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IN SITU GEL NOVEL APPROACH FOR NASAL DELIVERY

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ABSTRACT

Ocular drug delivery has been a major challenging and interesting field for the pharmaceutical scientists due to unique anatomy and physiology of eye. The major problem encountered in ocular drug delivery is the rapid loss of the drug through lachrymal drainage which results in poor bioavailability and therapeutic response of the drug. There are some static (different layers of the eye i.e. cornea, sclera, retina) and dynamic (blood aqueous and blood retinal barrier) barriers which also affect the bioavailability of the drug. In-situ gels are the liquid preparations which upon instillation undergoes phase transition in cul-de-sac of the eye to form a viscous gel and this occurs due to the environmental changes in the eye (i.e. due to change in temperature, change in pH and ion induced change). This review is to specify the basic anatomy and physiology of human eye, various approaches used for formulation of in-situ gels and polymers used in the formulation of in-situ gels.

INTRODUCTION

Oral drug delivery is the most desirable route for the drug administration. Whenever systemic effects are indented but oral bioavailability of some compounds has promoted the search of more effective route for the systemic delivery. Transmucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption.[(1)] Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route, this is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism and readily accessibility.[(2)] Nasal mucosa as an alternate route to achieve faster and higher drug absorption. Knowledge of the nasal mucosa high permeability and use of the nasal route for drug administration can be traced to ancient times. Realization of the nasal mucosa as a therapeutically viable alternate route came in the last two decades. The nasal mucosa itself and the drug delivery systems affect drug absorption through the nasal route, is invaluable. A stable, safe and effective nasal product can be developed through appropriate and adequate preformulation studies of drug.[(3)]In the last few years, the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs, especially those which are ineffective orally and must be administered by injection.

Advantages[(4,5)]

- Drugs that are orally not absorbed can be delivered to the systemic circulation by means of nasal drug delivery.
- Hepatic first pass metabolism is avoided.
- Easy accessibility and needle free drug application without the necessity of trained personnel facilitates self medication, thus improving patient compliance compared to parenteral routes.
- Drug degradation that is observed in the gastrointestinal tract is absent.
- The bioavailability of large drug molecules can be improved by means of absorption enhancer or other approach.
- Rapid drug absorption and quick onset of action can be achieved.
- The nasal bioavailability for smaller drug molecules is good.

- Drug possessing poor stability in GIT fluids are given by nasal route.
- Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- Polar compound exhibiting poor oral absorption may be particularly suited for this route of delivery.
- Convenient for the patients, especially for those on long term therapy, when compared with parenteral Medication.

Disadvantage[6,7]

- Nasal cavity provides smaller absorption surface area when compared to GIT.
- Relatively inconvenient to patient when compared to oral delivery system since there is a possibility of irritation.
- There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of improper technique of administration.
- Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.

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.[8] 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.[9]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 pseudo stratified epithelium where the long hairs may provide the function of filtering air borne particles. Respiratory area has a surface lined by a pseudo stratified 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. The olfactory segment is lined with a specialized type of

pseudo stratified 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. Bowman's glands are serous glands in the lamina propriety, whose secretions trap and dissolve odoriferous substances.[10] The total surface area of both nasal cavities is about 150 cm^2 and the total volume is about 15ml.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.

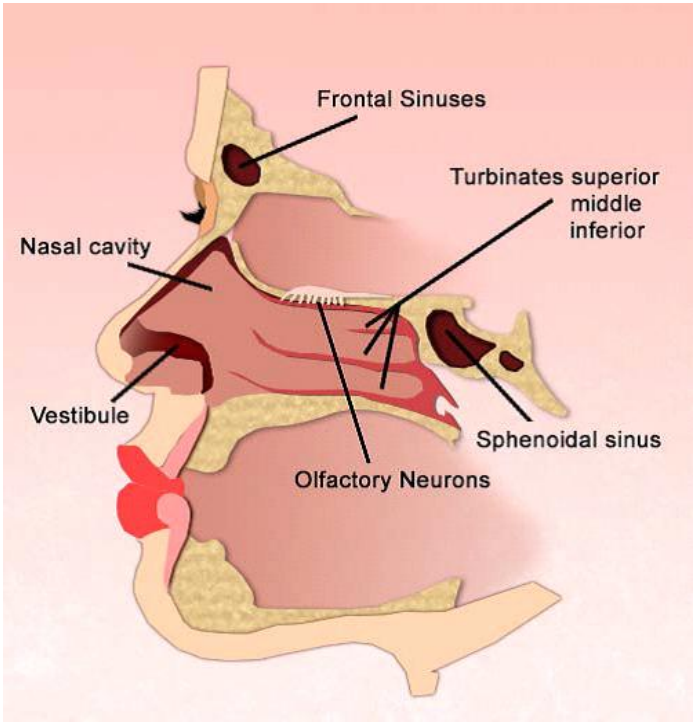

Figure:- Anatomy Of Nasal Cavity

Nasal Drug Delivery System

Intranasal 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.

Blood Supply to Nasal Cavity[11]

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.
- **Anteriorethmoidal 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.

Approaches of In Situ Gelling System

The various approaches for in situ gelling system

1. Stimuli Responsive In Situ Gelling System

- Temperature induced in situgel systems
- pH induced in situgel systems

2. Osmotically Induced In Situ Gelling System

3. Chemically Induced In Situ Gel System

- Ionic cross linking
- Enzymatic cross linking
- Photo-polymerization

1. Stimuli Responsive In Situ Gelling System

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

Temperature induced in situ gel system

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 vitro and in vivo. In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20–25 °C) andundergo gelation when in contact with body fluids (35– 37 °C), due to anincrease in temperature. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc.[12,13]

pH induced in situ gel systems

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the body fluid to pH 7.4. The polymers which shows pH induced gelation are cellulose acetate phthalate(CAP)Latex, Carbomer and its derivatives polyvinylacetyldiethyl aminoacetate (AEA),Polymethacrilic acid (PMMA), polyethylene glycol (PEG),pseudo latexes etc.[14,15]

2. Osmotically Induced In Situ Gelling System

In this method, gelling of the solution instilled is triggered by change in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel.The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations. The polymer which showsosmotically induced gelation are gellan gum, hyaluronic acid and alginates etc.[16,17]

3. Chemically Induced In Situ Gel System

The chemical reaction which forms in situ gel systems are Ionic crosslinking, enzymatic crosslinking and Photo-polymerization

Ionic cross linking

Certain ion sensitive polysaccharides such as carragenan, Gellan gum (Gelrite), Pectin, Sodium Alginate undergo phase transition in presence of various ions such as K+ , Ca2+, Mg2+,Na+**.** These polysaccharides fall into the class of ion-sensitive ones**.** For example, Alginic acid

undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction With guluronic acid block in alginate chains.[18,19]

Enzymatic cross linking

In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.[19,20]

Photo-polymerization

In situphoto-polymerization has been used in biomedical applications for over more than decade. A solution of monomers or reactive macromere and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromere because they rapidly undergo photo-polymerization in the presence of suitable photo initiator. Photopolymerizable systems when introduced to the desired site via injection get photocured in situ with the help of fiber optic cables and then release the drug for prolonged period of time. A photo-polymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney et al.[17,20]

Factors Affecting Nasal Drug Absorption[21,22]

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

I. Biological Factors

- 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

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

III. Physicochemical Properties of Formulation

- Dosage form
- Viscosity
- pH and mucosal irritancy

IV. Device Related Factors

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

Biological Factors[23]

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 visco elastic 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 onthe nature of the drug.

Physicochemical Properties Of Drugs[23]

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.

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[24]

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.

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 solution 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 ofnasal preparations. Drug carrier such as hydroxypropylcellulose was effective for improving 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, butylatedhydroxy 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.

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.

Mechanism Of Drug Absorption Through Nose

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. Subsequent to a drugs 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 various compounds investigated as enhancers in nasal drug delivery research are mentioned in Table 3.

Table No. 3: Various compounds used as enhancer in nasal drug delivery research[25]

Name of compound	Example
Surfactants	Sodium dodecyl sulphate (SDS), Polyoxy ethylene-9-lauryl ether, Phosphatidylcholines
Complexing and Chelating agents	Ethylene diaminetetraacetic acid (EDTA)
Cyclodextrins and derivatives	α-, β-, γ-cyclodextrin, DMβ-, HPβ-cyclodextrine
Fusidic acid derivatives	Sodium tauradihydrofusidate (STDHF)
Bile salts	Sodium taurocholate, Sodium glycocholate
Dry microspheres	Degradable starch microsphere Dextran microspheres

Nasal Formulations[26]

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.[27]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. 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 toa biological tissue. If the adhesive attachment is to a mucous coat the phenomenon is referredto as Mucoadhesion.[28]

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. 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.[(29)]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.

Theories Of Mucoadhesion[(30)]

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 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 coefficient is known to depend on molecular weight and cross-linking density.

Factors Affeceting Mucoadhesion

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

Material and Method[32]

Polymers: Thermoreversible polymers: - Pluronic and poloxamers are two main polymers.Mucoadhesive polymers: - which compatible with given drug.

Formulation excipients

Formulation excipients are chosen for various reasons. The most common reasons follow-

I. **Solubilizers:**co-solvents (glycols, alcohols, Transcutoletc), surfactants and cyclodextrin are used to improve the solubility of insoluble drugs.

II. **Buffer components:**various conventional buffer systems can be used to buffer nasal formulations. A high buffer capacity is important to maintain in situ formulation pH.

III. **Antioxidants:**according to stability of drug the antioxidants are used to prevent drug degradation in small quantities.

IV. **Flavour/taste:**some drugs may present problems with regard to aroma and taste. To avoid this problem particular flavour and taste masking agents are used.

V. **Preservative:**Nasal formulation usually contains preservatives to protect them from microbial contamination. Parabens, benzalkonium chloride, benzoyl alcohol are typically used as preservative.

VI. **Humectants:**To avoid any nasal irritation by formulation components, humectants are usually added to formulations. Examples - glycerin, sorbitol, mannitol.

VII. **Gelling/Viscofying agents:**commonly used agents for this purpose are methyl cellulose, carboxymethyl cellulose, carbopols and polyvinylalcohol.

Evaluation Of Nasal In Situ Gel System

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

Clarity [33]

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

Texture Analysis[33]

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[33]

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 to 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.

pH of the Gels[34)]

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[(34)]

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[(34)]

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[(33)]

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[(33)]

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 /cm2) = mg /A where m is the weight added to balance in grams, g is the acceleration due to gravity taken as 980 cm/sec2, A is the area of the tissue exposed and is equal to πr2 (r is the radius of the circular hole in the aluminium cap).

In vitro Nasal Diffusion Cell[(34)]

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 cm2. 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[(34)]

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 toobserve if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.

CONCLUSION

In situ gels offer the primary requirement of a successful controlled release product that is increasing patient compliance. Exploitation of polymeric in situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. Over the last decades, an impressive number of novel temperature, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use. Future use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems.

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