Review Article

Nasal Drug Delivery System

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ABSTRACT

Intranasal drug delivery is currently accepted to be helpful and reliable different to oral and parenteral routes. This route is additionally preferred for medication undergoing in depth initial pass result. Besides this; intranasal route has additionally been with success build a use for by passing the blood brain barrier [BBB] and later delivering drug molecules to central system [CNS]. Additionally, it decreases the lag time joined with oral drug delivery and offers noninvasiveness, self-medication, patient comfort and patient compliance that are hurdled in blood vessel drug medical care. This review can center of attention on anatomy of nasal, issue poignant nasal drug delivery and numerous bioavailability barriers in nasal drug delivery and numerous indefinite quantity forms and analysis of nasal formulation.

Keywords: Intranasal drug delivery, bioavailability, Nasal cavity.

INTRODUCTION

Intranasal administration offers a spread of engaging choices for native and general delivery of various therapeutic agents. The character of the nasal membrane provides a series of distinctive attributes, all of which can facilitate to maximize the patient's safety, convenience and compliance. The use of large-scale materials in drug delivery presents significant challenges, including in vivo volatility, low bioavailability and insolubility, poor body absorption, target-specific delivery issues and tonic efficacy, and potentially adverse drug effects. Therefore, exploitation new drug delivery systems for targeting drug to specific body components might be Associate in nursing possibility that may solve these crucial problems. Hence, applied science plays a big role in advanced drug/drug formulations, targeting space and their controlled drug unleash and delivery with large success.[1, 4]

As another to oral and channel routes, intranasal drug delivery has gained increasing attention within the last 20 years. Because of the massive extent, porous epithelium membrane, high total blood flow, the dodging of internal organ first-pass metabolism, and prepared accessibility of the nasal membrane, the intranasal route offers several blessings like simple and needle-free drug application, smart penetration of low molecular drug, fast absorption and quick onset of action, dodging of chemical and catalyst degradation, induction of native and distant tissue layer immune responses once vaccination, and direct nose-to-brain delivery.[2]

Advantages of nasal drug delivery system [3, 4]

- Absorption of drug is fast via extremely vascularised membrane.
- Accessibility of huge nasal tissue layer extent for dose absorption.
- Onset of action is fast.
- Non invasive and straight forward for administration.
- By pass the BBB.
- Degradation of drug ascertained in dirty dog is avoided.
- Internal organ initial pass metabolism is absent.
- Nasal bioavailability of tiny drug molecules is sweet.
- Bioavailability of huge drug molecules will be raised by suggests that of absorption enhancers.
- Unsuitable drug candidates for oral route will be with success given via nasal route.
- Alternate to channel route particularly for proteins and peptides.
- Convenient route for the patient on future medical care.
- Improved bioavailability.
- Facet effects are reduced thanks to low dose.
- Patient convenience and compliance is improved.
- A self-administration is feasible.
- Direct transport into circulation and system nervous central is feasible.

• Offers lower risk of drug

• doesn't have any complicated formulation demand

Limitations of nasal drug delivery system [3, 4]

• The range of transmission at nasal cavity is limited to 25–200 µL.

• High mass compounds can't be delivered through this route (mass interrupt ~1kDa).

• Adversely suffering from pathological conditions.

• Giant interspecies variability is ascertained in this route.

• Traditional defense mechanisms like mucociliary Clearance and ciliarey beating affects the permeability of drug.

• Irritation of nasal membrane by drug like Budesonide, Azilactine.

• restricted understanding of mechanisms and fewer developed models at this stage.

• General toxicity occurring thanks to absorption enhancers is nonetheless not established.

• Smaller absorption surface compared with dirty dog.

• Risk of nasal irritation thus inconvenient compared with oral route.

• Catalyst barrier to permeability of drug.

Profile of an 'ideal' drug candidate for nasal delivery [5]

An ideal nasal drug candidate ought to possess the subsequent attributes:

• Applicable binary compound solubility to supply the desired dose during a 25–150 ml per volume of formulation administration per nostril.

• Applicable nasal absorption properties.

• No nasal irritation from the drug.

• An acceptable clinical explanation for nasal dosage forms, e.g. fast onset of action.

• Low dose generally required (below 25 mg) A

• No harmful nasal metabolites.

• No offensive odors/aroma related to the drug.

• Appropriate stability characteristics.

Anatomy and physiology of nasal cavity [6, 7]

There are several challenges to thriving nasal delivery those aeries because of the complexness of the nose's physiology and performance. Physiology of the nose is shown in Figure1. The nose provides a way of warming, humidifying, and filtering the inhaled air before it reaches the lungs. It serves these functions by passing inhaled and invalid air over the massive area of the nasal cavity (approximately 180 cm2). additional oftentimes, the most operate of the nose is to be a primary line of defense, as a result of the mucus-coated membranes lining the cavum contain immunoglobulin, proteases, esterase, and plenty of different enzymes that facilitate break down contaminants before they'll be inspired and enter the body. Unfortunately, these defensive systems conjointly serve to forestall the delivery of drug. Air flow into the cavum comes in contact with the modality nerves that penetrate the cribriform plate on top of the concha. The modality neural bundle provides the sense of smell; consequently, it's also a potential route for delivering therapeutic agents on to the brain via intra- or extra neuronal pathways. The cavum is segmental by the superior, middle, and inferior structure (turbinate's) that has rough animal tissue linings. These cilia, 4–6 m long, beat with a frequency of the order of 1000 strokes/min, propelling mucous secretion secreted from the body fluid glands and foreign contaminants to the cavum, wherever it drains more down the esophagus and the gastrointestinal system. These cilia propel the mucous secretion through the nose at a rate of 5–6 mm/min . The secretion volumes vary from person to person, however it's typically accepted that 1 liter/day is secreted into the nose then swept wing posterior. This secretion rate will quite double once the nose is inflamed. The degree of the cavum is roughly 16–19 cm3. Therefore, a membrane turnover of quite2.5 times/hour is assumed with mucous secretion layer renewal occurring each 15 min. Thus, most of a drug treated within the cavum typically will be carried fully away in 10–80 min. complicating matters more, the patency of every nasal passage way changes with time, making another challenge to delivering drug. This cycle will last from 2 to 7 hours and determines the air flow into either side of the nose throughout inspiration and exhale. The temperature within the cavum is mostly 36_C, and also the pH typically varies between 5.5 and 6.5 in adults and 5.0 and 6.7 in infants and young kids, and tends to become additional alkali at lower temperature. At lower temperature, wherever alkali pH will occur, and also the mermaids activity decreases, which may increase survival of microorganism within the mucous secretion.

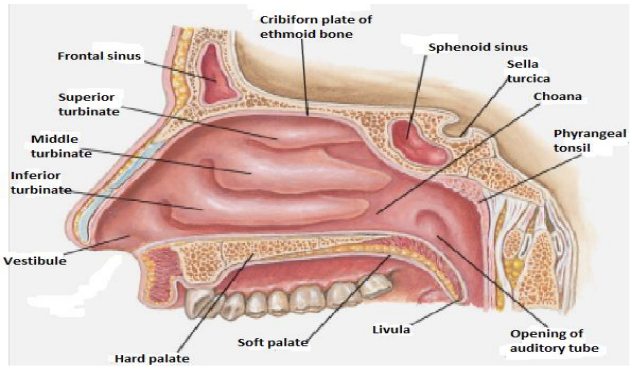

Figure 1: Anatomy of the nasal cavity

Atrium Intermediate space between nasal vestibule and metastasis regions is atrium. Its anterior section is well-grooved by a stratified squamous epithelial tissue and the posterior space by psudostratified columnare cells presenting microvill. Respiratory region Largest part of the

cavum is metastasis region, conjointly known as conches, is that the cavity and it's divided in superior, middle and inferior turbinate's that are projected from the lateral wall. The nasal metastasis membrane, thought-about the most important section for delivering drug systemically, is well-grooved by the animal tissue, basement membrane and lamina propria. The nasal metastasis animal tissue consists of pseudo stratified columnar animal tissue cells, globet cells, basal cells and mucosa and bodily fluid glands. Several of the animal tissue cells are lined on their apical surface with microvilli and the major half of them also has fine projections, known as cilia.[8]

Olfactory region Location of modality region is at thereof of the cavum and extends a brief manner down the septum and lateral wall. Its neuro-epithelium is that the solely a part of the CNS that's directly exposed to then external setting. Equally to the metastasis animal tissue, the modality one is additionally pseudo stratified but contains specialized modality receptor cells important for smell perception. Mucus membrane of nose associated its composition the nasal mucous secretion layer is just 5 µm thick and it is organized in 2 distinct layers: an external, viscous and dense, and an interior, fluid and serous. Generally, nasal mucous secretion layer consists of 95% of water, 2.5-3% of mucin and a couple of electrolytes, proteins, lipids, enzymes, antibodies, epithelial cells and bacterial product. Epithelial cells primarily there are 2 functions of these cells,

1. Offer a physical barrier to the invasion of infectious microorganisms and allergic particles.

2. Add conjunction with mucous secretion glands and cilia to secrete and take away mucous secretion and foreign particles from the cavum.

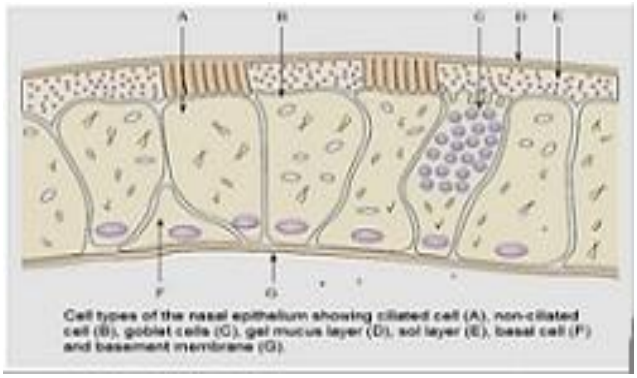

Figure 2: Structure of the Nasal Epithelium

Blood supply to nasal cavity Vasculature of the nasal cavity is richly equipped blood to meet the essential functions like heating and humidification, olfaction, mucociliary clearance and medical specialty functions. The nasal vascular bed is therefore designed that fast exchange of fluid and dissolved excipients between blood vessels and nasal tissue are often done easily. The capillary flow within the nasal mucous membrane was according to be 0.5 ml/g/min.
Sphenopalatine artery a branch of artery. Anterior artery a branch of artery ophthalmica. Branches of the maxillary artery supply the vestibule of the bodily cavity.

Mechanism of Drug Absorption from Nose

There is a pair of mechanisms for drug absorption from nose,

1. Aqueous route of transport

2. Lipoidal route of transported

Aqueous Route of Transport conjointly referred to as Para cellular route. It's slow and passive route and inverse the log-log relationship between relative molecular mass of water soluble compounds and intra nasal absorption. This route has poor bioavailability for those drugs that has relative molecular mass bigger than 1000D.

Lipoidal Route of Transport conjointly referred to as trancellular method. This route is to blame for the transport of lipotropic drug that shows a rate dependency on their lipophilicity. During this route drug crosses the semi permeable membrane by transport route via carrier mediate suggests that or through a transporter by gap the tight junctions.

Mechanism for Drug Delivery in to central nervous system via Intranasal Route[9]

Intracellular Route intracellular transport mediate route is slow and it takes hours to achieve the neural structure.

Extra Cellular Route the additional cellular transport mediate route causes fast entrance of drug into the brain (within minutes). There are 2 mechanisms for further cellular transport.

Mechanism: 1

Drug administered through intra nasally

↓

Transported along trigeminal region

↓

Drug reaches the olfactory bulb of trige`minal region

↓

Enters into regions of brain by diffution (facilitatedby peivascular pumb driven by arterial pump triven by arterial pressure)

Mechanism: 2

Drug when administered intranasally absorbed through olfactory cilia

↓

It binds with olfactory neurons and passes through olfactory neurons

↓

The axons of olfactory neurons terminates in to olfactory bulb and by passess

↓

It then enters in to other regions of brain (or olfactory tract which terminates in frontal lobe and other parts of brain)

Figure 3: Mechanism 1 and 2 showing Extracellular Transport

FACTORS INFLUENCING NASAL DRUG ABSORPTION [10, 11]

Various factors moving the general bioavailability of drug that are administered through the nasal route. Those are physiochemical properties of the drug, the anatomical and physiological properties of the nasal cavity and also the kind and characteristics of nasal drug delivery system.

•Physiochemical properties of drug

Molecular size

Enzymatic degradation in nasal cavity

Lipophilic-hydrophilic balance

• Delivery effect

Drug distribution and deposition

Formulation (Concentration, pH)

Viscosity

• Nasal effect

Environmental pH

Cold, rhinitis

Membrane permeability

1. Molecular size

The molecular size of the drug affects absorption of the drug through the nasal route. The lipotropic drug has direct relationship between the relative molecular mass and drug permeation where as water soluble compound shave inverse relationship. The speed of permeation is extremely sensitive to molecular size for compounds with MW ≥ 300 Daltons.

2. Enzymatic degradation in nasal cavity

Nasal cavity having exo-peptidases and end peptidases, exo-peptidases. Exo-peptidases capability to cleave peptides at their N and C terminal and endo-peptidases like aminoalkanoic acid and amino acid, which might attack internal amide bonds. Drugs like peptides and proteins are having low bio-availability across the nasal cavity; therefore this drug might have risk to endure catalyst degradation of the drug molecule within the lumen of the nasal cavity or throughout passage through the epithelial barrier.

3. Lipophilic-hydrophilic balance

The HLB nature of the drug affects the absorption method. By increasing lipophilicity, the permeation of the compound commonly will increase through nasal mucous membrane. Though the nasal mucous membrane was found to own some deliquescent character, it seems that this mucous membrane is primarily lipotropic in nature and the lipid domain plays a very important role within the barrier operate of those membranes. Lipophilic drug like buprenorphine, androgenic hormone and 17a-ethinyl-estrogen are nearly fully absorbed once administered intranasal route.

4. Formulation (pH, Concentration)

The pH of the formulation will have an effect on drug permeation. To avoid nasal irritation, the PH of the nasal formulation ought to be adjusted to 4.5–6.5 as a result of enzyme is found in nasal secretions, that is to blame for destroying bound microorganism at acidic pH. Underneath alkaline conditions, lysozym is inactivated and also the tissue is prone to microbic infection. In addition to avoiding irritation, it leads to getting economical drug permeation and prevents the expansion of microorganism. Concentration gradient plays vital role within the permeation method of drug through the nasal membrane because of nasal mucosal damage.

5. Viscosity

A higher viscosity of the formulation will increase contact time between the drug and also the nasal mucous membrane there by increasing the time for permeation. At identical time, extremely viscous formulations interfere with the traditional functions like ciliary beating or mucociliary clearance and therefore alter the permeability of drug.

6. Drug distribution and deposition

The drug distribution within the bodily cavity affects the potency of nasal absorption. The mode of drug administration may have an effect on the distribution of drug in bodily cavity that successively can confirm the absorption potency of drug. The absorption and bioavailability of the nasal dose forms depends on the positioning of disposition. The anterior portion of the nose provides a protracted nasal residential time for disposition of formulation, it enhances the absorption of the drug. The posterior chamber of bodily cavity can use for the deposition of dose kind and drug is eliminated by the mucociliary clearance method and thus how's low bioavailability. The positioning of disposition and distribution of the dose forms are depends on delivery device, mode of administration, physicochemical properties of drug molecule.

7. Environmental pH

The environmental pH conjointly affects the potency of nasal drug absorption. The unionized lipotropic kind crosses the nasal epithelial barrier via transcellular route, whereas the additional lipotropic ionizing kind passes through the aqueous para cellular route.

8. Membrane permeability

Nasal membrane permeability is that the necessary issue that affects the absorption of the drug through the nasal route. The water soluble drugs and notably massive relative molecular mass drug like peptides and proteins are having the low membrane permeability are in the main absorbed through the endocytotic transport and by passive diffusion through the aqueous pores (i.e. tight junctions).

9. Cold, rhinitis

The symptoms hyper secretion, itching and instinctive reflex primarily caused by the viruses, microorganism or irritants. Inflammation could be a most often associated common unwellness, it influence the bioavailability of the drug. It's caused by chronic or acute inflammation of the tissue layer of the nose. These conditions have an effect on the absorption of drug through the mucous secretion membrane due the inflammation.

NASAL DRUG DELIVERY SYSTEM DOSAGE FORMS [12, 13]

The selection of dosage form depends upon the drug getting used planned indication, patient population and last however not least, promoting preferences. Four basic formulations should be thought-about, i.e. solution, suspension, emulsion and dry powder systems.

1. Liquid nasal formulations Liquid preparations are the most widely used dosage forms for nasal administration of drug. They're primarily supported binary compound state formulations. Their humidifying impact is convenient and helpful, since several allergic and chronic diseases are usually connected with crusts and drying of mucose membranes. Microbiological stability, irritation and rhinitis are the major drawbacks related to the water based mostly indefinite quantity forms as a result of the specified preservatives impair mucociliary perform and also the reduced chemical stability of the dissolved drug substance and also the short continuance of the formulation within the cavum are major disadvantages of liquid formulations.

2. Instillation and rhinyle Catheters are used to deliver the drops to such as region of cavum simply. The formulation is placed within the tube. One end is placed in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth. Dosing of catheters is decided by the filling before administration and accuracy of the system and this can be primarily used for experimental studies only.

3. Compressed air nebulizers Nebulizer could be a device accustomed administers medication within the sort of a mist, indrawn into the lungs. The compressed air fills into the device, thus it's known as compressed air nebulizers. The common technical principle for all nebulizers is to use element, compressed air or ultrasonic power, as suggests that to interrupt up medical solutions/ suspensions into tiny aerosol droplets, used for direct inhalation from the mouth piece of the device. Nebulizers settle for their medication within the sort of a liquid resolution that is commonly loaded into the device upon use. Corticosteroids and Bronchodilators like salbutamol (Albuterol USAN) are usually used and generally together with ipratropium. These prescribed drugs are indrawn rather than bodily process. It's so as to focus on their impact to the tract that speeds onset of action of the medication and reduces aspect effects, compared to different intake routes. This device isn't appropriate for the general delivery of drug by patient himself.

4. Squeezed bottle Squeezed nasal bottles are primarily used as delivery devices for decongestants. They consist of a smooth plastic bottle with a straight forward jet outlet. Whereas pressing the plastic bottle the air within the instrumentality is ironed out of the little nozzle, there by atomizing a particular volume. By cathartic the pressure once more air is drawn within the bottle. This procedure usually leads to contamination of the liquid by microorganisms and nasal secretion sucked within. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are powerfully obsessed with the mode of administration. The variations between smartly and smoothly pressed applications influence the dose additionally because the drop size of the formulation. Thus, the dose is difficult to manage. So squeezed bottles with vasoconstrictors aren't suggested to be employed by youngsters.

5. Metered-dose pump sprays Most of the pharmaceutical nasal preparations within 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 drug, either regionally to typically alleviate cold or allergic reaction symptoms like nasal congestion or systemically. Though delivery strategies vary, most nasal sprays perform by indoctrination a fine mist into the nareis by the action of a non-automatic pump mechanism. The 3 main sorts obtainable for native impact are antihistamines, corticosteroids, and topical decongestants. Metered- dose pump sprays embody the instrumentality, the pump with the valve and also the mechanism. The dose accuracy of metered-dose pump sprays relies on the physical phenomenon and body of the formulation. For solutions with higher body, special pump and valve mixtures are obtainable within the market.

6. Powder dosage forms Dry powders are less often employed in nasal drug delivery. Major blessings of this indefinite quantity kind are the lack of preservatives and also the improved stability of the formulation. Compared to solutions, the administration of powders may lead to a chronic contact with the nasal membrane.

There are different types of powder dosage forms :

Insufflators Insufflators are the devices used to deliver the drug substance for inhalation. It is created by employing a straw or tube that contains the drug substance and typically it contains syringe conjointly. The achieved particle size of those systems is usually accrued compared to the particle size of the powder powder particles due to insufficient deaggregation of the particles.

Dry powder inhalers Dry powder inhalers (DPIs) are unit devices through that a dry powder formulation of a full of life drug is delivered for native or general result via the pneumonic route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in an exceedingly non polar volatile propellant or in dry powder dispenser that's fluidized once the patient

inhales. These are unit unremarkably accustomed treat metabolism diseases like respiratory disease, bronchitis, pulmonary emphysema and COPD and have conjointly been utilized in the treatment of diabetes. The medication is often control either in an exceedingly capsule for manual loading or a proprietary kind from within the dispenser. Once loaded or motivated, the operator puts the mouthpiece of the dispenser into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are unit a range of such devices. The dose that may be delivered is usually but a couple of tens of milligrams in an exceedingly single breath since larger powder doses may result in provocation of cough.

7. Pressurized MDI's a metered-dose inhaler (MDI) could be a device that delivers a selected quantity of formulation to the lungs, within the sort of a brief burst of aerosolized formulation that's inhaled by the patient. It's the foremost unremarkably used delivery system for treating respiratory disease, chronic obstructive pulmonary disease (COPD) and alternative respiratory diseases. The medication in an exceedingly metered dose dispenser is most ordinarily a medicament, adrenal cortical steroid or a mix of each for the treatment of respiratory disease and COPD. alternative medications less unremarkably used however conjointly administered by MDI are unit somatic cell stabilizers, like (cromoglicat or nedocromil).The advantages of MDIs are unit their movableness' and little size, accessibility over a good dose vary per effort, dose consistency, dose accuracy, protection of the contents which they're quickly prepared to be used. To use the dispenser, the patient presses downward on the highest of the canister, with their thumb supporting the inferior portion of the mechanism. The propellant provides the force to get the aerosol cloud and is additionally the medium within which the active part should be suspended or dissolved. MDIs more than 99 % of the delivered dose is contain propellant. Actuation of the device releases one metered dose of the formulation that contains the medication either dissolved or suspended within the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of those droplets, ends up in the generation of associate aerosol consisting of micrometer-sized medication particles that are unit then inhaled.

8. NASAL GELS Nasal gels are high-viscosity thickened solutions or suspensions. Till the recent development of precise dosing devices, there's not a lot of interest during this system. Reduction of post nasal drip due to high viscosity, reduction of taste effect due to decreased swallowing, reduction of anterior leakage of the formulation, reduction of irritation by the use of soothing/emollient excipients and increased absorption target delivery to mucosa. The deposition of the gel within the bodily cavity depends on the mode of administration. The formulation has low spreading capacities because of its viscosity. Without special application techniques, it only occupies a narrow distribution space within the bodily cavity, wherever it's placed directly. Recently, the primary nasal gel containing vitamin B for general medication has entered the market.

Evaluation of nasal drug formulations *In vitro* nasal permeation studies [10, 14]

Various approaches accustomed confirm the drug diffusion through nasal membrane from the formulation. There are 2 different ways to check diffusion profile of medication,

(A) *In vitro* diffusion studies the nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber having total capability of 60 cubic centimeters and a flanged top of concerning 3 mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The donor chamber is10 cm long with internal diameter of 1.13 cm, and a donor tube chamber has total capability of 60 cubic centimeter and a flanged top of concerning 3 mm; the lid has 3 openings, each for sampling, thermometer. The nasal membrane of sheep was separated from sub layer bony tissues and stoned in H2O containing few drops at genatamycin injection. When the entire removal of blood from mucosal surface, it's connected to donor chamber tube. The donor chamber tube is located in such a way that it contacts the diffusion medium in the receiver chamber. Samples (0.5 ml) from recipient chamber are with draw at planned intervals, and transferred to amber colored ampoules. The samples with drawn are suitably replaced. The samples are calculable for drug content by appropriate analytical technique. Throughout the experiment the temperature is held at 37°C.

B*) In vivo* Nasal Absorption studies Animal models for nasal absorption studies

The animal models utilized for nasal absorption studies are of 2 types, viz. whole animal or *in vivo* model, and an isolated organ insertion or *ex vivo* model. These models are mentioned intimately below:

Rat model: The surgical preparation of rat for in vivo nasal absorption study is done as follows: That are anaesthetized by intra peritoneal injection of Na Nembutal. Associate degree incision is formed within the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the esophagus towards the posterior region of the cavity. The nasopalatine is passage from tract in such way that the drug solution isn't drained from the nasal cavity through the mouth. The drug solution is administered by the cavity through nostril or through the cannulation tubing. Femoral vein is employed to collect the blood samples. Because all possible drainage channels are blocked, the drug is only absorbed through penetration and/or diffusion through the nasal mucous membrane and transferred into the circulation.

Rabbit model: The rabbit provide many advantages as associate degree animal model for nasal absorption studies: 1. This makes pharmacokinetic studies as with large animals (like monkey) 2. It is fairly inexpensive, readily available and easily maintained in laboratory

settings 3. The amount of blood is large enough (approx. 300ml) 4. To allow frequent blood sampling (l-2ml). Therefore, it permits full characterization of the absorption and determination of the pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or held in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anesthetized rabbit. The head of rabbit is held upright position and nasal Spray of drug solution is administered into each nostril. The temperature of the rabbit is maintained at 37°C throughout experiment with the assistance of a heating pad. The blood samples are collected by associate degree inward tubing within the marginal ear vein or artery.

***Ex vivo* Nasal insertion** Models surgical preparation is that the same as that's for *in vivo* rat model. Throughout the insertion studies, to reduce the loss of drug solution a funnel is placed between the nose and reservoir. The drug solution is placed during a reservoir kept at 37°C and is circulated through the cavity of the rat with a peristaltic pump. The insertion solution passes out from the nostrils (through the funnel) and runs once more into the reservoir. The drug solution within the reservoir is endlessly stirred. The number of drug absorbed is calculable by measurement the residual drug concentration within the perfusing solution. Rabbit also can be used because the animal model for *ex vivo* nasal insertion studies. The rabbit anaesthetized with parenteral uretliane-acepromazine. A midline incision is made into the neck and a polyethylene neonatal endotracheal tube cannulates the trachea. The esophagus is isolated and ligated. The distal end of the esophagus is closed with suture and flexible tygon tubing is incorporated into the proximal end and advanced to the posterior part of the nasal cavity. To prevent drug solution leakage from the cavity the nasopalatine tract (that connects cavity to the mouth) is closed with associate degree adhesive. The drug in isotonic solution is recalculated employing a peristaltic pump.

***In-vivo* bioavailability studies**

In-vivo bioavailability study is conducted on healthy male rabbits. Study consists of 3 groups every containing six rabbits and fasted for 24 h. first group treated with conventional preparation, second group was held as control (i.e. not received any test substances) and third group of test formulations. Water is given as desire during fasting and throughout the experiment. For the collection of blood samples the marginal ear vein of the rabbits used and sample of around 2 ml collected in heparin zed centrifuge tubes at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h after the drug administration. The blood samples are centrifuged at 3000 × g for 15 min to obtain the plasma and stored at -20°C until analysis. The extraction of drug from plasma can be carried out as reported previously and then analyzed using the HPLC method.

Pharmacokinetic analysis

Pharmacokinetic parameters are obtained from the plasma concentration vs. time plot. The area under the curve (AUC), the peak plasma concentration (C max) and the time to attain peak concentration (T max) can be obtained from these plots. The elimination rate constant (Kel) is determined from the semi logarithmic plot of plasma concentration vs. time. Elimination half-life (t1/2) can be calculated using the formula; t1/2 = 0.693/K el.

EVALUATION FOR GEL

Appearance

The formulations produced were visually inspected against white background for clarification, color in sol and gel form and for particulate matter, wherever present.

pH of gel

all formulated batch pH was calculated using pH meter which was previously calibrated using standard buffers of pH 4 & pH 7.26

Determination of mucoadhesive strength

The mucoadhesive strength of every formulation determined by measurement a force needed to detach the formulation from nasal membrane tissue. A section of sheep nasal membrane was placed on each of 2 glass slides using thread. 0.5 g of gel was placed on the primary slide and this slide placed below the height adjustable pan. Whereas another slide with mucosal section was connected in an inverted position to the underside of the same pan. All the slides with mucosal section were attached to the underside of the same pan. Both the slides with gel formulation kept in contact with each other, for 2 min to ensure close contact between them. Then the weight was kept rising in second pan until slides get separated from each other. The mucoadhesive force expressed as the detachment stress in dynes/cm^2 was calculated from the minimum weight that detached the mucosal tissue from the surface of each formulation.

Detachment stress (dyne/cm^2): m. g /A

Where, m = weight required for detachment of slide in grams, g = Acceleration due to gravity (980 cm/s2). A = Area of mucosa exposed.

Rheological studies

Viscosity of the prepared formulations was calculated by using Brookfield Cone and Plate Viscometer. The required spindle was lowered perpendicularly into the fixed quantity of gel which was to be calculated. The spindle was rotated at different speeds and the suitable speed was selected. The temperature was maintained at 25°C and then the viscosity was measured as the system was allowed to cool gradually.

Gelation study

This is the proportion of cations at which the liquid phase converted to gel. Gelation point was considered as the

proportion where formulations would not flow when test tubes were tilted to 90° angle, as the cations ions concentration was gradually increased.

***In vitro* release studies**

In vitro release study of the formulated in situ gel was performed in two chamber diffusion cells through dialysis membrane-70 with the molecular weight cut off 1200-1400 KDa. Diffusion cell having diameter 1.5 cm and 20 ml capacity consisted of an upper cylindrical cell open from above and diffusion membrane at its base. To prepare artificial membrane, section of dialysis membrane was soaked in PBS pH6.6 for hrs before mounting on diffusion cell. The content of the receiver compartment were placed at magnetic stirrer. The position of the donor compartment location has been modified so that dialysis membrane just touches the diffusion medium. An aliquot of 2-3 ml was withdrawn from receiver compartment at specific time interval and replaced with the same amount of fresh medium. Aliquots withdrawn were suitably diluted and calculated using UV spectrophotometer. *In vitro* drug release was carried out for 5-8 hrs. Membrane was in a two chamber cells. In situ gel formulation was placed within the donor compartment. Sufficient quantity of PBS 6.6 was placed in the receptor compartment. The temperature of the receiver compartment was maintained at the 37°C ±1.0^{0}C during experiment and the content of the receiver compartment was stirred using magnetic stirrer. The donor compartment site has been modified so that dialysis membrane easily contacts the diffusion medium. An aliquot of 2-3 ml was withdrawn from the receiver compartment at specific interval and replaced with the same amount of fresh medium. Aliquots collected were suitably diluted and calculated using UV spectrophotometer. *In vitro* drug release was carried out for 5-8 hrs.

***In vitro* permeation study**

Fresh nasal tissues were carefully removed from the nasal cavity of goat obtained from the local slaughter house. Tissue sample was placed in Franz diffusion cell displaying a permeation area of 1.76 cm and 6.6 pH phosphate buffer saline was added to the acceptor chamber and agitated with magnetic stirrer at 37^0 C. After every time interval, pure drug solution and formulation equivalent to 0.25%w/v of formulation was placed in the donor chamber. From the acceptor compartment sufficient quantity of sample aliquots were withdrawn at predetermined time interval up to 6 hrs replacing the sample volume with 6.6 pH PBS after each sampling, filtered and analyzed by UV spectrometer.

Evaluation for nasal spray

Drug Content (Assay)

The assay of drug substance within the complete container should be determined analytically with a stability indicating procedure. This test ensures accurate fabrication (e.g., formulation, filling, sealing). The acceptance criteria (assay limits as per official books) should be tight enough to create sure conformance in other related attributes (e.g., spray content uniformity). A suitable assay procedure should be designed to handle any degradation of the drug substance, adherence of the drug substance to the container and closure components, and so the potential effect of formulation evaporation and/or leakage.

Impurities and Degradation Products

The levels of degradation products and impurities should be calculated by means of stability indicating procedure(s). Specification should be set for individual and total degradation products and impurities. For identification and qualification thresholds, see the acceptable guidance. It should be noted that all associated impurities occur at the level 0.1% or greater. Described impurities and degradation products are those, either identified or unidentified, that are individually listed and limited within the drug product specification.

Preservative(s) and Stabilizing Excipient Assay

If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenyl ethyl alcohol) are utilized within the formulation, there should be a specific assay for these components with associated acceptance criteria (At a degree 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 guage the metering ability of the pump should be performed. The proper efficiency of the pump should be ensured primarily by the pump manufacturer, who should assemble the pump with parts of precise dimensions. Pump spray weight delivery should be check by the applicant for the drug product. In general, approval requirement for pump spray weight distribution will monitor the load of the individual sprays to within ±15 percent of the target weight and their mean weight to within ±10 percent of the target weight.

CONCLUSION

Basic information about nasal drug delivery system is mention during this text. INDD system might be a promising delivery system for the drugs with poor bioavailability and features a plus in conditions of patient compliance if compared to parenteral administration. This route of administration is especially appropriate to treat various neurodegenerative diseases as an example, Alzheimer's disease, Parkinson's disease as they require specific and rapid targeting of medication to brain. Development of a drug with a drug delivery system is influenced by several factors. Therefore for the avoidance of side effect and improve effectiveness of nasal products we should concentrate to basic research in nasal drug delivery.

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