REVIEW ARTICLE

Nose to Brain Drug Delivery: A Directed Approach for Delivering Drug into Brain

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Abstract

Poor/delayed bioavailability and hepatic first pass metabolism are the major concern when most common oral route is chosen for the delivery of drug, which is why alternate therapies are constantly sought for. Oral route known to have first dissolution of drugs in stomach followed by absorption in systemic circulation which may lead to delay in the effect of drug and reduce the efficacy and potency of the drug. When it is a matter of targeting to the brain, less lipophilic drugs have limited accessibility to the brain and thereby delays therapeutic effect. These limitations about brain targeting system suggest the requirement for the development of delivery system that will transport the medication in to the brain with adequate concentration to get pharmacological action. Drug delivery to brain through nasal mucosa is nowadays emerging way of transport of drug. This method devotes of first pass effect, improves absorption and requires minimal dose. Nasal *in situ* gel, after administration, converts rapidly into gel from liquid after contact with nasal mucosal region allowing adhering of drug in to nasal region. Nasal epithelium allows molecular mass up to 500 Da to pass and thus, the rapid drug accumulation in brain. This review focuses on nasal administration of medicines as a new method of drug transport into the brain. The mechanism of drug absorption through the mucous membrane of the nose, different types of nasal drug administration, methods of production, and polymers required are all described in this paper.

Key words: *In situ* gel, neural pathways, nose to brain drug delivery, olfactory neural pathway, trigeminal neural pathway, vascular pathway

INTRODUCTION

The most popular and simpler route of administration offering patient compliance and comfort is the oral drug delivery. However, a number of pharmaceutically active compounds, especially macromolecules due to size have limited bioavailability, which is attributable to low gastrointestinal permeability, prolonged first-pass metabolism, and chemical or protease degradation.[1] The oral route is known to cause medications to first dissolve in the stomach before being absorbed into the bloodstream, which may decrease the efficacy and potency of the drug and cause a delay in its effects.[2] Due to the desired side effects of oral bioavailability of most of the drugs, there is a search for a more effective way to deliver drugs into the body specially to brain.[1,3]

The blood-brain barrier is made up of astrocytes, which surround the capillary endothelium on the outside of the brain, pericytes, which are embedded in the capillary basement membrane, and endothelial cells from capillaries.[4] Therapeutic drug molecules are forced out of the brain by ATP-binding cassette transporters and P-glycoprotein, which prevent their accumulation.[2,4] Less lipophilic medications have decreased brain accessibility, which delays the therapeutic impact. These limitations emphasize the need for a dosage form to be developed that would carry the medication to the brain with enough concentration to produce a pharmacological effect. The drug molecules insisting for entry into brain must be extremely lipophilic in nature and have a molecular weight of <500 Da.

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Carrier mediated transport and receptor-mediated endocytosis are the most likely modes of drug administration for the central nervous system. This is because the paracellular route of administration is constrained by the tight confluence of capillaries. To implement these channels of medication entry into the brain, a drug delivery system needs to meet specific criteria. There are numerous treatments available for illnesses of the brain. In the event of treatment using pills, the patient must take pills 2–3 times a day. Due to a hectic schedule or emotional stress, patients frequently forget to take prescribed medication which is a major reason of non-completion of therapy.

NASAL DRUG DELIVERY

Nasal drug administration is a technique that targets multiple variables such as brain-targeted delivery, systemic drug delivery, and topical drug administration.[5] The various forms of nasal drug administration are; drops, sprays, gels, *in situ* gel, powders, inserts, insufflators, monodose powder inhaler, multidose dry powder system etc. Intranasal absorption enhances the efficacy of drugs by avoiding gastrointestinal and first-pass metabolism [Figure 1].

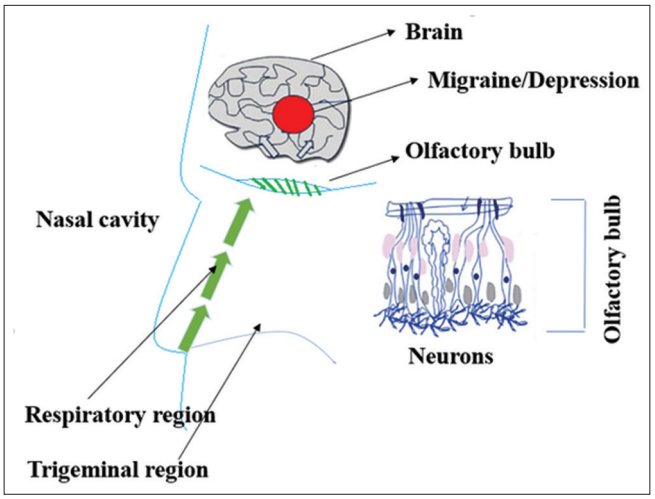

Figure 1: Routes of nasal drug delivery system

Advantages of nasal drug delivery system

1. It is a rapid, non-invasive, secure, and useful method of administering medication
2. It avoids the breaking down drugs in digestive tract
3. It avoids the first-pass metabolism in the liver
4. It allows direct delivery to the brain and spinal cord while reducing systemic drug exposure and its side effects
5. Drugs are quickly absorbed and start to work in the highly vascularized and porous nasal mucosa.
6. It increases patient compliance and self-medication
7. It is an alternative to parenteral delivery. It improves bioavailability of low molecular weight medicines.[6,7]

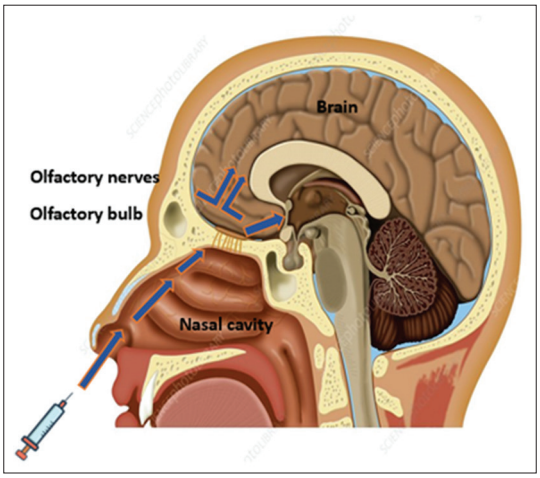

Figure 2: Anatomy of nasal cavity

Limitations of nasal drug delivery system

1. The physicochemical properties of the drug and its formulation must be taken into consideration because they have an impact on how well the medication is going to absorb into the nasal cavity.
2. Themucocilliary clearance causes the drug components to be rapidly removed from the nasal cavity which may result in mucocilliary toxicity.[7]
3. Only a very small amount (100–150 µL) of the drug formulation can be administered. This is the main issue for the drug requiring high dose for therapeutic action
4. Medicines with a high molecular weight could be less permeable to nasal passages.

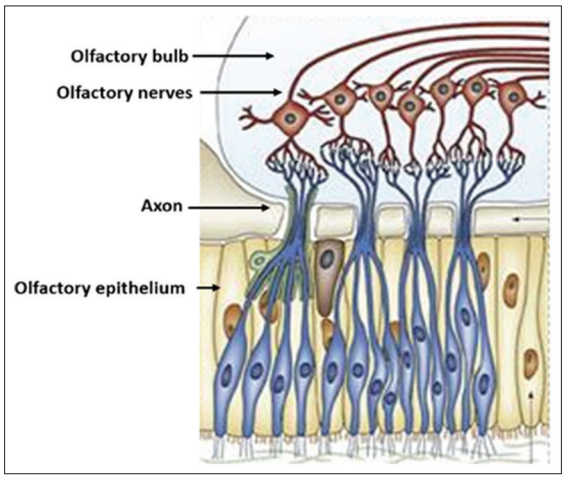

Figure 3: Enlarge aspects of olfactory nerves

Approaches to overcome above limitations

1. The first strategy involves chemically producing pro drugs, or chemical modification
2. It has the drawback of being quickly evacuated from the nasal cavity because ciliary action causes the medication to spend a brief period of time in the nasal mucosa. Mucoadhesive nanoparticles may be used to address this problem

3. A mucoadhesive formulation can be made using a polymer like chitosan to extend the formulation's residence time and increase nasal cavity permeability
4. Drugs having a molecular weight of <500 Da are suitable for administration through nasal way, because they encourage permeability across the nasal mucosa.

DIFFERENT PATHWAYS FOR NASAL DRUG DELIVERY SYSTEM

Various pathways through which absorption of drugs takes place are shown in Figure 2.[5]

Neural pathways

It involves mainly two pathways, that is, from the nasal mucosa to the brain, where the olfactory pathway and trigeminal neural pathways are linked.

Olfactory neural pathway

Drug material is transported to the cerebrospinal fluid or brain parenchyma through olfactory neural pathways. The major purpose of this pathway is to transport drug molecules that are lipophilic. The transport rate depends on the lipophilicity of the molecules.[8] Pharmaceuticals with molecular weights of 300–500 Da are responsible for this pathway. It improves the bioavailability of the drug without using an absorption enhancer, fluid-phase endocytosis and receptor-mediated endocytosis were notably detected throughout the sustentacular cells [Figure 3].[9]

Trigeminal neural pathway

The trigeminal pathway is a principal nerve pathway that terminates in the olfactory bulbs and activates the respiratory and olfactory epithelium of the nasal passages.[10] The trigeminal nerve consists of three divisions: Maxillary, ocular, and mandibular, which deliver sensory data from the nasal cavity, mouth, and CNS to the eyelids and corneal nervous system. The third integrates sensory and motor processes, as opposed to the first two, which are sensory processes.[11]

Vascular pathway

The medication is transported from the nasal to the cerebral systemic circulation by absorbing it into the already present capillary blood vessels just below the nasal mucous membrane. The mucosa of the nose has a lot of blood vessels. It is supplied with blood via arteries in the carotids, both internal and external, as well as the branches of the maxillary and facial arteries. The respiratory mucosa is the best location because it is ideal for drug adsorption into the systemic circulation, is larger than the olfactory mucosa, and receives blood from the anterior and posterior ethmoidal arteries, which are the smallest arteries in the ocular cavity.[12]

Drug delivery from the nose to the brain mechanism

There are three regions in the nasal cavity
(i) Vestibular area
(ii) Respiratory area
(iii) Olfactory region.[12]

1. Into the nose space the drugs reach via two main pathways, namely, a major pathway called the neuronal pathway and a minor pathway called the systemic circulation.
2. The amount of foreign particles is restricted by mucocilia present in the vestibular area (frontal part of the nasal cavity). This area is extremely rich in ciliated cells and mucus.
3. The respiratory region includes four main types of cells: Basal cells, Goblet cells, ciliated cells, and non-ciliated columnar epithelial cells. The breathing area is also composed of trigeminal sensory neurons and highly vascularized blood vessels.
4. In the respiratory region, medications are more easily absorbed into the bloodstream and transported throughout the body. Drugs are transported by trigeminal neurons from the nasal cavity to the pons and cerebrum of the brain, where they are, to a lesser extent, supplied to the olfactory and frontal brains.
5. A drug molecule initially passes through mucociliary clearance in the vestibular region before entering the nasal canal. To reduce the drug's mucociliary clearance, surface-engineered nanocarriers, mucoadhesive systems, and other specially designed intranasal devices are used.[13]
6. After reaching the respiratory and olfactory parts of the nasal cavity, the drug exits the body. Drugs are delivered from the nasal cavity to the brain through a number of pathways, including the olfactory nerve pathway, the trigeminal nerve pathway, the lymphatic/vascular system, and cerebrospinal fluid.

DIFFERENT TYPES OF NASALDRUG DELIVERYSYSTEMSDROPSANDSPRAYS

These formulations are generally used to treat local disorders. These are the examples of the easiest way of administration of drug in to the nose. Squeeze containers or similar type devices are used to administer the nostril/nasal drops. It has some drawbacks like mucociliary dysfunction, microbial development, and non-specific loss from the back of the throat or nose.[14] The likelihood of contamination during use and the accuracy of the given amount are the main limitations 0.5% w/v of ephedrine nasal spray is used to relieve nasal congestion. Nasal spray devices include an actuator, a piston, and a chamber. Nasal spray is more accurate than drops and generates exact doses in each spray.[15]

Nasal gels

Nasal gels are highly viscous, thick liquids, or suspensions. Nasal gels have some properties like reduction in viscosity because of postnasal drip, a decreased impact on taste because of decreased taking in, the elimination of anterior formulation loss, less irritation due to the use of soothing and emollient excipients, and targeted transport to the mucosa, hence improved absorption.[9] Folic acid and B12 are the first nasal gel launched in market.[16]

In situ gels

An *in situ* gel is the preparation that is present in solution form before being administered into the nasal cavity and transferred into gel after administration. *In situ* gelling formulations becomes the focused route of administration in recent years particularly in the domain of nasal drug delivery systems. Due to the environmental conditions, for example, the temperature, pH, magnetic field, and biological factors, they convert from a sol to a gel.[17,18] Ionic cross-linking or pH variations are responsible for the gelation, and the efficiency of gels also depends on their rheological properties, which are crucial for holding the gel in place at the application or absorption site.[8] In situ gel only needs 1–2 drops daily to provide relief, it is more practical than therapy. In situ formulations have been investigated for the administration of both systemic and local drugs.

Some advantages of in situ gels are: High compatibility with high molecular weight medications, less invasiveness; faster absorption at the site; direct delivery to the brain; and high medication levels at the desired place of action. This type of formulation shows a lower number of adverse consequences and also exhibits long-term medication release for an extended period of time, hence improving patient compliance.[19,20]

For example, Zolmitriptan *in situ* gel[21]

Carbopol *in situ* gel[22]

Nasal powder

Certain drugs have stability issues which limits their formulation in solution and suspension forms. Such types of drugs can be made stable by converting it in powder form.

The benefits of nasal powder include:

- The formulation is exceptionally stable.
- There is no preservative, and the acceptability of the nostril formulation depends on particle size, solubility, nasal irritancy, and aerodynamic qualities.[14]

For example, dexamethasone nasal powder.[23]

Nasal inserts

Nasal inserts are bioadhesive in nature and are in solid form employed in the administration of systemic drugs through the nose for a prolonged period of time. After administration of this dosage form, they absorb nasal mucosa fluid and convert into gel in the passageways that prevents the sensation of a foreign body.[24]

For example, Chitosan/xanthan gum nasal inserts.[25]

Insufflations

Insufflators are the tools used to administer the medication by inhalation. It is prepared with a syringe or tube that contains the psychoactive substance, as well as a straw or tube. Due to insufficient disaggregation of the particles, the observed particle size of these systems is frequently bigger than that of the powder particles' particle size.[17] For example, sodium cromoglycate (Rynacrom®) insufflator.[18]

Monodose powder inhaler

The monodose device for intranasally delivered powders ensures high-dose precision. With the new modification to this apparatus, freeze-dried powder that can lyophilize instantly can be applied. The various factors like pressure used in lyophilization, the apparatus affects the physical characteristics of freez-dried powder, which, in turn, impacts the powder's particle size and deposition.[26]

For example, Rivastigmine powder inhaler.[27]

Multidose dry powder systems

Novel techniques for administering numerous dosages of dry powder nasally have been created to improve patient compliance.

For example, Corticosteroid budesonide a topical nasal powder inhaler.[26]

Novel drug formulations

Novel formulations include nanoparticles, microspheres and liposomes for intranasal drug delivery. Various mucoadhesive polymers, enzymatic inhibitors, and nasal absorption enhancers improve the stability of the nasal cavity, membrane penetration, and retention time. It is uncertain if these formulations increases the absorption of medication by delivering the drug through the membrane in their encapsulation or whether they do so merely by enhancing the drug's stability and mucosal retention time.[28]

Microspheres

Microspheres are frequently been used in nasal formulations. The typical components of microspheres acting as building blocks are chitosan and alginate. In addition, microspheres may prolong the duration of the medicine's effects by preventing enzymes from metabolizing the drug and maintaining drug release.[29]

For example, Levocetrizine microspheres.[30]

Nanoparticles

A drug carrier or vaccine adjuvant with a diameter of 1–100 nm known as a nanoparticle which can be employed therapeutically to dissolve, entrap, encapsulate, adsorbed, or chemically bind the active ingredient. Intranasal drug delivery system incorporated with mucoadhesive nanoparticles is more efficient because of their tiny particle size, enhanced permeability, and capacity to sum up a range of substances. They can reduce mucociliary clearance, and offer a paracellular drug pathway to deliver the drug from the nose to brain.[6]

For example, Lorazepam nanoparticles.[24]

Nanoemulsions

A nanoemulsion refers to a stable, transparent mixture of two substances that are usually unable to dissolve in each other, specifically an oil-based substance and a water-based substance, which are combined using surfactant molecules. Nanoemulsions are the tiny emulsions which increases the permeability of nasal epithelial cells which results in accumulation of high quantity of drug into the brain.

According to study, cyclosporine-A nanoemulsion showed highest accumulation of drug in brain when administered by nasal route compared to those of the intranasal solution and IV administration of cyclosporine-A in Sprague-Dawley rats.[31] According to these results, cyclosporine-A nano emulsion may regulate transport straight from the nose to the brain without any systemic soaking.[32]

For example, Norcanthridin nanoemulsion.[33]

Liposomes

Liposomes are spherical-shaped vesicles that are composed of one or more phospholipid bilayers. They are able to incorporate hydhophyllic as well hydrophobic drugs in aqueous and lipid layer respectively. One advantage of liposomal drug system is a capacity to encapsulate tiny and big molecules having a broad variety pertaining to the ability to attract water as well lipid soluble drugs. It has discovered that it improves absorption through nose by increasing the membrane permeation of peptides like insulin and calcitonin.[34]

For example, Liposomes for pulmonary drug delivery system.[35]

POLYMERS USED FOR THE *IN SITU* GEL

pH sensitive polymers used in *in situ* gelling system

Carbopol

It is a polymer made of polyacrylic acid which forms gel at nasal pH level when pKa surpassed which is approximately 5.5.[36] These polymers convert itself into a sol-to-gel when they are exposed to a pH of 4.0–6.0 due to their pKa of 6.0. It get expand in water up to 1000 times their original volume and by 10 times their original diameter. The polymer expands when the pH of the solution rises since it is a pH-sensitive polymer. Triethanolamine, sodium hydroxide, or potassium hydroxide are used to counteract the gelling effect.[37]

Chitosan

Chitosan, a cationic polymer that is pH-dependent, is an amine-polysaccharide. Chitosan transforms into a pH-sensitive gel when it is combined with poly salts which have a single anionic head for ex-glucose phosphate salts.[38,39] Chitosan is a linear polysaccharide with cationic properties that decomposes into water-soluble carboxylate ions such as lactate, acetate, pyruvate, glyoxylate, citrate, malate, ascorbate, formate, and glycolate. The inclusion of nitrogen in its molecular structure, capacity to form polyelectrolyte complexes and canonicity is some of characteristics of chitosan responsible for the formation of gel.[40,41]

Pectin

The amount of galacturonic acid is the primary component of pectin that has been methoxylated. The degree of methoxylation impacts how well pectin works. Low methoxylated pectin in aqueous solution converted in to gel when the carboxyl groups on the backbone of the pectin make contact with Ca^{2+}, an "egg box" structure is produced.[42]

Thermo sensitive polymers used in *in situ* gelling system

Thermo-sensitive polymers react to little external changes in their environment and go through significant and unanticipated physical and chemical changes.[36] They undergo considerable and unwanted physicochemical changes in response to environmental changes.[43]

Thermo-sensitive polymers are the category of environmentally responsive polymer systems for drug

delivery that has received the most research. This is due to the ease with which temperature may be adjusted and used in both *in vitro* and *in vivo* environments. This system becomes gels when the temperature changes, continuing the medication release. These hydrogels are liquid at a temperature of about (20–25°C), but they start to form a gel at body fluid temperatures (35–37°C).

Temperature-sensitive polymers are of two types. Gels with a positive thermosensitive sign (+): This type of method has higher critical solution temperature and becomes hydrogel when the upper critical solution temperature is lowered.

Gels with negative thermosensitive sign: These are a system that has a lower critical solution temperature (LCST) and contract when heated over the LCST.[44,45]

Poloxamer

It is a tri-block copolymer soluble in water.[46] Studies of dynamic light scattering and ultrasonic velocity on the poloxamer 407 solutions reveal that aqueous poloxamer solutions convert into a gel as a result of inherent changes in micellar properties.[47]

Ethyl (hydroxyethyl) cellulose (HEC)

The hydrophilic and hydrophobic unit structure in the polymer backbone of HEC is distributed erratically. HEC is a non-ionic amphiphilic polysaccharide.[48] The thermal behavior of the HEC solutions is altered by the addition of an ionic surfactant (sodium dodecyl sulfate or cetyl triammonium bromide).[49]

Ion-activated *in situ* gel

These types of *in situ* gel cause gelation due to the phase transition in the presence of ions. An anionic polysaccharide (gellan gum) undergoes a phase change when monovalent and divalent cations (Ca_2^+, Mg_2^+, K^+, and Na^+) are present in the nasal discharge.[49]

Gellan gum

Before being used commercially, an anionic exocellular polysaccharide known as gellan gum goes through complete de-esterification during alkali treatment. The gelation process of gellan gum includes two steps.[50] The first step is the transition from random coil to double helical junction zones. The formation of junction points or the buildup of double helices is the second phase. These junction points cause gelation by forming complexes with cations as well as forming hydrogen bonds with water.[51]

In situ gel formation based on physical mechanism

- Swelling: *In situ* gelling may also occur due to the absorption of water from its surroundings and enlarging to fill a desired region
- Diffusion: In this mode, the polymer solution diffuses into the tissue surrounded by the polymer matrix which causes the precipitation.

In situ gel formation based on chemical reactions

Enzymatic activity, photo-initiated processes, and precipitation in inorganic solids from supersaturated ionic solutions are few examples of the chemical reactions that are responsible for the formation of *in situ* gel.

Ionic crosslinking

Polymers may transit into another phase when certain ions are present. Ion-sensitive polysaccharides are a category of polysaccharides.

For example, Gellan gum, a commercially available anionic polysaccharide also known as Gelrite® which solidifies in the presence of monovalent and divalent cations (Ca_2^+, Mg_2^+, K^+, and Na^+).

METHOD OF FORMULATION[39]

Cold method

This process involves mixing the drug with a sufficient volume of double-distilled water and cooling it down to 4°C overnight. The *in situ* gelling polymer is gradually added and continuously agitated. After that, the prepared dispersion solution is refrigerated until a solution becomes clear. This method is applied for the gelling polymer, namely, Poloxamer, chitosan, or carbopol. The polymeric solution of poloxamer maintains a solution at low temperature and changes into gel at high temperature due to its thermosensitivity. Due to the precipitation reaction polypropylene oxide chain in the poloxamer diminishes at high temperatures which leads to precipitation.[52]

Hot method

The hot method is used for the polymers such as pectin or gellan gum. At higher temperatures chains present in gellan gum get solubilize in water, acquire a random-coil shape with high segmental mobility and stay in solution form. The sol-gel transformation occurs on the cooling of the gellan gum solution due to the presence of K+ or Ca2+ ions. Similarly, in the case of pectin, it requires a higher temperature for de-methoxylation, which promotes the solubility or dissolution of the pectin.

EVALUATION OF *IN SITU* GELS

Clarity

Clarity is evaluated visually against a black or white background.

Viscosity

Viscosity of the gel can be performed using a variety of viscometers such as Brookfield viscometer, cone, and plate viscometer with different spindle and speed.[6]

Texture analysis

The viscosity, consistency, and cohesiveness of gels are evaluated using a texture analyzer, which is significantly used to display the syringe ability of the solution so that the formulation can be easily injected during the pharmacokinetic study. To maintain close contact with a surface, gels need to have greater adhesiveness ratings.

pH of gel

The amount of formulation is placed in a beaker, small quantity of Triethanolamine or NaOH is used to maintain the pH of the formulation to get the nasal pH in the range of 5.5–6.5.

Drug content

About 1 ml of the prepared formulation is taken and diluted with 10 ml of distilled water in a 10 ml volumetric flask. UV visible spectroscopy is used to determine the drug content in the sample.

Sol-to-gel transition temperature and gelling time

In situ gel formulation is placed in a sample tube at a specific temperature and then heated at specific rate. The sol-to-gel transition can be concluded as the temperature at which phase transition of the sol meniscus is seen first. The meniscus should not move when you tilt the tube, which is an indication that gel has formed.[53]

Gel strength

This parameter is measured using a Rheometer. A specific amount of gel is placed in a beaker. Slowly lifting the beaker containing the gel causes a probe to be inserted into it. Changes in the probe having load are observed to check how deep the probe is buried under the surface of gel.

Sterility testing

For the sterility testing, the formulation is incubated for 14 days at 30–35°C in a fluid thioglycollate medium to check for bacterial growth and at 20–25°C in a soybean casein digest medium to check for fungal growth.

Accelerated stability studies

For the accelerated stability study, the formulation is temporarily stored in amber-colored vials sealed with aluminum foil. According to ICH state regulations, accelerated stability was performed at 40 ± 2°C and 75 ± 5% RH.

In vitro drug release studies

For the *in situ* gel formulations, drug release studies are conducted with dialysis membrane using Franz diffusion cell apparatus. A dialysis membrane separates the donor compartment and receptor compartment, which each makeup one-half of the cell. The formulation of the required quantity is placed in the donor compartment and the acceptor compartment is filled with the dissolution medium. The diffusion cell is allowed to rotate at 50 rpm. At the predetermined time interval, the solution is withdrawn and replaced with the same volume. Absorbance was taken on a particular wavelength. The drug release from the entire volume of the receptor solution is estimated using analytical methods.[54]

Available patents on Intranasal administration drug devices[55]

Table 1.

Marketed products of nasal *in situ* gels[46]

Table 2.

NASAL DRUG DELIVERY: NEEDS AND FUTURE PROSPECTS

Drug delivery methods that are currently accessible are not widely accepted or complied. Improved solubility or stability, enhanced bioavailability, and biological half-life are the

Table 1: Available patents on intranasal administration drug devices [54]

Type	Patent No.	Year	Assignee	Dosage form
Nasal drug delivery device	9550036 B2	2017	Impel Pharmaceuticals Inc.	Intranasal
Nasal medicine inhaler	359,555	1993-	Nippon Glaxo Limited, Tokyo, Japan	Intranasal
Drug delivery in the nervous system	US 2005/0027110 A1	2003	Gray Cary Ware & Fredenrich LLP USA	Intranasal
Pre-filled nasal drip device	USD610253S1	2020	Daikyo Seiko, Ltd.	Intranasal

Table 2: Marketed products used through nasal route[55]

Sr No.	Drug	Brand name	Dosage forms	Manufacturer	Indications
1	Multiple ingredients	Zicam	Solution (Spray)	Church & Dwight , Inc	Used to prevent cough and cold
2	doxycycline hyclate	Atridox	Solution (Spray)	Tolmar therapeutics Inc	Periodontal treatment product with sub gingival Delivery

present needs of industry.[56] High drug release and prolong drug residence time at the application site are the key difficulties of biopharmaceutical industry to improve safety, efficacy, and compliance. Preservative-free methods, Atomized mist technologies, and integrated formulation development are all crucial parameters for the drug delivery through the nasal cavity. Hence, the new technologies may include better nasal formulations which releases drug at specific site, carrier based systems and enhanced spray formulations.[57]

For nasal medicine delivery to be successful, scientists must work on the creation of the following:

1. Targeted delivery methods that take advantage of the drug's capacity for variation to boost efficacy and decrease negative effects
2. Biotechnology and advanced technologies are being used in new macromolecule delivery methods
3. Consolidated or enhanced nasal drug formulations
4. Integrated device development for effective therapeutic drug delivery.[20]

CONCLUSION

In situ gelling formulations composed of polymeric materials which are capable of undergoing a sol-to-gel transformation on exposure to biological stimuli and emerged as new drug delivery techniques for nasal medication administration. It has been proven that use of mucoadhesive polymers *in situ* gelling preparations increases medication absorption by enhancing residence in the nasal cavity. Nanoparticles in *in situ* gel exhibit mucoadhesive capabilities to lengthen their stay in the olfactory mucosa. To increase the loaded nanoparticle's residence period inside the nasal cavity, better formulation techniques are required. The overall quantity of the medicine supplied also relies on how much of it travels through the olfactory mucosa and how much of it is distributed throughout the brain, which is another crucial element.

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