Review Article

A Review on *In-Situ* Nasal Gel Drug Delivery System

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ABSTRACT

Oral route is the most common and preferred route for the administration of majority of drugs in the body, but drug targeting to the respective organ imposes the problem for administration through the oral route. For the improvement of drug safety and efficacy in our body the development of new delivery system called in situ gelling nasal drug delivery system is developed. The present reviews focused on the anatomy of nasal system and criteria required of drug candidate to prepare a gel i.e. in situ gel. The present review also focused on the approaches regarding formulation of in situ gel with respect to physiological temperature, pH, and physicochemical conditions. The main role played by the polymers like cellulose, pectin etc. in a body, absorption of drug by various ways and the various factors that affect the absorption are also discussed here. Various evaluation parameters also consider during preparation of in situ gel.

Keywords: Nasal Anatomy and Physiology, Approaches In Situ Gel, Polymers Used In In-Situ Gel, Strategies to Increase Nasal Drug Absorption.

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.[1] The generation of a new drug molecule is an expensive and time consuming process. Hence the safety and efficacy ratio of "old" drugs can be improved by delivering these drugs at controlled and slow delivery or targeted delivery. This leads to the development of In situ gelling nasal drug delivery systems[2]. The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurvedic system of Indian medicines[3] Transmucosal route of drug delivery [i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity] preoral administration for systemic administration, nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption.[4] 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.[5] Due to the non invasive nature and increased patient comfort and compliance they are preferred for long term therapy as the parenteral route is considered inconvenient.[2] In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects.[3] The nasal delivery seems to be a favourable way to circumvent the obstacles for blood-brain barrier [BBB] allowing the direct drug delivery in the bio phase of central nervous system [CNS] active compounds.[3] Intranasal delivery of large molecular weight biologics such as protein, gene vectors, and stem cells is a potentially useful strategy to treat variety of disease of CNS including stroke, Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, and psychiatric disorders.[12]

Majority of products available are used for treatment of allergic rhinitis, migraine, cold, pain etc. The various formulations given by nasal route includes nasal gel, spray, powders, solution, drops etc[5].

Gel

Gel is the state which exists between solid and liquid phase. The solid component comprises a three dimensional network of inter-linked molecules which immobilizes the liquid phase[6].

In Situ gel

In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In situ gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot[6].

Principle of Gelling

The principle involving the In situ gelling of nasal formulations is that the nasal formulations imbibe in the nasal fluid after administration and forms gel into the nasal cavity. In the nose, the mucus lower layer comes and goes around the cilia, forwarding the propulsion phase, backward in the preparatory phase. At the propulsion phase, cilia extremity scrapes the upper layer

of mucus penetrating it almost 0.5 mm. ciliary activity zones then occur at various intervals. Cilia situated backwards help to remove any obstacle if there is any interference in the propulsion phase. After the formation of the gel, dissolution occurs and or the mucociliary removal towards the nasopharynx occurs.[5]

Ideal Drug Candidate[3,8]

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

Advantages[1,2,8]

1. Absorption of drug is rapid due to highly vascularised mucosa.
2. Availability of large nasal mucosal surface area.
3. Onset of action is rapid.
4. Administration of dose is easy and Non-invasive.
5. Bypass the Blood Brain Barrier.
6. Degradation of drug observed in GIT is avoided.
7. Hepatic first pass metabolism is absent.
8. Nasal bioavailability of small drug molecules is good.
9. Bioavailability of large drug molecules can be increased by means of absorption enhancers.
10. Alternate to parenteral route especially for proteins and peptides.
11. For the patient on long term therapy this route Convenient.
12. Improved bioavailability as compared to oral route.
13. Side effects are minimum due to low dose.
14. Patient convenience and compliance is improved.
15. A self-administration of drug dose is possible.
16. Direct transport into systemic circulation and CNS is Possible.

Disadvantages[1-6,12]

1. Delivery volume in nasal cavity is restricted to 25–200 µl.
2. High molecular weight compounds cannot be delivered through this route [mass cut off ~1kDa].
3. Adversely affected by pathological conditions.
4. Large interspecies variability is observed in this route.
5. Normal defence mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
6. Drugs like Budesonide, Azilactine are liable to cause Irritation of nasal mucosa.
7. Limited understanding of mechanisms and less developed models at this stage.
8. Systemic toxicity occurring due to absorption enhancers is yet not established.
9. Smaller absorption surface compared with GIT.
10. Possibility of nasal irritation hence inconvenient compared with oral route.
11. Enzymatic barrier to permeability of drug.

Nasal Anatomy and Physiology[1,3,6, 9,10-13]

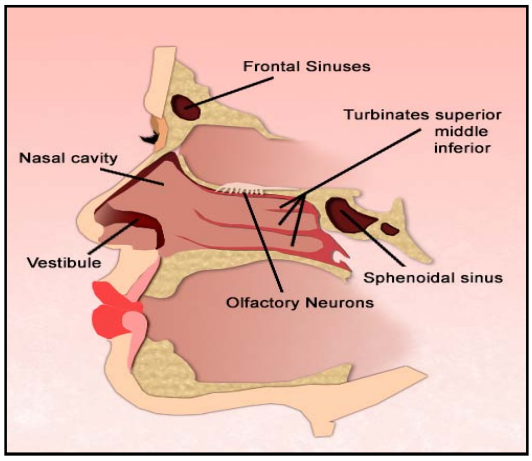

Figure 1: Anatomy of nasal cavity.

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.[13] In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways[7].

The human nasal cavity has a total volume of 15-20ml and a total surface area of approximately 150cm^2. Nose is divided into two nasal cavities via the septum. The volume of each cavity is about 7.5 ml and has a surface area around 75 cm^2. pH of the mucosal secretions ranges from 5.0 to 6.7 in children and 5.5 to 6.5 in adults. The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min[9] both symmetrical halves consist of four areas nasal

vestibule, atrium, respiratory region and olfactory region.[7]

Nasal Vestibule

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm^{2}[3] this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands[7] is responsible for filtering out the air borne particles[4,5] It is considered to be less important of the three regions with regard to drug absorption.

Atrium

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.[5,7]

Respiratory Region

The nasal respiratory region is the largest part of the nasal cavity, also called conchae[9]. The respiratory region is the most important for systemic drug delivery.[10-12]

The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells.[8]

The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each of the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically.[7,8]

Olfactory Region

The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall[3,7,9] it is of about 10 cm^{2} in surface area and it plays a vital role in transportation of drugs to the brain and the CSF.[2,6,13]

When the drug is administered intranasally, it can enter into the brain via three different paths. The first one is the systemic pathway by which the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing BBB [especially lipophilic drug]. The others are the olfactory region and the trigeminal neural pathway by which drug is transported directly from the nasal cavity to CNS [cerebrospinal fluid and brain tissue]. There are different mechanism by which the drugs across the olfactory membrane to reach CNS.

The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism depends on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neurons.[8]

Mucus Membrane of Nose and Its Composition

The nasal mucus layer is only 5 µm thick. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.[3]

Epithelial Cells

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.[1]

Basically there are two functions of these cells:

1. Provide a physical barrier to the invasion of infectious microorganisms and allergic particles;
2. Work in conjunction with mucus glands and cilia to secrete and remove mucus and foreign particles from the nasal cavity.[3]

Blood Supply to Nose

Nasal vasculature is richly supplied with blood to fulfil the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The capillary flow in the nasal mucosa was reported to be 0.5 ml/g/min.[1,3]

Approaches in Situ Gel[5,6,10]

In Situ Gel Formation Based on Physiological Stimuli

Temperature Induced In Situ Gel Systems

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] and undergo gelation when in contact with body fluids [35– 37 °C] Due to an increase in temperature.

pH Triggered Systems

Formation of In situ gel based on physiologic stimuli is formation of gel induced by pH changes.

All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental 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.[5] Swelling of hydrogel increases as the external pH increases in the case of weakly acidic [anionic] groups, but decreases if polymer contains weakly basic [cationic] group[7]. The majority of anionic pH-sensitive polymers are based on PAA [Carrboro®, carbomer] or its derivatives.[9]

Table 1: Types of Thermosensitive Polymer.

Types of thermoresponsive sol-gel polymeric system	Properties of gel System	Common Polymers
Negatively Thermosensitive	have a lower critical solution temperature [LCST] and contract upon heating above the LCST.	poly[Nisopropylacrylamide] [PNIPAAm]
Positively Thermosensitive	has an upper critical solution Temperature [UCST]; such a hydrogel contracts upon cooling below the UCST.	poly[acrylic acid][PAA] and polyacrylamide [PAAm]
Thermally Reversible	Polymer solution is a free flowing liquid at ambient temperature and Gels at body temperature.	poly [ethylene oxide]-b-poly [propylene oxide]-b-poly[ethylene oxide] Pluronics®, Tetronics®, Poloxamers.

In Situ Formation Based on Physical Mechanism

Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol [glycerol mono-oleate], which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bioadhesive properties and can be degraded *in vivo* by enzymatic action.[10]

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone [NMP] has been shown to be useful solvent for such system.[10]

In Situ Formation Based on Chemical Reactions

Ionic Cross Linking

Certain ion sensitive polysaccharides such as carrageenan, 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.

Enzymatic Cross Linking

In situ formation catalysed 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.

Photo-Polymerization

Photo-polymerization is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromer 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 macromers because they rapidly undergo photo-polymerization in the presence of suitable photo initiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful systems. These systems can be designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence *in vivo*. The photo-reactions provide rapid polymerization rates at physiological temperature.

Polymers used in In-Situ Gel[1,5,9,10,12]

Ideal Polymers

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

Cellulose Derivative

There are many pharmaceutical grade derivatives of cellulose widely used in different Administration routes. Several cellulose derivatives have proved to be effective on enhancing. The intranasal absorption of drugs, including soluble cellulose derivatives such as Hydroxypropyl methylcellulose, hydroxypropyl cellulose [HPC], methylcellulose [MC], and Carboxymethyl cellulose [CMC], and insoluble cellulose derivatives such as ethyl cellulose and microcrystalline cellulose [MCC].

Using celluloses as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective on increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs.

Gellan Gum

Gellan gum [commercially available as Gelrite TM or KelcogelTM] is an anionic deacetylatedexocellular polysaccharide secreted by Pseudomonas elodea with a

tetra saccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. The formulation consisted of Gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming an in situ gel.

Pluronic F-127

Poloxamers or Pluronic [marketed by BASF Corporation] are the series of commercially available dysfunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic polyethylene oxide.

Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid.

Pluronics or Poloxamers also undergo In situ gelation by temperature change. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week.

Sodium Alginate

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid[M]and α-L-guluronic acid [G] residues joined by 1, 4-glycosidic linkage. Dilute aqueous Solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain.

Polyacrylates

Polyacrylates have been investigated very frequently in many drug administration routes, like Nasal drug delivery systems, due to their excellent mucoadhesive and gel-forming capability. Polyacrylates may also temporarily open the tight junctions between the epithelial cells during the swelling progress in the nasal cavity and improve the paracellular absorption of drugs.

Chitosan

Chitosan is [2-amino-2-deoxy-[1→4]-β-d-glucopyranan] a biodegradable, thermosensitive, Polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell.

Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption due to their excellent mucoadhesive properties. It was also confirmed that coating Micro- and nano particulates with chitosan could improve drug adsorption to mucosal Surfaces. Recent studies have shown that only protonated, soluble chitosan can trigger the opening of tight junctions and thereby facilitate the paracellular transport of hydrophilic mannitol.

Pectin

Pectin's are a family of polysaccharides, in which the polymer backbone mainly comprises α-[1-4]-D-glucuronicacid residues. The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. The potential of an orally administered In situ gelling Pectin formulation for the sustained delivery of Paracetamol has been reported.

Xanthum Gum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris.

The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.

Mechanism of Drug Absorption[1,3,5,9,11,12]

The absorbed drugs from the nasal cavity must pass through the mucus layer. It is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin which has the tendency to bind to the solutes, hindering diffusion.

A] First mechanism- also known as paracellular transport this utilizes the aqueous route of transport and is slow and passive. This route is not suitable for the drugs having molecular weight greater than 1000 Daltons due to poor bioavailability.

B] Second mechanism–also known as transcellular route which utilizes the lipoidal route for transport of lipophilic drugs.

C] Drugs also cross cell membranes by an active transport route via carrier mediated or transport through the opening of tight junctions.

Intra Nasal Drug Delivery[7]

Intranasal drug delivery several approaches should be considered, attending, specifically, to the nature of pathologic condition [acute or Chronic] and intended effects of drug treatment [local, systemic or at CNS].

Local

Intranasal administration of medicines is the natural choice for the treatment of topical nasal Disorders. Among the most common examples are antihistamines and corticosteroids for rhino sinusitis, and nasal decongestants for cold symptoms. In these cases, intranasal route is the primary option for drug delivery because it allows a rapid symptom relief with a more favourable adverse-event profile than oral or parenteral routes.

Systemic

The intranasal administration is an effective way to systemically delivery of drugs as an alternative to oral and intravascular routes. Consequently, the number of drugs administered as nasal formulations intended to achieve systemic effects has widely increased. Some prominent examples include analgesics [morphine], cardiovascular drugs as Propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and Ketorolac, and antiviral drugs [acyclovir]. These include, for instance, zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.

Vaccine

Nasal mucosa is the first site of contact with inhaled antigens and, therefore, its use for vaccination, especially against respiratory infections, has been extensively evaluated.

In fact, nasal vaccination is a promising alternative to the classic parenteral route, because it is able to enhance the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin A. In upper airways, the systemic and local immunological responses are mainly mediated by the nasal associated lymphoid tissue situated underneath the nasal epithelium.

CNS Delivery through Nasal Route

The tight junctions of the BBB surrounding the brain is one of such mechanisms, resulting in a greater transendothelial electric résistance [1500-2000 $\Omega.cm^2$] compared to that of other tissues like skin, bladder, colon, lungs [3-33$\Omega.cm^2$].

The obstacle imposed by those brain protective mechanisms has increased the interesting developing strategies to overcome them when brain drug exposure is required. In this context over the last few years, intranasal route has emerged as a promising approach for brain delivery of drugs. The absence of gastrointestinal and hepatic presystemic elimination is advantage in this delivery system.

Factors Affecting Nasal Drug Absorption[1,3,7-9]

Nasal Biological Factor

Physiological Factors

Blood Flow

Vasoconstriction effect decrease nasal drug absorption by diminishing the blood flow.

Nasal Secretions

Viscosity of nasal secretion and Solubility of drug in nasal secretions influence the drug absorption through nasal.

PH of the Nasal Cavity

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. PH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.

Mucociliary Clearances

Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MCC; whereas, increased MCC decreases drug permeation.

Pathological Conditions

Table 2: pathological condition and mucociliary clearance

Pathological conditions	Mucociliary clearance
Asthma	Increased: inflammatory process and irritation Decreased: epithelial damage
Viral and bacterial Infections	Compromised: loss of cilia and change of mucus properties

Physico Chemical Properties of Drug

Molecular Weight and Size

The rate and degree of nasal absorption of polar drugs is low and highly dependent of the molecular weight. Permeation of polar drugs with a molecular weight of less than 300 Da is not considerably influenced by their physicochemical properties.

By contrast, the rate of permeation is highly sensitive to molecular size if it is higher than 300 Da; an inverse relationship exists between rates of Permeation and molecular weight.[9]

Solubility

As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions.[3]

Lipophilicity

The permeation of the compound normally increases through nasal mucosa with Increase in Lipophilicity.[3] If Lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity.[7]

Pka and Partition Coefficient

As per the pH partition theory, unionized species are absorbed better compared with ionized specie nasal absorption of weak electrolytes depends on their ionization degree and the largest absorption occurs for the non-ionized species.[7]

Formulation Properties

Dosage Form

Solution and suspension sprays are preferred over powder sprays because the last one easily prompted the development of nasal mucosa irritation. Recently, gel

devices have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa.[7]

Viscosity

Contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.[3]

pH and Mucosal Irritancy

Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria.[3,7]

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.[1]

Volume of Solution Applied

The nostrils can retain only a limited volume beyond which 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.

Strategies to Increase Nasal Drug Absorption[3,7,10-12]

The methods to improve the bioavailability through nasal route. These works was mainly focused on the limitations of nasal route. Followings are some approaches which have been used successfully for the improvement of nasal drug absorption.

Nasal Enzymes Inhibitors

The metabolism of drug in the nasal cavity can be minimized by using various kinds of enzyme inhibitors for minimization of activity of nasal enzymes. Example of enzyme inhibitor includes protease and peptidase, used as inhibitors for the formulation of peptide and protein molecule.

Structural Modification

Drug structure can be modified without changing the pharmacological activity to improve the nasal absorption. Chemical modifications were mainly used to modify the drug structure.

Permeation Enhancer

Various types of permeation enhancers have been investigated to improve the nasal Absorption likes surfactants, cyclodextrins, fatty acids, bile salts, phospholipids, etc.

Particulate Drug Delivery

These are used as carriers for the encapsulation of drug. These carriers was found suitable for prevention of exposure of drug and improve the retention capability in to nasal cavity. These carriers may include microspheres, liposomes, nanoparticles and neosomes.

Prodrug Approach

Prodrugs are the inactive chemical moiety which becomes active at the target site. This Approach is mainly used to improve the physicochemical properties such as taste, odour, solubility, stability.

Bioadhesive Polymer

Bioadhesive polymers are used to improve the nasal absorption of the drug. They improve the retention time of the drug inside the nasal cavity by making an adhesive force between Formulation and nasal mucosa. Bioadhesion leads the minimization of mucociliary clearance of formulation.

In Situ Gel

These formulations generally controlled the problems of administration along with conversion into gel by the influence of stimuli includes temperature, pH and ionic concentration. Thick consistency of gel makes the formulation difficult to drain by the influence of ciliate movement.

Evaluation[1,2,5,6,9,10]

Clarity

The clarity of formulated solutions can be determined by visual inspection under black and White background.[1,5,6]

Texture Analysis

The firmness, consistency and cohesiveness of formulation are assessed using texture analyser which mainly indicates the syringeability of the formulation can be easily administered *in-vivo*.[10]

pH of the Gel

For determining the pH of the formulation of nasal in situ gel, taken 1 ml quantity of each Formulation transferred into a different beaker and diluted it with distilled water up to 25 ml and then pH of each formulation was determined by using pH meter.[6]

Drug Content[6]

1 ml of formulation was taken in 10 ml volumetric flask. And then it was diluted with 10 ml of distilled water then volume adjusted to 10 ml, 1 ml from this solution again diluted with distilled water up to 10 ml after this absorbance of prepared solution was measured at particular wavelength of the drug by using U.V visible spectrophotometer.

Viscosity Measurement

Viscosity of nasal in situ gel was measured by using (cone and plate viscometer) programmable Brookfield viscometer.[6,10]

Gelling Temperature

This test is especially for the thermosensitive In situ gel. In this 2 ml in situ gel transferred to test tube and placed into water bath then the temperature of water bath

increased slowly and constantly. Gel was allowed to equilibrate for 5 minute at each setting, and then formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90° angle, this is known as a gelation temperature.[6,9]

Gel Strength

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.[1,6,10]

In Vitro Nasal Permeation Studies

The *in-vitro* permeation studies are performed by the diffusion studies in a diffusion cell made of glass which consists of a donor and receiver compartment. The nasal mucosa of the sheep is used in the diffusion studies.[2]

In Vivo Nasal Absorption Studies

A number of animal models are used for the *in-vivo* studies; these include the rat model, rabbit model, dog model, sheep model, monkey model.[2]

Histopathological Studies

Two mucosa tissue pieces (3 cm^2) were mounted on in vitro diffusion cells. One mucosa was used as control (0.6 ml water) and the other was processed with 0.6 ml of optimized organogel (conditions similar to *in vitro* diffusion). The mucosa tissues were fixed in 10% neutral carbonate formalin (24 hours), and the vertical sections were dehydrated using graded solutions of ethanol. The subdivided tissues were stained with haematoxylin and eosin. The sections under microscope were photographed at original magnification ×100. The microscopic observations indicate that the organogel has no significant effect on the microscopic structure of the mucosa. The surface epithelium lining and the granular cellular structure of the nasal mucosa were totally intact. No major changes in the ultra-structure of mucosa morphology could be seen and the epithelial cells appeared mostly unchanged.[10]

Advancement in the Nasal Dosage Forms

Nasal Drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. Due to ease of self-administration it is becoming more popular.

Nasal Sprays

Suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal both solution and spray can deliver an exact dose.

Nasal Powders

These formulations are developed when there is problem with stability. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug.

Nasal Gels

The nasal gel showed growing interest due to reduction of post-nasal drip, high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.

Nasal Inserts

Nasal inserts are novel, Bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.

CONCLUSION

The present article is focus on the studying all the parameters/element of in-situ gelling system. Sustained and prolonged release of the drug, good stability and biocompatibility, patient compliance characteristics make the in situ gel dosage forms very reliable In situ gel has some of the merits over the injectable administration and oral route are non-invasiveness and quick onset of action. The mucoadhesive polymers used in the gelling system are most importance as the targeting the drug in the specific region of body.

To develop the a good in-situ nasal gel we must consider the type of approach used, factors that affect the dosage form, evaluation parameters strategies to modify the nasal absorption, etc.

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