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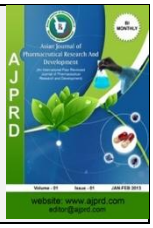

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Review Article

An Overview of Mucoadhesive Thermoreversible Nasal Gel

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A B S T R A C T

Nasal drug is a supportive delivery technique to acquire therapeutic related levels of the medicine in the blood and an sufficient bioavailability. The Drugs have been nasally administrated for entertaining and therapeutic function since premature period. Administration through Nasal route offers a striking route of drug administration for achieving total systemic drug effects to the oral and parenteral route. Nasal drug delivery include rather the large surface area of the nasal cavity and which promotes quick absorption and relatively high blood flow. To improve nasal drug absorption many attempts have been completed in the recent years to develop the residence time of therapy formulations in the nasal cavity. To get better nasal drug absorption many attempts have been completed in the recent years to enhance the residence time of remedy formulations in the nasal cavity, out of them thermoresponsive in situ gel formulation approaches are one of the very important and effective.

Keywords: Mucoadhesive, thermoreversible, *in situ* nasal gel, Nasal DDS.

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INTRODUCTION

The nasal route is a significant mode of drug delivery and nasal cavity has been widely explored for more than three decades. This route is a potential alternative route to parenteral or oral administration for therapeutically active drugs. The nasal route has shown remarkable advantages with an increasing number of products existing for administration through the route for systemic and local administration that include a rapid and high systemic availability. This drug delivery system avoid first pass metabolism by the liver, and the opportunity of targeting drugs directly from the nasal cavity to the brain [1].

In current years many drugs have been shown to achieve improved systemic bioavailability through nasal route than by oral administration Therapy through intranasal administration has been an usual form of healing in the Allopathic & Ayurvedic system of Indian Medicine [2]

In current time many drugs have been shown to reach better systemic bioavailability through nasal route than by oral administration. Nasal delivery is considered to be a promising administration route to get faster and superior stage of medicine absorption. Nasal mucosa has been considered as a potential since nose has a great surface area existing for remedy absorption [3].

Nasal drug delivery - It is a helpful delivery technique to get therapeutic related levels of the medicine in the blood and an adequate bioavailability [4].

The Drugs have been nasally administrated for recreational and therapeutic function since early period. Administration through Nasal route offers an attractive route of drug administration for achieving total systemic drug effects to the oral and parenteral route.

Nasal drug delivery include rather the large surface area of the nasal cavity and which promotes rapid absorption and relatively high blood flow. To improve nasal drug absorption many attempts have been completed in the recent years to enhance the residence time of remedy formulations in the nasal cavity.[5]

Advantages of Nasal Drug Delivery System & Nasal Route:

Nasal drug delivery system nasal absorption of drug offer significant attractive alternative advantages over oral administration parenteral & injection [6]-

- The drug direct entry into systemic circulation through transnasal delivery.
- The rate and amount of absorption as well as time profiles vs plasma concentration are comparable with I.V. administration.
- Nasal drug delivery system improved bioavailability of drug.
- Nasal drug delivery systems are available friendly for user easy noninvasive use.
- Nasal drug delivery system bypass hepatic first – pass metabolism and drug enters direct into system circulation.
- Gastrointestinal degradation of drug that is absent in nasal drug delivery system.
- Through nasal drug delivery system achieve quick onset of action and rapid absorption of drug.
- To improve bioavailability of drug molecules by means of absorption enhancer.
- Drug molecules have good bioavailability through nasal route.
- Drugs that are lesser absorption through oral rote can be delivering to the systemic circulation with the help of nasal drug delivery system.
- Improved compliance& convenience.
- Rapid onset of action and rapid drug absorption via highly-vascularized mucosa.
- Self-administration& Improved bioavailability.
- Reduced side effects of drug through nasal drug delivery system and also reduce dose of drug.
- Administration of drug through nasal route is easy.
- Avoidance of the first-pass metabolism gastrointestinal tract.

LIMITATIONS [2,7]:

- Remedial agents may be at risk to partial degradation in the nasal mucosa may cause irritation to the mucosa.
- Release of drug is predictable to reduce with rising molecular weight of drug.
- The histological toxicity of absorption enhancers used in nasal drug release system is not yet clearly well-known.
- Nasal cavity provides lesser absorption exterior area when compare to GIT.
- Nasal blocking due to cold or allergies may interfere with this method of delivery. Frequent use of this way may result in mucosal damage.

Types of formulation for Nasal drug delivery systems [2,8]

1. Nasal suspensions and emulsions
2. Nasal drops and sprays
3. Nasal gels
4. Nasal powders.
5. Nasal microparticles
6. Nasal liposomal.
7. Nasal micellar

1. Nasal suspensions and emulsions:

Suspensions are rarely used or investigated as nasal drug delivery systems. oral drug delivery it has been reported by several authors that emulsions were superior to suspensions in enhancing the bioavailability of poorly soluble drugs and the trend is similar with nasal formulations. Absorption enhancement has been attributed to solubilisation of the drug and the lipophilic absorption enhancers in the composition. Similarly, other low solubility compounds have been formulated in emulsions to increase the drug solubility, e.g. diazepam and testosterone. a nano-suspension to target the brain through the nose. Formulation as a nanosuspension facilitated bypassing of the blood-brain barrier (BBB) for particles ranging between 1-500 nm. Moreover, recently researchers have also reported nasal administration of nano-emulsions for brain targeting [2,8].

2. Nasal drops and sprays:

Nasal drops are one of the simplest and most convenient Delivery systems among all formulations. Nasal drops can be delivered with a pipette or by a squeezy bottle. These formulations are the main limitation is the lack of precision in the administered dosage and the risk of contamination usually recommended for the treatment of local conditions, but challenges include microbial growth, mucociliary dysfunction and nonspecific loss from the nose or down back the throat. Both solution and suspension formulations can be formulated into nasal sprays. Nasal spray systems consist of a chamber, a piston and an operating actuator. Nasal sprays are comparatively more accurate than drops and generate precise doses a nasal spray can deliver an exact dose from 25 to 200 µm .Several studies have shown that nasal sprays can produce consistent doses of reproducible plume geometry. Formulation properties such as thixotropy, surface tension and viscosity can potentially influence droplet size and dose accuracy. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly. Other factors such as the applied force, orifice size and design of the pump can also affect the droplet size which can impact the nasal deposition of sprays [2,8].

3. Nasal gels:

Nasal gels are high-viscosity thickened solutions or suspensions. A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. The semi-solid characteristics of gels can be defined in terms of two dynamic mechanical properties: elastic modulus G' and viscous modulus G" .The rheological properties of gels depend on the polymer type, concentration and physical state of the gel. Bioadhesive polymers have shown good potential for nasal formulations and can control the rate and extent of drug release resulting in decreased frequency of

drug administration and improved patient compliance Formulation, reduction of irritation by using soothing emollient excipients and target delivery to mucosa for better absorption [2,8].

4. Nasal powders:

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability Particulate nasal dosage forms are usually prepared by simply mixing the drug substance and the excipients , by spray-drying or freeze- drying of drug .Dry-powder formulations containing bioadhesive polymers for the nasal delivery of peptides and proteins Water-insoluble cellulose derivatives and Carbopol 934P were mixed with insulin and the powder mixture was administered nasally. The powder took up water, swelled, and established a gel with a prolonged residence time in the nasal cavity. . The advantages to the nasal powder dosage forms are the absence of preservative and superior stability of the formulation [2,8].

Powers formulation dependent on [2,8].-

- Solubility
- Particle size
- Aerodynamic properties
- Nasal irritancy

5. Nasal microparticles:

Using microparticles as another way of prolonging the residence time in the nasal cavity was introduced in 1987. It was suggested that an increased contact time could increase the absorption efficiency of drugs. As proposed, the relative intranasal bioavailability of human growth hormone in sheep was increased from 0.1% for the solution to 2.7% for the degradable starch microsphere formulation with addition of absorption enhancer.

6. Nasal liposomal:

Liposomes have also been investigated as nasal drug delivery systems and absorption enhancing effects were found for insulin and calcitonin in vitro permeability studies. The enhancement effect was attributed to increased nasal retention of peptides. The best carrier effect for calcitonin was demonstrated with cationic liposomes as they were found to adhere intimately to the nasal mucosal surface, facilitating the penetration of the encapsulated drug. Similar observations were made for desmopressin-loaded cationic liposomes which resulted in enhanced antidiuretic effects in rats compared with anionic liposomes and solutions. Insulin for liposomes showed increased nasal absorption of high membrane fluidity compared to more rigid particles. However, the absorption enhancing effect of liposomes is difficult to separate from the enhancing effects of the single components. Moreover, proliposomes have also shown potential in nasal drug delivery.

Proliposomes are dry, free-flowing granules. Composed of sorbitol as carrier and lipids that form a liposomal dispersion on contact with water. Their advantages are the combination of a fast onset (surface drug) and prolonged drug action (encapsulated drug) as demonstrated for propranolol and nicotine.

Types of liposomes-

- Cationic Liposomes
- Anionic Liposomes
- Proliposomes

7. **Nasal micellar:**

Different types of adjuvants can affect the drug absorption (described earlier, see section 5.1) and are often required to reach therapeutic plasma levels when hydrophilic macromolecular drugs such as peptides and proteins are delivered by the nasal route. Among other surfactants used, bile salts are often used as enhancers, e.g. as micellar solutions. Tengamnuay and Mitra described the use of micelles of sodium glycocholate and micelles thereof mixed with fatty acid (linoleic acid) as absorption enhancers for the model dipeptide (D-Arg2)- kyotorphin and for insulin in rats. The effect of mixed micelles was synergistic and superior compared to the single enhancer. Mixed micelles of sodium glycocholate and linoleic acid reduced the blood glucose level after nasal insulin administration to 47% of the glucose level after an identical nasal dosage of unenhanced insulin. Pure sodium glycocholate resulted in a reduction to 55%. Regarding the mechanism, in a difference to the membrane solubilizing effect of pure bile salts, the mixed micelles were proposed to have an effect on the nasal paracellular pathway. Hereby, the bile salts were considered to act as solubilizing agents for the fatty acids thus making them more available at the nasal mucosa. The absorption modifying effect of mixed micelles was reversible after 20- 40 min and the morphological alterations of the nasal mucosa were only mild to moderate after 5 h of exposure. Liposomes have also been investigated as nasal drug delivery systems and absorption enhancing effects were found for insulin and calcitonin in vitro permeability studies. The enhancement effect was attributed to increased nasal retention of peptides. The best carrier effect for calcitonin was demonstrated with cationic liposomes as they were found to adhere intimately to the nasal mucosal surface, facilitating the penetration of the encapsulated drug . Similar observations were made for desmopressin-loaded cationic liposomes which resulted in enhanced antidiuretic effects in rats compared with anionic liposomes and solutions. insulin for liposomes showed increased nasal absorption of high membrane fluidity compared to more rigid particles. However, the absorption enhancing effect of liposomes is difficult to separate from the enhancing effects of the single components. Moreover, proliposomes have also shown potential in nasal drug delivery.

FACTORS INFLUENCING NASAL DRUG ABSORPTION

A. Factors Related to Drug
B. Factors Related to Formulation
  a) Physicochemical Properties of the Formulation
  b) Dosage form Used for Developing the Formulation

FACTORS RELATED TO DRUG

Lipophilicity On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa.

Although the nasal mucosa was found to have some hydrophilic character, it appears that this mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. In one study it was found that lipophilic compounds alprenolol and propranolol were well absorbed from the nasal mucosa, in contrast to the hydrophilic drug metoprolol. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. A number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinyloestradiol**,** have been shown to be completely or almost completely absorbed nasally in animal models. A correlation between lipophilicity and nasal drug absorption has been demonstrated using several compounds.

Chemical Form

The chemical form of a drug can be important in determining absorption. For example, conversion of the drug into a salt or ester form can alter its absorption. Huang et al. studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions.

Molecular Weight

In the case of lipophilic compounds, a direct relationship exists between the MW and drug permeation whereas watersoluble compounds depict an inverse relationship. it can be concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug, which will mostly permeate through aqueous channels of the membrane. By contrast, the rate of Permeation is highly sensitive to molecular size for compounds with MW = >300 Da.

Partition Coefficient and pKa

As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same holds true in the case of nasal absorption. Jiang et al. conducted a study to determine the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The results showed that a quantitative relationship existed between the partition coefficient and the nasal absorption constant. The nasal absorption of weak electrolytes such as salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile, substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid . Similarly, when the absorption of benzoic acid was studied at pH 7.19 (99.9% of the drug existed in ionized form) it was found that 10% of drug was absorbed indicating that the ionized species also permeates through nasal mucosa. Based on all of these observations, the authors accounted partition coefficients as a major factor governing nasal absorption and supported that other transport pathways for hydrophilic drugs might be of importance [2,8].

Solubility & Dissolution Rate

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared, no absorption takes place [2,8].

FACTORS RELATED TO FORMULATION [2,8,9]

1) Physicochemical Properties of the Formulation

a) pH and Mucosal Irritancy

The pH of the formulation, as well as that of nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 .In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.

b) Osmolarity

Ohwaki et al. studied the effect of osmolarity on the absorption of secretin in rats and found that absorption reached a maximum at a sodium chloride concentration of 0.462 M because shrinkage of the nasal epithelial mucosa was observed at this salt concentration. This results in increased permeation of the compound resulting from structural changes and was further confirmed when sorbitol was used as an osmoregulatory agent. The authors found that permeation of secretin subsequently decreased and, therefore, isotonic solutions are usually preferred for administration.

c) Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

B) Factors Related to Formulation

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2) Dosage form Used for Developing the Formulation

The selection of dosage form depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences.

Some of these delivery systems and their important features are summarized below:

a) Nasal Drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

b) Nasal Sprays

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 mL. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation.

c) Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of post-nasal drip due to 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.

d) Nasal Powders

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage forms are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers.

Generally, the absorption enhancers act via one of the following mechanisms:

• Inhibit enzyme activity;

• Reduce mucus viscosity or elasticity;

• Decrease mucociliary clearance;

• Open tight junctions; and

• Solubilize or stabilize the drug.

Absorption enhancers are generally classified as physical and chemical enhancers. Chemical enhancers act by destroying the nasal mucosa, very often irreversibly, whereas physical enhancers affect nasal clearance reversibly by forming a gel. The enhancing effect continues until the gel is swallowed. Examples of chemical enhancers are chelating agents, fatty acids, bile acid salts, surfactants and preservatives. Osmolarity and pH may accelerate the enhancing effect. Davis and Illum have given a detailed account of the absorption enhancers that can be used for enhancing nasal absorption of drug molecules. The main agents used for enhancing nasal absorption of drugs have been summarized.

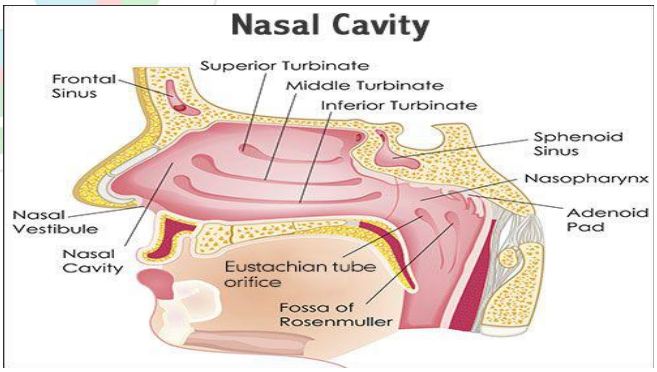

Figure 1.1: Structure of Nasal cavity [8]

FACTORS INFLUENCING NASAL DRUG ABSORPTION [2,8,9]

A) Factors Related to Drug

a) Lipophilicity

On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that this mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. In one study it was found that lipophilic compounds alprenolol and propranolol were well absorbed from the nasal mucosa, in contrast to the hydrophilic drug

metoprolol. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. A number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinyloestradiol**,** have been shown to be completely or almost completely absorbed nasally in animal models. A correlation between lipophilicity and nasal drug absorption has been demonstrated using several compounds.

b) Chemical Form

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c) Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions.

d) Molecular Weight

In the case of lipophilic compounds, a direct relationship exists between the MW and drug permeation whereas watersoluble compounds depict an inverse relationship. it can be concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug, which will mostly permeate through aqueous channels of the membrane. By contrast, the rate of permeation is highly sensitive to molecular size for compounds with MW = >300 Da.

e) Partition Coefficient and pKa

As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same holds true in the case of nasal absorption. Jiang et al. conducted a study to determine the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The results showed that a quantitative relationship existed between the partition coefficient and the nasal absorption constant. The nasal absorption of weak electrolytes such as salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile, substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid. Similarly, when the absorption of benzoic acid was studied at pH 7.19 (99.9% of the drug existed in ionized form) it was found that 10% of drug was absorbed indicating that the ionized species also permeates through nasal mucosa. Based on all of these observations, the authors accounted partition coefficients as a major factor governing nasal absorption and supported that other transport pathways for hydrophilic drugs might be of importance.

f) Solubility & Dissolution Rate

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared, no absorption takes place.

Factors affecting Nasal Drug Absorption:

Many factors affect the systemic bioavailability of nasally administered drugs. The factors can be attributed to the physicochemical properties of the drugs and the characteristics of other ingredient of delivery system has been discussed in relevant section i.e. dosage forms and type and characteristics of selected nasal drugs delivery system. These play significant role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. **The factors influencing nasal drug absorption are as follows [2,8,9]-**

1. Physicochemical properties of drug

- Chemical form of drug.
- Polymorphism
- Molecular weight
- Particle size
- Solubility & dissolution rate.

2. Nasal effect

- Membrane permeability
- Environmental pH
- Mucociliary clearance
- Cold, rhinitis

3. Delivery effect

- Formulation (Concentration, pH, osmolarity)
- Delivery effects
- Drugs distribution and deposition.
- Formulation effect on mucociliary clearance.
- Toxic effect on ciliary function and epithelial membranes

Pharmacokinetics of Nasal Absorption [2,8,9]:

Factors reported to affect the pharmacokinetic parameters following intranasal administration are:-

1. Physiology-related factors, such as

a) Speed of mucus flow

b) Presence of infection

c) Atmospheric conditions

2. Dosage form related factors such as

a) Concentration of active drug

b) Physicochemical properties of active drug

c) Density/ viscosity properties of formulations

d) pH/toxicity of dosage form

e) Pharmaceutical excipients used

3. Administration related factors such as

a) Size of droplet

b) Size of deposition

c) Mechanical loss into the oesophagus

d) Mechanical loss into other regions in the nose

e) Mechanical loss anteriorly from nose

LITERATURE SURVEY

Some extensive review of literatures were carried out and it has been mentioned as below-

Therese Nimi N, Deepa Manohar R (2019) reported that oral route is considered as most convenient and preferred route of administration for the systemic action. Due to poor bioavailability and hepatic first pass metabolism of certain drug, other routes are mainly preferred over oral route, such as parenteral route, transmucosal route and transdermal route. Intranasal route considered as an attractive route due to similar concentration time profile of drug as that of the intravenous route. In-situ nasal gel where drug is administered as a low viscous solution upon contact with nasal mucosa the polymeric conformation change occur and gel formation has been occur. Various triggered polymers are used for the gel formation such as poloxamer, chitosan, carbopol [10].

Agrawal A & Maheshwari RK (2011) developed a mucoadhesive in situ nasal gel containing domperidone with enhanced drug loading and transnasal permeation properties, which were achieved by improving drug solubility using the concept of mixed solvency. Poloxamer 407 was used as thermosensitive polymer and carbopol 934P as mucoadhesive polymer. Initially solubility of domperidone was enhanced in aqueous solution by using various solubilizers like sodium citrate (SC), urea (UR), polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), propylene glycol (PG) etc, individually and as a combination of two, three, and four solvents, respectively. Maximum solubility of domperidone was achieved at 30% w/w solvent concentration, containing mixed blend of PVP K30 (7.5% w/w) + PEG 400 (7.5% w/w) + PEG 600 (7.5% w/w) + Propylene Glycol (7.5% w/w), enhancing solubility of domperidone by 172.20 times as compared to its solubility in water. In situ gel was prepared by cold technique. Evaluation of the prepared gel was carried out, including properties like phase transition temperature, viscosity, in vitro drug release, drug content, transnasal permeation and stability studies. In vitro drug release studies of aqueous solution of mixed blend were performed and permeability coefficient was found to be 1.576 × 10-02 cm/hr and flux was found to be 8.64 µg/cm2hr. Similarly in vitro studies for in situ nasal gel were performed and percent cumulative drug release was 73.05±0.57% in 6 h. Transnasal drug permeation studies results in flux value of 7.04 µg/cm2hr and percent cumulative drug permeated across the membrane as 86.62±0.992%. The results from stability studies revealed that the prepared thermogel showed no significant decrease in drug content and no physicochemical change was observed upon storage in different temperature conditions resulting as a stable formulation [11].

Ebru Altuntaş and Gülgün Yener (2017) developed a mucoadhesive thermoreversible nasal gel with a tailored gelling temperature to provide the prolonged contact between mometasone furoate and the nasal mucosa and in order to prevent drainage of the formulation. For this purpose, in situ gel containing a thermo gelling polymer poloxamer 407 (Pluronic® F-127) and a mucoadhesive polymer Carbopol® 974P NF was prepared. In this content, formulations were designed to have gelation temperature below 34°C to obtain gelation at intranasal cavity. Evaluation of the prepared in situ gels was carried out by the determination of sol-gel transition temperature, rheological and mechanical characteristics, mucoadhesion strength, drug content, physicochemical stability, in vitro release profiles, and ex vivo permeation across sheep nasal mucosa of formulations. Consequently, the in situ gel (CP5) which had favorable gelation temperature (30.1 ± 0.24°C), rheological and mechanical characteristics, in vitro release profile (T%100 180 min), and mucoadhesion strength (0.289 ± 0.0069 mJ) was developed. Consequently, the in situ gel system has been concluded as a promising approach in order to improve the therapeutic effects of intranasal mometasone furoate administration [12].

Amir F *et al.* (2017) reported that poloxamers are triblock copolymers with a center block of hydrophobic polypropylene oxide (PPO) flanked by two hydrophilic polyethylene oxide (PEO) blocks. Among this family of copolymers, poloxamer 407 is a non-ionic surfactant with reversible gelation properties above a particular polymer concentration and a particular temperature. The gelation phenomenon is reversible and characterized by a sol-gel transition temperature (Tsol-gel). Below Tsol-gel, poloxamer407 aqueous solutions remain fluid and the solution turns to a semi-solid material above this temperature which is shown in the fig.ii. The thermogelation is due to hydrophobic interactions between the poloxamer 407 copolymer chains. By elevating the temperature, the poloxamer 407 copolymer chains start to aggregate into a micellar structure. The formation of micelle structures is a result of the dehydration of the hydrophobic PPO repeat units and defines the initial step of gelation. Tsol-gel is concentration dependent and increases by a reduction of the poloxamer 407 concentration in aqueous solution until a lower level is reached at which point poloxamer 407 does not gel anymore [13].

Maryam K (2014) reported that carbopol is a polyacrylicacid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopol (poly acrylic acid) is a well-known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline Ph [14].

Swati Jagdale *et al.* (2016) optimized controlled release *in situ* nasal delivery for timolol maleate. HPMC and Poloxamer 407 were selected as polymer in formulation of thermoreversible *in situ* nasal gel. Nasal route had shown better systemic bioavailability due to its large surface area, porous endothelial membrane, high total blood flow, and avoidance of first-pass metabolism. Timolol maleate is a beta blocker used primarily in the treatment of hypertension. Drug undergoes extensive hepatic first-pass metabolism (80%).The drug has half-life of 4 hrs. Oral

bioavailability of timolol maleate is 61%. Optimization was carried out using 32 factorial designs. It was observed that formulations f1 and f4 revealed the highest % drug release, that is, 93.57% and 91.66%, respectively. Factorial design study indicated that the drug release and viscosity were most significant dependent factors. *Ex vivo* diffusion study through nasal mucosa indicated 67.26 ± 2.10% and 61.07 ± 2.49% drug release for f1 and f4 formulations. f1 was the optimized batch. This batch thus can act as a potential nasal delivery with enhanced bioavailability for the drug [15].

Blessing Atim Aderibigbe (2018) reported that in situ-based gel drug delivery systems that can bypass the blood-brain barrier, deliver the therapeutics to the desired site, reduce peripheral toxicity and control drug release kinetics have been developed. Some of the therapeutics used to treat neurological diseases suffers from poor bioavailability. Preclinical reports from several researchers have proven that the delivery of drugs to the brain via the nose-to-brain route using in situ gels holds great promise. However, safety issues on the toxicity of the nasal mucosa, transportation of the drugs to specific brain regions and determination of the required dose are factors that must be considered when designing these gels. This review will be focused on in situ-based gels that are used for the delivery of therapeutics via the nose-to-brain route, preclinical reports and challenges [16].

Wang Y *et al.* (2017) reported that neurodegenerative diseases are becoming prevalent as the population ages. Geniposide could inhibit oxidative stress, reduce apoptosis, protect neuron, and has been used for therapy of the neurodegenerative diseases. The bioavailability of geniposide by nasal route is greater than that by oral administration. However, mucociliary clearance is a rate-limiting factor for nasal route administration. The objective of this study was to develop and evaluate a mucoadhesive, thermoreversible *in situ* nasal gel of geniposide. The poloxamers (P407, P188) and the hydroxypropyl methylcellulose were used as thermoreversible and mucoadhesive polymers, respectively. Borneol was used as a permeation enhancer. The hydrogel was prepared with the cold method and optimized by the response surface methodologycentral composite design. Gelation temperature, pH, clarity, gel strength, mucoadhesive strength, *in vitro* and *ex vivo* release kinetics of formulations were evaluated. The optimized amounts of poloxamer407 (P407), poloxamer188 (P188) and hydroxypropyl methylcellulose were determined to be 19.4±20.5%, 1.1±4.0% and 0.3±0.6% respectively. The secondorder polynomial equation in terms of actual factors indicated a satisfactory correlation between the independent variables and the response ($R2$ = 0.9760). An ANOVA of the empirical second-order polynomial model indicated the model was significant (P<0.01). P407, P188, P407×P188, P4072 and P1882 were significant model terms. The effects of P407 on gelation temperature were greater than those of other independent variables. The pH values of all the formulations were found to be within 6.3±6.5 which was in the nasal physiological pH range 4.5±6.5. The drug content, gel strength, mucoadhesive strength of the optimized formulations were 97±101%, 25±50 sec and 4000±6000 dyn/cm2 respectively. The *in vitro* release kinetics of cumulative release of geniposide was fitted to the zeroorder model. The *ex vivo* cumulative release kinetics of geniposide was fitted to the Weibull model. This study concludes that the release of geniposide is controlled by gel corrosion, and that the permeation of geniposide is time-dependent. The more residence time, mucoadhesive, thermoreversible *in situ* nasal gel of geniposide for neurodegenerative diseases is of compliance and potential application [17].

Richa Srivastava *et al.* (2017) developed thermo-reversible *in-situ* gel for the treatment of allergic rhinitis (AR). The objective of the present investigation was to develop a mucoadhesive *in-situ* gel with reduced nasal mucocilliary clearance to improve the local effect of the polyherbal extract in the treatment of allergic rhinitis (AR). The prolonged residence of drug formulation in the nasal cavity is one of utmost importance for intranasal drug delivery. The prepared formulations were subjected for gelling temperature, gelling time, viscosity, gel strength, pH, drug content, mucoadhesive strength, spread ability and irritancy studies. In the study the pluronic F127 (PF127) based mucoadhesive *in-situ* nasal gels containing *Moringa olifera* (MO) and *Embelia ribes (ER) extracts* were used having antioxidant and anti-inflammatory effect. A polyherbal thermosensitive *in-situ* hydrogel was designed and evaluated by the mixing of pluronic F127, poly (ethylene glycol) (PEG400) and Xanthan gum with a small amount of (hydroxypropyl methylcellulose) HPMC K4M and Carbopol 934. Total 13 thermosensitive *in-situ* gels of extracts were prepared through combination of HPMC K4M or Carbopol or xanthan gum and PF127. All the preparations were investigated, and the selected method for gel formation underwent the thermal transition from sol to hydrogel. The mucoadhesive gel after being administered into the nasal cavity, get transformed into the viscous hydrogel at body temperature, which diminished nasal mucociliary clearance and prolonged the duration of action. The *in-situ* nasal herbal gel prepared by combination of different concentration of to HPMC K4M or carbopol or xanthan gum with PF127 (10% w/v) produces the better and effective gel. The findings of evaluation parameter indicate that the in-situ gel prepared by combination with corbopol were better quality compared to HPMC K4M and xanthan gum. From these findings, it can be concluded that *in-situ* herbal nasal gels may be potential drug delivery systems for *Moringa olifera* and *Embelia ribes* extracts to overcome first-pass metabolism and thereby to improve the bioavailability. The mucoadhesive *in-situ* gel system is a promising approach for the intranasal delivery of polyherbal extracts for the therapeutic effects improvement of Allergic rhinitis [18].

Monica Rao *et al.* (2017) worked to increase the bioavailability of ropinirole and avoid patient discomfort by formulating thermoreversible *in situ* nasal gel. Parkinson's disease is a degenerative disorder of the central nervous system (CNS). The most obvious symptoms are movement-related such as shaking, rigidity, slowness of movement and difficulty with walking, rigid muscular movements and difficulty in chewing and swallowing especially solid dosage forms. Ropinirole is an anti-Parkinson drug that has low oral bioavailability which is primarily due to first-pass

metabolism. Thermoreversible nasal gels were prepared by cold method using Pluronic F-127 and hydroxy methyl propyl cellulose (HPMC K4M) as gelling agents. Formulations were evaluated for various parameters such as drug content, pH, gelling time, gelling temperature, gel strength, mucoadhesive force, *ex vivo* diffusion, histological studies and *in vivo* bioavailability. Formulations displayed gelation at nasal temperature and the gelation time was found to be less than mucociliary clearance time. The nasal residence time was seen to be increased due to mucoadhesion and increased gel strength. The nasal gel formulations showed *ex vivo* drug release between 56–100% in 5 h. Histological study of sheep nasal mucosa revealed that the gel had a protective effect on the mucosa unlike plain ropinirole which showed evidence of moderate cellular damage. A fivefold increase in bioavailability in brain was observed on nasal administration as compared to IV route. Thermoreversible *in situ* nasal gel was found to a promising drug delivery for Parkinsonian patients [19].

Sabale A. *et al.* (2020) reviewed on nasal delivery, which is an alternative to oral or parenteral administration due to certain limitations such as absorption of the drug, drug targeting to particular organs can cause a problem for administration through oral route. The nasal route has also been successfully used for bypassing the blood-brain barrier and afterword delivering drug molecules to the central nervous system. Also, lag time related to oral drug delivery is reduces by this route and offers noninvasiveness, self-medication, patient comfort, and patient compliance. Extend drug delivery can be attained by different new dosage forms like in situ gel. In situ formulations are drug delivery systems. The in-situ gelling system is a process in which the solution forms of a gel before administration in the body, but once administrated, it undergoes gelation in-situ, to form a gel. In situ gelling system becomes very popular nowadays because of their several advantages over conventional drug delivery systems like a sustained and prolonged release of a drug, reduced Frequency of administration, improved patient compliance and comfort. The *in situ* gel-forming polymeric formulations offer several advantages like sustained and prolonged action reduced Frequency of administration, in comparison to conventional drug delivery systems. From a manufacturing point of view, the production of such systems is less complex and thus lowers the investment and manufacturing cost. Various evaluation parameters are considered during the preparation of *In-Situ* gel [20].

Kempwade, A., Taranalli, A (2014), formulated and evaluated in situ thermoreversible intranasal gel of an antimigraine drug rizatriptan benzoate. The poloxamer 407 and carbopol 934 were used as thermoreversible and mucoadhesive polymers respectively. The gels were prepared with cold method. The phase transition temperature was determined with visual method. The gels were evaluated for their pH, mucoadhesive strength, in vitro release and ex vivo drug permeation through goat nasal mucosa. The histopathological study of the nasal mucosa was carried out to check for its damage during drug permeation. The 18 % w/v poloxamer solution was found to be showing phase transition at physiologic conditions (34–35 °C). As the percentage of carbopol 934 was increased from 0.1 to 0.5 % w/v the gelling temperature was found to be decreased. All formulations were showing mucoadhesive strength above 4,000 dynes/cm2. Drug permeation studies have indicated that the drug permeation rate can be increased by using carbopol 934 above 0.3 % w/v concentration. The histopathological evaluation of nasal mucosa after drug permeation study has not shown any evidence of damage. Thus in situ thermoreversible mucoadhesive gel of rizatriptan benzoate can be a promising approach to treat migraine [21].

Sheri Peedikayil Sherafudeen & Prasanth Viswanadhan Vasantha (2015) formulated and evaluated mucoadhesive *in situ* nasal gels of loratadine. This drug delivery system may overcome the first-pass metabolism and subsequently improve the bioavailability of the drug. A total of 16 formulations of *in situ* nasal gels were prepared using different polymeric ratios of hydroxypropyl methylcellulose (HPMC K-100) and xanthan gum. All formulations had a clear appearance in the sol form, with gelling temperature of the nasal gels ranging between 33.1 ± 0.43 and 34.8 ± 0.82 °C. The gelling time of all the formulations varied from 4.0 ± 0.21 to 11.3 ± 0.22 s; the drug content was >95%. The pH of the formulations ranged between 5.6 ± 0.004 and 6.0 ± 0.003, i.e. no mucosal irritation is expected as the pH was in the acceptable range. Mucoadhesive strength was adequate (3010.89 ± 1.21-6678.89 ± 0.45 dyne/cm2) to provide prolonged adhesion. *In vitro* drug release studies showed that the prepared formulations could release the drug for up to 10 h with all of them following Higuchi kinetics. The accelerated stability studies indicated that the gels were stable over the six months test period. The DSC and XRD analysis revealed that there was no drug-polymer interaction. From these findings it can be concluded that *in situ* nasal gels may be potential drug delivery systems for loratadine to overcome first-pass metabolism and thereby to improve the bioavailability [22].

Amit Jadhav *et al.* (2018) worked was related to overcome the hepatic first pass metabolism by formulating in-situ nasal gel along with caffeine to get cumulative effect. Rizatriptan benzoate undergo hepatic first pass metabolism. Formulation was developed to decrease the mucociliary authorization by using thermo-reversible polymer in gel, thus increase the contact time with nasal mucosa and humanizing the absorption of drug. Gels were prepared by cold technique process and evaluate by Appearance, Viscosity, Gelation Temperature, Permeation Studies, Drug Content, Gel strength etc. The gelation temperature of all studied gel formulations were found in range. pH of gel was in the range and drug content was found between 90-98.86%. Gel strength was found in range of 60-120 sec [23].

Kailas K Mali *et al.* (2015) developed a mucoadhesive *in situ* gel of Granisetron hydrochloride (GH) with reduced nasal mucocilliary clearance in order to improve the bioavailability of the antiemetic drug, granisetron

hydrochloride. The prolonged residence of drug formulation in the nasal cavity is of utmost importance for intranasal delivery of drug. The *in situ* gelation upon contact with nasal mucosa was conferred via the use of the thermogelling Pluronic flake 127 (PF 127). Moringa gum (MG), carboxymethyl tamarind gum (CMTG) and sodium alginate (SA) was used to modulate mucoadhesion whereas drug release of optimized formulation was modified by 0.3% polyethylene glycol 6000 (PEG 6000). Results revealed that as the concentration of mucoadhesive polymer increased the mucoadhesive strength increased and gelation temperature decreased significantly. Preformulation studies showed that addition of GH in 18% PF 127 gels modulated gelation temperature significantly while mucoadhesive polymers alters mucoadhesion. Formulation F6, F11 and F15 showed more than 80% of drug diffusion at 240 min. Gelation temperature and mucoadhesive strength of all three formulations were found in the range of 30-31 □ C and 963.66±9.60 to 991.33±10.26 dyne/cm2 respectively. Formulation F11 showed optimum results and further histopathological evaluation reveled formulation is safe for use. Addition of PEG 6000 increased drug diffusion in formulation F11 with flux 0.034 mg.cm2/min. This study concluded the potential use of CMTG as mucoadhesive *in situ* nasal gel in terms of ease of administration, accuracy of dosing, prolonged nasal residence and improved nasal bioavailability [24].

Inayat Bashir Pathan *et al.* (2017) developed an ion sensitive *in situ* nasal gel of Fluoxetine hydrochloride for brain delivery. A 3^2 factorial design was used to investigate effect of independent variable on dependent variables. Formulations were evaluated for gelation study, viscosity, gel strength, mucoadhesion strength, drug content, *ex-vivo* drug permeation, *in vivo* pharmacodynamic and stability study. The results revealed that as the concentration of gellan gum and HPMC were increased, there was increase in viscosity and mucoadhesive strength and decrease in percent release. The optimized formulation F4 showed highest drug release 94.24 %. In locomotor activity and forced swim test study, the *in situ* gel treated rats showed significant responses as compared to control group. Histopathological examinations showed no evidence of nasal mucosal damage. The *in situ* nasal gel was stable after 3 months. It was concluded that, the *in situ* nasal formulations of Fluoxetine hydrochloride which enhanced nasal absorption and patient compliance for the treatment of depression [25].

P. K. Lakshmi and K. Harini (2019) developed a thermo-reversible nasal *in situ* gel of atomoxetine hydrochloride (AH) with reduced nasal muco-ciliary clearance in order to improve residence time and targeting the brain through nasal mucosa for the treatment of attention-deficit hyperactivity disorder (ADHD). *In situ* gel formulations were prepared using different concentrations of the thermo-gelling poloxamer 407 and mucoadhesive polymers. Temperature-triggered ionic gelation is the mechanism involved. Taguchi L9 OA experimental design was employed for the optimization of the effect of independent variables (Poloxamer 407 and Carbopol 934P) on the response (gelation temperature). *In situ* gel formulation F4 is having 20% poloxamer 407 and 0.3% carbopol 934P and formulation F6 having 20% poloxamer 407 and 0.2% HPMC K100 were optimized based on evaluation parameters. The gelation temperature of F4 and F6 was found to be 37°C ± 0.4 and 37°C ± 0.2, drug content 98.34 and 98.33% and drug release was 83.18, 82.4% in 4 hrs with a flux of 436.9 and 428.1 µg.cm2/hr respectively. The release pattern of drug followed first-order kinetics with Higuchi release mechanism. The value of 'n' from Korsemeyer equation indicated the anomalous diffusional drug release. This study concluded that in situ gel enhanced the nasal residence time and thus may improve the bioavailability of the drug through nasal route by avoiding first pass metabolism [26].

Mahmoud M Omar et al (2019) reported that sumatriptan succinate (SUT) is a potent drug used for relieving or ending migraine and cluster headaches. SUT bioavailability is low (15%) when it is taken orally owing to its gastric breakdown and bloodstream before reaching the target arteries. The aim of the study was to enhance SUT bioavailability through developing an intranasal transferosomal mucoadhesive gel. SUT-loaded nanotransferosomes were prepared by thin film hydration method and characterized for various parameters such as vesicle diameter, percent entrapment efficiency (%EE), *in vitro* release and ex vivo permeation studies. The in-situ gels were prepared using various ratios of poloxamer 407, poloxamer 188, and carrageenan and characterized for gelation temperature, mucoadhesive strength, and rheological properties. The prepared transferosomes exhibited percent entrapment efficiencies (%EE) of 40.41±3.02 to 77.47±2.85%, mean diameters of 97.25 to 245.01 nm, sustained drug release over 6 hours, and acceptable ex vivo permeation findings. The optimum formulae were incorporated into poloxamer 407 and poloxamer 188-based thermosensitive in-situ gel using carrageenan as a mucoadhesive polymer. Pharmacokinetic evaluation showed that the prepared in-situ gel of SUT-loaded nano-transferosomes gave enhanced bioavailability, 4.09- fold, as compared to oral drug solution. Based on enhancing the bioavailability and sustaining the drug release, it can be concluded that the in-situ gel of SUT-loaded nano-transferosomes were developed as a promising non-invasive drug delivery system for treating migraine [27].

CONCLUSION:

The Drugs have been nasally administrated for recreational and therapeutic function since early period. Administration through Nasal route offers an attractive route of drug administration for achieving total systemic drug effects to the oral and parenteral route. Nasal drug delivery include rather the large surface area of the nasal cavity and which promotes rapid absorption and relatively high blood flow. To improve nasal drug absorption many attempts have been completed in the recent years to enhance the residence time of remedy formulations in the nasal cavity, out of them thermoresponsive in situ gel formulation approaches are one of the very important and effective.

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