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CONTEMPORARY INVESTIGATION ON NASAL SPRAY DRUG DELIVERY SYSTEM

Md. Mehdi Hasan*[1], Md.Mizanur Rahman[2], A K lutful Kabir[3], Ajoy Kumar Ghosh[2], Mahbub Hasan[2], Md. Salimul Karim[1], Harun Ar Rashid[1]

[1]Department of Pharmacy, Faculty of Health science, Northern University Bangladesh, Dhaka -1205, Bangladesh.
[2]Department of Pharmacy, Stamford University Bangladesh, Dhaka-1217, Bangladesh.
[3]Department of Pharmaceutical Technology, Faculty of Pharmacy, University Of Dhaka, Dhaka-1000, Bangladesh.

ABSTRACT

Nasal route has been a preferred choice of administrating certain types of drugs. It has been explored as an alternative route for administration of vaccines and biomolecules such as proteins, peptides and non-peptide drugs, hence it has attracted the interest of scientific community. Nasal route is beneficial for the drugs which are unstable on oral administration because they are significantly degraded in GIT or metabolized by first pass effect in liver. Nasal route is alternative to parenteral therapy and also useful for long term therapy. Nasal mucosa is highly vascularized and most permeable giving rapid absorption and onset of action. Nasal route is noninvasive, widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. Nasal route gives good absorption of small molecules, then that of large molecules can be increased by absorption promoters. Thus, Intranasal therapy holds a great promise of research to understand the potentiality and limitation of it and possible use of this route for delivering different drugs. The aim of this review is to discuss the prospect of nasal spray as an innovative drug delivery system for local or systemic drug administration. It is expected that this review will help to understand and further to develop suitable intra- nasal formulations to achieve specific therapeutic objectives.

Key Words:- Nasal route, pharmacokinetic parameters, nasal absorption enhancers, Factors , Excipients ,Formulation, Evaluation, Models.

INTRODUCTION

The focus of this review is to evaluate possibility of nasal spray as an innovative drug delivery system for the future. Nasal drug delivery has received a significant attention in recent years as a convenient and reliable route; not only for local but also for the systemic administration of drugs. The nasal cavity is one of the easily accessible route, which is generally well tolerated. The abundance of blood vessels in the nasal mucosa contributes to drug absorption, which is almost equal to intravenous injections in some instances.

Corresponding Author

Md. Mehdi Hasan
Email:- mehdinub@yahoo.com

The nasal cavity offers a number of distinctive advantages for systemic delivery such as (Duquesnoy C *et al.*, 1998; Eller N *et al.*, 1998; Slot WB *et al.*, 1997):

I- A large surface area for drug absorption.
II- Convenience and good patient compliance.
III- Rapid attainment of therapeutic drug levels in the blood.
IV- High drug permeability, especially for lipophilic and low molecular weight drugs.
V- Avoidance of harsh environmental and gastrointestinal conditions.
VI- Bypassing of hepatic first-pass metabolism.
VII- Potential direct drug delivery to the brain along the olfactory nerves.

VIII- Direct contact site for vaccines with lymphatic tissues.

The nasal cavity is an easily accessible route which is generally well tolerated (Knoester PD *et al.,* 2002). The abundance of blood vessels in the nasal mucosa contributes to drug absorption, which is almost equal to intravenous injections in some instances. The nasal route of drug delivery can be used for both local and systemic drug delivery (Casettari L *et al.,* 2014).

For instance, localized nasal drug delivery is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions. A diverse range of drugs including corticosteroids, anti-histamines, anti-cholinergic and vasoconstrictors can be administered locally. At this point a need of innovative drug delivery system emerges.

In recent years, achieving a systemic drug action using the nose as the entry portal into the body has received more attention. A wide range of pharmaceutical dosage forms including solutions, gels, suspensions, emulsions, liposomes and micro particles can be used to achieve systemic drug actions. These dosage forms are mostly designed to exploit the advantage of a rapid onset of action when administered via nasal route. For example, morphine and ketamine can be delivered intra-nasally to achieve rapid analgesic effects. Nasal spray can be the most efficient drug delivery system among all. Moreover, vaccines can also be administered using the nose as a potential route, such as those for influenza (Herman N *et al.,* 2015).

Anatomy and physiology of nose

The nose is the primary entrance to the respiratory tract, allowing air to enter into the body for respiration. The nasal cavity is 120-140 mm deep, runs from the nasal vestibule to the nasopharynx and is divided into two by a cartilaginous wall called nasal septum. The nose has a surface area of around 160 cm2 and a total volume of ~16-19 ml (Aulton ME *et al.,* 2013). The nose serves as the mean of bringing warm humidified air into the lungs. It is the primary organ for filtering out particles in the inspired air, and it also serves to provide a first-line immunologic defense as it brings the inspired air into contact with the mucous-coated membrane. The nose has three main regions: vestibular, turbinate and olfactory regions). The vestibular region is the anterior part of the nose and it is the narrowest part of the nasal cavity. The vibrissae cover most of this area which renders it capable of filtering out particles with an aerodynamic particle size larger than 10 µm that may be inhaled with air. In the vestibular region, the surface lining changes from skin, at the first part of the passage, to a stratified squamous epithelium . The turbinate region is a large vascular part of the nose and can be divided into superior, middle and inferior regions (Figure 1). It is lined with a pseudostratified columnar epithelium. It is composed of mucus secreting, ciliated, non-ciliated and basal cells (Figure 2). The ciliated and non-ciliated cells are covered with non-motile microvilli, which are responsible for increasing the surface area, thus, this is the region where the drug absorption is optimal. Ciliated cells are covered with approximately 100 motile cilia which are responsible for mucus transport so mucociliary clearance prevails. Once drug (as particles or in solution) find their way to the muco-ciliary area, they will be cleared from nasal cavity and then have limited access to the absorption site (SINGH L *et al.,* 2015; Prajapati ST *et al.,* 2015; Mundlia J *et al.,* 2015).

The olfactory region is an area comprising about 8% of the total surface area of the nasal epithelium and is made of a non-ciliated, pseudostratified columnar epithelium. It is important for transporting drugs to the brain and cerebrospinal fluid (CSF). There is a mucus layer of 5 µm in thickness covering the epitheliumcells which traps unwanted particles. The mucous secretion consists of mucin, water, salts, proteins such as albumin, immunoglobulin, lysozyme, and lactoferrin, and lipids. The pH of the nasal secretions ranges from 5.0 to 6.5 (Aulton ME *et al.,* 2013)

Biopharmaceutical Consideration

The easy accessibility and higher surface area makes the nose a potentially viable drug delivery organ. Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives. Therefore, before product development, important biopharmaceutical aspects need to be considered-firstly, whether it is intended for:

- Localized delivery
- Systemic delivery
- Single or repetitive administration

The feasibility of being able to achieve the therapeutic objectives will determine whether the development of a nasal delivery system is appropriate (Eller N *et al.,* 1998; Knoester PD *et al.,* 2002; Kublik H *et al.,* 1998). Comprehending the factors that can affect drug deposition, retention and absorption are essential to enable intelligent design of nasal formulations. Numerous physiological, anatomical, and pathological conditions must also be considered. Different types of nasal formulations available in the UK at the time of publication are enlisted in Table 1 (Electronic Medicines Compendium., 2015). However, a major challenge in designing nasal drug delivery formulations is to introduce the drug into a suitable vehicle system that provides drug stability and ideal dispensing characteristics. Elements

such as selection of specific pharmaceutical excipients, delivery devices and processing methods need careful consideration. A schematic illustration of all the key parameters of a successful nasal formulation is shown in Figure 3.

Advantages of Nasal Drug Delivery System: (Chein WY *et al.*, 1989; Gopinath PG *et al.*, 1978)

- Drug degradation that is observed in the gastrointestinal tract is absent.
- Hepatic first – pass metabolism is absent.
- Rapid drug absorption and quick onset of action can be achieved.
- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- The nasal bioavailability for smaller drug molecules is good.
- Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
- Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
- Large nasal mucosal surface area for dose absorption
- Rapid drug absorption via highly-vascularizedmucosa
- Rapid onset of action
- Ease of administration, non-invasive
- Avoidance of the gastrointestinal tract and first- pass metabolism
- Improved bioavailability
- Lower dose/reduced side effects
- Minimal aftertaste
- Improved convenience and compliance
- Self-administration
- New patent coverage for drug formulations about to expire

Although traditional nasal drug delivery methods offer significant advantages over injection or oral administration, they face challenges that limit efficacy and applications.

- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved.
- A self-administration is possible.
- Direct transport into systemic circulation and CNS is Possible.
- Offers lower risk of overdose
- Does not have any complex formulation requirement

CNS is Possible.

• Offers lower risk of overdose
• Does not have any complex formulation requirement

Limitations of nasal drug delivery system (Chajed S *et al.*, 2011):

- Delivery volume in nasal cavityis restricted to 25–200 μL.
- High molecular weight compounds cannot be delivered through this route (mass cut off ~1kDa).
- Adversely affected by pathological conditions.
- Large interspecies variability is observed in this route.
- Normal defense mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
- Irritation of nasal mucosa by drugs like Budesonide, Azilactine.
- Limited understanding of mechanisms and less developed models at this stage.

Systemic toxicity occurring due to absorption enhancers is yet not established.

- Smaller absorption surface compared with GIT.
- Possibility of nasal irritation hence inconvenient compared with oral route.
- Enzymatic barrier to permeability of drug.

Profile of an 'ideal' drug candidate for nasal delivery: (Behl CR. *et al.*, 1998)

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 administration per nostril.
- 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.

Mechanism of Drug Absorption:

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles easily pass through the mucus layer; however, large particles may find some difficulties. Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer as a result of environmental or physiological changes (Shinichiro H *et al.*, 1981). Subsequent to a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa. These include transcellular or simple diffusion across the membrane, paracellular transport via

movement between cell and transcytosis by vesicle carriers. Several mechanisms have been proposed, but para cellular and transcellular routes dominate. (Duvvuri S *et al.,* 2003).

Paracellular transport is slow and passive. There is an inverse correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was reported for drugs with a molecular weight greater than 1000 Daltons (Huang C *et al.,* 1985).

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. (Duvvuri S *et al.,* 2003). Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity.

Factors affecting Nasal Drug Absorption (Chein YW *et al.,* 1989; Proctor DF *et al.,* 1977; Gopinath PG *et al.,* 1978):

Many factors affect the systemic bioavailability of nasally administered drugs. The factors can be attributed to the physicochemical properties of the drugs and the characteristics of other ingredient of delivery system has been discussed in relevant section i.e. dosage forms and type and characteristics of selected nasal drugs delivery system. These play significant role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are as follows.

1. Physicochemical properties of drug
- Chemical form of drug.
- Polymorphism
- Molecular weight
- Particle size
- Solubility & dissolution rate.

2. Nasal effect
- Membrane permeability
- Environmental pH
- Mucociliary clearance
- Cold, rhinitis

3. Delivery effect
- Formulation (Concentration, pH, osmolarity)
- Delivery effects
- Drugs distribution and deposition.
- Formulation effect on mucociliary clearance.

Toxic effect on ciliary function and epithelial membranes Pharmacokinetics of Nasal Absorption:

Factors reported to affect the pharmacokinetic parameters following intranasal administration are: -

1. Physiology-related factors, such as a) speed of mucus flow
- presence of infection
- atmospheric conditions

2. Dosage form related factors such as
- concentration of active drug
- physicochemical properties of active drug
- density/ viscosity properties of formulations
- pH/toxicity of dosage form
- pharmaceutical excipients used

3. Administration related factors such as
- size of droplet
- size of deposition
- mechanical loss into the oesophagus
- mechanical loss into other regions in the nose
- mechanical loss anteriorly from nose

Factors Influencing Nasal Drug Absorption

A) Factors Related to Drug

a) Lipophilicity

On increasing lipophilicity, the permeation of the com- pound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic char- acter, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. In one study it was found that lipophilic compounds alprenolol and propranolol were well absorbed from the nasal mucosa, in contrast to the hydrophilic drug metoprolol. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. A number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinyl- oestradiol (Hussein NR., 2014) have been shown to be completely or almost completely absorbed nasally in animal models. A correlation between lipophilicity and nasal drug absorption has been demonstrated using several compounds (Jadhav KR *et al.,* 2007).

b) Chemical Form

The chemical form of a drug can be important in deter- mining absorption. For example, conversion of the drug into a salt or ester form can alter its absorption, studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

c) Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the poly- morphic stability and purity of drugs for nasal powders and/or suspensions.

d) Molecular Weight

In the case of lipophilic compounds, a direct relationship exists between the MW and drug permeation whereas water- soluble compounds depict an inverse relationship. Based on the reports by (Yamamoto A *et al.,* 1993) it can be concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug, which will mostly permeate through aqueous channels of the membrane. By contrast, the rate of permeation is highly sensitive to molecular size for com- pounds with MW = >300 Da.

e) Partition Coefficient and pKa

As per the pH partition theory, unionized species are ab- sorbed better compared with ionized species and the same holds true in the case of nasal absorption (Jiang XG *et al.,* 1997) conducted a study to determine the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The results showed that a quantitative relationship existed between the partition coefficient and the nasal absorption constant (Jiang XG *et al.,* 1997). The nasal absorption of weak electrolytes such as salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile, substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid (Hirai S *et al.,* 1981). Similarly, when the absorption of benzoic acid was studied at pH 7.19 (99.9% of the drug existed in ionized form) it was found that 10% of drug was absorbed indicating that the ionized species also permeates through nasal mucosa (Hirai S *et al.,* 1981). Based on all of these observations, the authors accounted partition coefficients as a major factor governing nasal absorption and supported that other trans- port pathways for hydrophilic drugs might be of importance.

f) Solubility & Dissolution Rate:

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared, no absorption takes place.

B) Factors Related to Formulation

1) Physicochemical Properties of the Formulation

a) pH and Mucosal Irritancy:

The pH of the formulation, as well as that of nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 (Arora P *et al.,* 2002). In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.

b) Osmolarity

Ohwaki et al. studied the effect of osmolarity on the absorption of secretin in rats and found that absorption reached a maximum at a sodium chloride concentration of 0.462 M, because shrinkage of the nasal epithelial mucosa was observed at this salt concentration (Ohwaki T *et al.,* 1987).This results in in- creased permeation of the compound resulting from structural changes and was further confirmed when sorbitol was used as an osmoregulatory agent. The authors found that permeation of secretin subsequently decreased (Ohwaki T *et al.,* 1989) and, therefore, isotonic solutions are usually preferred for administration.

c) Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

Drug Absorption Enhancement

Many drugs having high water solubility have poor permeability across nasal epithelia and may present insufficient bioavailability. To enhance their permeation and bioavailability permeation enhancers are frequently employed. In principle, permeation enhancers induce reversible modifications on the structure of the epithelial barrier. Although the exact mechanism of drug absorption/permeation enhancement is not well known, it is widely accepted that these materials modify the permeability of epithelial cell layer by modifying the phospholipid bilayer (Davis SS *et al.,* 2003).

Enhancement of nasal absorption:

Several methods have been used to facilitate the nasal absorption of drugs:

- Structure modification: The chemical modification of a drug molecule has been commonly used to modify the

physicochemical properties of drug and could also be utilized to improve the nasal absorption of drug.

- Salt or ester formation: Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents (Rashid HA *et al.,* 20 16). The drug could be converted to form a salt or an ester for better transnasal permeability. For example, nasal absorption could be improved significantly by forming a salt with increased solubility in nasal fluid or an ester with enhanced uptake by nasal epithelium.

- Formulation design: Proper selection of pharmaceutical excipients in the development of nasal formulation could enhance the formulation stability and/or the nasal bioavailability of drug.
- Surfactants: Incorporation of surfactant into nasal dosage forms could modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug. Survey of the literature indicates that surfactants have been extensively evaluated for the possibility of enhancing the nasal absorption of drugs, including peptide and protein drugs. A number of surfactants have been reported to enhance the absorption of drugs through the nasal mucosa to a level sufficient to achieve their systemic effects mild surfactants at low concentrations may only alter membrane structure and permeability whereas certain surfactants at high concentrations may disrupt and even dissolve biological membranes**.**

Strategies to improve nasal absorption (Ibrahim A *et al.,* 2010):

There are many barriers present in nasal cavity which interfere with absorption of various drugs. There are some methods which have been successfully used for the improvement of nasal drug absorption.

- Nasal enzymes inhibitors: Various kinds of enzyme inhibitors are utilized to minimize metabolism of drug in nasal cavity which minimize activity of enzymes present in nasal cavity includes protease and peptidase, used as inhibitors for the formulation of peptide and protein molecule.
- Structural modification: Modification of drug structure can be done without changing the pharmacological activity for improvement of nasal absorption.
- Permeation enhancer: Permeation enhancers are of different categories and have been investigated to improve the nasal absorption like surfactants, fatty acids, phospholipids, cyclodextrins, bile salts, etc.
- Particulate drug delivery: Carriers are used for the encapsulation of drug which prevent exposure of a drug to nasal environment and improve the retention capacity in nasal cavity. Some examples of carriers may include microspheres, liposomes, nanoparticles and niosomes.
- Prodrug approach: Inactive chemical moiety is called prodrug which becomes active at the target site. Prodrugs are mainly used to improve taste, odor, solubility and stability.
- Bioadhesive polymer: To improve the nasal residence and absorption of the drug bioadhesive polymers are used. They improve the retention time of the drug inside the nasal cavity is increased by making an adhesive force between formulation and nasal mucosa, which leads to minimization of mucociliary clearance of formulation.
- In situ gel: These are the formulations which get converted into gel upon instillation into nasal cavity by the influence of stimuli includes temperature, pH and ionic concentration.

Consistency of the gel is thick which makes the formulation difficult to drain by the influence of ciliate movement.

Excipients used in Nasal Formulation: (Sachin C *et al.,* 2011)

Commonly used excipients that are frequently added to nasal preparations are can be listed as below:

1. Bioadhesive polymers: It can be defined as a compound that is capable of interacting with biological material through interfacial firces and being retained on such material for prolonged periods of time. If the biological material is a mucus membrane, the bioadhesive material is termed as a mucoadhesive. On molecular level, mucoadhesion can be explained on the basis of attractive molecular interactions involving forces such as Van Der Waals, Electrostatic interactions, Hydrogen Bonding, and Hydrophobic interactions.

2.Hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

3. Penetration enhancer: Chemical penetration enhancers are widely used in the nasal drug delivery. Classification of chemical penetration enhancer includes, following

- Solvents
- Alkyl methyl sulphoxides
- Pyrrolidones
- 1- Dodecyl azacycloheptan-2-one
- Surfactants

Mechanism of penetration enhancers is as follows,

- Increasing cell membrane permeability
- Opening tight junction and formation of intracellular aqueous channels

- Increasing lipophilicity of the charged drug by forming ion pair
- Inhibiting proteolytic activity.

4. Buffers: Nasal formulations are generally administered in small volumes ranging from 25 to 200 µL with 100 µL being the most common dose volume. Hence, nasal secretions may alter the pH of the administrated dose. This 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.

5. 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 polyglycolyzed C8- C10 glyceride) can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP–ß-Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In such cases, their impact on nasal irritancy should be considered.

6. Preservatives: Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Mercury-containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in nasal systems.

7. Antioxidants: A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxytoluene and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program.

8. Humectants: Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Certain preservatives/ antioxidants among other excipients 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 are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

9. Surfactants: Incorporation of surfactant into nasal dosage forms could modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug.

Research and development in nasal drug delivery:

Most of the over the counter nasal preparation are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area, population and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

Liquid Nasal Formulation

Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair mucociliary function (Zia H *et al.,* 1993) and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations (Hardy JC *et al.,* 1985). The several types dosage forms available in liquid form are de- scribed below.

1. Instillation and rhinyle catheter: Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulation in the tube and kept tube one end was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth (Harris AS *et al.,* 1986). Dosing of catheters is determined by the filling prior to admin-istration and accuracy of the system and this is mainly used for experimental studies only.

2. Compressed air nebulizers: Nebulizer is a device used to administer medication in the form of a mist inhaled into the lungs. The compressed air is filling into the device, so it is called compressed air nebulizers. The common technical principal for all nebulizers, is to either use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the

device (Knoch M *et al.*, 2002). Nebulizers accept their medicine in the form of a liquid solution, which is often loaded into the device upon use. Corticosteroids and Bronchodilators such as salbutamol (Albuterol USAN) are often used, and sometimes in combination with ipratropium (Hickey AJ, 2004). The reason these pharmaceuticals are inhaled instead of ingested is in order to target their effect to the respiratory tract, which speeds onset of action of the medicine and reduces side effects, compared to other alternative intake routes This device is not suitable for the systemic delivery of drug by patient himself.

3. Squeezed bottle: Squeezed nasal bottles are mainly used as delivery de- vice for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly de- pendent on the mode of administration. The differences between vigorously and smoothly pressed application influence the dose as well as the droplet size of the formulation. Thus the dose is hard to control. Therefore squeezed bottles with vasoconstrictors are not recommended to be used by children (Mygind N *et al.*, 1978).

4. Metered-dose pump sprays: Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand- operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants Metered- dose pump sprays include the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

Powder Dosage forms:

Dry powders are less frequently used in nasal drug de- livery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a pro- longed contact with the nasal mucosa. The types of powder dosage forms are described below:

1. Insufflators: Insufflators are the devices to deliver the drug sub- stance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules (Hughes BL *et al.*, 1993).

2. Dry powder inhaler: Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales (Alagusunda-ram M *et al.*, 2010).These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough.

3. Pressurized MDIs: A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as (cromoglicate or nedocromil) (Hickey AJ, 2004).The advantages of MDIs are their portability and small size, availability over a wide do- sage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use (Newhouse MT, 1991).

To use the inhaler the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate the aerosol cloud and is also the medium in which the active component must be suspended or dissolved. Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled .

Nasal Drops and Sprays

Nasal drops are one of the simplest and most convenient delivery systems among all formulations. The main limitation is the lack of precision in the administered dosage and the risk of contamination during use (Washington N *et al.,* 2001). Nasal drops can be delivered with a pipette or by a squeeze bottle. These formulations are usually recommended for the treatment of local conditions, but challenges include microbial growth, mucociliary dysfunction and non-specific loss from the nose or down back the throat (Hussein NR., 2014). Nasal spray systems consist of a chamber, a piston and an operating actuator. Nasal sprays are comparatively more accurate than drops and generate precise doses (25 -200 µl) per spray. Several studies have shown that nasal sprays can produce consistent doses of reproducible plume geometry. Formulation properties such as thixotropy, surface tension and viscosity can potentially influence droplet size and dose accuracy. Other factors such as the applied force, orifice size and design of the pump can also affect the droplet size which can impact the nasal deposition of sprays.

Nasal Gels

A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. The semi-solid characteristics of gels can be defined in terms of two dynamic mechanical properties: elastic modulus G' and viscous modulus G" (Chaturvedi M *et al.,* 2011). The rheological properties of gels depend on the polymer type, concentration and physical state of the gel. They can range from viscous solutions (e.g. hypromellose, methylcellulose, xanthan gum and chitosan) to very hard, brittle gels (e.g. gellan gum, pectin and alginate). Bioadhesive polymers have shown good potential for nasal formulations and can control the rate and extent of drug release resulting in decreased frequency of drug administration and improved patient compliance. In situ gel-forming polymeric formulations are drug delivery systems that are in solution form before administration in the body, but once administered, undergo in situ gelation, to form a gel. The formation of gels depends on factors like temperature modulation, pH change and presence of ions from which the drug gets released in a sustained and controlled manner. Fluid gels are potential alternative to in situ gels. These fluid gels are essentially structured liquids containing a gel forming polymer. They are prepared by applying a shear force to the polymer solution during the gelation process. This results in gelled particles suspended in an un-gelled polymer solution.

Nasal Suspensions and Emulsions

Suspensions are rarely used or investigated as nasal drug delivery systems. Analogous to marketed aqueous ophthalmic suspensions of the soft corticosteroid, loteprednoletabonate (e.g. Alrex®, Bausch and Lomb Pharmaceuticals), a nasal aqueous suspension of same drug containing microcrystalline sodium carboxymethylcellulose for stabilisation and retention in the nasal cavity was patented by Senju Pharmaceuticals Inc., Osaka, Japan and was intended for the local treatment of allergic rhinitis. Moreover, a nasal suspension for the delivery of insulin was investigated by (Ando et al. 1998) . Here, soybean-derived steryl glycoside and sterol mixtures (1%) were used as absorption enhancers and pharmacological bioavailabilities of 6.7% and 11.3% were achieved. However, for oral drug delivery it has been reported by several authors that emulsions were superior to suspensions in enhancing the bioavailability of poorly soluble drugs and the trend is similar with nasal formulations. Absorption enhancement has been attributed to solubilisation of the drug and the lipophilic absorption enhancers in the composition. Similarly, other low solubility compounds have been formulated in emulsions to increase the drug solubility, e.g. diazepam and testosterone.

Used a nano-suspension to target the brain through the nose. Formulation as a nanosuspension facilitated bypassing of the blood-brain barrier (BBB) for particles ranging between 1-500 nm. Moreover, recently researchers have also reported nasal administration ofnano-emulsions for brain targeting (Shinde R L *et al.,* 2015).

Nasal Micellar and Liposomal Formulations

Different types of adjuvants can affect the drug absorption and are often required to reach therapeutic plasma levels when hydrophilic macromolecular drugs such as peptides and proteins are delivered by the nasal route **(**Ponti DE *et al.,* 1991). Among other surfactants

used, bile salts are often used as enhancers, e.g. as micellar solutions. Tengamnuay and Mitra described the use of micelles of sodium glycocholate and micelles thereof mixed with fatty acid (linoleic acid) as absorption enhancers for the model dipeptide (D-Arg2)-kyotorphin and for insulin in rats. The effect of mixed micelles was synergistic and superior compared to the single enhancer. Mixed micelles of sodium glycocholate and linoleic acid reduced the blood glucose level after nasal insulin administration to 47% of the glucose level after an identical nasal dosage of unenhanced insulin. Pure sodium glycocholate resulted in a reduction to 55%. Liposomes have also been investigated as nasal drug delivery systems and absorption enhancing effects were found for insulin and calcitonin in vitro permeability studies. The enhancement effect was attributed to increased nasal retention of peptides. The best carrier effect for calcitonin was demonstrated with cationic liposomes as they were found to adhere intimately to the nasal mucosal surface, facilitating the penetration of the encapsulated drug. Similar observations were made for desmopressin-loaded cationic liposomes which resulted in enhanced antidiuretic effects in rats compared with anionic liposomes and solutions. Proliposomes are dry, free-flowing granules composed of sorbitol as carrier and lipids that form a liposomal dispersion on contact with water. Their advantages are the combination of a fast onset (surface drug) and prolonged drug action (encapsulated drug) as demonstrated for propranolol and nicotine (Jung BH *et al.,* 2002).

Nasal Micro particles

Using microparticles as another way of prolonging the residence time in the nasal cavity was introduced in 1987 (Illum *et al.,* 1987). It was proposed that microspheres of albumin, starch, and DEAE-dextran (diethyl aminoethyl-dextran) absorbed water and formed a gel-like layer which was cleared slowly from the nasal cavity. Three hours after administration, 50% of the delivered amount of albumin and starch microspheres and 60% of the dextran microspheres were still present at the site of deposition. It was suggested that an increased contact time could increase the absorption efficiency of drugs.

Moreover, recently solid lipid nanoparticles have also shown promising results and were shown to increase the brain targeting of rosmarinic acid following nasal delivery for potential management of Huntington's disease (Bhatt R *et al.,* 2015).

Application of Nasal Drug Delivery System: (Blumgart, H.L *et al.,* 1924; Schipper *et al.,* 1991)

1. Through nasal route: Diabetes mellitus is a chronic disease that usually requires multiple insulin injections to achieve adequate glycaemic control. This represents a major cause of reduced compliance to treatment. Consequently, other routes for insulin administration have been explored. During recent years, much progress in the development of inhaled insulin has been made. Inhaled insulin has favorable properties, such as rapid onset of action, improved bioavailability and good tolerability, thereby providing satisfaction and ease of administration.

However, long-term safety of inhaled insulin needs to be assessed, and the cost would be higher than inject able insulin. Nasal, oral and transdermal insulin are undergoing early phases of pharmacological development. The purpose of this review is to describe the latest developments in the area of non-invasive routes for insulin delivery. A large number of patients with diabetes worldwide require daily dose of insulin. Insulin therapy, using the vial and syringe method is complicated and time consuming. To find an alternative way to deliver insulin will elude the researchers to replace inject able insulin by more comfortable, noninvasive and less strenuous delivery method, which can provide in pharmacokinetically consistent manner. The present article reviews the various alternatives for insulin delivery.

2. Insulin gel administered through nasal route: The objective of the present study was to formulate insulin gel for intranasal administration and to evaluate with respect in-vitro release study and hypoglycaemic activity in animal model and healthy human volunteers. The insulin gel was formulated using the combination of carbopol and hydroxypropylmethylcellulose as gelling agent. The in-vivo efficacy of insulin gel administered intranasally was assessed by measuring the blood glucose levels at specified time intervals in rats and humans. The use of bioadhesive nasal gel containing insulin not only promoted the prolonged contact between the drug absorptive sites in the nasal cavity but also facilitated direct absorption of medicament through nasal mucosa. Absorption of the drug through the nasal mucosa high in the first 0.5 to 1.5 hrs of the study with a sharp decline in blood sugar and rise in insulin values corresponding to that decline in blood sugar. This study further demonstrates that administration of insulin intranasally in gel form is a pleasant and painless alternative to inject able insulin.

3. Cancer pain management through nasal route: Cancer pain management necessitates the use of opioids when pain is moderate or severe. Opioids need to be versatile and effective. Newer formulations may improve patient compliance and may be more conductive to the

management of transient flares of pain; they also may be tailored to treat certain special populations and may be particularly effective in certain clinical situations.

For e.g. Newer opioids have been developed for transdermal, nasal and nebulized administration, providing a needle-less means of controlling pain in those unable to take oral medications. However, newer opioid formulations are not a substitute for good pain management strategies and will not control pain unless provided in adequate doses and schedules. Newer opioid formulations have niche roles in clinical practice, and pain palliative specialists need to be aware of new developments in opioids and delivery systems.

4. Antibiotics andmucolytics are delivered to the nasal cavity: Decongestants, antibiotics and mucolytics are delivered to the nasal cavity, their intended site of action. Due to its accessibility, relatively large surface area 160 cm2 and rich vascular supply of the nasal mucosa, the nasal route of administration is attractive for many drugs for systemic absorption, including proteins and peptides. For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration (Hasan MM *et al.,* 2016). Due to rich blood supply, drugs absorbed via the nasal route have a rapid onset of action, which can be exploited for therapeutic gain. The nasal delivery is also recommended in order to avoid degradation in the gastro intestinal fluid, metabolization in the gastrointestinal tract or biotransformation by the first pass effect. The ease of administration via the nasal route may also lead to increased patient compliance. Nasal devices such as metered doses nasal sprays have been developed that are simple for patient to use. Patient with swallowing difficulty and\or children can be treated with less difficulty with nasal drug delivery system.

Nasal drug delivery can:

- Promote rapid onset of action.
- Avoid gastrointestinal tract or first pass metabolism
- Enhance patient compliance

5. Microsphere as nasal drug delivery system:

All types of microspheres that have been used as nasal drug delivery system are water insoluble but absorb water into the sphere matrix, resulting in swelling of the spheres and the formulation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microsphere also exerts a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. Starch and dextran microspheres have been administered repeatedly and can be classified as safe dosage forms.

6. Utility of insoluble powder formulation for nasal systemic drug delivery: Insoluble powder formulations improve nasal bioavailability predominantly by retarding drug elimination from the absorption site and appear to be effective for nasal systemic drug delivery.

7. Nasal drug and vaccine delivery technology: OptiNose is a drug company with breakthrough technology to transform the static nasal drug delivery market.

8. Potential application for the OptiNose nasal drug.

The bioadhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state).

Examples of some bioadhesive polymers employed for nasal drug delivery systems

a) Carbopol(car boxy polyethylene)
b) Sodium carboxy methyl cellulose (SCMC)
c) Hydroxypropyl cellulose(HPC)
d) Hydroxypropylmethyl cellulose(HPMC)
e) Hydroxyl ethyl cellulose(HEC)
f) Methyl cellulose(MC) g) Sodium hyaluronate h) Guar gum
i) Sodium alginate j) Polycarbophil
k) Starch
l) Dextran m) Chitosan

9. Delivery of diagnostic drugs:

Nasal drug delivery system also play very important role in the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route better for systemic release of medicament into blood circulation, so can get quick results with less toxicity. Phenolsulfonphthalein is a diagnostic agent used to diagnose the kidney function of the patients. Pancreatic disorders of the diabetic patients were diagnosed by using the ‘Secretin’. And the secretory function of gastric acid was determined by Pentagastrin, diagnostic agent.

Evaluation of Nasal Drugs: (Chien YW *et al.,* 1987; Blumgart HL., 1924; Stovall R *et al.,* 1976)

(A) In vitro nasal permeation studies: Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. The two important methodologies to study the diffusion profile of the drug are discussed here,

In vitro diffusion studies (Stovall R *et al.,* 1976; Beht *et al.,* 1998):

The nasal diffusion cell is fabricated in glass. The water- jacketed recipient chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The 10 cm long donor chamber, and a donor tube chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 openings, each for sampling, thermometer, and a donor tube chamber the 10 cm long donor chamber tube has internal diameter of 1.13 cm. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops at genatamycin injection.

After the complete removal of blood from muscosal surface, is attached to donor chamber tube. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber. At predetermined intervals, samples (0.5 ml) from recipient chamber are with draw and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. Throughout the experiment the temperature is maintained at 37oC.

(B) In Vivo Nasal Absorption studies:

Animal models for nasal absorption studies: The animal models employed for nasal absorption studies can be of two types, viz., whole animal or in vivo model and an isolated organ perfusion or ex vivo model. Public or animal health should be the first priority of a recall operation rather than the root cause(s) and full extent of the quality defect (Hasan MM *et al.,* 2016). These models are discussed in detail below:

Rat Model: The surgical preparation of rat for in vivo nasal absorption study is carried out as follows: The rat is anaesthetized by intraperitoneal injection of sodium pentobarbital. An incision is made in the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the esophagus towards the posterior region of the nasal cavity. The passage of the nasopalatine tract is sealed so that the drug solution is not drained from the nasal cavity through the mouth. The drug solution is delivered to the nasal cavity through the nostril or through the cannulation tubing. The blood samples are collected from the femoral vein. As all the probable outlets of drainage are blocked, the drug can be only absorbed and transported into the systemic circulation by penetration and/or diffusion through nasal mucosa.

Rabbit Model (British national formulary, 2000)**:** The rabbit offers several advantages as an animal model for nasal absorption studies:

1. It is relatively cheap, readily available and easily maintained in laboratory settings
2. It permits pharmacokinetic studies as with large animals (like monkey)
3. The blood volume is large enough (approx. 300ml)
4. To allow frequent blood sampling (l-2ml)

Thus it permits full characterization of the absorption and determination of the pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, the rabbit is anaesthetized by an intramuscular injection of a combination of ketamine and xylazine. The rabbit's head is held in an upright position and the drug solution is administered by nasal spray into each nostril. During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

Dog Model (Schipper *et al*., 1991)**:** The dog is either anaesthetized or retained hi the conscious condition depending on the drug characteristics and the purpose of experiment. The dog is anaesthetized by intravenous injection of sodium thiopental and the anesthesia is maintained with sodium Phenobarbital. A positive pressure pump through a cuffed endotracheal tube gives the ventilation. The body temperature is maintained at 37-38°C by a heating pad. The blood sampling is carried out from the jugular vein.

Sheep Model (Junginger, 1990)**:** The sheep, rabbit and dog models are more practical and suitable for investigating nasal drug delivery from sophisticated formulations. They permit better evaluation of theparameters there involved. The in vivo sheep model for nasal delivery is essentially parallel to that for the dog model. Male in-house bred sheep are employed since they are free from nasal infections.

Monkey Model (Junginger, 1990)**:** Monkeys (approx. 8 kg) are anaesthetized, tranquillized or maintained in the conscious state as per the experimental purpose. The monkey is tranquillized by intramuscular injection of

ketamine hydrochloride or anaesthetized by intravenous injection of sodium Phenobarbital. The head of the monkey is held in an upright position and the drug solution is administered into each nostril. Following the administration, the monkey is placed in a supine position in a metabolism chairfor 5-10 min. throughout the course of study the monkey breaths normally through the nostrils. The blood samples are collected through an indwelling catheter in the vein.

Ex vivo Nasal Perfusion Models (Aulton ME *et al.*, 2002)**:** Surgical preparation is the same as that is for in vivo rat model. During the perfusion studies, a funnel is placed between the nose and reservoir to minimize the loss of drug solution. The drug solution is placed in a reservoir maintained at 37°C and is circulated through the nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs again into the reservoir. The drug solution in the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution. The drug activity due to stability problems may be lost during the course of experiment. This is especially true for peptide and protein drugs that may undergo proteolysis and aggregation. Rabbit can also be used as the animal model for ex vivo nasal perfusion studies. The rabbit is anaesthetized with parenteral uretliane-acepromazine. A midline incision is made in the neck and the trachea is cannulated with a polyethylene neonatal endotracheal tube. The esophagus is isolated and ligated. The distal end of the esophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive to avoid drainage of drug solution from the nasal cavity. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

Table 1. Current formulations for nasal drug delivery: (Electronic Medicines Compendium, 2015)

Indication	Active pharmaceutical ingredient	Formulation
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder and diluent for reconstitution-aqueousspray Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Endometriosis Ovarian stimulation	Nafarelin acetate	Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone - dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Nocturia associated with multiple sclerosis The diagnosis and treatment of vasopressin- sensitive cranial diabetes insipidus. Establishing renal concentration capacity.	Desmopressin acetate	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

Table 2. Nasal drug absorption enhancers and mechanisms: (Electronic Medicines Compendium .,2015)

Class of compound	Example	Possible action
Fatty acids	Dideconoylphosphatidylcholine, lysophosphatidylcholine	Membrane disruption
Surfactants	Sodium lauryl sulphate, saponin, polyoxyethylene-9-lauryl ether	Membrane disruption
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Open tight junctions, enzyme inhibition, mucolytic activity
Cyclodextrines and derivatives	α-, β-, γ-cyclodextrin DMβ-, HPβ-cyclodextrin	Open tight junctions, membrane disruption
Enzyme inhibitors	Bestatin, amastatia	Enzyme inhibition
Bio-adhesive materials	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions

Figure 1. Sagittal section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E). Reproduced with permission from ref (UGWOKE M *et al.*, 2001).

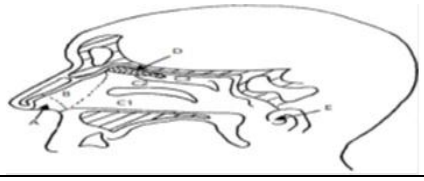


Figure 2. Cell types of the nasal epithelium with covering mucous layer showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), mucous gel-layer (D), sol layer (E), basal cells (F) and basement membrane (G). Reproduced with permission from ref. (UGWOKE M *et al.*, 2001).

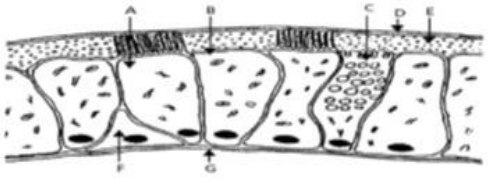
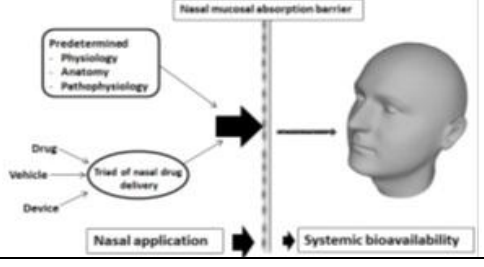


Figure 3. Consideration of formulation elements of nasal product development



CONCLUSION

Nasal spray is a promising alternative to other route of administration. In near future intranasal therapy will have more priority for its promising results and future promises of delivering drugs with specific objectives. Nasal spray can be a great choice for long treatment of illnesses such as diabetics, osteoporosis and others. A growing demand is already in the market for an alternative drug delivery system and nasal spray can be a better substitute then other drug delivery system. Obviously bioavailability of nasal drug product is the major challenge which demands more attention for research. Reduction of certain side effects and improved effectiveness can open up a new aspect for achieving therapeutic objectives. As discussed in the above review, nasal spray upholds a great promise as an innovative drug delivery system and it is expected that in near future nasal spray will fulfill the demand of global pharmaceutical market. As highlighted in this review article, there are hurdles like technical and practical issues, to be overcome through further research.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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