WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Volume 3, Issue 2, 1143-1149. Review Article ISSN 2278 – 4357

NASAL INSERTS DRUG DELIVERY SYSTEM: A REVIEW

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Article Received on
16 November 2013,
Revised on 20 December 2013,
Accepted on 19 January 2014

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ABSRTACT

Nasal drug delivery system is a useful delivery system for the drugs that are in low doses. Nasal drug delivery system provides easy application of drug with self administration. Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via nasalroute. Nasal inserts are prepared by lyophilization. The process of lyophilization involves a container closed with an impermeable membrane pierced with one or more holes through which the material in the container can be lyophilized. The advantages of nasal inserts are-Pain free and self administered, Convenient and easy to use, safe. The nasal inserts can be evaluated by-water uptake study, invitro drug release study, bioadhesive potential of inserts, differencial scanning calorimetry. drug content determination, surface $p^{H.}$ Nasal inserts are small device and light in weight. Disadvantages of nasal inserts are.-all drugs cannot be given by nasal route, Frequent use of this routes leads to nasal mucosal damage, Drug cannot be withdrawal if once administered.

Keywords-Nasal inserts, lyophilisation, surface p^{H}, sustainable, mucosal damage, nasal route.

INTRODUCTION[1,2]

Nasal drug delivery system is a useful delivery system for the drugs that are in low doses. Nasal drug delivery system provides easy application of drug with self administration.Nasal inserts are small device and light in weight. Nasal inserts are prepared by lyophilisation of

polymers. Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via nasal route. The principle of dosage form to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation. They consist of a sponge like hydrophilic matrix, in which the drug is embedded. It allows easy dosing with high potential for systemic administration that helps prevent hepatic first pass metabolism. When the nasal inserts comes into contact with highly vascularized nasal mucosa absorbs water and swells. Nasal inserts are prepared by lyophilization.The process of lyophilization involves a container closed with an impermeable membrane pierced with one or more holes through which the material in the container can be lyophilized. These holes are sufficiently large to allow the escape of water vapor from the material kept in the container. Nasal inserts are not rigid in structure. So that they are convenient, easy to use, pain free and self administered formulation and patient friendly. The aim of this study was to investigate the ability of polymers to form inserts by lyophilisation and to characterize the inserts with respect to bioadhesion potential, wetting time, water uptake behavior, drug release, mechanical properties, and the physical state of polymer and drug in the insert.

Anatomy and physiology of nose[1]

The human nasal cavity has a total volume of about 16 to 19 ml and total surface area of about 180cm2. It is divided into two nasal cavities via the septum. Some of the regions are described as follows;

1.The respiratory region

The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

2. The vestibular region

It is located at the opening of nasal passages and is responsible for filtering out the airborneparticles. It is considered to be the least important of the three regions with regards to drug absorption.

3. The olfactory region

It is of about 10 cm2 in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. Human olfactory region comprises of thick connective tissue lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, bowans bundle and blood vessels whereas epithelium consists of three different cells i.e. basal cells, supporting cells and olfactory receptor cells etc. Neurons are interspersed between supporting

cells. The olfactory receptor cells are bipolar neurons with a single dendritic and extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium. The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10 to 15 minutes the pH of the mucosal secretions ranges from 5.5 to 6.5 in adults. Numerous enzymes for instance, Cytochrome P-450, Carboxylesterases and Glutathione S-transferase are present in nasal cavity.

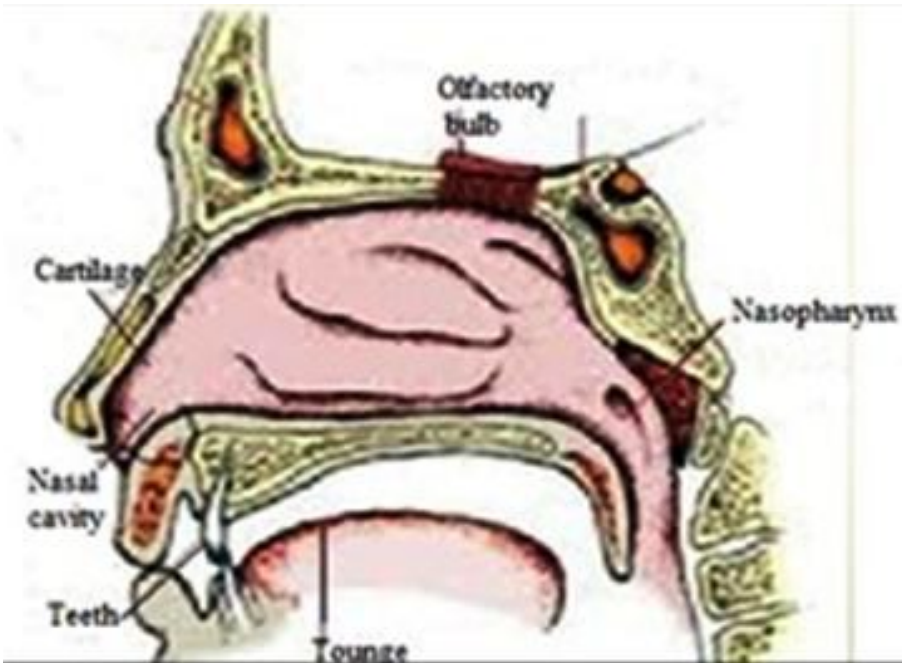

Fig. 1: Anatomy and Physiology of Nose

ADVANTAGES OF NASAL INSERTS[3]

1.Convenient and easy to use

2.Safe

3.Pain free and self administered

4.Precise single dose

5.Sustainable

DISADVANTAGES OF NASAL INSERTS[3]

1. All drugs cannot be given by nasal route.

2. Frequent use of this routes leads to nasal mucosal damage.

3. Drug cannot be withdrawal if once administered.

4. Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability.
5. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
6. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
7. Nasal cavity provides smaller absorption surface area when compared to GIT.
8. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
9. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
10. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

METHOD OF FORMULATION OF NASAL INSERTS[2]

The nasal inserts can be formulated by freeze drying or lyophilization method, and it can be formulated by following steps.

Step1- preparation of gel solutions

Drug and solvent (1% w/w) was first dissolved in about one third of the required amount of distilled water. The required weight of individual polymer were then added slowly with constant stirring to the obtained uniform gels and the resulted solution was made up to the desired volume and stirred to homogeneity, which was then stored at 4°C overnight to allow the removal of air bubbles.

Step2-preparation of *nasal inserts*

Aliquots of the prepared gel solution were filled into the polypropylene tubes (bullet shaped)with internal diameter of 1 cm at the tube mouth and 3.5 cm in length) as moulds. The tubes were lyophilized for 24 h in a freeze-dryer with the pre-set cycle stages; freezed for 4 h,at30°C,driedfor20h,withvacuum50mTorrandcondensertemperatureat50°C.Theinsertswereth enstored in a desiccator until use.

EVALUATION OF NASAL INSERTS[4,5]

The nasal inserts can be evaluated by following evaluation parameter

1.Water uptake study- A sponge (5 cm × 6.5 cm × 3 cm) was fully soaked in the hydration medium (phosphate buffer with pH of 6.0) and placed in a petri dish filled with the same buffer to a height of 1 cm in order to keep the sponge soaked during the experiment. Circular filter paper (d = 55 mm, Whatman No.41) was also soaked in the medium and positioned on the top of sponge. This experimental setup was equilibrated for 30 min. Accurately weighed inserts were then placed on the filter paper and the water uptake was determined as the increase in the weight of insert (weight of hydrated insert and wet filter paper minus weight of wet filter paper) over the initial dry insert weight.

2.Viscosity measurement of polymer solutions

The gel/sol samples were left undisturbed overnight and then equilibrated to 22°C ± 1°C for 1 h in a water bath before the measurement. The viscosity of the resultant polymer solutions were then determined with a Brookfield viscometer DV-II LV (Spindle NO.64).

3.In-vitro drug release

A locally fabricated diffusion cell mimicking the humidity properties of the nasal mucosa was used for the drug release studies. The lower end of a glass tube (inner diameter = 3.5 cm, surface area = 9.61 cm2) was closed with the cellulose acetate membrane (Millipore 0.22 µm pore size). This tube was placed vertically in a release medium container (filled with 50 mL phosphate buffer with pH of 6.0) and adjusted exactly to the height of the release medium surface so that the cellulose acetate membrane was wetted but not submersed. Briefly, the receptor compartment contained Phosphate buffer solution (PBS) with pH of 6 at 37°C and the donor compartment contained air saturated with moisture generated using the temperature and closed system nature of the experimental setup. The nasal insert was placed on the cellulose acetate membrane (Millipore 0.22 µm pore size) maintained just in contact with the liquid phase of the receptor compartment, which was constantly agitated with a Teflon coated magnetic bead. Samples of 1 mL were withdrawn at the regular time intervals from the receptor compartment and analyzed spectrophotometrically (using a UV double beam spectrophotometer) at 309 nm. Each sample taken from the receptor compartment was replaced immediately with 1 mL of fresh medium.

4. Bioadhesive potential of inserts

A hundred g of a hot agar solution (1%w/w, in phosphate buffer with pH of 6.0) was casted on a petri plate and left to gel at 4-8°C in a refrigerator for 3 h. The agar gel was then equilibrated for 1 h to the test conditions of 22°C and 79% relative humidity (saturated

ammonium chloride solution) in a chamber. The inserts which were placed on the top of the agar gel, moved downward due to the gravity after the glass plate was turned into a vertical position. The displacement in mm was measured as a function of time (n = 3). The adhesive potential was inversely related to the displacement of the insert.

5. Surface pH

The inserts were left to swell for 2 h on the surface of agar plate. Agar solution was prepared by dissolving 2%w/v agar in SNF by heating under stirring, then poured into a Petri dish for gel formation at room temperature. Surface pH, was measured by means of a pH paper placed on the surface of the swollen inserts. The measurements were performed in duplicate.

6. Differential scanning calorimetery

DSC analyses were performed for drug, polymers, physical mixtures (keeping the same ratio between drug and polymer as present in the inserts), and the tested formulations. Samples of 3 mg each were placed in aluminum pan and heated at the rate of 10°C/min to 400°C. The instrument was calibrated with Indium and dry N2 was used as carrier gas with aflow rate of 25 ml/min.

7. Drug content

Drug content was determined by dissolving the inserts in simulated nasal fluid (SNF of pH 6.5 was composed of7.45 mg/ml NaCl, 1.29 mg/ml KCl and 0.32 mg/mlCaCl2.2H2O) under continuous shaking for 24 h in a thermostated shaking water bath maintained at 37°C. The resulting solution was filtered through a millipore filter 0.45 µm and the amount of drug was then determined spectrophotometricaly at λ max 276 nm.

8.Hydrophilicity of inserts

The hydrophilicity of the in situ gelling inserts was tested by measuring their moisture absorption capacity. Preweighed inserts were placed above a saturated solution of ammonium chloride at room temperature (relative air humidity of 79%).The inserts were weighed after 48 h and moisture content calculated from the weight increase.

CONCLUSION

Nasal inserts are a new solid dosage form for the application of drugs via the nasal mucosa. The nasal inserts were displaying porous structure and good bioadhesive strength to overcome the nasal mucociliary clearance. Nasal inserts were smooth in appearance, uniform

in regard to thickness, weight, and drug content, as well as non-irritating to nasal mucosa. The developed nasal inserts exhibited satisfactory mucoadhesivecharacteristics, water uptake, and extended drug release.

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