures, and proposed acceptance criteria, is addressed in ICH Q6A (71) and Q6B (72). In addition, stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied (32). The characteristic tests used in the development process in the USA and Europe are detailed in Table 4.

Table 3 – Development characterization tests in nasal drug products in USA and Europe. Adapted (2).

Characterization Test	FDA	EMA
Stability	X	X
Temperature cycle testing	X	X
Priming, re-priming	X	X
Micro/bioburden	X	X
Extractables	X	X
Leachables	X	N/A

USP testes, 601, 87, 88, 661, 381…	X	N/A
Drop testing, vibration, shipping, air transport tests	X	X
Effect of orientation	X	X
Plume geometry	X	N/A
Profiling near exhaustion	X	X
Performance in the hands of different users	X	X
Particulates	X	N/A

Once approved and marketed, nasal drugs must demonstrate ongoing quality. For that reason, the products are routinely controlled and compared regulatory expectations for marketed nasal product specifications (2). In Table 3 are detailed the routine tests required by FDA and EMA.

Table 4 – Routine control tests for nasal drugs products. Adapted (2).

Control Test	FDA	EMA
Priming, re-priming	X	X
Dose weight (through life)	X	X
Leakage	X	X
Dimensional, metrology	X	X
Droplet/particle size distribution	X	X
Spray pattern	X	N/A
Extractables	X	X
Microbial limits	X	X

7. Approved Medicines

The following molecules constitute the intranasal administrated medicines currently approved in Portugal. Most of the marketing approved drugs have similar indication and don't need a prescription in order to collect them from Pharmacies.

a. Azelastine - Allergodil®; Azep®; Snizdil®

Azelastine nasal spray is a second-generation intranasal antihistamine and selectively antagonizes histamine receptor-1. Azelastine has mast-cell stabilizing and anti-inflammatory properties (73). Azelastine nasal spray is an effective, rapid-acting, and well-tolerated drug to improve nasal symptoms due to the congestion of human nasal mucosa in patient with allergic rhinitis (AR). Allergodil®; Azep®; Snizdil® are nasal sprays that don't need medical prescription. Azep® is not marketed in Portugal but has marketing approval (74–76)

b. Azelastine and Fluticasone – Azecort®; Dymista®

Current recommendations for management of AR emphasize the use of intranasal corticosteroid or antihistamine medication orally or intranasally (77). Despite these available therapies, patients often report inadequate symptom relief or difficulty with adherence to therapy (78). Azecort® and Dymista® are a combination intranasal antihistamine and corticosteroid spray that represents an alternative therapeutic option for the management of AR for patients that do not respond to monotherapy (79,80). Azecort® is not marketed in Portugal but has marketing approval (79) but Dymista® is a drug available with medical prescription (80).

c. Beclometasone - Neo-Sinefrina Alergo®

Intranasal corticosteroids are a recommended treatment in persistent rhinitis and in moderate/severe intermittent rhinitis. They have shown to reduce nasal congestion, rhinorrhea, sneezing, itching and can also relieve ocular symptoms. Among the several corticosteroid intranasal sprays available, beclomethasone dipropionate is one of the most known and prescribed (81). Neo-Sinefrina Alergo® is a nasal spray that has marketing approval in Portugal since 1976 and is commercialized without the need of a prescription (82).

d. Budesonide – Aeromax Nasal®; Cetix Spray Nasal®; Pulmicort Nasal Aqua®

Budesonide is an intranasal corticosteroid available for the treatment of AR. Budesonide is quickly metabolized to less-active metabolites, have minimal systemic absorption and, for that reason, have minimal systemic adverse effects(83). Aeromax Nasal®, is a marketed medicine since 2001 that needs prescription (84). Cetix Spray Nasal® and Pulmicort Nasal Aqua® are drugs that do not need medical prescription but are available only for pharmacies dispense (85,86).

e. Cromoglycic Acid - Fenolip®

Cromoglycic acid is an antiallergic drug which inhibits the degranulation of mast cells, thereby blocking the release of inflammatory mediators. Thus, cromoglycic acid prevents the development of allergic reactions rather than reducing acute symptoms and its onset of action is about four to seven days (87). Fenolip® is a nasal spray indicated for treating rhinitis without needing a prescription (88).

f. Desmopressin - Dsavp Desmopressin®

The desmopressin, a vasopressin analogue, is used for the treatment of diabetes insipidus. It has a potent antidiuretic effect, minimal side effects and lacks the vasopressor effects of its parent molecule (89). The nasal spray Dsavp Desmopressin® is a medicine approved in 1979 and is prescribed for diabetes insipidus caused by the deficiency of the antidiuretic hormone. However Dsavp Desmopressin® is not marketed in Portugal (90).

g. Dimethindene and phenylephrine - Vibrocil®

Nasal preparations containing the direct sympathomimetic agent phenylephrine and the highly potent H1 antagonist dimetindene are commonly used to relief nasal congestion caused by various conditions including common cold, sinusitis and allergies (91). Vibrocil® is a nasal spray with marketing approval in 1966 without a prescription needed in Portugal (92).

h. Esketamine - Spravato®

Esketamine have demonstrated efficacy for treatment-resistant depression (93). Spravato® is a nasal spray marketed approved in Portugal since 2019 for patients that do not respond to

two different antidepression drugs. Spravato® is part of the medicines that need a special prescription (item a), that refers to medicines used only on hospitals due to its pharmacological characteristics, its novelty or for public health reasons (94). In July of the present year, a guide for professional healthcare was released in order to minimize the risks (95).

i. Fentanyl - Instanyl®; PecFent®

Fentanyl nasal spray is approved for the treatment of breakthrough cancer pain in patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain (96). Instanyl® has marketing approval since 2011 but is not commercialized in Portugal (97). Contrarily, PecFent® is commercialize under the special item b of prescription. This means that PecFent® is intended for pathologies whose diagnosis is made only in a hospital environment or in differentiated establishments with adequate means of diagnosis, although the administration and monitoring of patients may take place outside these places (98). In January of 2021 the second version of the guide for the health professional was released as additional risk minimization measures (99).

j. Fluticasone - Flutaide®; Vibrocil Anti-Alergias®

As was mentioned before, intranasal corticosteroids are recommended therapy for patients with mild to persistent and any moderate to severe presentation of AR symptoms (100). Flucatione proprionate is a widely used intranasal corticosteroid, that has a needed prescription form, known as Flutaide® (101), and a freely prescription form - Vibrocil Anti-Alergias® (102).

k. Fluticasone Furoate – Avamys®

Fluticasone furoate nasal spray is an intranasal corticosteroid with an enhanced affinity for the glucocorticoid receptors and low systemic bioavailability (103). Avamys® was marketed approved in 2008 for AR symptoms and needs prescription in Portugal (104).

l. Glucagon - BAQSIMI®

Glucagon is a key pancreatic hormone that in concert with insulin serves as a central regulator of glucose metabolism. Glucagon counters insulin’s effects on glucose metabolism

and serves as a rescue medicine in the treatment of hypoglycemia (105). BAQSIMI® is indicated for severe hypoglycemia in adults and children older than four years old. The nasal powder was approved in 2019 in Portugal (106) and in May 2021, the demonstration device leaflet came out as an additional risk minimization measure to healthcare professionals (107).

m. Lidocaine - Lidonostrum Bomba-Spray 10%®; Xilonibsa Spray 10%®

Lidocaine was unique in its short onset of action as a local anesthetic with an excellent safety and tolerability profile (108). The spray solutions has many indications, but regarding nasal application, it is indicated for the prevention of pain associated with otorhinolaryngology procedures such as maxillary sinus puncture and minor surgery in the nasal and pharyngeal cavity (109).

n. Mometasone – Nasomet®; Rhinizill®

Mometasone furoate is an intranasal corticosteroid used in the treatment of rhinitis and rhinosinusitis (110). Since 2015, mometasone has been a needed prescription product approved. Rhinizill® is not commercialized in Portugal (111) but Nasomet® and many generic brands medicines are (112).

o. Mupirocin - Bactroban®

Mupirocin is an antibiotic from monocarboxylic acid class used as antibacterial agent against methicillin-resistant Staphylococcus aureus (113). Marketing approved since 1994, Bactroban® is a nasal cream prescription dependent indicated for eradication of staphylococci in nasal carriers (114)

p. Naxolone - Nyxoid®

Naxolone is a specific morphinic antagonist compound (115), and is an emergency therapeutic indicated for known or suspected opioid overdose manifested by respiratory and/or central nervous system depression in non-clinical and healthcare settings. Single dose nasal spray Nyxoid® was marketed approved in 2017 in Portugal and requires medical prescription. In 2018, educational material for training and support of the Nyxoid® administration was made

available to specialized technical teams and non-governmental organizations working in integrated response centers (116).

q. Phenylephrine - Neo-Sinefrina®

Phenylephrine is a pure α-agonist (117) and is widely used for the treatment of nasal congestion (118). Nasal drops Neo-Sinefrina® are indicated for all situations were nasal congestion is concerned: rhinitis and sinusitis (119).

r. Thyme Essential Oil, Benzoin Tincture and Eucalyptus Tinture – Vaporil®

Vaporil® is compost by thyme essential oil, benzoin tincture and eucalyptus tincture. The major constituent of thyme essential oil is thymol, which is a medicinal plant with several therapeutic properties such as antimicrobial, antioxidant, anticarcinogenesis, anti-inflammatory, and antispasmodic activities (120). Benzoin Tincture provides simpler and better adhesion to the nasal skin (121). Finally, Eucalyptus Tinture has antibacterial, antiviral and antifungal components and is used against the colds, influenza, rhinitis and sinusitis symptoms (122). Vaporil® is a nasal spray approved in 2008 in Portugal and is independent from medical prescription (123).

s. Oxymetazoline - Bisolspray Nebulicina Adulto®; Ilvico Respir®; Nasorox®; Nasorhinathiol®; Rinerge®; Vicks Sinex Aloé®; Zolinol®

Oxymetazoline is a widely used intranasal decongestant that when applied topically, induce nasal vasoconstriction, reduced nasal turbinate volume, increased nasal patency which is experienced by patients as freer breathing through the nose (124). There are many products containing oxymetazoline; the first marketed approved in Portugal was Rinerge® in 1970, a nasal spray, and the last one was Zolinol® in 2020 that is nasal drops. All of them do not require medical prescription (125–131)

t. Oxytocin - Syntocinon®

Oxytocin was the first peptide hormone to be biochemically described and synthesized with abundant evidence for diverse functions and health benefits (132). Syntocinon® is a nasal spray indicated to stimulation of expelling milk in patients with difficulties in breastfeeding, prevention and treatment of breast engorgement and prevention of puerperal mastitis (133).

u. Procaterol - Onsudil®

Procaterol is a short-acting β2-agonist that can improve the pulmonary function stable chronic obstructive pulmonary disease (COPD) patients treated with a long-acting bronchodilator (134). Onsudil® is a nasal spray marketed approved in 1990 that requires medical prescription. Onsudil® is indicated for dyspnea and other symptoms caused by reversible airway obstruction in asthma or exacerbation of COPD (135)

v. Tramazoline - Rhinospray®

Tramazoline is a α2-selective agonists and is very used in decongestant products (136). Rhinospray® is a nasal spray approved in 1965 for the relief of nasal congestion associated with the common cold (137).

w. Triamcinolone – Nasacort®; Telfast Spray Nasal®

Triamcinolone has been evaluated in clinical trials and found to be beneficial in minimizing nasal secretory response, reducing inflammation in medical treatment of rhinosinusitis (138). Nasacort® was approved in 1997 but is not commercialized nowadays in Portugal (139). Diversely, Telfast Spray Nasal® was marketed approved in 2011 and, although it does not required a medical prescription, it is only available in pharmacies (140).

x. Influenza, live attenuated - Fluenz Tetra®

Fluenz Tetra® is a intranasal vaccine, approved in 2013, indicated in prophylaxis of flu in children and adolescents aged 24 months or over and under 18 years. However, it is not commercialized in Portugal (141).

y. Xylometazoline - Actifed Descongestionante®; Nasex®; Seaxyl®; Snup®; Vibrocil Actilong®; Xymeral®

Xylometazoline hydrochloride is a well-established nasal decongestant that belongs to the pharmacotherapeutic group of sympathomimetic drugs and acts selectively on α-adrenergic

receptors (142). There are various approved nasal products, nasal drops or sprays, and none requires medical prescription (143–147).

z. Xylometazoline and Ipratropium Bromide – Nasitrim Duoeffect®; Vibrocil ActilongDuo®

Xylometazoline is an alpha (α)-agonist, a sympathomimetic agent that helps to relieve nasal congestion by locally constricting blood vessels in the nasal mucosa and ipratropium is an anticholinergic agent that reduces the amount of watery nasal discharge produced from the nasal mucos (148). Thus, Nasitrim Duoeffect® and Vibrocil ActilongDuo® are nasal sprays marketed that do not need prescription and are indicated for symptomatic treatment of nasal congestion and rhinorrhea associated with colds (149,150).

aa. Xylometazoline and Dexpanthenol – Nasex Duo®; Septanazal®; Vibrocil ActilongProtect®

Nasal decongestant sprays containing xylometazoline, that have a rapid onset of action, and dexpanthenol, that promotes cell proliferation and protects the epithelium, have demonstrated beneficial synergetic effects on the symptoms of acute rhinitis (151). Nasex Duo®, Septanazal® and Vibrocil ActilongProtect® are nasal sprays approved and marketed in Portugal that do not requires medical prescription (152–154).

bb. Zolmitriptan - Zomig Nasal®

Zolmitriptan has shown to be highly effective and well tolerated in the acute treatment of migraine with or without aura in adults (155). Although its' approval in 2002, Zomig Nasal® is not commercialized in Portugal (156).

8. Current Challenges

The administration of drugs through the nasal mucosa is an attractive method for local and systemic drug delivery for treating acute and chronic medical conditions. Despite its attractiveness, nasal drug absorption still faces significant challenges (15).

The toxic potential of intranasal products must be evaluated. While necrosis and inflammation of nasal tissues are of acute concern, allergenicity, immunogenicity, and carcinogenicity represent potential delayed manifestations. Solvents and excipients are obvious potential contributors to toxicity, but it should also be noted that the high concentrations of drug that are applied intranasally may cause local toxic effects. The toxicities of prodrug/enzyme combinations will need to be carefully evaluated. Finally, the toxic potential of a formulation may depend on whether it is targeted towards systemic drug absorption or direct nose-to-brain absorption (157).

Optimizing drug formulation and delivery device development can unlock the potential for innovative inhaled medicines that can revolutionize patients' lives (158), and many models have been created in order to study and predict the behavior of the nasal mucosa with various drugs and absorption during the development of new intranasal formulations (159–163).

9. Conclusion

The nasal cavity has a large surface area and is highly vascularized. Drugs absorbed by the nasal mucosa pass directly into the systemic circulation, avoiding first-pass metabolism by the liver. Despite the potential of the nasal route, the mucus and epithelial barrier, mucociliary clearance and enzymatic activity represent some of the limitations. Increasing the residence time of the drug product in the nasal cavity may improve drug absorption. Many approaches were presented in this review but there are also some concerns, such as the potential toxicity in the nasal mucosa. The physicochemical properties of the drugs are also an important factor that affects the nasal drug absorption, since a number of lipophilic drugs have been shown to be almost completely absorbed from the nasal mucosa. The nasal route of administration will probably have great potential for the future development of peptide preparations and other drugs that otherwise should be administered parenterally.

However, with regulatory demands increasing, professional guidance is needed and should be provided by manufacturers of nasal drug delivery systems to support pharmaceutical companies in finding the optimum formulation. Even though such support cannot exempt marketers form performing proper due diligence on the finished product, it is obvious that time to market can be reduced substantially if available resources are utilized in a proper cooperation mode.

Nonetheless a considerable number of products and several innovations for intranasal administration have been developed in recent years. This underlines the continuous attractiveness of the nasal administration mode. Careful and concurrent considerations of all elements in the formulation triad, such as drug, vehicle system and delivery device are the basis of successful formulation development.

In summary, an analysis of the available literatures has revealed that the intranasal route is an attractive approach and is very applicability. However, it was also stated that nasal drug delivery presents several limitations and must be overcome to develop successful intranasal medicine.

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