

AN OVERVIEW: FORMULATION AND PRODUCT DEVELOPMENT OF NASAL SPRAY

Mukesh Bhatt* and Ganesh Kumar Bhatt

Shri Guru Ram Rai Institute of Technology and Sciences, Dehradun, Uttarakhand, India.

Article Received on
03 April 2017,

Revised on 23 April 2017,
Accepted on 13 May 2017

DOI: 10.20959/wjpr20176-8557

*Corresponding Author

Mukesh Bhatt

Shri Guru Ram Rai Institute
of Technology and Sciences,
Dehradun, Uttarakhand,
India.

ABSTRACT

The intranasal delivery is suitable route for administration of the drug for local, systemic as well as CNS drug delivery. Advantages of nasal spray dosage form such as it is cost-effective, easy to use/carry and self-administrable, it has high patient compliance make this dosage form rising opportunity for nasal drug delivery. This article rough idea the appropriate aspects of nasal anatomy, physiology and histology, and the biological, physicochemical and pharmaceutical factors that must be considered during the formulation development of nasal spray.

KEYWORDS: Nasal Spray, Nasal drug delivery system and formulation.

INTRODUCTION

The nasal delivery of drugs in the recent decade been considered as a approaching route of administration to achieve higher bioavailability and increased level of drug absorption. The systemic effects achieved of the drugs administered by this route grants an alternative for the drugs given by parenteral delivery which can be sometimes not convenient or the oral delivery which can decrease bioavailability. This has appealed a great fervor for the development of nasal delivery of drugs. The highly permeable monolayer of the nasal epithelium, the richly vascularised submucosa and avoidance of hepatic first-pass metabolism has proved to be valuable for the drug administration via the nasal route. Other important features include accessible surface area of the nasal cavity and the rich blood flow which promotes rapid absorption. Hence, the rationale behind this article is to provide an expansive review covering the many aspects of nasal drug delivery.

ADVANTAGE

1. Reach directly into Systemic blood circulation and avoid first pass hepatic and intestinal metabolism
2. Drug degradation is absent in GIT tract
3. Drug absorption is very fast and quick onset of action
4. Smaller size of drug molecules having higher bioavailability.
5. It provides good penetration of, especially Lipophilic, low molecular weight drugs through the nasal mucosa.
6. Lipophilic drug easily penetrate in BBB

LIMITATIONS

1. Dose is limited because of relatively small area available for the absorption of drug.
2. Time available for drug absorption is limited.
3. Diseased condition of nose impairs drug absorption.
5. Absorption surface area is less when compared to GIT.
6. Nasal irritation
7. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
8. Certain surfactants used as chemical enhancers may interrupt and even dissolve Membrane in high concentration.

Nasal Anatomy and Physiology**1) Nasal vestibule**

In this area of nasal cavity, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region.

2) Atrium

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.

3) Respiratory region

It is divided in superior, 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. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air and also offers physical and enzymatic protection of the nasal epithelium against several foreign compounds, including drugs. The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin an antibodies that confer immunological protection against bacteria and virus.

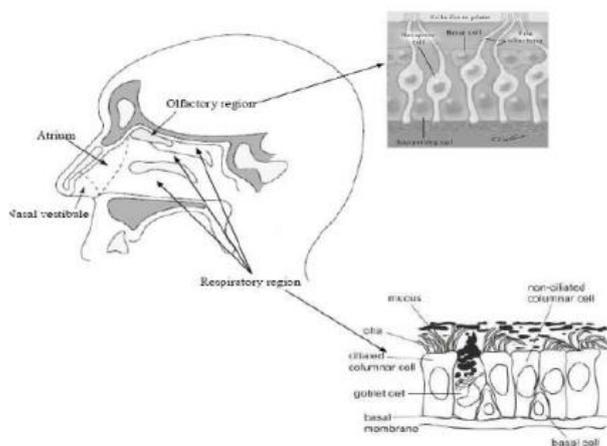


Fig no: 1 Anatomy of nasal

4) Olfactory region

The olfactory region is located in the roof of the nasal cavity and extends a short way down the Septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly

exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception.

Factors Influencing Nasal Drug Absorption

Biological Factors

Structural features

Biochemical changes

Physiological factors

Blood supply and neuronal regulation

Nasal secretions

Mucociliary clearance and ciliary beat frequency

Pathological conditions

Environmental conditions

Membrane permeability

Physicochemical Properties of Drugs

Molecular weight

Size

Solubility

Lipophilicity

pKa and Partition coefficient

Chemical form of the drug

Polymorphism

Chemical state

Physical state

Physicochemical Properties of Formulation

Physical form of formulation

pH

Osmolarity

Volume of solution applied and drug concentration

Viscosity

Formulation of nasal spray

Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects. Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, and drug product). Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition. Energy is required for dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice. The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product. Both solution and suspension formulations can be formulated into nasal sprays.



Fig no 2: Pictorial diagram of nasal spray

1) Active Pharmaceutical Ingredient

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.

- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

2) Excipients used in nasal spray formulations

There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are as follows:

a) Buffers: Nasal secretions may alter the pH of the administered dose which can affect the Concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ. Examples of buffer used in nasal spray sodium phosphate, Sodium citrate, citric acid.

b) Solubilizers: Aqueous solubility of drug is always a limitation for nasal drug delivery in Solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolized C8- C10 glyceride) can be used to enhance the solubility of drugs. Other compounds can be used like, the use of surfactants or cyclodextrins such as HP- β -Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with Lipophilic absorption enhancers. In these cases, their impact on nasal irritancy should be considered.

c) Preservatives: Most nasal formulations are aqueous based so needs preservatives to prevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

d) Antioxidants: A small quantity of antioxidants may be required to prevent drug Oxidation. Commonly used antioxidants are sodium bisulfite, butylated hydroxytoluene, Sodium metabisulfite and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation.

e) Humectants Because of allergic and chronic diseases there can be crusts and drying of mucous membrane. Certain preservatives/antioxidants are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal

products. Humectants avoid nasal irritation and do not affect drug absorption. Common examples include Glycerin, Sorbitol and Mannitol.

PHYSICAL PROPERTIES OF FORMULATION

Nasal spray formulation are classify into two types:-

1. Solution
2. Suspensions

And both can be either aqueous or non aqueous. When formulating aqueous nasal spray product, it is critical to control properties such as pH, buffer capacity, Osmolarity and viscosity. The US FDA Chemistry, Manufacturing and Controls (CMC) Guidance on nasal spray recommends measurement of pH, Osmolarity and viscosity as the part of the drug product specification.

Characterization of Nasal Spray

pH

The pH of the nasal formulation is very important mainly to avoid irritation of the nasal mucosa, to prevent the growth of pathogenic micro organism, to sustain normal physiological ciliary movement. Lysozyme which is present in nasal secretion that is responsible for destroying certain micro organisms at acidic pH, under alkaline pH, Lysozyme is deactivated and the nasal tissue is susceptible to microbial infection. It is therefore pH of the formulation was adjusted between 4.5 - 6.5 and pH of the all prepared formulations was measured for pH using by digital pH meter.

Osmolality

For formulations containing an agent to control the tonicity or for products having a label claim regarding tonicity, the osmolality of the formulation should be tested and controlled at release.

Clarity test

The test was performed to find out whether the colloidal dispersion is free from the particulate matter or not. The dispersion in the test tube was observed against black and white background under light using clarity testing apparatus. Particulate matter may originate during manufacturing, from formulation component, container and closure component. Level of particulate matter in the drug product was increased with time, temperature and stress.

Sterility

The test for sterility was designed to reveal the presence of microorganisms in the colloidal dispersions. Soya bean casein digested media was used in this study in order to find out both bacteria and fungi. One portion of intended media was used for detection of bacteria at 37°C for 24h and another portion used for the detection of fungi at 23°C for seven days.

Pump delivery

The formulation has been filled into a container having a single nozzle (0.2 mm diameter) was actuated for 10 times in a pre-weighed weighing bottle. After actuation the weight of the weighing bottle was reweighed and the difference was calculated.

Viscosity

For formulations containing an agent contributing to the viscosity, this parameter should be tested and controlled at release and on stability. The contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation. Also high viscosity of formulations interferes with normal ciliary beating and/or MCC and thus, increases the permeability of drugs.

Spray Content Uniformity (SCU)

The spray discharged from the nasal actuator should be thoroughly analyzed for the drug substance content of multiple sprays from beginning to the end of an individual container, among containers, and among batches of drug product. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. This test is designed to demonstrate the uniformity of medication per spray, consistent with the label claim, discharged from the nasal actuator, of an appropriate number ($n = 10$ from beginning and $n = 10$ from end) of containers from a batch. The primary purpose is to ensure SCU within the same container and among multiple containers of a batch. For acceptance of a batch the amount of active ingredient per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations 10 containers, none of the determinations is outside of 75 to 125 percent of the label claim, and the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim. If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim, but none are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim, an additional 20 containers should be

sampled for second tier testing. For the second tier of testing of a batch, the acceptance criteria are met if the amount of active ingredient per determination is not outside of 80 to 120 percent of the label claim for more than 6 of all 60 determinations, none of the 60 determinations is outside of 75 to 125 percent of label claim, and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

Spray Pattern and Plume Geometry

Characterization of spray pattern and plume geometry is important for evaluating the performance of the pump. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design of the pump, the size of the metering Chamber and the characteristics of the formulation.

Plume geometry testing requires images taken from a sideward view of the emitted spray parallel to the axis of the plume, whereas for the evaluation of the spray pattern, an image of an axial cross-section of the plume at a defined distance to the nozzle is compulsory.

Particle Size Distribution

For suspension nasal sprays, the specification should include tests and acceptance criteria for the Particle size distribution of the drug substance particles in the formulation. For example, microscopic evaluation can be used and such an examination can provide information and data on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth.

CONCLUSION

The intranasal route is an reachable alternative route for drug administration. The development of drugs for directly target the brain in order to achieve a good therapeutic effect in CNS with reduced systemic side effects. It has advantages in terms of reduces systemic exposure and hence side effects and avoiding first-pass metabolism. Nasal spray drug products Contain active ingredients dissolved or suspended in Solutions or mixtures of excipients in nonpressurized dispenser that deliver a spray containing a metered Dose of the active ingredient. Vital characterization Test for nasal spray includes spray pattern, droplet size Distribution, spray content uniformity these depend on Formulation as well as device properties.

REFERENCE

1. Santosh thorat formulation and product development of nasal spray: An Overview 2016; 4(8d): 2976-2985.
2. Sachin chhajed, sagar sangale and s.d. barhate advantageous nasal drug delivery system: a review (2011).
3. Senthil kumar k, manoj varma g, vudaykiran a, r arun kumar and b sudhakar nasal drug delivery system - An Overview.
4. Rakesh n and arshad bashir khan targeted drug delivery systems mediated through nasal delivery for improved absorption: an update.
5. M. Menaka, v. P. Pandey, a. Anton smith formulation development and evaluation of ondansetron hydrochloride nasal spray(2013).
6. Per gisle djupesland nasal drug delivery devices: characteristics and performance in a clinical perspective—a review (2012).
7. M.alagusundaram, b.chengaiiah¹, k.gnanaprakash¹, s.ramkanth¹, c.madhusudhana chetty¹, d.dhachinamoorthi² nasal drug delivery system - an overview(2010).
8. Muhammad u. Ghorji, mohammed h. Mahdi, alan m. Smith, barbara r. Conway, nasal drug delivery systems: An Overview 2015.
9. Latika nasare, kamlesh niranjane, anuradha nagdevte, sumedh mohril nasal drug delivery system: an emerging approach.
10. For brain targeting 2014.
11. aishwarya j jadhav, sheetal b gondkar, ravindra b saudagar a review on nasal drug delivery system(2014).
12. Jayesh k. Kakad, prasad k. More¹, sheetal b. Gondkar², ravindranath b. Saudagar a recent review on nasal drug delivery system.
13. kisan r. Jadhav, manoj n. Gambhire¹, ishaque m. Shaikh¹, vilarsrao j. Kadam¹ and sambjahi s. Pisal² nasal drug delivery system-factors affecting and applications.