REVIEW ON IN-SITU NASAL GEL DRUG DELIVERY SYSTEM

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ABSTRACT

The critique was carried out to discuss in detail about the in-situ gel nasal drug delivery system as these system have better systemic bioavailability through nasal route as compared to oral route of administration. In-situ gel may be novel indefinite quantity kind for nasal delivery of varied medication. It’s infusing into the nasal cavity as low viscous solution and after someday it forms gel once it contact with the nasal mucosa membrane. The most advantage of victimization nasal delivery is shunning of first pass metabolism, high porosity of some medications in nasal epithelium tissue, fast drug absorption across this membrane, rapid onset of action, improved patient compliance and comfort, sustained and prolonged action in compared to different drug delivery systems. The formation of gel depends on factors like temperature modulation, pH change, presence of ions, ultra violet irradiation, polymorphism, dissolution rate, solubility, viscosity and osmolarity. The review was targeted on anatomy and physiology of nose, advantages, disadvantages, mechanism of drug delivery to the nose, forms of dosage kind for nasal delivery, barriers in nasal drug delivery, factors influencing nasal absorption, mucoadhesive polymer ustilized in nasal drug delivery system and analysis of in-situ gel nasal drug delivery system.

KEYWORDS: In-situ gel, nasal mucosa, Bioavailability, novel dosage form, first pass metabolism.
INTRODUCTION
The most commonly used route of administration for systemic effect is oral administration. But for some drug the systemic effect was not in desirable condition due to oral bioavailability and promoted for the search of more effective route for systemic delivery.[1] Usually the nasal cavity is used for the treatment of local diseases they are rhinitis, migraine, cold, pain and nasal congestion. In recent years it has been proved that many drugs achieved better systemic bioavailability through nasal route.[2] The various formulations used by nasal route are nasal gel, spray, powders, etc. Transmucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption[1] This is due to the anatomy and physiology of nasal passage that is porous endothelial membrane, large surface area, high total blood flow, the avoidance of first pass metabolism and readily accessibility.[3][4] In-situ is a Latin term which means ‘In its original place or in position’. In-situ gel is a type of dosage form in which the medicament is in solution form before administration into the body, after administered it undergoes gelation to form a gel.[5] Due to its accessibility, nasal drug administration is considered as an alternative route for systemic circulation instead of intravenous administration[6] Nasal drug delivery also provides a way to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly.[7] The nasal route is an attractive not only for delivery of vaccines due to large surface area and low proteolytic activity but also it improves the patient compliance and decrease the production cost compared to parenteral production.[8] Due to their high permeability the nasal route show only smaller molecular weight drugs the absorption will be more. For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane so the drugs cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier.[9] Penetration enhancers such as surfactants, bile salts and phospholipids increases the drug penetration but in site of clinical use the toxicity test proved that the permeation enhancers has some limitation due their irreversible damage.[10,11] Even though the number of challenges for the researchers to overcome some disadvantages in conventional nasal products and to make effort for the new nasal formulation.

Gel[12]
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.
In-situ gel\textsuperscript{[12]}

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

ADVANTAGES OF NASAL DRUG DELIVERY\textsuperscript{[13]}

- Rapid drug absorption
- Non-invasive
- Easy administration
- Good bioavailability
- Improved patient compliance and convenience.
- Large surface area for drug absorption
- Rapid action
- Less side effects
- The nasal drug is used when the drug which are not suitable for oral route.
- Crosses blood brain barrier.
- First pass metabolism is avoided.

DISADVANTAGES OF NASAL DRUG DELIVERY\textsuperscript{[13]}

- Removal of drug is not possible in nasal cavity.
- Less number of drugs are given by nasal route.
- Nasal irritant drugs are not given through this route.
- Less than 25-200 μl volume of drugs given by this route.
- Lower molecular weight drugs are only given by this route.
- Frequently use of this route causes mucosal damage.
- The drug absorption may cause allergic problems.
- The reached amount of drug may vary in different regions (brain, spinal cord).
PROFILE OF AN ‘IDEAL’ DRUG CANDIDATE FOR NASAL DELIVERY[14]

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

ANATOMY AND PHYSIOLOGY OF NOSE[15]

The nose is divided into two cavities by presence of septum between them and it extends posterior to the nasal pharynx. The surface area of nasal is about 150 cm2 and the volume of nasal cavity is approximately 15 ml. Nose has three regions they are vestibular, respiratory and olfactory. The most anterior part of the nasal cavity is vestibule; it opens through the nostril breathing and olfactory plays a major role of human nose in transportation of drugs to the brain. Except for systemic drug delivery the respiratory region is very important. The respiratory epithelium consists of basal cells, mucus secretion containing goblet cells, rough
columnar and non-ciliated columnar cells. These cells facilitate active transport processes like exchange of water, ions between the cells and cilia motility. The cilia are a hair like microvilli that is three hundred in numbers. They supply large surface area for the drug absorption and the movement of cilia is like a wave and it helps to transport the particles to the throat for intake. Below the epithelium the blood vessels, nerves, serous glands, secretory glands are found. There is a presence of capillaries network that is responsible for drug absorption. The epithelium linked by a mucus secretion layer is revived each ten to fifteen minutes. The pH of the mucus secretion ranges from 5.5 to 6.5 and for youngsters it ranges from 5.0 to 6.7. The mucus layer entrapped the particles which are cleaned by the cilia that they cleared among 20 minutes.

**PRINCIPLE INVOLVED IN IN-SITU GELLING**\(^{[16]}\)

The principle concerned in in-situ gelling of nasal formulation is that the nasal fluid is absorbed by the nasal formulation once administration and forms gel within the nasal cavity. The formation of nasal gel avoids the foreign body sensation. The bioadhesive properties of the gels are used for maintaining contact between gel and mucosa membrane. It acts as un harness dominant matrix and acts as sustained delivery system. Cilia present backwards facilitate to gel rid of the obstacle if there is any interference present within the propulsion state. Once the formation of gel, dissolution and mucociliary removal happens. So there is no have to compelled to take away the dosage kind after it has been depleted of drug.

**BLOOD SUPPLY TO NASAL CAVITY**\(^{[17]}\)

Nasal vasculature is ever such supplied with blood to implement the essential functions of the nasal cavity like as heating and humidification, olfaction, mucociliary clearance and immunological functions. Blood provide 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.
- **Anterioethmoidal 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.

**IN-SITU GEL FORMULATION**[18][19]

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

**Stimuli response in situ gelling system**

**Thermally triggered system**

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

**pH triggered systems**

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

**Osmotically induced in situ gelling system**

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

**Chemically induced in situ gel system**

**Ionic cross linking**

Some ion sensitive to polysaccharides like as carrageenan, Gellan gum, pectin, sodium alginate endure activity transition within the presence of assorted ions such as K⁺, Ca²⁺, Mg²⁺, Na⁺. These polysaccharides represent the category of ion-sensitive ones.

**Enzymatic cross linking In situ**

Formation catalyzed by natural enzymes has not been zetetic wide however appears to have some benefit over chemical and photochemical approaches. For instance, an enzymatic
method operates expeditiously beneath physiological conditions while not want for potentially harmful chemicals like as monomers and initiators.

**Photo-polymerization**
In situ photo-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 photo cured in situ with the help of fiber optic cables and then release the drug for prolonged period of time.

**MECHANISM OF NASAL DRUG DELIVERY**[20][21][22]
The first step concerned within the absorption of the drug in the nasal cavity is crossing the mucus membrane, as are little small, uncharged corpuscle was passing entirely the mucus simply. But charged large molecule does not pass easily through the mucus membrane. The protein present in the mucus layer is Mucin, which binds with the solutes that delay the diffusion and structural changes in the mucus layer are also possible because of environmental changes (i.e. pH, temperature, etc.).[20] During the drug passage in mucus there are several mechanisms for absorption n across the mucosa thus includes simple diffusion, Paracellular transport between cell and transcytosis by vesicle carriers. The restrictions to the drug absorption are essential for metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly. The first mechanism is known as a paracellular route which involves an aqueous route for transportation. This is the slow and passive route. There is a log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The drugs with a molecular weight greater than 1000 Daltons are having poor bioavailability.[21] The second mechanism is known as a trans cellular route which involves transportation through the lipoid route and it is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. The drugs cross the cell membrane by active transport through carrier-mediated or opening of tight junctions.[22]
FACTORS AFFECTING NASAL DRUG ABSORPTION\textsuperscript{[23,24]}

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

**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

**Physicochemical Properties of Drugs**
- Molecular weight
- Size
- Solubility
- Lipophilicity
- pKa and Partition coefficient

**Physicochemical Properties of Formulation**
- Dosage form
- Viscosity
- pH and mucosal irritancy

**Device Related Factors**
- Particle size of the droplet/powder
- Size and pattern of disposition
Biological Factors\textsuperscript{[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 viscoelastic mucus layer towards nasopharynx while less viscous lower layer of mucus is relatively stationary. Secondly, broad ranges of metabolic enzymes are present in the nasal mucosa. This can limit the bioavailability of nasally administered drugs, however; the level of activity of these enzymes is lower as compared to that found in GIT and liver. Moreover pathological conditions like inflammation, the respiratory disorder additionally have an affect on the absorption of drugs from nasal cavity and pH of nasal cavity also affects permeation of drug. A change in the hydrogen ion concentration of mucus can affect the ionization and increase or decrease the permeation of drug depending on the nature of the drug.

PHYSICOCHEMICAL PROPERTIES OF DRUG\textsuperscript{[23]}
Various physicochemical characteristics of drug can also affect nasal absorption of the drug.

Molecular Weight and Size
The 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 the absorption of the 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 development is related to with the rise in lipophilicity following esterification that augmented the speed 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.

**Physical Form of Formulation**
Nasal drug absorption depends on the physical sort of the formulation. The necessary parameter in formulation development is that the viscosity of the formulation. Generally, a more viscous formulation will provide less efficient systemic nasal drug delivery. In the nasal delivery of desmopressin, an 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.

**pH of Formulation**
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 little volumes starting from 25 to 200 μl with 100 μl being the foremost common dose volume. Hence, nasal secretions could alter the
Hydrogen ion concentration of the administered dose. This will have an effect on the concentration of unionized drug out there for absorption. Therefore, an adequate formulation buffer capacity is also needed to keep up the pH.

**Osmolarity**

Drug absorption are often suffering from by tonicity of the formulation. Shrinkage of the epithelial cells has been ascertained within the presence of hypertonic solutions. The hypertonic saline solution also inhibits or stop the ciliary activity. Low pH includes a similar impact as that of hypertonic solutions. Generally, an isotonic formulation is preferred.

**GELLING/ VISCOFYING AGENT OR GEL FORMING CARRIERS**[24]

Some formulations need to be gelled or made more viscous to increase nasal residence time. Increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Drug carrier such as hydroxypropylcellulose was effective for improving 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 the aqueous basis and require preservatives to stop microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzyl alcohol a number of the normally 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 wetness is crucial for preventing dehydration. Therefore, mugginess can be particularly especially in gel primarily based nasal products to avoid nasal irritation and are not probably to have an effect on drug absorption. Some common humectants used embody glycerin, sorbitol and mannitol.

Absorption Enhancers
When it becomes tough for a nasal product to accomplish its needed absorption profile, the utilization of absorption enhancers is suggested. 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 could also be needed once a drug adduces docile membrane permeableness, massive 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.

EVALUATION OF IN SITU GEL\cite{25,26,27}
In situ gels may be evaluated and characterized for the following parameters.

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

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

CONCLUSION
Nasal drug delivery is a novel platform and it is alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment. Development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetes, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Bioavailability of nasal drug products is one of the major challenges in the nasal product development. In contrast, a huge amount of money is investigated by pharmaceutical companies in the development of nasal products, because of growing demand of nasal drug products in global pharmaceutical market. So for the avoidance of side effect and improve effectiveness of nasal products we should pay attention to basic research in nasal drug delivery.

REFERENCES


