Review on Nasal Drug Delivery System and Their Application

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ABSTRACT
Nasal drug delivery has received a great deal of attention as a convenient, reliable, and promising method for the systemic administration of drugs. It is especially for those molecules which are ineffective orally and only effective if administered by injection. The nasal route of drug delivery has advantages over the other alternative systems of non-invasive drug administration. The present review is an attempt to provide some information concerning nasal drug delivery system such as limitations, advantages, mechanism of drug absorption, anatomy of nasal cavity, factors affecting of nasal drug delivery, strategies to enhance nasal absorption, strategies to extend duration of drug formulations within the nasal cavity, leading to improved nasal drug absorption, novel drug formulations, sorts of nasal drug delivery system with uses of nasal drug delivery in various diseases, and recent advancement of nasal delivery systems.

Keywords- NDDS, Nasal therapy, Spray, ADME process.

I. INTRODUCTION
The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called ‘Nasya karma’ has been recognized form of treatment in the Ayurvedic system of Indian medicines [1]. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects [3, 4]. The low metabolic environment of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. In addition to that, nasal administration minimizes the lag time associated with oral drug delivery and offers noninvasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy. [5] It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100% [6], on the other hand absorption of hydrophilic drugs can be increased by means of absorption enhancers. [7] Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity [8]. The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS) active compounds. It has also been considered to the administration of vaccines [9]. Buserelin, desmopressin, calcitonin, insulin, luteinizing hormone releasing hormone, growth hormone and adreno-corticotrophic hormone are some of the peptides that have been successfully administered through the nasal route. Apart from these, steroids (corticosteroids, estradiol, progesterone, testosterone, and so on) [10].
II. THE USE OF NASAL DRUG DELIVERY

The easy accessibility and available surface area make the nose a possibly viable drug delivery organ.[11] Pharmaceutical product development is an essential task which is directly dependent on its therapeutic objectives. The aspects to be considered for product development depend on whether it is intended for:

- a) Local delivery
- b) Systemic delivery
- c) Single or repetitive administration.

**Local delivery**

Nasal delivery is a logical delivery choice for local (or topical) treatment as it provides the minimal potential for systemic adverse effects when compared to the oral route of administration, and hence, relatively low doses are effective when administered through nasal route with less systemic toxic effects. Prominent therapeutic classes of drugs delivered are decongestants for cold nasal symptoms and antihistamines and corticosteroids for allergic rhinitis [12].

**Systemic delivery**

The intranasal administration of drugs is an effective way for the systemic availability of drugs as compared to oral and intravascular routes of administration. It provided fast and extended drug absorption than oral and parenteral administration. Therapeutic classes of drugs delivered include analgesics (exmorphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone, and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of a migraine and cluster headaches [9, 14-15].

**Nasal vaccines**

During inhalation nasal mucosa is the first site of contact with inhaled antigens, and therefore, its use for vaccination, especially for respiratory infections, has been extensively evaluated.[16] In fact, nasal vaccination is a promising alternative to the classic parenteral route because it can enhance the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin A. Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectorised influenza, Group B meningococcal native, attenuated respiratory syncytial virus, and parainfluenza.

**Different factors affecting nasal drug absorption**

Various factors affect bioavailability of nasally administered drugs as follows:

**I Biological Factors [4]**
- Structural features
- Biochemical changes

**II Physiological factors**
- Blood supply and neuronal regulation
- Nasal secretions

- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental conditions
- Membrane permeability

**III Physicochemical Properties of Drugs [4]**
- Molecular weight
- Size
- Solubility
- Lipophilicity
- pKa and Partition coefficient
- Chemical form of drug.
- Polymorphism.
- Chemical state.
- Physical state.

**Modifying drug structure**

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption. Here, a modification of physicochemical properties such as molecular size, molecular weight, pKa, and solubility is favorable for nasal drug absorption [17,18,19].

Designing of nasal formulation depends on the therapeutic need of the particular drug molecule, duration of action, and duration of therapy. Both controlled release and conventional release drug delivery are possible through nasal route. The requirement of the pharmaceutical excipients depends on the mode of drug delivery, that is, local or systemic drug delivery [20]. A wide range of nasal formulations are available and many studies have been done so far, some of these delivery systems and their key features are summarized below.

**Nasal drops**

They are the most convenient and simple system developed for nasal drug delivery. Nose drops can be delivered with a squeezy or by a pipette a bottle. These pharmaceuticals formulations are often recommended for treating local conditions, which include suffering some challenges such as microbial growth, mucosal dysfunction, and non-specific loss of the nose or lower back [21]. The featured disadvantage of this system is the lack of the dose precision, and therefore, nasal drops may not be useful for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays. Nasal sprays Solution and suspension are formulated into nasal sprays. Availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm. The morphology particles size (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly [22].

**Nasal gels**

Until the recent development of precise dosing device, there was not a lot of interest during this system. Nasal gels are high viscosity thickened solutions or suspensions[23]. The benefits of a nasal gel include the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing,
reduction of anterior leakage of the formulation, reduction of irritation using soothing/emollient excipients, and target to mucosa for higher absorption.

**Nasal powder**

This dosage form may be formulated if solution and suspension dosage forms cannot be formulated, for example, due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of superior stability and preservative of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties, and nasal irritancy of the active drug and excipients. Local application of the drug is another advantage of this system [24].

**Liposomes**

These are phospholipid vesicles composed by bilayer enclosing one or more aqueous compartments, in these compartments drug can be entrapped or adsorbed. Microspheres Microsphere has an important role in nasal drug delivery with enhancing absorption, sustained release, and also has great importance because it protects the drug from enzymatic degradation.[25].

**Physicochemical properties of formulation:**

**Physical form of formulation:**

Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation[26]. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.

**Evaluation parameters**

(For Nasal Spray dosage form - Inhalation Solutions, Suspensions, and S prays)

**Appearance, Color, and Clarity:** The appearance of the content of the container (i.e., formulation) and the container closure system (e.g., pump components, inside of the container) should conform to their respective descriptions as an indication of the drug product integrity. If any color is associated with the formulation (either present initially or from degradative processes occurring during shelf life) then a quantitative test with appropriate acceptance criteria should be established for the drug product by the manufacturer [27].

**Identification:** A specific identification test(s) is recommended to verify the identity of the drug substance in the drug product. Chromatographic retention time alone is not an adequate method to ensure the identity of the drug substance in the drug product[28]. If the drug substance is a single enantiomer, then at least one of the methods should be specific for this property.

**Drug Content (Assay):** The assay of drug substance in the entire container should be determined analytically with a stability indicating procedure. This test provides assurance of consistent manufacturing (e.g., formulation, filling, sealing). The acceptance criteria (assay limits as specified in official books) should be tight enough to ensure conformance in other related attributes (e.g., spray content uniformity)[29]. A suitable assay procedure should be designed to address any degradation of the drug substance, adherence of the drug substance to the container and closure components, and the potential effect of formulation evaporation and/or leakage.

**Impurities and Degradation Products:** The levels of degradation products and impurities should be determined by means of stability indicating procedure(s). Acceptance criteria should be set for individual and total degradation products and impurities[30]. For identification and qualification thresholds, refer to the appropriate guidance. All related impurities appearing at levels of 0.1 percent or greater should be specified. Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification.

**Preservative(s) and Stabilizing Excipient(s) Assay:** If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenylethyl alcohol, edetate) are used in the formulation, there should be a specific assay for these components with associated acceptance criteria (At a concentration of 0.10 percent or 1.0 milligram per day).

**Pump Delivery:** A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the metering ability of the pump should be performed. The proper performance of the pump should be ensured primarily by the pump manufacturer, who should assemble the pump with parts of precise dimensions[31]. Pump spray weight delivery should be verified by the applicant for the drug product. In general, pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within ±15 percent of the target weight and their mean weight to within ±10 percent of the target weight.

**S pray Content Uniformity (SCU):** The spray discharged from the nosepiece should be thoroughly analyzed for the drug substance content of multiple sprays from an individual container, among containers, and among batches of drug product[32]. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. The number of sprays per determination should not exceed the number of sprays per single dose. A single dose represents the minimum number of sprays per nostril specified in the product labeling.

To ensure reproducible in vitro dose collection, the procedure should have controls for actuation parameters (e.g., stroke length, depression force). The test may be performed with units primed following the instructions in the labeling. The amount of drug substance delivered from the nosepiece should be expressed both as the actual amount and as a percent of label claim. This test is designed to demonstrate the uniformity of medication per spray (or minimum dose), consistent with the label claim, discharged from the nosepiece, of an
appropriate number (n = 10 is recommended) of containers from a batch. The primary purpose is to ensure SCU within the same container and among multiple containers of a batch.

The following acceptance criteria are recommended:
The amount of active ingredient per determination is not outside of 80–120 percent of label claim for more than 1 of 10 containers, none of the determinations is outside of 75–125 percent of the label claim, and the mean is not outside of 85–115 percent of label claim[33]

If 2 or 3 of the 10 determinations are outside of 80–120 percent of the label claim, none is outside of 75–125 percent of label claim, and the mean is not outside of 85–115 percent of label claim, an additional 20 container should be sampled (second tier)[34]. For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80–120 percent of the label claim for more than 3 of all 30 determinations, none of the 30 determinations is outside of 75–125 percent of label claim, and the mean is within 85–115 percent of label claim[35].

Foreign Particulates: For both solution and suspension nasal sprays, there should be validated tests and associated acceptance criteria for foreign particulates. Foreign particulates may originate during manufacturing, from formulation components, and, in particular, from the container and closure components[36]. Levels of foreign particulates in the drug product may increase with time, temperature, and stress.

Microbial Limits: The microbial quality should be controlled by appropriate tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator pathogens[37]. Acceptance criteria should be reflective of the data for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production), but at a minimum should meet the recommended microbial limits acceptance criteria in USP, Microbiological Attributes for Non-sterile Pharmacopeial Articles.

Furthermore, appropriate testing should show that the drug product does not support the growth of microorganisms and that microbiological quality is maintained throughout the expiration dating period. [38][39][40]

### III. CONCLUSION

The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding the first pass metabolism. The quality control of Nasal Spray is critical area where high standards are to be maintained therefore evaluation of different parameters discussed in this review shows strict pharmacovigilance as far as such type of dosage forms are concerned. Impurities and Degradation Products, Preservative(s) and Stabilizing Excipient(s) Assay, Pump Delivery, Spray content uniformity, Spray Content Uniformity (SCU) through Container Life, Spray Pattern and Plume Geometry, Droplet Size Distribution, Particle size distribution (suspension), Microscopic Evaluation (Suspensions), Foreign Particulates, Microbial limit, Preservative Effectiveness, Net Content and Weight Loss (Stability), Leachables (Stability), PH, Osmolality. The acceptance criteria for these parameters have been recognized by officials books all over the world. The attempts to deliver corticosteroid hormones through the nasal route for systemic absorption have triggered further studies and strict control over the delivered dosage.

**FUTURE PROSPECTUS**

It is not surprising to find a lot of research focusing to develop nasal drug delivery system and its contribution in therapeutic management. In general, a concise overview of the pharmacotherapy of nasal drug delivery system has highlighted that in spite of the availability of new drugs and several specialized devices.

**REFERENCES**

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