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A comprehensive review on over-the-counter medication nasal spray and scope of development

Sarvesh Rahate[1*], Sakshi Hirkane[2], Akash Lashkar[3], Trapti Shrivastava[4]
[1,2,3]*Sagar Institute of Pharmacy& Technology, Gandhinagar, Bhopal, M.P., India (462036)*
[4]*Dept. of Biotechnology, Sagar Institute of Pharmacy & Technology, Gandhinagar, Bhopal, M.P., India*
**Corresponding Author: SarveshRahate*

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ABSTRACT: Globally the pharmaceutical innovations are in search for better and point outcomes for the treatment in medications. The game play in the arena of pharmaceuticals is in the constant search of novel drug delivery systems having overwhelming therapeutic effects on the existing issues of systems. The suitability of the drug administration and enhanced patient amenableness, and the drug – receptor compatibility is an essential strategy of the drug delivery systems via the nasal route of administration. Though the drug – receptor compatibility is as important as in other route of administration too. The anatomy and physiology of the nasal cavity provide unique advantages for accessing targets for local, systemic, and potentially central nervous system drug delivery. Therefore, the advantages and the challenges should be kept in consideration at all the points and that must be discussed to overcome to reach these targets. In India, Oxymetazoline Hydrochloride marketed under brand name **Otrivin Oxy Fast Relief**(refer to FIGURE 1) nasal sprays is easily available as OTC medicines.

KEYWORDS: Nasal spray, Oxymetazoline Hydrochloride, nasal cavity, inhalation, nasal administration, olfactory response.

I. INTRODUCTION

Drugs have been administered nasally for therapeutic and recreational purposes since ancient times. Psychotropic drugs and hallucinogens were snuffed for these purposes by the people of Indian origin and South American origin, and this practice is currently widespread among abusers of cocaine and heroin. Nasal spray drug products represent a small portion of the overall drug delivery market. However, these hold the potential of delivery systems to easily drive the whole market to a greater extent. There are number non-invasive delivery routes – pulmonary, transdermal, needle-free, buccal and others – for which optimised technologies are under development. Among these routes, the proven track record of nasal drug delivery technologies to pass the concept stage in this quest, and go on to facilitate the development and launch of viable product candidates, stands out. Many nasal products for the topical treatment of conditions such as rhinitis and sinusitis have of course been marketed for decades.

The young and ageing population considering in any of the demographics, facing challenges certainly increase the demand and growth of home health care and self-administration of drug therapy giving the nasal spray administration quite a wide spectrum to enter as the Over-the-counter (OTC) medication a priority in geriatric as well as paediatric. This makes the drug developer show a keen interest in route of administration that is obviously patient friendly and cost effective to the patient expenditure on treatment.

Where other routes often offer such benefits at the expense of desirable pharmacokinetics, nasally administered formulations have true potential for rapid onset of action, high bioavailability and direct "nose-tobrain" delivery. This potential arises predominantly because of the complicated structure of the nasal cavity, which has evolved to carry out multiple functions.

About 2% of the drugs that are conveyed through nasal route are due to the reason for availability of large surface area. In comparison to alternative routes of drug delivery, nasal route is found more prominent. A range of nasally delivered products has been on the market during recent decades. These products belong to therapeutic areas such as allergic rhinitis treatment, migraine relief, hormone replacement therapy (HRT) and common cold relief.

The advantages of delivery via the nasal route are numerous. It is clearly a convenient, non-

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invasive administration route but this is not what sets it apart. Where other routes often offer such benefits at the expense of desirable pharmacokinetics, nasally administered formulations have true potential for rapid onset of action, high bioavailability and direct "nose-to-brain" delivery.

Inhalation sprays are intended for delivery to the lungs by oral inhalation for local and/or systemic effects. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multi-dose presentations.

FIGURE 1.Otrivin Oxy Fast Relief, GlaxoSmithKine Pharmaceutical Ltd.

II. METHOD

In this section of our article, we will see the overview of physiology of nasal cavity; understand its working and principles. The anatomy and physiology of the nasal cavity provide unique advantages for accessing targets for local, systemic, and potentially central nervous system drug delivery. Along with this we will throw a light on action of locally and systemically acting drug products.This potential of the Nasal Sprays arises predominantly because of the complicated structure of the nasal cavity, which has evolved to carry out multiple functions. They include physical protection of the lower airways (by filtering out large particles), immune protection, and optimisation of the temperature and humidity of air before it enters the lungs. What is more, the nose is an amazing and delicate sensory organ, able to detect minute traces of countless substances in the air via the olfactory nerves that enter the roof of the nose through the cribiform plate.

To go more in detail for the better understanding for the development of nasal spray, firstly take a dive into the nasal physiology (refer to FIGURE 2). Breathing and olfaction are the prime functions of the nasal cavity in humans and animals.The human nasal cavity is lined with mucus layer and hairs which are involved in those functions of trapping the inhaled particles and pathogens. These tiny hairs are known as nostrils. More of the functions of nasal structure are resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances classified under the essential functions of nasal structure The nasal cavity of human is around the total volume of 15-20 mL i.e. each cavity has nasal volume of 7.5 - 10 mL and approximates 150cm^2 of total surface area of the cavity. One more important thing, the nasal cavity is vertically separated in to the two halves by a wall known as **Septum** or the **Nasal Septum**.

Each of the nasal halves consists of four areas that are mentioned as follows and that are distinguished according to their anatomic and histological characteristics:

Nasal vestibule:The nasal vestibule is the most anterior part of the nasal cavity; it is adjacent to the atrium, the intermediate region. In this particular section of Nasal Cavity, there are nasal hairs present, these are known as vibrissae, which majorly function for the filtration of inhaled particles. In known language, these vibrissae are said to be the nostrils. The general characteristics of nasal vestibule easily afford the high resistance against the suspended environmental substances that are toxic to an extent, but simultaneously at the same time the absorption of substances including drugs becomes very difficult in this region.

Atrium: The atrium is the intermediate area between the nasal vestibule and respiratory region. The stratified squamous and transitional types are mainly found in the anterior third of each cavity. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudo-stratified columnar cells presenting microvilli.

Respiratory region: The respiratory region contains ciliated cells, mucous secreting goblet cells, and basal cells. It is divided in superior,

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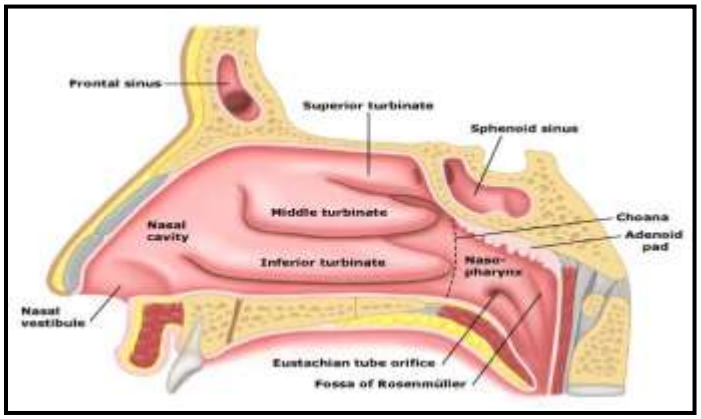
middle and inferior turbinate's which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air.The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria.

Olfactory region: The olfactory region is located in the roof of the nasal cavity and extends a short way down the Septum. . The neuro-epithelium of olfactory is the only part of the Central Nervous System (CNS) that is directly exposed to the external environment. Similarly to therespiratory epithelium, the olfactory region is also pseudo-stratified but it contains the specialized olfactory receptor cells which are very important for the perception of smell.

FIGURE 2. The Human Nasal Physiology



III. RESULTS

The nasal administration of drug offers an interesting alternative for achieving systemiceffects in comparison to the parentral route, which can be inconvenient for the oral administration that can result in unacceptably low bio availabilities. The nasal epitheliumis a highly permeable monolayer, the sub-mucosa is richly vascularised, and hepatic first-passmetabolism is avoided after nasal administration. Other attractive and yet important features include the rather large surface are of the nasal cavity which is of 150cm^2 and the relatively high blood flow, promoting the rapid absorption of the drug. Furthermore, self-medication is easy and convenient i.e. the patient can easily administer the formulation by himself.

By delivering directly the drug to site of action, in this nasal drug delivery offers greater convenience pattern and assured safety. It is a noni-invasive and a painless method of drug administration, which is quite encouraging greater compliance compared to other routes of drug administration. Another advantage of nasal drug delivery for patients taking multiple drugs is that a nasally delivered drug may act as an adjunct to another drug given orally or intravenously administered.

Nasal delivery also offers the opportunity to bypass the blood–brain barrier and deliver drugs

directly to the central nervous system. This barrier prevents systematically delivered drugs, whether delivered orally, intravenously, or by other routes, from reaching significantconcentrations in the brain. Two cranial nerves, the olfactory nerve and the trigeminal nerve,pass through the nasal cavity. An intra-nasally delivered drug could use these pathways to reach the tissue present in the central nervous system and achieve levels that are necessary to be of therapeutic benefit to the patient. Additionally, there are other potential vascular,

cerebro-spinal, or lymphatic pathways as routes to the central nervous system (CNS).

New opportunities in the nasal drug delivery systems administration include the possibility for direct nose-to-brain delivery, that are requiring dose particle deposition in the olfactory region. However, researchers working in this area currently face a dilemma but time on again there have been successful attempts in this direction of nasal drug delivery. Traditionally, nasal formulations ideally have particle sizes above 20-30 µm to minimise the degree of deposition in the lower airways, which increases as particle size

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decreases. But at the same time, to reach the olfactory region requires dose particle sizes below 5 µm. A new nasal delivery method is therefore needed to prevent deposition of fine particle nasal dose in the lower airways.

IV. DISCUSSION

The drug substances like oxymetazoline, which are considered of imidazole class, are acting on the alpha-adrenergic receptors of nasal mucosal arterioles leading to decreased flow of blood. In the recent days, various natural as well as synthetic polymers are widely used in nasal drug delivery. The present work described the formulation development and evaluation of nasal solution dosage form for the use of oxymetazoline as a model drug. The meter dose spray formulation helps to deliver known amount of formulation.

Imidazole derivatives such as oxymetazoline are readily absorbed across mucosal membranes, especially in children. Oxymetazoline**binds to α_1- and α_2-adrenoceptors**, which are Gq-protein-coupled receptors that promote vascular smooth muscle contraction by increasing intracellular calcium levels in response to ligand activation.Molecular formula: **$C_{16}H_{25}ClN_2O$**. The Chemical Structure for Oxymetazoline Hydrochloride is as follows (refer to FIGURE 3).

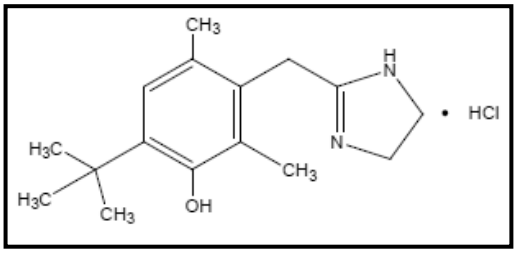

Figure 3: Chemical Structure of Oxymetazoline Hydrochloride

The Oxymetazoline Hydrochloride (Otrivin Oxy) has proven to be an effective nasal decongestant in India. Though, biological factors must be considered affecting the nasal drug absorption. Various factors affect bioavailability of nasally administered drugs as follows:

Biological Factors: Structutal Features and Biochemical Changes. There are different sections of each of the nasal cavity: the nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. These structures and the type of cells present, density and number of cells present in that region influence the permeability. Enzymatic barrier to the delivery of drugs is the nasal mucosa because of the presence of a large number of enzymes in it.Oxidative and conjugative enzymes, peptidases and proteases are some of the prime enzymes present in the nasal mucosa. Protease and peptidase were responsible for the pre-systemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin.

Physiological Factors: Blood Supply & Neuronal Regulation, Nasal Secretion, Mucociliary Clearance, Pathological Conditions and Environmental Conditions. The nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion, regulating the rise in amount of drug to be permeated and low blood supply due to sympathetic stimulation gives relaxation, regulating the fall in amount of drug to be permeated. The increased permeability of a compound is due to parasympathetic stimulation. Nasal secretions are produced by anterior serous and seromucus glands, the permeability of drug through the nasal mucosa secretion is affected by the viscosity of nasal secretion, solubility of drug in the secretion, and most important is the pH of the nasal cavity, where in variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species. When saying of Mucociliary clearance (MCC), a substance is nasally administered, it is cleared from thenasal cavity in nearly about ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa. Considering pathologic conditions, Mucociliarydisfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, and atrophic rhinitis also affects the

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drug permeation, altering absorption from the nasal cavity in different ways. Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability.

Process and Development of a Nasal Spray Formulation factors should be taken into consideration to obtain successful nasal absorption of drugs includes the concentration of the drug. Nasal spray drug products contain the therapeutically active ingredients or the Active Pharmaceutical Ingredient (API) i.e. the drug substances that is dissolved or suspended in solutions or mixtures of several excipients (e.g., preservatives, viscosity modifiers, emulsifiers, and buffering agents) in non-pressurized dispensers thatdeliver a spray containing a metered dose of the Active Pharmaceutical Ingredient (API).

Nasal absorption enhancers are required to be non-irritating, nontoxic and non-allergenic or at least to have immediately reversible effects. Moreover they should be potent in nature, compatible with the drug and other excipients in the formulation and systemically inert in the concentrations. Lack of odour, taste and influence on mucociliary clearance are other important requirements for nasal drug delivery. For any manufacturer, it is of utmost important that the enhancers and other excipients used in the development of the formulation must be qualified for over all safety profile.

V. RESULTS

Nasal drug delivery can be affected by several factors e.g. Biological Factors, Physiological factors, Physicochemical Properties of Drugs, Physicochemical Properties of Formulation. Attributes of the novel nasal approach include a large surface area for introduction of drug to the bloodstream, rapid onset of therapeutic drug levels, potential for direct-to-central nervous system delivery, no first-pass metabolism, and non-invasiveness to maximise patient comfort and compliance.

VI. CONCLUSION

Both the paediatric nasal formulations as well as the geriatric nasal formulation are developed by utilizing the factorial design approach. There are several benefits of nasal sprays and considering their potential benefits, and nasal administration of the drug we should expect to see a more novel range of nasal products reaching the market in the near future. Probably it will include not only for more local treatment of drug but also provide systemic protection alternatives. The development of drugs would be for directly targeting the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects

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