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Nasal In-Situ Gel: A Novel Drug Delivery System

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ABSTRACT

Over the past few decades, advances in the in situ gel technologies have spurred development in many medical and biomedical applications including controlled drug delivery. Many novel in situ gel based delivery matrices have been designed and fabricated to fulfill the ever increasing needs of the pharmaceutical and medical fields. In situ gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultraviolet irradiation from which the drug gets released in a sustained and controlled manner. Nasal delivery is a promising drug delivery option where common drug administrations such as intravenous, intramuscular or oral are inapplicable. Recently, it has been shown that many drugs have better bioavailability by nasal route than the oral route. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. The physiology of the nose presents obstacles but offers a promising route for non-invasive systemic delivery of numerous therapies and debatably drug delivery route to the brain. Thus this review focuses on nasal drug delivery, various aspects of nasal anatomy and physiology, nasal drug absorption mechanisms, various nasal drug delivery systems and their applications in drug delivery.

KEYWORDS

Nasal In Situ Gel, Absorption Enhancer, Nasal Formulation, Mucoadhesive Drug Delivery System, Microsphere Based Drug Delivery System.

INTRODUCTION

The most desirable and convenient method of drug administration is the oral route because of their ease of administration. However, in many instances oral administration is not desirable when the drug undergoes significant degradation via first pass effect in liver. Hence, lack of systemic absorption through the gastrointestinal tract led to research on alternate routes of drug delivery such as parenteral, intramuscular, subcutaneous, intranasal, transdermal etc.[1]

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Intranasal (IN) administration is a needle free and hence an ideal alternative to the parenteral route for systemic drug delivery. Nasal mucosa consists of a rich vasculature and a highly permeable structure for systemic absorption. Drug administration through the nasal cavity is easy and convenient. Avoidance of first pass metabolism is the main advantage of nasal route of drug delivery.[2]

Intranasal delivery is non-invasive, essentially painless, does not require sterile preparation and it is easily and readily administered by the patient or a physician for e.g. in an emergency setting. Given these positive attributes, it is logical to consider intranasal administration when developing new therapeutics or when

extending the life or improving the profile of an existing drug. [3, 4]

ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

In studying drug absorption from the nasal mucous membrane, it is essential to have a clear understanding of anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used.[5] The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12-14 cm. In this passage the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. There are 3 distinct functional zones in the nasal cavities, viz. vestibular, respiratory and olfactory regions.[6]

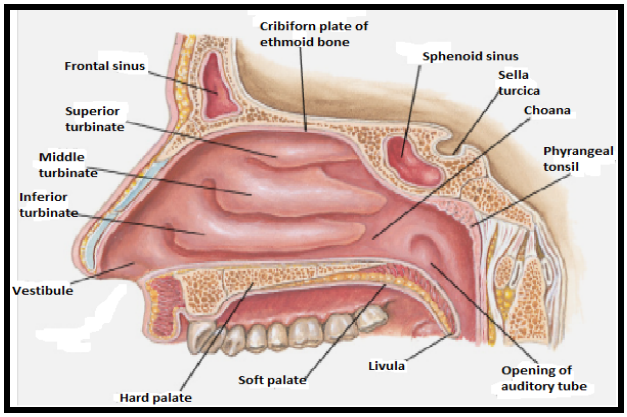

Figure 1: Anatomy of the Nasal Cavity

The zones are arranged anteroposteriorly in the sequence of order. The vestibular area serves as a baffle system and its surface is covered by a common pseudostratified epithelium where the long hairs may provide the function of filtering air borne particles. Respiratory area has a surface lined by a pseudostratified columnar epithelium and is normally covered by a dense layer of mucus that is constantly moving towards the posterior apertures of the nasal cavity by a powerful system of motile cilia.[6] The olfactory segment is lined with a specialized type of pseudostratified columnar epithelium known as olfactory epithelium, which contains receptors for the sense of the smell. This segment is located along the dorsal roof of the nasal cavity. Olfactory mucosal cell types include: bipolar neurons, supporting (sustentacular) cells, basal cells and Bowman's glands. The axons of the bipolar neurons form the olfactory nerve (cranial nerve I). Bowman's glands are serous glands in the lamina propria, whose secretions trap and dissolve odoriferous substances.[7]

The total surface area of both nasal cavities is about 150 cm^2 and the total volume is about 15 ml. Approximately 1.5 cm from the nares (nostrils) is the narrowest portion of the entire airway, the internal ostium (or nasal valve) with a cross-sectional area of about 30 mm^2 on each side. The nasal valve accounts for approximately 50% of the total resistance to respiratory airflow from the nostril to the alveoli.[7]

Each of the two nasal cavities is limited by the septal wall and the lateral wall dominated by inferior, middle and superior turbinates (Figure 1). They are important for maintaining the slit-like cavity thus facilitating humidification and temperature regulation of inspired air. Under and lateral to each of the turbinates are passages called the inferior, middle and superior meatus. The inferior and middle meatus receive the openings of the nasolacrimal duct and the paranasal sinuses. The mucous membrane in a meatus will not be hit by an ordinary intranasal spray. The individually variable caliber and shape of the lumen of the nasal cavities make it difficult to give uniform recommendations for intranasal drug administration.[5]

Nasal Epithelium

The nostrils are covered by skin, the anterior one-third of the nasal cavity by a squamous and transitional epithelium, the upper part of the cavity by an olfactory epithelium and the remaining portion by a typical airway epithelium which is ciliated, pseudostratified and columnar.[5]

The epithelial cells in the nasal vestibule are stratified, squamous and keratinized with sebaceous glands. Due to its nature, the nasal vestibule is very resistant to dehydration and can withstand noxious environmental substances

and limits permeation of substances. The atrium is a transitional epithelial region with stratified, squamous cells anteriorly and pseudostratified columnar cells with microvilli posteriorly.[8]

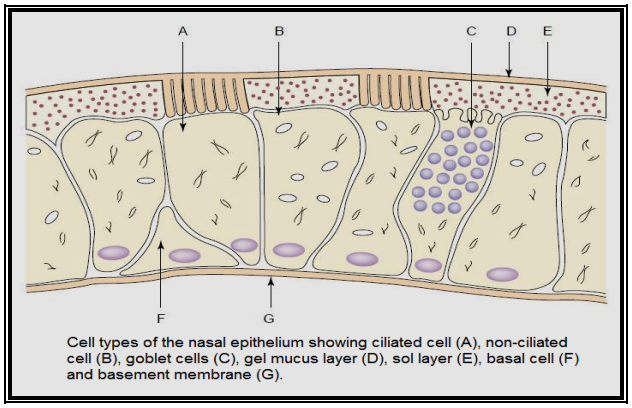

Figure 2: Structure of the Nasal Epithelium

The nasal airway epithelium consists of four major cell types: basal cells, ciliated and non-ciliated columnar cells, goblet cells and basement membrane. Basal cells are the progenitors of the other cell types and lie on the basement membrane and do not reach the airway lumen. They are believed to help in the adhesion of columnar cells to the basement membrane. Columnar cells are related to neighbouring cells by tight junctions apically and in the uppermost part by interdigitations of the cell membrane. All columnar cells, ciliated and non-ciliated are covered by about 300 microvilli uniformly distributed over the entire apical surface. These short and slender fingers like cytoplasmic expansions increase the surface area of the epithelial cells thus promoting exchange processes across the epithelium. The microvilli also prevent drying of the surface by retaining moisture essential for ciliary function. The cilia have a typical ultra structure, each ciliated cell containing about 100 cilia, 0.3 μm wide and 5 μm in length. The anterior one-third of the nasal cavity is non-ciliated.[8]

Cilia start occurring just behind the front edge of the inferior turbinate and the posterior part of the nasal cavity as well as the paranasal sinuses is densely covered by cilia. Another cell type, characteristic of an airway epithelium is the goblet cell. The goblet cell contribution to the volume of nasal secretion is probably small compared to that of the submucosal glands. Goblet cells probably respond to physical and chemical irritants in the microenvironments. The basement membrane is the layer of the collagen fibrils on which the epithelium rests.[5] The olfactory epithelium is a pseudostratified columnar in type and consists of specialized olfactory cells, supporting cells and both serous and mucous glands. The olfactory cells are bipolar neurons and act as peripheral receptors and first-order ganglion cells.[6]

Blood Supply to Nasal Cavity [9]

Nasal vasculature is richly supplied with blood to fulfill the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. Blood supply comes from branches of both the internal and external carotid artery including branches of the facial artery and maxillary artery. The named arteries of the nose are,

- **Sphenopalatine artery**, a branch of maxillary artery.
- **Anterior ethmoidal artery**, a branch of ophthalmic artery.
- **Branches of the facial artery** supplying the vestibule of the nasal cavity.

The lamina propria in the nasal mucosa is rich in blood vessels. They differ from the vasculature in the tracheobronchial tree in three ways. First is venous sinusoid in the nose. Second is arteriovenous anastomosis in the nose. Third are the nasal vasculature shows cyclical changes of congestion giving rise to the nasal cycle. Porosity of the endothelial basement membrane has been described as a characteristic of nasal blood vessels. The capillaries just below the surface epithelium and surrounding the glands are well suited for rapid movement of fluid through the vascular wall.

Mucus Secretion and Mucociliary Clearance[10]

The submucosal glands which secrete the greater quantity of nasal mucus comprise both mucus cells, secreting the mucus gels and serous cells, producing a watery fluid.

Table 1: Structural Feature of Different Sections of Nasal Cavity and Their Relative Impact on Permeability[6]

Region	Structural Features	Permeability
Nasal vestibule	• Nasal hairs (vibrissae) Epithelial cells are stratified, squamous and keratinized Sebaceous glands present	Least permeable because of the presence of Keratinized cells
Atrium	• Transepithelial region Stratified squamous cells present anteriorly and pseudo stratified cells with microvilli present posteriorly	Less permeable as it has small surface area and stratified cells are present anteriorly
Respiratory region (inferior turbinate middle turbinate superior turbinate)	• Pseudostratified ciliated columnar cells with microvilli (300 per cell), large surface area • Receives maximum nasal secretions because of the presence of seromucus glands, nasolacrimal duct and goblet cells • Richly supplied with blood for heating and humidification of inspired air, presence of paranasal sinuses	Most permeable region because of large surface area and rich vasculature
Olfactory region	• Specialized ciliated olfactory nerve cells for smell perception • Receives ophthalmic and maxillary divisions of trigeminal nerve • Direct access to cerebrospinal fluid	Direct access to cerebrospinal fluid
Nasopharynx	• Upper part contains ciliated cells and lower part contains squamous epithelium.	Receives nasal cavity drainage

Mucus is also released from the goblet cells as mucus granules which swell in the nasal fluids to contribute to the mucus layer. Mucus secretion is a complex mixture of many substances and consists of about 95% water, 2% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozyme and lactoferrin and <1% lipids. About 1.5 to 2 liter of nasal mucus is produced daily. This mucus blanket about 5 mm thick consists of two layers, a lower sol layer and an upper gel layer. The viscosity of both layers affects ciliary beating and the efficiency of transporting the overlying mucus, the mucociliary clearance (MCC). The nasal mucus performs a number of physiological functions,

- It covers the mucosa and physically and enzymatically protects it.
- The mucus has water-holding capacity.
- It exhibits surface electrical activity.
- It permits efficient heat transfer.
- It acts as adhesive and transports particulate matter towards the nasopharynx.
- It behaves as an adhesive.
- It acts as a retainer for the substances in the nasal duct.

Nasal ciliary clearance is one of the most important physiological defense mechanisms of the respiratory tract to protect the body against any noxious materials inhaled from reaching the lungs.

When such materials adhere to or dissolve in the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the GIT. Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the MCC. It consists of a coordinated interaction between the overlying mucus layer and the methachronal wave like movement of the underlying cilia. Optimum physicochemical properties of the mucus and movement of the cilia are required for effective and efficient MCC. Although there is a lot on inter-individual differences in MCC rate, this has been estimated at 6 mm/min. Maintaining optimal MCC is very important in order to prevent respiratory tract infections. The MCC can be influenced by environmental and pathological conditions. Factors that can increase ciliary beat frequency (CBF) and mucus production or decrease mucus viscosity will all lead to increase in MCC. Environmental conditions like temperature (below or above 23°C), inhalation of sulphur dioxide and cigarette smoke all decrease MCC. All the pathological and environmental conditions above will ultimately alter nasal drug delivery and the performance of nasal mucoadhesive formulations and should be taken into account during product development.

NASAL DRUG DELIVERY SYSTEM [11]

Intranasal (IN) delivery is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some drugs. Hence there has been a surge of interest that has led to many investigations involving the nasal cavity as a feasible site for the administration of much therapeutic agents.

Advantages [11]

- The nasal epithelium is thin, porous (especially when compared to other epithelial surfaces) and highly vascularised. This ensures high degree of absorption and rapid transport of absorbed substances into the systemic circulation for initiation of therapeutic action.
- A porous endothelial basement membrane that poses no restriction to transporting the drug into general circulation.
- Absorbed substances are transported directly into the systemic circulation thereby avoiding the first pass metabolic effect generally experienced following oral drug administration.
- In some cases, drugs can be absorbed directly into the CNS after nasal administration bypassing the tight blood brain barrier.
- Generally, the enzymatic activity of the nasal epithelium is lower than that of the GIT or liver and higher bioavailability of drugs especially proteins and peptides can be achieved. In addition, enzyme inhibitors are more effective following nasal than oral application because of a higher degree of dilution in the latter than in the former.
- Realization of pulsatile delivery of some drugs like human growth hormone, insulin, etc. is higher with NDD.
- The nose is amenable to self-medication that not only lowers the cost of therapy but improves patient compliance as well. The risk of Overdosage is low and nasal lavage can be used to remove unabsorbed excess drug.
- Reformulation of existing drugs as NDD products offers companies the possibility to extend the life cycle of their products.

Limitation [11]

- Only a limited amount of the formulation can be administered intranasally. Application of large quantities will disturb the normal functioning of the nose (olfaction and humidification of inspired air).
- The dosing regimen as a result of drainage of the solution or expulsion of the dose due to sneezing.
- The high porosity of the nasal epithelium is still not sufficient for absorption of all compounds especially hydrophilic ones and large molecules like proteins.
- In addition, the nasal mucosa is enzymatically active albeit to a lesser extent compared with the GIT.

- The potential toxicology or irritancy of the drug product is a very important point that should be thoroughly investigated.
- Drug absorption and permeability of the different regions of the nasal cavity is quite different. Also deposition posteriorly will result in faster clearance by the MCC. The MCC is a very important physiological function of the nose that works strongly against NDD.

Another limitation of nasal drug delivery includes rapid mucociliary clearance of the therapeutic agent from the site of deposition resulting in a short span of time available for absorption. However, it can be overcome by using bioadhesive polymers that increase residence time of the formulation in the nasal cavity thereby improving absorption.

Mechanism for Drug Permeation [12, 13]

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. Mucin the principle protein in the mucus has the potential to bind to solutes and hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.). Subsequent to a drug's passage through the mucus, there are several 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. Obstacles to drug absorption are potential 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 involves an aqueous route of transport which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.

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.

FACTORS AFFECTING NASAL DRUG ABSORPTION [9, 12]

Factors influencing absorption are related to nasal physiology, physicochemical characteristics of drugs and formulation aspects.

I. Biological Factors [9]

- Structural features
- Biochemical changes
- Physiological factors
  - ✓ Blood flow
  - ✓ Nasal secretions
  - ✓ pH of the nasal cavity
  - ✓ Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental factors
  - ✓ Temperature
  - ✓ Humidity

II. Physicochemical Properties of Drugs [9]

- Molecular weight
- Size
- Solubility
- Lipophilicity
- Pka and Partition coefficient

III. Physicochemical Properties of Formulation [12]

- Dosage form
- Viscosity
- pH and mucosal irritancy
- Osmolarity
- Volume of solution applied

IV. Device Related Factors [12]

- Particle size of the droplet/powder
- Size and pattern of disposion

BIOLOGICAL FACTORS [9]

Physiological factors include firstly mucociliary clearance is one of the major factor responsible for the clearance of the drugs from the nasal cavity and it involves combined action of mucus layer and cilia, tips of cilia are in contact with and transport the superficial viscoelastic mucus layer towards nasopharynx while less viscous lower layer of mucus is relatively stationary. Secondly broad ranges of metabolic enzymes are present in the nasal mucosa. This can limit bioavailability of nasally administered drugs however; level of activity of these enzymes is lower as compared to that found in GIT and liver. Moreover pathological conditions like rhinitis, common cold can also affect absorption of drugs from nasal cavity and pH of nasal cavity also affects permeation of drug. A change in the pH of mucus can affect the ionization and increase or decrease the permeation of drug depending on the nature of the drug.

PHYSICOCHEMICAL PROPERTIES OF DRUGS [9]

Various physicochemical characteristics of drug can also affect nasal absorption of the drug.

Molecular Weight and Size

Extent of the absorption of the drug depends on molecular weight particularly for hydrophilic compounds. Nasal route is suitable for efficient delivery of drugs up to 1000 Daltons. Absorption reduces the significantly if the molecular weight is greater than 1000 Daltons except with the use of penetration enhancers. It has been reported that a good linear correlation exists between the log percentage drug absorbed nasally and the log molecular weight of water soluble compounds suggestion the participation of aqueous channels in the nasal absorption of water soluble molecules. It has been reported that particle size greater than 10 µm are deposited in the nasal cavity. Particles that are 2 to 10 µm can be retained in the lungs and particles of less than 1 µm are exhaled.

Solubility and Dissolution

Drug solubility is a major factor in determining absorption of drug through biological membranes. It not only limits the drug absorption but it can also limit a formulator's ability to formulate a product if the drug is not sufficiently soluble in the desired vehicles. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Particles deposited in the nostrils need to be dissolved prior to absorption. If the drug remains as particles in nostrils or if they are cleared away from the nasal cavity, one may not observe absorption of the drug.

Chemical Form

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. For example, conversion of a drug into a salt or ester form can alter its absorption. This phenomenon is associated with the increase in lipophilicity following esterification which increased the rate and extent of nasal absorption.

Partition Coefficient and pKa

A quantitative relationship between the partition coefficient and nasal absorption is constant. As per the pH partition theory, unionized species are absorbed better compared with ionized species and same holds true in the case of nasal absorption. The extent of absorption is PH dependent, being higher at a pH lower than the pKa and decreases beyond the pKa. In general, the authors found that the nasal absorption increase with the lipophilicity of the permeant. Various studies indicate that the drug concentrations in the cerebrospinal fluid (CSF) rise with an increase in lipophilicity or partition coefficient of the drugs.

PHYSICOCHEMICAL PROPERTIES OF FORMULATION [12]

Drug Concentration, Dose and Dose volume

Drug concentration, dose and dose volume of administration are three interrelated parameters that impact the performance of the nasal delivery system. Nasal absorption of L-Tyrosine

was shown to increase with drug concentration in nasal perfusion experiments. 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 drug is increasing by increasing formulation volume there may be a limit as to what extent nasal absorption can be increased. The nostrils can retain 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.

Physical Form of Formulation

Nasal drug absorption depends on the physical form of the formulation. The important parameter in formulation development is viscosity of the formulation. Generally a more viscous formulation will provide less efficient systemic nasal drug delivery. In nasal delivery of desmopressin, addition of the viscous agents may produce a somewhat more sustained effect. It would seem logical that more viscous formulations e.g. gels should be more appropriate for locally acting drugs.

Formulation pH

The pH of the formulation as well as that of nasal surface can affect a drug's permeation. The pH of the nasal formulation is important for the following reasons,

- To avoid irritation of the nasal mucosa.
- To allow the drug to be available in unionized form for absorption.
- To prevent the growth of pathogenic bacteria in the nasal passage.
- To maintain functionality of excipients such as preservatives.
- To sustain normal physiological ciliary movement.

Lysozymes are found in nasal secretions which are responsible for destroying certain bacteria at acidic pH. Under alkaline conditions lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5.

Buffer Capacity

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 administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH.

Osmolarity

Drug absorption can be affected by tonicity of the formulation. Shrinkage of the epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of hypertonic solutions. Generally an isotonic formulation is preferred.

Gelling / Viscofying Agents or Gel Forming Carriers

Some formulations need to be gelled or made more viscous to increase nasal residence time. Increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Drug carrier such as hydroxypropylcellulose 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.

Solubilizers

Aqueous solubility of a drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol, medium chain glycerides and Labrasol can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP-β-Cyclodextrins 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.

Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzyl alcohol are some of the commonly used preservatives in nasal formulations.

Antioxidants

Depending upon the stability profile of a given drug in the formulation chosen, it may be necessary to use antioxidants to prevent drug degradation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxy toluene and tocopherol.

Humectants

Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel based nasal products to avoid nasal irritation and are not likely to affect drug absorption. Some common humectants used include glycerin, sorbitol and mannitol.[14]

Absorption Enhancers

When it becomes difficult for a nasal product to achieve its required absorption profile, the use of absorption enhancers is recommended. The selection of absorption enhancers is based upon their acceptability by regulatory agencies and their impact on the physiological functioning of the nose. Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation. Once a suitable enhancer is identified, its optimal concentration should be experimentally determined. Generally higher concentrations of enhancers are likely to result in nasal irritation and damage to the nasal mucosa. On the other hand, lower enhancer concentrations would generally provide lower or no improvement of absorption[1]. The various compounds investigated as enhancers in nasal drug delivery research are mentioned in Table 2.[1]

Table 2: Various Compounds Investigated As Enhancers in Nasal Drug Delivery Research[1]

Surfactants	Sodium dodecyl sulfate (SDS), Polyoxy ethylene-9-lauryl ether, Phosphatidylcholines
Complexing and Chelating agents	Ethylene diamine tetraacetic acid(EDTA)
Cyclodextrins and derivatives	α-, β-, γ-cyclodextrin, DMβ-, HPβ-cyclodextrin
Fusidic acid derivatives	Sodium Tauradihydrofusidate (STDHF)
Bile salts	Sodium taurocholate, Sodium glycocholate
Dry microspheres	Degradable starch microsphere, Dextran microspheres

NASAL FORMULATIONS [15]

Designing of nasal formulation depends upon the therapeutic need of the particular drug molecule, duration of action and duration of therapy. Both controlled release and conventional release drug delivery are possible through nasal route. Requirement of the pharmaceutical excipients depend upon the mode of drug delivery i.e. local or systemic drug delivery. Wide range of nasal formulations has been studied so far and these include,

1. Nasal drops
2. Nasal powders
3. Nasal sprays (solution/suspension)
4. Nasal mucoadhesive particulate delivery (micro/nanoparticles, liposomes)
5. Nasal gel
6. Nasal ointments
7. Nasal microemulsions

MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers which become adhesive on hydration and hence can be

used for targeting a drug to a particular region of the body for extended period of time.[16]

Bioadhesion is an integral phenomenon in which two materials at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue then the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye. [16]

The potential of the drug delivery system to localize a drug at the site of absorption for an extended period of time and to promote intimate contact between the formulation and the underlying absorbing tissue has great appeal to both local and systemic effects. Good considered bioadhesion is the phenomenon in which two materials at least one being of biological nature are held together for extended periods of time by interfacial forces. Bioadhesion has been defined as the attachment of synthetic or biological macromolecules to a biological tissue. If the adhesive attachment is to a mucous coat the phenomenon is referred to as Mucoadhesion.[17]

Mechanism of Mucoadhesion

Several theories have been put forward to explain the mechanism of polymer-mucus interactions that lead to mucoadhesion. To start with the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative.[8]

Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration there is a dissociation of hydrogen bonds of the polymer chains. The polymer-water interaction becomes greater than the polymer-polymer interaction thereby making the polymer chains available for mucus penetration. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links and is inversely related to the cross-linking density. [18, 19]

Theories of Mucoadhesion [20]

1. Electronic Theory: The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical charge forms at the interface and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.

2. Adsorption Theory: The adsorption theory of bioadhesion proposes that adhesion of a polymer to a biological tissue results from (i) primary chemical bonds that are somewhat permanent and therefore undesirable in bioadhesion (ii) van der Waals, hydrogen, hydrophobic and electrostatic forces which form secondary chemical bonds.

3. Wetting Theory: Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer or use of a surfactant.

4. Diffusion Theory: The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers and the

diffusion co-efficient is known to depend on molecular weight and cross-linking density.

Factors Affecting Mucoadhesion [17]

The mucoadhesive power of a polymer is affected by the nature of the polymer and also by the nature of the surrounding media. The factors influencing the mucoadhesion are as follows,

I. Polymer Related Factors

- Molecular weight
- Concentration of active polymer
- Flexibility of polymer chains
- Special confirmation
- Swelling

II. Environment Related Factors

- pH of the polymer-substrate interface
- Applied strength
- Initial contact time

III. Physiological Factors

- Mucin turnover
- Disease state

Methods for Measuring Mucoadhesion [17]

Several test methods have been reported in literature for studying mucoadhesion. These tests are important during the design and development of a bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis and bioadhesive bond strength. The methods reported are as follows,

1. *In vitro / Ex vivo* methods

- Methods based on measurement of tensile strength.
- Methods based on measurement of strain strength.

2. Other *In vitro* Methods

- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Falling liquid film method
- Colloidal gold staining method
- Viscometric method
- Thumb test
- Adhesion number
- Electrical conductance

3. *In vivo* Methods:

- Use of radio isotope
- Use of gamma scintigraphy

Advantages of Mucoadhesive Drug Delivery Systems [17]

1. These dosage forms are readily localized in the region applied to improve and enhance the bioavailability of drugs.
2. The dosage forms facilitate intimate contact of the formulation with the underlying absorption surface. This allows modification of the tissue permeability for absorption of macromolecules such as peptides and proteins. Inclusion of penetration enhancers such as sodium glycholate, sodium taurocholate and protease inhibitors in the mucoadhesive dosage forms resulted in the better absorption of the peptides and proteins.
3. Mucoadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.

Mucoadhesive Polymers

Bioadhesive polymers have been used extensively in nasal drug delivery systems to provide dosage forms retention. Bioadhesive polymers are defined as polymers that can adhere to a biological substrate. Diverse classes of polymers have been investigated for their potential use as mucoadhesive.[21]

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks joint by cross linking agents. The polymers should possess optimal polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual

adsorption and interpenetration of polymer and mucus to take place.[21]

Ideal polymers for mucoadhesive drug delivery system should have the following characteristics, [22]

- The polymers and its degradation products should be nontoxic and non-absorbable from the gastrointestinal tract.
- It should be a nonirritant to the mucous membranes.
- It should preferably form a strong non-covalent bond with the mucin epithelial cell surface.
- It should adhere quickly to moist tissue and should possess some site specificity.
- It should allow easy incorporation of the drug and offer no hinderance to its release.
- The polymer must not decompose on storage or during shelf life of the dosage form.
- The cost of the polymer should be not too high, so that prepared dosage form remains competitive.
- It should show bioadhesive properties in both dry and liquid state.
- It should possess an optimum molecular weight to the bioadhesion.
- It should be able to accommodate both oil and water soluble drugs for the purpose of controlled drug delivery.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.
- It should show specificity for attachment to an area or cellular site.
- It should show specificity and stimulate endocytosis.
- It should be inert and compatible with the environment.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.
- It should possess a wide margin of safety both locally and systemically

Table 3: Mucoadhesive Polymers Used In Nasal Drug Delivery[22]

Polymers	**Bioadhesive property**
Carboxymethylcellulose	+ + +
Carbopol 934	+ + +
Polycarbophil	+ + +
Tragacanth	+ + +
Poly(acrylic acid/divinyl benzene)	+ + +
Sodium alginate	+ + +
Hydroxy ethyl cellulose	+ + +
Gum karaya	++
Thermally modified starch	++
Pectin	++
Polyvinyl pyrrolidene	+
Acacia	+
Polyethylene glycol	+
Psyllium	+
Amberlite-200 resin	+
Hydroxypropyl cellulose	+
Chitosan	+

MICROSPHERE BASED DRUG DELIVERY SYSTEM

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm. They are made of polymeric, waxy or other protective materials i.e. biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatine; the synthetic polymers include polylactic acid and polyglycolic acid. Microspheres are small and have large surface to volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important often dictating their activity. [23]

Microparticles are of two types:

Microcapsules: The entrapped substance is completely surrounded by a distinct capsule wall.

Microspheres: The entrapped substance is dispersed throughout the microsphere.

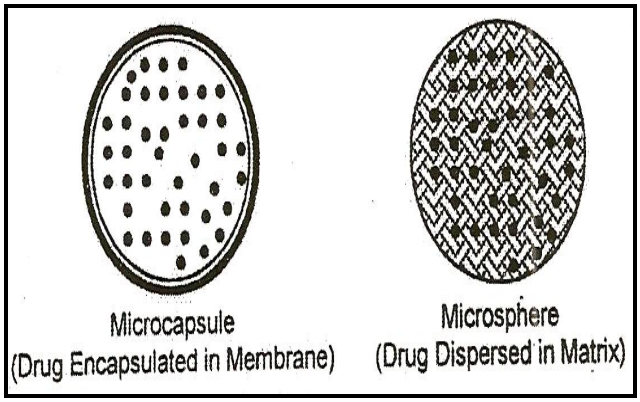

Figure 3: Differentiations between Microcapsules and Microsphere

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. However, the success of these microspheres is limited due to the short residence time at the site of absorption. It would therefore advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres.[24]

General Method of Preparation of Microspheres [25]

The microspheres can be prepared by using any of the several techniques enlisted following. But the choice of the technique mainly depends on the nature of the polymer used for the intended use and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below,

- The particle size requirements.
- The drug or the protein should not be adversely affected by the process.
- Reproducibility of the release profile and the method.
- No stability problem.
- There should be no toxic products associated with final product.

General Methods are:

- Single emulsion technique
- Polymerization techniques
  - ✓ Normal polymerization
  - ✓ Interfacial polymerization
- Phase separation/coacervation techniques
- Spray drying and spray congealing
- Solvent evaporation
- Chemical and thermal cross-linking
- Freeze drying

Loading of Drug [25]

The active components are loaded over the microspheres principally using two methods i.e. during the preparation of the microsphere or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and

surface adsorption. Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross-linking agent, surfactant, stabilizers, etc.), heat of polymerization, agitation intensity, etc. Percent incorporation in preformed microspheres is relatively less but the major advantage of loading method being there is no effect of process variables. The loading is carried out in pre-formed microspheres by incubating them with high concentration of the drug in a suitable solvent. The drug in these microspheres is loaded via penetration or diffusion of the dug through the pores in the microspheres as well as adsorption on their surface. The solvent is then removed, leaving drug loaded microspheres.

Drug Release Kinetics [25]

Release of the active constituents is an important consideration in case of microspheres. Many theoretically possible mechanisms may be considered for the release of drug from the microparticles.

1. Liberation due to polymer erosion or degradation
2. Self-diffusion through the pores
3. Release from the surface of the polymer
4. Pulsed delivery initiated by the application of an oscillating or sonic field

In most of the cases, a combination of more than one mechanism for drug release may operate. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The drug could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second pore diffusion mechanism and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuses into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors, viz. the macromolecule: polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. The pore diffusion method is named so because the dispersed protein/drug creates a water filled pore network through which the active principle diffuses out in a controlled manner. In case of the biodegradable polymers, the release is controlled by both the erosion as well as diffusion process. The polymer erosion i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix. This plasticization of the matrix finally leads to the cleavage of the hydrolytic bonds. The cleavage of the bond is also facilitated by the presence of the enzyme (lysozymes) in the surroundings. The erosion of the polymer may be either surface or bulk leading to the rapid release of the drug/active compound. The rate and extent of water uptake thereof determines release profile of the system and depends on type of the polymer, porosity of the polymer matrix, protein/drug loading, etc.[25]

EVALUATION OF NASAL IN SITU GEL SYSTEM

In situ gels may be evaluated and characterized for the following parameters,

Clarity [23]

The clarity of formulated solution was determined by visual inspection under black and white background.

Texture Analysis [23]

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringeability of sol so the formulation can be easily administered *in vivo*.

Gelation Point [23]

It is temperature at which the liquid phase makes a transition to gel. A gelation temperature range suitable for thermoreversible nasal gel

would be 30□36°C. Gelation point was considered as the temperature where formulations would not flow when test tubes were tilted to 90° angle as the temperature was gradually increased. While in case of pH & ion dependant polymer there is change in pH or contact with nasal fluid they get change from sol to gel.

pH of the Gels [24]

The pH of each batch was measured using pH meter which was calibrated using buffers of pH 4 and pH 8 before the measurements.

Content Uniformity [24]

Weighed amount of the formulation was dissolved in medium and after suitable dilution the absorbance was measured using UV/visible spectrophotometer. The amount of the drug present in the formulation was calculated by measuring the absorbance of a standard solution of known concentration of drug prepared in distilled water.

Rheological Studies [24]

Viscosity of the prepared formulations was measured by using Brookfield Viscometer. The gel under study was placed in the small sample holder and the spindle was lowered perpendicularly into it. The spindle was rotated at varying speeds and the suitable speed was selected.

Gel Strength [23]

This parameter can be evaluated using a Rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker from the sol form. This gel containing beaker is raised at a certain rate so 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.

Measurement of Gel Strength [23]

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength was then placed onto the in situ gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation. Weights that detached the two vials using the following equation,

Detachment stress (dynes /cm^2) = mg /A

where *m* is the weight added to balance in grams, *g* is the acceleration due to gravity taken as 980 cm/sec^2, A is the area of the tissue exposed and is equal to πr^2 (*r* is the radius of the circular hole in the aluminium cap).

In vitro Nasal Diffusion Cell [24]

The nasal diffusion cell was fabricated in glass. Drug release from gel was tested with nasal diffusion cell using dialysis membrane (mol.wt.12, 000-14,000 kDa) with permeation area of 0.785 cm^2. 20ml of diffusion medium was added to the acceptor chamber. Gel containing drug equivalent to its dose was placed in donor compartment. At predetermined time points, 1ml sample was withdrawn from the acceptor compartment replacing the sampled volume with diffusion medium after each sampling. The samples were suitably diluted and measured spectrophotometrically. The concentration of drug was determined from a previously constructed calibration curve.

Fourier Transform Infrared Spectroscopy and Thermal Analysis [24]

During gelation process the nature of interacting forces can be evaluated using this technique by employing KBr pellet method. Thermogravimetric analysis can be conducted for *in situ* forming polymeric systems to quantitate the percentage of water in hydrogel. DSC is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.

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