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NASAL GEL AS PROMISING MUCOSAL DRUG DELIVERY

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ABSTRACT

Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, high permeability of some drugs in nasal epithelium, quick drug absorption across this membrane, rapid onset of action, improved patient compliance and comfort, sustained and prolonged action in comparison to other drug delivery systems. In-situ gel is a novel dosage form for nasal delivery of various drugs. The nasal administration of drugs, including numerous compound, peptide and protein drugs, for systemic medication has been widely investigated in recent years. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in rapid systemic drug absorption. It is infusing into the nasal cavity as low viscous solution and after sometime it forms gel when it contact with the nasal mucosa. The formation of gel depends on factors like temperature modulation, pH change, presence of ions, ultra violet irradiation, polymorphism, dissolution rate, solubility, viscosity and osmolarity. The review was focused on anatomy and physiology of nose, advantages, disadvantages, mechanism of drug delivery to the nose, types of dosage form for nasal delivery, barriers in nasal drug delivery, factors influencing nasal absorption, mucoadhesive polymer used in nasal drug delivery system and evaluation of in-situ gel nasal drug delivery system. These drug delivery systems have the ability to control the rate of drug clearance

from the nasal cavity as well as protect the drug from enzymatic degradation in nasal secretions.

KEYWORDS: In-situ gel, nose, bioavailability, first pass metabolism.

INTRODUCTION

The most commonly used route of administration for systemic effect is oral administration. But for some drug the systemic effect was not in desirable condition due to oral bioavailability and promoted for the search of more effective route for systemic delivery. Usually the nasal cavity is used for the treatment of local diseases they are rhinitis, migraine, cold, pain and nasal congestion. In recent years it has been proved that many drugs achieved better systemic bioavailability through nasal route. The various formulations used by nasal route are nasal gel, spray, powders, etc. Transmucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption.[1] This is due to the anatomy and physiology of nasal passage that is porous endothelial membrane, large surface area, high total blood flow, the avoidance of first pass metabolism and readily accessibility. In-situ is a Latin term which means 'In its original place or in position'. In-situ gel is a type of dosage form in which the medicament is in solution form before administration into the body, after administered it undergoes gelation to form a gel. Due to its accessibility, nasal drug administration is considered as an alternative route for systemic circulation instead of intravenous administration.[2]

Nasal drug delivery also provides a way to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly. The nasal route is an attractive not only for delivery of vaccines due to large surface area and low proteolytic activity but also it improves the patient compliance and decrease the production cost compared to parentral production. Due to their high permeability the nasal route show only smaller molecular weight drugs the absorption will be more.[1,3] For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane so the drugs cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier. Penetration enhancers such as surfactants, bile salts and phospholipids increases the drug penetration but in site of clinical use the toxicity test proved that the permeation enhancers has some limitation due their irreversible damage. Even though the number of challenges for

the researchers to overcome some disadvantages in conventional nasal products and to make effort for the new nasal formulation.[3]

ADVANTAGES OF NASAL DRUG DELIVERY[1,7]

The major advantages associated with nasal drug deliver include.

- Rapid absorption, higher bioavailability, therefore, lower doses.
- Fast onset of therapeutic action.
- Avoidance of liver first pass metabolism.
- Avoidance of metabolism by the gastrointestinal tract.
- Avoidance of irritation of the gastrointestinal membrane.
- Reduced risk of overdose.
- Non-invasive, therefore, reduced risk of infectious disease transmission.
- Ease of convenience and self-medication.
- Improved patient compliance.
- Can be a beneficial adjunct product to an existing product.

DISADVANTAGES OF NASAL DRUG DELIVERY[1,5]

- Mucociliary clearance reduces the residence time of drug.
- Not applicable to all drugs.
- Insufficient absorption due to lack of adequate aqueous solubility.
- Require high volume of dose (25-200 ml) depending on aqueous solubility of drug.
- Few drugs can cause nasal irritation.
- Few drugs may undergo metabolic degradation in the nasal cavity.
- Less suitable for chronically administered drugs.
- Drugs requiring sustained blood levels should not be considered for nasal drug delivery.

IDEAL DRUG CANDIDATE FOR NASAL DELIVERY[1,4,6]

- Appropriate aqueous solubility to provide the desired dose in a 25-150 µl volume of formulation administered 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 metabolite, No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

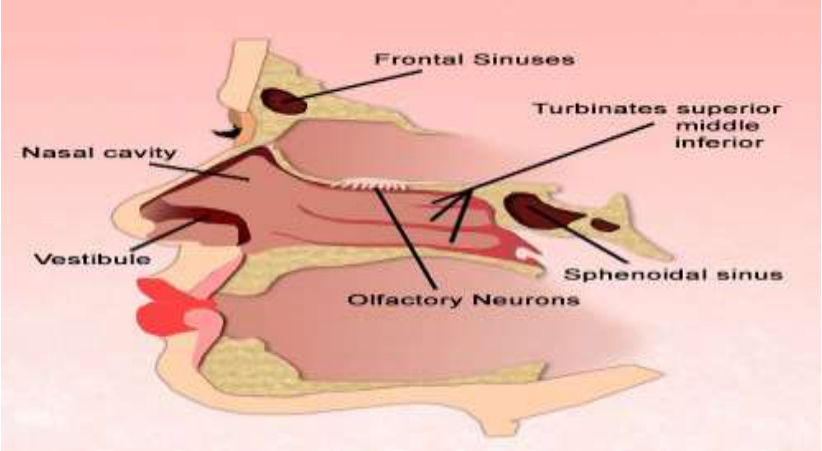

Fig 1: ANATOMY OF NASAL CAVITY[2]

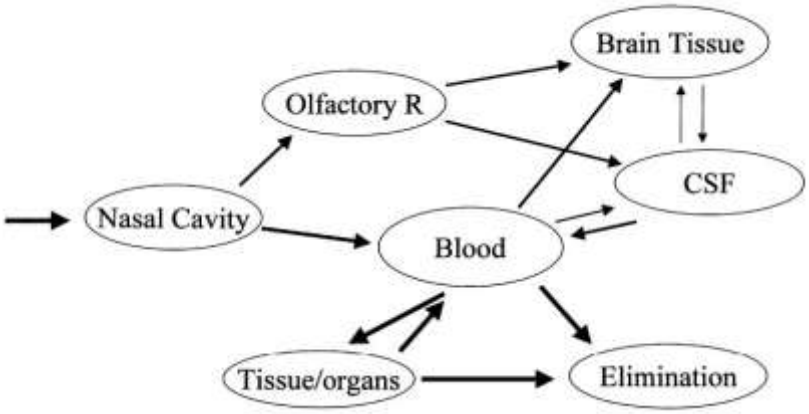

Fig 2: CONNECTIVITY OF NASAL CAVITY TO OTHER ORGANS[3]

PHYSICOCHEMICAL PROPERTIES OF DRUGS WHICH AFFECT THEIR NASAL DELIVERY

1. Drug molecular weight and size

The permeation of drugs having molecular weight less than 300Da is not significantly influenced by the physicochemical properties of the drug as they will mostly permeate through aqueous channels of the membrane. On the other hand, the rate of permeation is highly sensitive to molecular weight for compounds more than 300 Da. The bioavailability of intranasally administered peptides and proteins including insulin may be low because of high molecular weight and hydrophilicity.[5]

2. Drug solubility and dissolution rate

Like other routes of administration, the nasal absorption can take place only after the drug's dissolution. The dissolution rate is important in determining nasal absorption of powder and suspensions dosage forms. Rapid dissolution is very crucial for the drug particles after nasal

administration otherwise the particles will be subjected to rapid clearance from the airway with subsequent reduction of the bioavailability.[5,6]

3. pKa and the partition coefficient of drug

The nasal membrane is predominantly lipophilic, hence, the rate and extent of absorption of a drug across a biological membrane is influenced by its lipophilicity. Normally, the permeation of the compound through nasal mucosa increases with increasing lipophilicity. Low molecular weight lipophilic drugs are absorbed quite efficiently across the nasal epithelium, whereas larger hydrophilic drugs, such as peptides and proteins, have substantially lower bioavailability because they are not easily transported across nasal membrane thereby enhancing mucociliary clearance. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity, hence, with accelerated mucociliary clearance the contact time with nasal membrane diminishes resulting in a reduced permeation through the wall. In general, the passage across biomembrane is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site. According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. The nasal absorption of week electrolytes depends on their ionization degree and the largest absorption occurs for the non-ionized species. For polar drugs partition coefficient is the major factor influencing the permeability through nasal mucosa.[5,7]

4. Chemical state: pro-drugs

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. If a drug does not have the desired absorption properties, several options can be considered to improve the drug's delivery. Pro-drug technique has been employed to increase the lipophilicity. The aliphatic pro-drug of acyclovir provides a classical example of this process, which resulted in an increased drug bioavailability. However, it should be noted that the 140-fold increase in partition coefficient of the drug was only associated with 30% increase in bioavailability. It should also be emphasized that the ester form of the pro-drug can show greater increase in transnasal drug transport but premature hydrolysis of such ester in the nasal cavity provides the main limitation of this technique. Water-soluble prod-rugs of 17β-estradiol have been evaluated after intranasal administration. These pro-drugs were capable of producing high levels of estradiol in the cerebrospinal fluid (CSF), compared to an equivalent intravenous dose. These data suggest

that the drug can reach the CSF via a direct pathway through the nasal cavity and as a result may have a significant value in the treatment of Alzheimer's disease.[4,5]

5. Physical state: particle size and morphology

Particle size and morphology of drug particles constitute important properties for particulate nasal drug products. Particle size and morphology are related to the drug dissolution and should be controlled to obtain suitable drug dissolution properties in the nostrils. In vitro dissolution rates in suitable simulated fluid(s) should be considered. Particle size and morphology are also important to minimize the feel of grittyness and possibly irritation to the nasal cavity. Too fine particles, below five microns may be inhaled into the lungs and should be avoided for nasal products. Generally, particles in the 5-10 micron range are deposited in the nostrils.[4,8]

6. Polymorphism

An evaluation and study of the polymorphic forms of drugs administered in particulate form is an important parameter to be considered in nasal drug product development. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes. The effect of polymorphism on the nasal drug absorption has not been explored to date. However, in view of the information available on other biological membranes, this factor should be considered.[5,9]

FORMULATION PROPERTIES WHICH AFFECT NASAL DRUG DELIVERY

The specific formulation properties which affect drug absorption depend on the route of administration and the type of dosage form selected.

1. Types of dosage forms and delivery systems

Nasal drops are the simplest and the most convenient nasal pharmaceutical form, but the exact amount of drug delivered is not easily quantified and often result in overdose. Moreover, rapid nasal drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powders sprays because the last one easily prompted the development of nasal mucosa irritation. Recently, gel devices have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. This enhances the drug residence time and diminishes mucociliary clearance, thereby, potentially increases nasal absorption. Over the last few

years, specialized systems such as lipid emulsions, microspheres, liposomes and films have also been developed to improve nasal drug delivery.[10]

2. Drug concentration, dose and volume of administration

There should be clear positive relationship between absorption - and drug concentration upto a certain level. Such a relationship is not always observed. There are many other confounding factors which can influence the nasal membrane transport mechanism and provide a modified absorption profile. In general, higher nasal absorption or therapeutic effect was observed with increasing dose. It is important to note how the dose is varied. If the dose is increased by increasing formulation volume, there may be a limit as to what extent nasal absorption can be increased. The nostrils can remain only a limited volume, beyond which a formulation will drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15 ml with an upper limit of 0.20 ml.[5,11]

3. Physical form of formulation

Nasal drug absorption depends on the physical form of the formulation. A powder form was found to be more effective than liquid formulations because powder is not readily washed out with the nasal secretions.[3,12]

4. Viscosity

As formulation viscosity increases, the contact time between drug and nasal mucosa enhances and, thereby, the potential of drug absorption increases. At the same time, high viscosity of formulations interferes with normal ciliary beating and/or mucociliary and, thus, incrases the permeability of drugs. This has been observed during nasal delivery of insulin, acyclovir and metoprolol. However, sometimes, enhancing formulation viscosity does not enhance the drug absorption. Generally, a more viscous formulation will provide less efficient systemic nasal drug delivery. They observed that although the residence time enhanced as viscosity increased the drug absorption diminished. This observation has been attributed to a decrease in the drug diffusion from the formulation. On the other hand, it has also been reported that the viscosity of the solution may provide a larger therapeutic period of nasal formulations.[13]

5. Formulation pH

The extent of nasal absorption depends on the pKa of drug and pH at the absorption site, contributing for that also the pH of formulation. It is important to adjust nasal formulations to appropriate pH for the following reasons.

- To avoid irritation of the nasal mucosa
- To avoid efficient drug absorption
- To prevent growth of pathogenic bacteria in the nasal passage.

To avoid nasal irritation, formulation pH should be adjusted between 4.5 and 6.5. The nasal surface pH is 7.39 and the pH of nasal secretions is 5.5-6.5 in adults and 5.0-6.7 in infants and children. The physiological properties of drugs should be kept in mind in deciding on formulation pH. Most drugs are absorbed well in their un-ionized form. While it is desirable keep the formulation pH between 4.5 and 6.5, at times a pH lower than 4.5 may have to be chosen to keep an appreciable drug fraction in the un-ionized form.[4]

6. Formulation osmolarity

Studied the effects of osmolarity, among other factors, on the nasal absorption of secretin in rats. They found that the absorption was affected by the concentration of sodium chloride in the formulation and the absorption reached a maximum at a 0.462 M sodium chloride concentration. Shrinkage of epithelial cells of the nasal mucosa was observed at this salt concentration. At a formulation pH of about 3, the observed effects may have been a combination effect of the low pH and the salt concentration.[5]

7. Formulation excipients

In nasal formulations, a wide variety of pharmaceutical excipients can be found and they are selected accordingly to their functions. Solubilizers, buffer components, antioxidants, preservatives, humectants, gelling/viscosifying agents, and flavoring or taste masking agents are some of the most usual excipients. Although they are responsible for several nasal irritations, antioxidants, preservatives, humectants and flavouring or taste masking agents are not expected to alter nasal drug absorption.[4,5]

BIOLOGICAL FACTORS WHICH AFFECT NASAL DRUG ABSORPTION

1. Nasal blood flow

The nasal mucosa is supplied by rich vasculature and presents a large surface area making it an optimal local for drug absorption. The blood flow rate influences significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane, reaching the general circulation. Indeed, bearing in mind that most of drug absorption takes place by diffusion, the blood flow is essential to maintain the concentration gradient from the site of absorption to blood. Hence, it is well known that vasodilation and

vasoconstriction may determine the blood flow and, consequently, the rate and extent of drug to be absorbed. The blood vessels in the nasal mucosa are surrounded by adrenergic nerves which act as alpha adrenoceptors. Stimulation of these receptors has been shown to decrease blood flow and blood content in the nose of animals and humans. The nasal blood is affected by several external and physiological factors such as ambient temperature, humidity, presence of vasoactive drugs, trauma, and inflammation as well as psychological factors such as emotion, fear, anxiety, and frustration. The nasal flow is sensitive to different locally or systemically acting drugs. Drugs such as oxymetazoline and clonidine decrease blood flow whereas histamine, albuterol, isoproterenol, phenylephrine and fenoterol are shown to increase the blood flow. Such effects are important in determining nasal drug absorption due to their effect on blood flow.[9,14]

2. Enzymatic activity in the nose

Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect. However, they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of cytochrome P450 dependent monoxygenase, lactate dehydrogenase, oxidoreductase, hydrolases, acid phosphatase and esterase. It has been reported that cytochrome P450 isoenzymes metabolized the drug such as cocaine, nicotine, alcohols, progesterone and decongestants. Similarly, proteolytic enzymes (aminopeptidases and proteases) were found and they are belived to be the major barrier against the absorption of peptide drugs, such as calcitonin, insulin and desmoprssein. Thus, enzymes exist in the nasal mucosa may affect the pharmacokinetic and pharmacodynamic profile of nasally applied drugs .In this context, although the nasal first-pass metabolism is usually weaker than hepatic and intestinal ones it cannot be ignored.[5]

3. Mucociliary clearance

The function of mucociliary clearance system is to remove foreign substances and particles from the nasal cavity, consequently preventing them from reaching the lower airways. Nasally administered formulation can be cleared from the nasal cavity with a half-life of clearance of about 15 min with the result of limiting time available for absorption . The normal mucociliary transit time in humans has been reported to be 12-15 min. Rapid mucocliliary clearance of drug formulations that are deposited in the nasal cavity is thought to be an important factor underlying the low bioavailability of intranasally administered drugs. Some drugs, hormonal changes in the body, pathological conditions, and formulation

factors especially rheology are reported to affect mucociliary clearance and in turn exert significant influence on drug permeability.[15]

4. Physical condition of the nasal mucosa

The condition of the nasal mucosa can have an important effect on drug absorption. There are times when the mucosa is crushing, bleeding, or dry. One may be suffering from rhinorrhea, sinitis, or nasal infection. In people suffering from severe nasal allergies, an excessive nasal secretion can wash away the formulation before the drug has a chance of getting absorbed through the mucosa or before acting locally.[3]

NASAL GELS

A gel is a soft, solid or semisolid like material consisting of two or more components, one of which is a liquid, present in substantial quantity. The semisolid characteristics of gels can be defined in terms of two dynamic mechanical properties: elastic modulus G' and viscous modulus G". The rheological properties of gels depend on the polymer type, concentration and physical state of the gel.[9] 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. Moreover, the prolonged contact time afforded at the site of absorption can improve drug bioavailability by slowing down mucociliary movement. The mechanism of mucoadhesion in the nasal cavity can be explained by a number of theories, but it is generally accepted that the mechanism is based on two key stages, the contact and consolidation stages. So, when formulations containing bioadhesive polymers are instilled in the nasal cavity, they can spread over the nasal epithelium. Due to the increased surface contact, the polymer chains can diffuse within the mucus. This creates sufficient contact for entanglement. Secondary chemical bonds are then formed between the polymer chains and mucin molecules[9]. Various biocompatible and biodegradable polymers have been used to formulate mucoadhesive systems. These include polyvinyl alcohol, chitosan, carbopol, alginate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch and gellan gum. Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin, insulin , scopolamine hydrochloride, mometasone furoate , carvedilol , sumatriptan succinate, vaccines and proteins . Ozsoy et al., 2000 has investigated the formulation of ciprofloxacin

hydrochloride using hydroxypropyl methylcellulose (HPMC) and the results suggested that the bioavailability of ciprofloxacin gel formulation prepared with HPMC was almost identical to the oral route. In spite of most gels exhibiting shearthinning behaviour (pseudoplasticity), some gel formulations with suitable rheological properties cannot be easily delivered using a normal nasal spray device. *In situ* gelation can be used to overcome this problem, and has been investigated for the nasal delivery of mometasone furoate, carvedilol and influenza vaccine. In such systems, the viscosity of the formulation must be low enough to allow dispensing from nasal spray device and viscous enough for adhesion on the application site. *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 ungelled polymer solution. These can be formulated to behave as a viscoelastic liquid whilst maintaining a true gel microstructure within the gel particles.[8]

Ideal Drug Candidate for nasal gel[6,12]

- The drug has aqueous solubility to provide the desired dose in a 25-150 µl volume of Formulation administered per nostril.
- Appropriate nasal absorption properties.
- The drug should not cause nasal irritation.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, ≤ 25 mg per dose.
- The drug must not possess toxic nasal metabolites.
- No offensive odours/aroma associated with the drug.
- Suitable stability characteristics.

Advantages of nasal gel[8,12]

- Absorption of drug is rapid due to highly vascularised mucosa.
- Availability of large nasal mucosal surface area.
- Onset of action is rapid.

- Administration of dose is easy and Non-invasive.
- Bypass the Blood Brain Barrier.
- Degradation of drug observed in GIT is avoided.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Alternate to parenteral route especially for proteins and peptides.
- For the patient on long term therapy this route Convenient.
- Improved bioavailability as compared to oral route.
- Side effects are minimum due to low dose.
- Patient convenience and compliance is improved.
- A self-administration of drug dose is possible.
- Direct transport into systemic circulation and CNS is Possible.

Disadvantages of nasal gel[6,8]

- Delivery volume in nasal cavity is restricted to 25– 200µl.
- 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 defence mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
- Drugs like Budesonide, Azilactine are liable to cause Irritation of nasal mucosa.
- 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.

Properties of nasal gel[16]

- It should be low viscous.
- It should be free flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as a spray.
- Nasal in-situ gel should have long residence time.

- The nasal in-situ gel follows phase transition mechanism and to stand with the shear forces in the nasal cavity wall.

Table 1: TYPES OF GEL[1,3]

Class	Description	Example
Inorganic	Usually two-phase system	Bentonite magma
Organic	Usually single-phase system	Carbopol, tragacanth
Hydrogel	Organic hydrogel natural and synthetic gums inorganic hydrogel	Methyl cellulose, Sodium carboxymethyl cellulose, Pluronic, Bentonite gel, Veegum
Organogel	Hydrocarbon type animal, vegetable fats soap base greases hydrophilic organogel polar nonionic	Petrolatum,Mineraloil/Polyethylene gel, Cocoa butter aluminium stearate with heavy mineral oil gel carbowax bases

MECHANISM OF NASAL DRUG DELIVERY

The first step involved in the absorption of drug in nasal cavity is crossing the mucus membrane, because small, uncharged particles were passing through the mucus easily. But charged large molecule does not pass easily through the mucus membrane. The protein present in the mucus layer is Mucin, which binds with the solutes that delays the diffusion and structural changes in the mucus layer are also possible because of environmental changes (i.e. pH, temperature, etc.).[1]

During the drug passage in mucus there are several mechanisms for absorption across the mucosa thus includes simple diffusion, Para cellular transport between cell and transcytosis by vesicle carriers. The restrictions to the drug absorption are essential for metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly. The first mechanism is known as paracellular route which involves an aqueous route for transportation. This is slow and passive route. There is log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The drugs with a molecular weight greater than 1000 Daltons are having poor bioavailability[1,3]

The second mechanism is known as transcellular route which involves transportation through the lipoid route and it is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. The drugs cross the cell membrane by active transport through carrier mediated or opening of tight junctions.[1,4]

IN-SITU GEL

In situ is a Latin word which means in position. It is defined as a liquid formulation generating a solid or a semisolid depot after administration. In situ gel forming system are those which are when exposed to physiological condition will shift into a gel phase. This new concept was suggested for the first time in the early 1980s. Gel formation occurs through the cross linking of polymer chains that can be achieved by covalent bond formation or non covalent bond formation. Both natural and synthetic polymers were used in the formation of in situ gels. In situ gel systems are capable of producing sustained release relatively constant plasma profiles.[7]

Advantages of in situ gel

- Prolong drug release.
- Easy to administer.
- Less frequency of administration.
- Less systemic side effects.
- Reduced number of application.

Principle involved in in-situ gelling

The principle involved in in-situ gelling of nasal formulation is that the nasal fluid is absorbed by the nasal formulation after administration and forms gel in the nasal cavity. The formation of nasal gel avoids the foreign body sensation. The bioadhesive properties of the gels are used for maintaining contact between gel and mucosa. It acts as release controlling matrix and acts as sustained delivery system. Cilia present backwards help to remove the obstacle if there is any interference present in the propulsion phase. After the formation of gel, dissolution and mucociliary removal occurs. So there is no need to remove the dosage form after it has been depleted of drug.

In-situ gel formulation[2,7,10,12]

There are many mechanisms for formulating in-situ gels are discussed as follows:

1. Thermally triggered system

Under this mechanism, in-situ gel is formed by using polymer that changes from solution to gel by changing physiological temperature of the body. When the temperature increases the biomaterials used to form in-situ gel leads to transition from sol to gel and produce in-situ gel

2. pH triggered systems

In-situ gel is also prepared by changing pH of the gel based on physiological stimuli and here pH sensitive polymers were used. If the polymer contains weakly acidic groups the swelling of hydro gel increases as the external pH increases but it decreases if the polymer contains weakly basic groups.

3. Osmotically induced in situ gelling system

In this method, gelling of the instilled solution is triggered by change in the ionic strength. The rate of gelation is depends on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence as the mono or divalent cations. The polymers are induced gelation are gellan gum, hyaluronic acid and alginates etc.

4. Chemically induced in situ gel system

a. Ionic cross linking

Some ion sensitive to polysaccharides such as carrageenan , Gellan gum, pectin, sodium alginate undergo phase transition in the presence of various ions such as K+, Ca2+, Mg2+, Na+. These polysaccharides fall into the class of ion-sensitive ones.

b. Enzymatic cross linking -

In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiological conditions without need for potentially harmful chemicals such as monomers and initiators.

c. Photo- polymerization

In situ photo-polymerization has been used in biomedical applications.

Polymers used in In-Situ Gel[2]

1. The polymers and its degradation products should be nontoxic and non-absorbable from the gastrointestinal tract.
2. It should adhere quickly to moist tissue and should possess some site specificity.
3. It should be a non-irritant to the mucous membranes.
4. It should possess a wide margin of safety both locally and systemically.
5. The cost of the polymer should be not too high, so that prepared dosage form remains Competitive.

List of polymers used in in-situ gel

- Cellulose derivative
- Gellan gum
- Pluronic F-127
- Sodium alginate
- Polyacrylate
- Chitosan and Carbopol

EVALUATION OF IN SITU GEL

1. Clarity

The clarity of formulated solution can be determined by the visual method that is inspection under black and white background.[1,17]

2. Viscosity

The viscosity and rheological characters of the formulation either in solution or in gel made with artificial tissue fluid which depends on route of administration were determined by different viscometer like Brookfield viscometer, cone and plate viscometer.

Brookfield viscometer is used to determine the viscosity of in situ gel before and after gelation. Shear rate varies from 1 to 1000/s. about 2 ml of sample is used to apply on the plate and to ensure that the shearing of formulation does not occur. The readings were noted and average of at least three reading is taken as a point.[1,4]

3. Gel- strength

This can be evaluated using a Rheometer. Depending on the mechanism of the gelling agent used, from the sol form, a specified amount of gel is prepared in a beaker. This gel containing beaker is raised at a certain rate, pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.[4,18]

4. Determination of gelation temperature

The gelation may be defined as that the temperature at which the liquid phase makes a transition to gel. The liquid formulation is kept in a sample tube, immersed in a water bath and heated at a specific temperature and then heated at a specified rate. The samples shall be examined for gelation, which is said to have occurred when the meniscus would no longer

move upon tilting through 90°C. The gel melting temperature is a critical temperature when the gel starts flowing upon tilting through 90°C shall be recorded. Gel Formation is indicated by a lack of movement of meniscus on tilting the tube.[1,19]

5. pH of gel

The pH of in situ nasal gel is measured by using pH meter.[1]

6. Drug content

Phosphate buffer saline solution is used to dilute in situ nasal gel (10 mg) in 100 ml of volumetric flask and then dissolve the gel by shaking. By using Whatman filter paper, in situ nasal gel is filtered and pipette out 1 ml of filtrate and dilute to 100 ml with phosphate buffer saline solution at pH 6.4. Spectrophotometrically drug content is estimated by using standard curve.[1,7]

7. In vitro drug release studies

For the in situ gel formulations by oral, ocular or rectal routes, the drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment.

In the acceptor chamber, 20 ml of phosphate buffer saline at 34^0C is added and a mixture of 95 per cent O_2 and 5 per cent CO_2 is bubbled through the system to ensure the oxygenation and agitation. The temperature of the system is maintained at 34^0C. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique. For injectable in situ gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed.[1,7]

8. Determination of Mucoadhesive Strength

Force which is required to detach the gel from nasal mucosa tissue is measured to determine the mucoadhesive strength of in situ nasal gel. With the help of two glass slides, a section of sheep nasal mucosa is fixed on each of two slides using thread. On the first slide 50 mg of gel is placed and then fixing this slide below the height adjustable pan is done, on the other side of the pan another slide with mucosal section is placed in inverted position. Both slides are placed in contact with each other for 2 minutes to ensure the intimate contact between them.

The mucoadhesive force is determined from the minimal weight that detaches the mucosal tissue from surface of each formulation.[1,8]

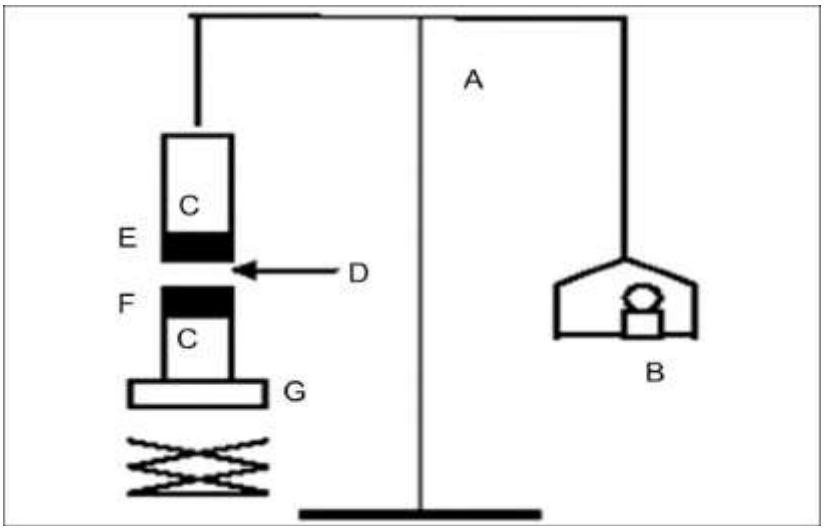

Fig 3: MODIFIED BALANCE, B WEIGHTS, C GLASS VIAL, E, F MEMBRANE, G HEIGHT ADJUSTABLE PAN[8]

Detachment stress (dynes/cm2) = mg/A

Where, m = weight required for detachment in gram,

g= Acceleration due to gravity (980 cm/s2),

A = Area of mucosa exposed

9. Histopathological Evaluation of Mucosa

Phosphate buffer is used for incubation of histopathological evaluation of tissue for 6 hours and formulation is compared with tissue incubated in diffusion chamber. 10 per cent buffered formalin solution is used to fix tissue and then embedded in paraffin following routine processing. Glass slides are used to cut the sections. Hematoxylin and eosin are used for staining of tissue. Light microscope is used for detecting tissue damage by examining the tissue sections.[1,7,20]

APPLICATION OF NASAL DRUG DELIVERY SYSTEM

- **Local delivery**

For the natural treatment of topical nasal disorders the drug is administered through nasal route. Among the most common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In fact, relatively low doses are effective when administered through nasal route with less systemic toxic effects.[21]

- **Systemic delivery**

The intranasal administration of drugs is an effective way for systemic availability of drugs as compared to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption, and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration. Examples include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.[22]

- **Nasal vaccines**

Nasal mucosa is the first site of contact with inhaled antigens and therefore, its use for vaccination, especially against respiratory infections, has been extensively evaluated. In fact, nasal vaccination is a promising alternative to the classic parenteral route, because it is able to enhance the systemic levels of specific immunoglobulin G and nasal secretary immunoglobulin A. Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and parainfluenza 3 virus.[23]

- **CNS delivery through nasal route**

Intranasal route has promising approaches for delivery of drugs to the brain. The delivery of drugs to the CNS from the nasal route may occur via olfactory neuroepithelium. The transport via trigeminal nerve system from the nasal cavity to CNS has also been described. Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumors, epilepsy, pain and sleep disorders.[24,25]

CONCLUSION

Over last decade, the nasal cavity has become one the promising and potentially versatile route for delivering drugs. In particular, its unique capability of extending the drug release, by passing the hepatic firstpass metabolism and direct delivery of drugs to brain holds great promise in the field of drug delivery. A growing body of evidence relating to nasal drug delivery suggest it might the used for challenging drugs which can facilitate the pharmaceutical manufacturing and drug delivery challenges. Various pharmaceutical dosage forms and their potential to be utilised for local or systemic drug administration has been discussed in their review article. It is intuitively expected that this review will help to

understand and further to develop the intranasal formulations to achieve specific therapeutic objectives. However, a number of technical and practical issues, which are also highlighted in this review article, remain a hurdle to be overcome in order for the full potential to be realized.

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