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Review on Strategies and Prospective of in Situ Nasal Gel

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ABSTRACT

Nowdays many drugs have best systemic bioavailability through nasal route as compared to oral administration. In these intranasal drug delivery enables dose reduction and rapid attainment of therapeutics, bloods levels, quicker onsets of pharmacological activity, and fewer side effects. The recent advancement of nasal drug delivery system has increased tremendously and is gaining significant importance. The anatomy of nasal route, advantages, disadvantages, mechanism of action, limitation, factors affecting nasal delivery, applications and future trends of nasal drug delivery system in local delivery, systematic delivery, nasal vaccines and CNS delivery are lucidly. The important aspects of biological, physicochemical and pharmaceutical and pharmacological factors of nasal cavity that must be considered during the process of discovery as well as development of new drugs for nasal delivery as in corporation into appropriate different nasal pharmaceutical formulation are also discussed. Nasal route is more suitable for those drugs which cannot be administered orally due to more gastric degradation or hepatic first pass metabolism of the drug. Intra nasal delivery is non-invasive technique, essentially painless, does not require sterile preparation, and is easily and readily administered by the patients or a physician, as in emergency setting. Further addition, intranasal drug delivery reduces dose size increase rapid nasal delivery of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects. There are various approaches in nasal drug, delivering a therapeutic substance to the target site.

KEYWORDS: *In situ nasal gel, Bioavailability, Drug delivery, Pharmacological activity, Rapid action*

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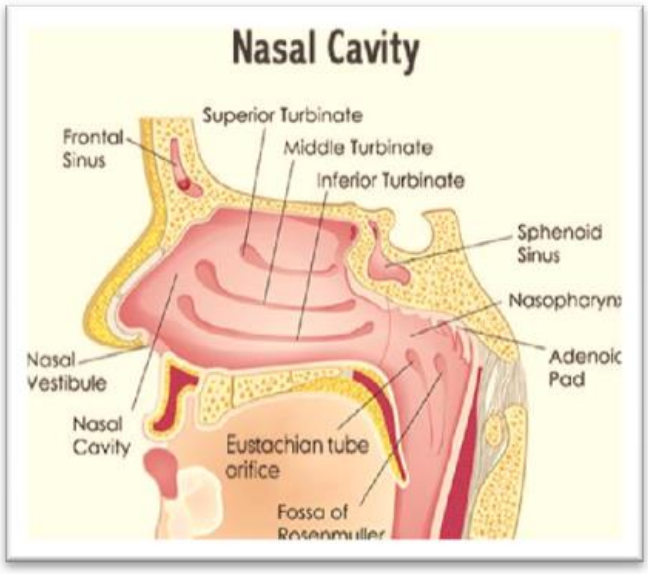
INTRODUCTION

In recent years many drugs have been shown to better accomplish systemic bioavailability through nasal route than by other administration. Nasal therapy is the acknowledged form of treatment in the Ayurveda of Indian medicine, and also called as NASAYA KARMA. Nasal drug delivery which is practiced since years, has been given a new attain of life. It is a useful delivery method for drugs that are active in low doses and show no least oral bioavailability such as proteins and peptides. One of the reasons for less absorption of peptides and proteins via the nasal route is fast movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism. The nasal route avoids hepatic first pass elimination associated with the oral delivery. It is easily accessible and suitable for self-medication.[1] The early 1980s saw the introduction of the nasal route as a promising systemic delivery alternative to other conventional drug delivery routes. Nasal route is easily accessible, convenient, and consistent with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, escaping the hepatic first pass elimination. The oral administration of protein and peptide drug is not possible because they are significantly reduced in the gastrointestinal tract or considerably metabolized by the first-pass effect in the liver. Intranasal drug delivery offers assuring substitute route for administration of such drugs. Many advanced and effective approaches to the CNS delivery of drugs have developed in recent years. Nasal delivery is one of the most determined delivery opportunities for brain targeting as brain and nose compartments are linked to each other via olfactory/trigeminal path via peripheral circulation. Direct nose to brain transport results into quick and/or greater uptake in the brain, which delivers an alternative selection of self-medication. Synthesis of more lipophilic analogues, enzyme inhibitors, permeation enhancers, colloidal, bioadhesive and NDDS like microemulsion, liposomes and nanoparticles could help in abolishing certain pharmaceutical challenges like low bioavailability, local irritation and toxicity upon long term treatment. With all its inherent advantages intranasal route has been indicated as the most promising approach for delivery of drugs to the brain/CNS [2]. Oral route is the most desirable and convenient method of drug administration as facilitate manufacture and administration. Failure of satisfactory absorption through the gastrointestinal tract lead to alternate routes of drug delivery in research. Researchers developed the parenteral route of drug administration to elucidate the above problem. For the past few decades, the transdermal route has been selected for delivery of specific drugs. However, its application is limited due to low permeability of the skin to many drugs [3].

Anatomy of nose

The external nose has a pyramidal shape, which may vary greatly depending on race. The change in the shape of the nose has been widely studied by plastic and reconstruction

surgeons. Even though this outer structure may not have an apparent significance for intranasal administration of drugs and vaccines, it is important for the design of delivery, and for understanding the administration techniques. The external nasal anatomy can be differentiated into bony, cartilaginous, and soft tissue components. The soft tissue component of the nose is composed of skin, fibro adipose tissue and muscles of facial expression, regulated by the facial nerve. The skin over the nasofrontal angle is thick or dense [4]. The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm^2, and is divided into two nasal cavities by the septum. The volume of each cavity is nearly 7.5 ml, having a surface area around 75 cm^2. Formulation of drug administration into the nasal cavity, a solute can be accumulated in one or more of anatomically distinct regions, the vestibular, respiratory and olfactory regions [5]. The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. The nasal cavity contains three main regions which are nasal vestibule, olfactory region and respiratory region. The surface area in the nose can amplify about 150 cm by the lateral walls of the nasal cavity consisting a folded structure, it is a very high surface area compared to its small volume.



This folded structure involves three turbinates: the superior, the median and the inferior. The most important nasal airway have the narrow passages, ordinarily it is 1-3 mm wide and these narrow structures are beneficial to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; non olfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is enclosed with skin-like stratified squamous epithelium cells, where as respiratory region, which has a typical airways, epithelium guarded with numerous microvilli, resulting in a large surface area available for drug absorption and transport [6]. The major functions of the nasal cavity are breathing and olfaction [7]. Nasal respiratory sites compared to olfactory sites includes Extravasation which was size-dependent at all sites but the differences between sites can largely be qualified to two principal physiological characteristics: (i) differences in relative capillary vascular density, i.e. vascularity, and (ii) differences in vascular permeability determined by the characteristic average capillary wall pore size [8]. The nasal cavity is linked with arteries, veins, lymphs and neurons. Superior coronary supplied the upper lip and provides two vessels into the nose: inferior artery of the septum, which supplies blood to the anterior part or the nasal septum which supplies the ala of the nose [9].

Nasal cycle & nasal control

The nasal cycle (NC)

It is the natural congestion and decongestion of the nasal mucosa during the day, where congestion of one side is attended by reciprocal decongestion of the contralateral side. It is based on the dilation/ contraction of the venous cavernous tissue in the submucosa of the turbinates and septum, but also of the ethmoid sinuses. It is known that almost 70-80% of adults face a regular NC, but a true periodicity/reciprocity exists only in 21-39% of the population. NC is measured an ultradian rhythm of side-to-side nasal mucosal enlargement with a phase length ranging from 30 min to 6h. As first described, in an ideal cycle, the two air routes should show reciprocal variations of equal amplitude, 180° out of phase, with an identical period and similar mean airflow, with total nasal flow remaining constant [10].

NC control:

Congestion and decongestion of the nasal venous cavernous tissue is under the control of the ANS. Nasal venous sinusoids have a dense adrenergic innervation, and stimulation of these fibres causes the release of noradrenaline, which results in vasoconstriction and in a reduction of nasal airway resistances (NAR). Physiologically, there is a sympathetic tone at the level of the nasal venous sinusoids and the transection or a local anaesthesia of the cervical sympathetic nerves evokes ipsilateral nasal congestion. High spinal cord injury (>T1) is associated with immediate loss of the NC, which appears to slowly recover with time. Selective block of the stellate ganglion is able to alter the NC of the homolateral side, heading to a swelling of the inferior concha attended by a pronounced increase of NAR, with a moderate rise of NAR in the contralateral side [10].

Nose-to-brain delivery

The BBB and the cerebrospinal fluid (CSF) are two physiological barriers that separate the brain from its blood supply, regulating the internal environment. The tight junctions between the BBB capillary endothelial cells are r++esponsible for the restrictions to the drugs passage into the brain. Only low molecular weight and lipophilic molecules can cross easily the BBB. Macromolecules, such as peptides and proteins, do not have access to the CNS through the BBB. In this context, the nasal route arises as a promising alternative, providing a direct access to the brain with no need of bypassing the BBB. As mentioned, the drugs passage from the nose to the brain occurs by the olfactory bulb, with consequent transport via axons along the neurons. Nonetheless, some of the nasal administered drugs are absorbed preferentially in the respiratory epithelium, due to the high density of blood vessel. The nose-to-brain mechanism has been extensively investigated for the development of formulations that improve brain targeting [11].

Passage of drugs via nasal mucosa

The passage of drugs via the nasal mucosa is mostly accomplished in three ways, which are paracellular,

transcellular and transcytotic. The first channel is the paracellular transport, which is associated with the intercellular spaces and tight junctions. Paracellular transport is an important pathway particularly for absorption of peptides and proteins, so it has been described that the paracellular route should be reversibly opened to enrich nasal absorption of peptides, and mucosal absorption enhances due to the hydrophilic characteristic of drugs. The second passage route is the transcellular route which is due to passive diffusion or active transport mechanism. It is important in absorption of lipophilic molecules or the molecules that are acknowledged by the membrane (active carrier transport). The third passage route is transcytosis. Here, the particle is taken into a vesicle and shifted to the cell. Finally, it is accumulated in the interstitial space.[12]

Mechanism of nasal absorption

The absorbed drug from the nasal cavity passes across the mucus layer. It is the first step in absorption. Small, unchanged drugs simply pass through this layer but large, charged drugs take much time to cross it. The principle protein of the mucus is mucin. It has the affinity to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are probable as a result of environmental changes like change in pH and temperature. Many absorption mechanisms were advised earlier but only two mechanisms have been predominantly used, such as- [13].

First mechanism:

It includes an aqueous route of transport, which is also well-known as the paracellular route but slow and passive. It has an inverse corelation between intranasal absorption and the molecular weight of water soluble compounds. The molecular weight more than 1000 Daltons show low bioavailability [1].

Second mechanism:

It involves transport through a lipoidal path known as the transcellular process. It is accountable for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs can also cross cell membranes by an active transport path via carrier-mediated means or transport through the opening of tight junctions. For example chitosan, a natural biopolymer from shell fish opens tight junctions between epithelial cells to simplify the drug transport [1].

To date, the accurate mechanisms of nose to brain delivery have not been completely understood. Pathways involving nerves connecting the nasal routes to the brain and spinal cord are important as well as routes involving the vasculature, cerebrospinal fluid, and lymphatic system. Thus, it seems that a combination of these pathways should be responsible, one may predominate depending on the properties of the drug, the characteristics of the formulations, and the delivery device used. The delivery of substances from the nose to the CNS may occur via olfactory neuroepithelium and may include paracellular, transcellular, and/or neuronal transport. The paracellular way refers to the transfer of substances across an epithelium through tight junctions between sustentacular cells or the fissures between sustentacular cells and olfactory neurons. This route is slow and passive, it is responsible for the transport of hydrophilic drugs, and it shows rate dependency on the molecular weight of a molecule. The transcellular process is accountable for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. This pathway includes transport across the sustentacular cells, most likely by receptor-mediated endocytosis, fluid phase endocytosis, or by passive diffusion. It is rapidly mediated and at a high rate [13].

Principle of gel

Main principle of in-situ gelling for nasal formulation is to be applied in nasal cavity. In this process after administration of drug solution is transferred into gel in nasal cavity [14].

Properties of nasal in situ gel

1. It should have long residence time.
2. It should be low viscous.
3. Free flowing allow for reproducible administration to nasal cavity.
4. In this in-situ gel formulation follows phase transition mechanism and shear forces in nasal cavity wall [14].

Advantages, disadvantages & limitation

Advantages:

1. Drug degradation that is noticed in the gastrointestinal tract is absent.
2. Hepatic first pass metabolism is avoided.
3. Rapid absorption drug and fast onset of action can be achieved.
4. The bioavailability of higher drug molecules can be enhanced by means of absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is high.
6. Drugs that are orally degraded can be delivered to the systemic circulation by nasal drug delivery.
7. Reports so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8. Compatible for the patients, especially for those on long term therapy, when compared with parenteral medication.
9. Drugs possessing poor stability in gastro intestinal track fluids are given by nasal route.
10. Polar compounds exhibiting poor oral absorption may be mostly suited for this route of delivery [6].

Disadvantages:

1. There is a possibility of irritation when compared to the oral delivery system since.
2. There is a possibility of irritation when compare to the oral delivery system.
3. The substance and constituents added to the dosage form may cause local side effects and irreversible damage of the cilia on the nasal.
4. The nasal cavity provides a smaller absorption surface area when compared to gastrointestinal tract.
5. There is possibility of irritation when compared to the oral delivery system.
6. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract due to the improper administration.
7. Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.[16]

Limitation

1. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly found.
2. It may be inconvenient to patients when compared to oral dose delivery as there is a possibility of nasal irritation.
3. Nasal cavity poses smaller absorption surface area when compared to GIT.
4. There is a possibility of local side effects in the nasal cavity and irreversible damage of the cilia on the nasal mucosa, both from the substance and from components added to the dosage form.
5. Certain surfactants used as chemical enhancers may interrupt and also dissolve in membrane with high concentration.
6. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration[16]

Method of prepration of insitu nasal gel

Cold Method and Hot Method

In cold method, the drug is mixed with sufficient quantity of double distilled water and kept overnight at 4^0C in a refrigerator. The in situ gelling polymer is added slowly with continuous stirring. The dispersion is then stored in a refrigerator uptill clear solution is formed and finally volume is adjusted. This method is carefully chosen when poloxamer, chitosan or carbopol is used as a gelling polymer. Considering the fact that polymeric dispersion of poloxamer remains as solution at lower temperature and gets converted into gel at higher nasal temperature, because the solubility of polypropylene oxide chain of poloxamer decreases at high temperature which results in precipitation or salting out of polymer. Similarly, chitosan also requires low temperature to remain as solution at room temperature, its hydrophobicity increases with increase in temperature.[17]

In hot method: This method is utilized when gellan gum or pectin is used as a gelling polymer. At higher temperature, gellan chains dissolve in water and assume a random-coil conformation with a high segmental mobility at high temperature and remain as a solution at higher temperature. Sol—gel transition occurs on cooling gellan gum solution in the presence of ions like K+ or Ca2+. Similarly, pectin also requires higher temperature for its demethoxylation, which helps in the formation of solution or dissolving of pectin [17].

Table no:1 Factors affecting nasal absorption:-[16]

Nasal barriers	Factors to be comsidered
1. Physiological barrier	
A. Nasal mucus	Viscosity, pH of mucous and drug/dosage form-mucous interaction
B. Nasal epithelium barrier	Molecular weight, ionization constant and mode of transport
C. Mucocillary clearance	Nasal residence time and nature of dosage form
D. Pathophysiology	Volume of nasal serection and permiablity of epithelium
E. Nasal metabolism	Nature of the molecules (e.g, protein, peptides)
F. Efflux transport system	Nature of drug molecules and nose to brian absorption
2. Physiological barriers	
A. Drug solubility and dissolution	Nature of dosage form, dose, pKa and polymorphism
B. Molecular weight and sized	Less bioavailability with molecular weight more than 1000
C. pH and pKa	Affect the nose to blood and nose to brain absorption
D. Compound lipophilicity	Unionized pH favors for absorption
3. Formulation factors	
A. Drug concentration, dose, volume	High concentarion for better bioavailability, maximum dose in minimum vehicle
B. Osmolarity	Isotonic solution prevents epithelial damage and toxicity
C. Site of absorption	Site of absorption based on viscosity, position of head, volume, delivery device, desposition at anterior chamber prolong the nasal residential time.

Approaches

A. Stimuli Responsive In Situ Gelling System

Physical or chemical modifications in response to small external changes in the environmental conditions.

➢ **Temperature induced in situ gel system**

1. Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in-vivo and in-vitro.
2. These hydrogels are liquid at room temperature (20°-25°C) and undergoes gelation when in contact with body fluids (35°-37°C), due to increase in temperature. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose).

➢ **PH inducing in situ gelling system**

1. Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an significant indication, which can be addressed through pH-responsive materials.
2. Gelling of the solution is triggered by change in pH. At pH 4.4 the formulation is free from is a free running solution which go through coagulation when the pH is raised by the body fluid to pH 7.4. The polymers are namely cellulose and its derivatives polyvinyl acetate, polyethylene glycol are pH induced gelating polymers.

➢ **Osmotically Induced In Situ Gelling System**

In this method, gelling of the solution instilled is activated by changes in the ionic strength. It is expected that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms clear gel in the presence of the mono or divalent cations. The polymer

which shows osmotically induced gelation is gellan gum and alginates.

B. Chemically Induced In-Situ Gelling System

The chemical reaction which forms in-situ gel systems are ionic crosslinking, enzymatic cross linking and photopolymerization

- **Ionic cross linking**

Ion sensitive polysaccharides such as carragenan, gellan gum, pectin, sodium alginate undergo phase transition in presence of various ions such as K^+, Ca^{2+}, Na^+. These polysaccharides drop into the class of ion-sensitive ones. For example, Alginic acid go through gelation in presence of divalent cations example Ca^{2+} due to the interaction with guluronic acid block in alginate chains.

- **Enzymatic cross linking**

In Situ formation catalyzed by natural enzymes has not been investigated broadly but seems to have some advantages over chemical and physicochemical approaches. For example an enzymatic process operates effectively under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

- **Photo polymerization**

Photo polymerizable systems when introduced to the desired site via injection get photo cured in-situ with the help of fiber optic cables and then release the drug for prolonged period of time. A photo polymerization, biodegradable hydrogels as a tissue permeable material and controlled release carrier [14].

Polymer used in formulation

1. Permeation enhancers

The permeation enhancers are mostly used for the development of absorption of the active medicament. Mostly, the absorption enhancers act via one of the following mechanisms:

A. Inhibit enzyme activity;
B. Reduce mucus viscosity or elasticity;
C. Decrease mucociliary clearance
D. Open tight junctions
E. Solubilize or stabilize the drug.

The mechanism of action of absorption enhancer is increasing the rate of absorption at which drug permits through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should achieve this while causing no damage or permanent change to nasal mucosa**.**

Qualities of Ideal penetration enhancer

1. It should main to an effective increase in the absorption of the drug.
2. It should not cause of permanent damage or alteration to the tissues.
3. It should be non irritant and nontoxic.
4. It should be effective in small quantity.
5. The enhancing effect should occur when absorption is required.
6. The effect should be temporary and reversible.
7. It should be compatible with other excipients.

Different penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetenic acid derivatives, cyclodextrins and glycols [6].

Formulation factors

Formulation pH

The amount 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 development of pathogenic bacteria in the nasal passage
- To avoid nasal irritation, formulation pH should be adjusted between 4.5 and 6.5.
- The pH of nasal surface is 7.39 and the nasal secretions pH 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 like key on formulation pH.
- Most drugs are absorbed well in their un-ionized form. While it is required maintain 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 [3].

Formulation excipients

In nasal formulations, a wide variety of pharmaceutical excipients can be found and they are selected subsequently in their functions. Solubilizers, buffer components, antioxidants, preservatives, humectants, gelling/viscosifying agents, and flavoring or taste masking agents are certain common excipients. Although they are responsible for several nasal irritations, antioxidants, preservatives, humectants and flavoring or taste masking agents are not expected to alter nasal drug absorption [3].

Buffer capacity

Nasal formulations are mostly administered in small volumes ranging from 25µL to 200µL. Hence, nasal secretions may change the pH of the administered dose. This can alter the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ [5].

Clarity

Abbe's refractometer used to measure the refractive index of liquids. The clarity of solutions, that is, formulations before gelling, was determined in name of refractive index using Abbes refractometer. The calibration of refractometer was done by using water as reference standard. The refractometer scale was adjusted in such a way that the cross wire of the telescope was exactly on the boundary between the bright and dark regions.

pH

Digital pH meter was calibrated by using pH buffer of 4 and 7. Twenty milliliter of each formulation was taken in beaker and glass electrode was sufficiently dipped into the samples of formulations. Then, pH of the solution was determined in triplicate.

Drug content

By using double beam UV visible spectrophotometer the drug contents of formulations was determined. One milliliter of preparation was taken in capacity of 10ml volumetric

flask, diluted with double distilled water and volume adjusted to 10ml. One milliliter quantity from this solution was again diluted with 10ml of double distilled water. Finally, the absorbance of prepared solution was measured by UV visible spectrophotometer.

Mucoadhesive strength

It is the force needed to detach the formulation from nasal mucosal tissue. The mucoadhesive force, the detachment stress of the formulation was determined by a modification of the mucoadhesive force measuring device. The modified balance technique using two-glass vials and sheep nasal mucosa was used. A nasal mucosa with thickness of 0.6mm and surface area 2.835cm^2 was cut from the olfactory region of sheep nasal cavity and instantly secured with the mucosal side out onto each glass vial using a thread. The vials were stored at 32^{0}C –34^{0}C for 10min. One vial was attached to one side of balance and 0.5ml of gel sample was placed between the two mucosal membranes attached to the bottom of the vials. The minimum weight of water required to break the mucosal adhesion was measured.

Mucoadhesive Strength (dynes=cm^2) = mg/A.

Where m is weight needed for detachment in g, g is acceleration due to gravity (980cm/s^2) and A is surface area of mucosa exposed (cm^2).

Gel strength determination

A sample of (50g) was placed in a 100-ml graduated measuring cylinder and gelled in a thermostatically controlled water bath at 32^{0}C–34^{0}C by addition of simulated nasal fluid. The weight of 35grams was then taken onto the disk whose diameter was 2.3cm, clearance from side wall of cylinder 0.4cm, thickness 0.5cm and this disc was put onto the gel. The gel strength was measured as the time (seconds) required to moving the piston 5cm down through the gel. Gel strength is associated to molecular weight a degree of cross-linking, etc. If more than five minutes to drop the apparatus into the gel, additional weights were placed on top of the apparatus and gel strength was described by the slight weights that pushed the apparatus 5cm down through the gel [17].

Spreadability

Spreadability is the area traveled per unit time (cm2/min) by the gel formulation. Whatmanns filter paper (0.45mm) is used for determination of spreadability of solution formulations. 1ml graduated pipette with rubber bulb was clamped upright to the stand in such a way that the tip of pipette was at 2cm above the horizontal surface of round shape filter paper. 0.1ml sol formulation was dropped at midpoint of filter paper. At fixed time interval, 20s, the surface area covered by the formulation was measured [17].

In vitro drug release

In vitro drug diffusion study of various formulations was performed using Franz diffusion cell. Dialysis membrane having molecular weight cut-off range of 12000–14000 kDa was used as diffusion membrane. Dialysis membrane was allowed to soak in phosphate buffer pH 6.4 for 24h before experiment. Diffusion cell was filled with 21ml phosphate buffer pH 6.4 and dialysis membrane was mounted on cell. The gel containing drug equivalent to 10mg was placed onto donor chamber. The temperature was maintained at 32^{0}C–34^{0}C by circulating water bath. Samples of 1ml were withdrawn at different time intervals replaced with same volume of fresh solution, filtered and amount of drug was determined by UV visible spectrophotometer.[18]

Ex-vivo permeation studies

Fresh nasal mucosa from olfactory region was carefully detached from the nasal cavity of sheep obtained from the local slaughter house. Nasal mucosa was put into phosphate buffer pH 6.4. Tissue samples were placed on diffusion cells immediately. Phosphate buffer solution pH 6.4 at 34^{0}C was added to the acceptor chamber. Formulation equivalent to 10mg drug was placed in the donor chamber. At predetermined time points, 1 ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer pH 6.4 after each sampling, for a period of 5h. The samples withdrawn were filtered and used for analysis. Blank samples (without drug) were run at the same time throughout the experiment to check for any interference. The amount of permeated drug was determined using a UV-visible spectrophotometer.[18]

Histopathological evaluation of nasal mucosa

Fresh nasal mucosa was carefully removed from the nasal cavity of sheep and was stored in 10% of formalin solution. Phosphate buffer pH 6.4 and isopropyl alcohol were used as negative and positive controls, respectively. Histological studies were carried out on sheep nasal mucosa that had been used for ex vivo permeation study which was treated with 1ml optimized in situ gel for 5h. Afterward, tissue were cut and stained with eosin. Sections were examined under a light microscopy to detect any damage to the tissue during in vitro permeation.[18]

Gelling time

The method exists in sol form before administration and after administration it turns into gel form. Gelling time is the time acquired for the transformation of sol to gel form. Time for gelation is recorded by placing 2ml of prepared formulation in a test tube and adding small amount of simulated nasal fluid, maintaining the temperature at 37ºC and visually observing the gel formation, and onset of time for gelation is recorded as gelling time in seconds [18].

Polymers used in formation of in situ nasal gel

Pectin

The functionality of pectin is determined by the degree of methoxylation which in turn is the percentage of galacturonic acid (major component of pectin) that is methoxylated. The mechanism of gelation of aqueous solution of pectin with low degree of methoxylation is as follows: the carboxyl groups of pectin backbone interact with Ca^{2+} and induce the formation of 'egg box' structure. Here is an initial dimerization steps of two homogalacturonic chains by cooperative bridging of parallel facing chains across Ca^{2+}. This is possible due to rigid nature of homogalacturonic chains and binding of first calcium cation by two pectin chains facilitates their alignment with respect to each other, which in turn permits the easier binding of a next calcium ion, and so on along the sequence. The most favorable arrangement is the antiparallel orientation of the two chains, and this initial dimer association is strongly stabilized by hydrogen bonding, in addition to electrostatic interaction. The minimum number of successive non-methoxylated galacturonic acid residues necessary to form a cooperative egg box has been estimated to be 6 -20 [15].

Carbopol

Carbopol shows sol to gel transition in aqueous solutions as the pH is raised above its pKa. The acidic carboxyl groups of the polymer partially dissociate in water and begin to uncoil to produce a flexible coil structure. In acidic conditions, a small proportion of the carboxyl groups present on the polymer dissociate, producing a flexible coil structure. In an alkaline senario, the carboxyl groups ionize, generating negative charges along the polymer backbone. Electrostatic repulsion of the anionic group is reason for uncoiling and expansion of the molecule which results in polymer swelling and gel formation. Further adding of carbopol thins the gel because the cations screen the carboxyl groups and so the electrostatic repulsion decreases [19].

Gellan gum

Gellan gum is an anionic exocellular polysaccharide which is completely de-esterified by alkali treatment for commercial use and this deacylated gellan gum has following tetrasaccharide repeat units: (1,3)b-D-glucose, (1,4)b-Dglucuronic acid, (1,4) b-D-glucose, (1,4)a-L-rhamnose, has lower sol to gel transition temperature and stronger gel strength than the native one. The gelation of gellan gum in aqueous solutions contains two steps. The first step is the formation of double helical junction zones by conformation change from random coil and the second step is the aggregation of the double helices to form junction points, which results in gelation by complexation with cations and hydrogen bonding with water Divalent cations such as Ca2+, produces strongest gel with low acyl gellan when compared with monovalent cations. In the presence of divalent cations, gelation occurs with the subsequent aggregation of double helices mediated by cations and the sol--gel transition appears at temperatures lower than coil--helix transition. By contrast, divalent cations immediately interact with gellan chains segments as cooling takes place, forming ordered structures at temperatures higher than the coil--helix transition.[15,19].

Chitosan

Chitosan is a linear polysaccharide which becomes watersoluble after the formation of carboxylate salts, such as formate, acetate, lactate, malate, citrate, glyoxylate, pyruvate, glycolate and ascorbate due to its cationic nature. Due to the presence of nitrogen in the molecular structure, cationicity and capacity to form polyelectrolyte complexes is the unique property of chitosan which is responsible for the in situ gel formation. Various divalent anions such as polyol-phosphate, sulfate, oxalate, molybdate or phosphate are liable for the gelation of chitosan aqueous solutions. Mostly, b-glycerophosphate is used because It maintains the chitosan solubility at physiological pH and the temperature-sensitive character of these chitosan. The b-glycerophosphate solution permits fast hydrogel formation on heating. The b-glycerophosphate addition to chitosan aqueous solution modulates electrostatic and hydrophobic interactions, and hydrogen bonding between chitosan chains, which are the main molecular forces involved in gel formation. Chitosan is a linear polysaccharide which becomes watersoluble after the formation of carboxylate salts, such as formate, acetate, lactate, malate, citrate, glyoxylate, pyruvate, glycolate and ascorbate due to its cationic nature. Due to the presence of nitrogen in the molecular structure, cationicity and capacity to form polyelectrolyte complexes is the unique property of chitosan which is responsible for the in situ gel formation. Many divalent anions such as polyol-phosphate, sulfate, oxalate, molybdate or phosphate are liable for the gelation of chitosan aqueous solutions. Mostly, bglycerophosphate is used because itmaintains the chitosan solubility at physiological pH and the temperature-sensitive character of these chitosan. The b-glycerophosphate solution allows rapid hydrogel formation on heating. The bglycerophosphate addition to chitosan aqueous solution modulates electrostatic and hydrophobic interactions, and hydrogen bonding between chitosan chains, which are the main molecular forces involved in gel formation.[15]

Poloxamer

Poloxamer is commercially offered as pluronic and the gelation mechanism (s) of its aqueous solution have been investigated by various techniques. Ultrasonic velocity and dynamic light scattering measurements on the poloxamer 407 solutions indicated that the intrinsic changes in micellar properties, such as aggregation number and micellar symmetry cause aqueous poloxamer solutions to form a gel. It was also concluded that decrease in the critical micelle concentration arise by increasing temperature. In recent studies on aqueous solution of poloxamer done by light-scattering, smallangle X-ray scattering, rheology, small-angle neutron scattering and dielectric behavior measurement, clearly indicated the unimers to micelles transition, and the occurrence of gelation when the micellar volume fraction increased to critical value (0.5) for hard-sphere crystal formation. As the temperature further increased, the aggregation conformation of poloxamer hydrogels changed from spherical micelles closely packed in a cubic lattice into the rod-like micelles packed in a hexagonal system, which resulted in decrease of the intermicellar interactions. When the temperature was further increased, the sol to gel transition occurred due to reduction of inter-micellar interactions caused by partial dehydration of the polyethylene oxide blocks.[15]

Ethyl (hydroxyethyl) cellulose

EHEC is a non-ionic amphiphilic polysaccharide which consists of unevenly distribution of both hydrophilic and hydrophobic units in the polymer backbone. It has been stated that the EHEC solutions entirely changed their thermal behavior with the addition of an ionic surfactant, like cetyl triammonium bromide and sodium dodecyl sulfate. In the presence of ionic surfactants, the surfactant is bound to the polymer and this endows an apparent polyelectrolyte character to the initially non-ionic character. Small-angle neutron scattering determined that there is a temperature induced association and gelation of semi-dilute solutions of EHEC in the occurrence of an ionic surfactant. In the presence of ionic surfactants, it is further expected that the formation of mixed micelles between the hydrophobic groups in EHEC and the amphiphilic surfactants creates the conditions necessary to induce a sol to gel transition as the temperature is increased.[19]

Sodium alginate

Alginate is a non-branched, high-molecular weight binary copolymer of (1–4) glycosidically linked β-D-mannuronic acid and α-L-glucuronic acid monomers. The high acid content allows alginic acid to undergo spontaneous and mild gelling in the presence of divalent cations, such as calcium ions. These mild gelling properties are pH dependent and permit the encapsulation of many molecules or even cells

within alginate gels with minimal negative effect. Further, the carboxylic acid groups of alginic acid are highly reactive and can be appropriately moderated for various applications. Alginate surface is negatively charged; therefore, when positively charged polymers are added to the alginate solution, they can form a poly-cation and poly-anion complex, which will enhance the overall stability of the microcapsules.[20]

Phosphatidylcholines (PC)

Phosphatidylcholines are surface-active amphihilic compounds produced in biological membranes and liposomes. Several reports have appeared in the literature showing that these phospholipids can be used as enhancers for systemic nasal drug delivery[21].

Application

- Intranasal administration considers a simple, economic, convenient and non invasive path for fast drug delivery to systemic circulation.
- Treatment of epilepsy and schizophrenia
- Treatment of migraine
- As an antidepressant
- Treatment of angina pectoris and neurological deficit
- Treatment of amnesia
- Intranasal delivery of peptides[14]

In situ nasal gel (for CNS)

- The Delivery of Anti-Parkinson Drugs.
- The Delivery of Anti-Migraine Drug.
- The Delivery of Anti-Alzheimer's Drug.
- The Delivery of Anti-Depressant Drug.
- The Delivery of Anti-Schizophrenia Drug.[17]

Conclusion

The nasal mucosa gives several advantages for controlled drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage. First-pass metabolism in the liver and presystemic elimination in the GI tract can be avoided. The area is well suited for a retentive formulation and has better patient compliance. The drug targeting to the brain should be evaluated for their safety and risk-benefit proportion for the patients. Now the safety issue has been given great importance by the researchers during the research stage, and this issue will become critical when the drug is to be delivered is for a long term therapy. With the appropriate formulation and dosage form design, the permeability and the local environment of the mucosa can be controlled and manipulated to accommodate drug permeation. Nasal drug delivery is an well-organized alternate route for systemic delivery of orally inefficient drugs. Similarly it offers non-invasive delivery of potent peptide and perhaps protein drug molecules. The intranasal route is an available alternative to parenteral routes. The need for safe and effective nasal permeation and absorption enhancers is a major component for a promising future in the area of nasal drug delivery. It reduces systemic exposure and thus reduces the side effects.[7]

Future trend

The next generation of biomaterials looks toward the event and clinical use of smart materials which is in a position to permit better control over processes occurring post-implantation. The host site can itself control the material around local changes in pH, ionic strength or other specific molecular interactions. the employment of supramolecular assemblies of responsive polymers (e.g shell or core cross-linking structures) could also be utilized to achieve long-term structural stability. The detection motifs exhibiting more sensitive and selective responses should be further developed and incorporated into responsive polymer matrices, aimed toward sensing and discriminating subtle changes within the gradients also temperature and pH, glucose, bioactive small molecules then additional biorelevant macromolecular species. The development of pH-responsive polymers is centered on systems capable of selectively detecting various analytes at the same time. The challenge remains to optimize material responses and to incorporate these into medical devices to substantiate that these novel smart materials reach their application potential, both in vitro and in vivo. in vivo uses became more thoroughly investigated, with promising work towards disease therapies and targeted drug delivery[7]. The treatment of neurological diseases is challenging because of the number of genes associated, the progressive nature of the disease and the in sufficient knowledge of the mechanisms and biomarkers associated with these diseases.(22)

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