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INTRA NASAL DRUG DELIVARY SYSTEM: SCOPE, METHODS AND APPLICATIONS

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ABSTRACT

Nasal drug delivery has garnered attention from the scientific community because it may be investigated as a substitute delivery method for vaccines and biomolecules including proteins, peptides, and non-peptide medicines. In Ayurvedic medical system, intranasal therapy is a recognized mode of treatment. Medications that are unstable when administered orally can benefit from being administered via the nasal route because they are digested by first pass action in the liver or extensively degraded in the GIT. A good long-term therapeutic option is the nasal route, which is also an alternative to parenteral therapy. Because of its high vascularization and high permeability, the nasal mucosa allows for quick absorption and activity. Since the medication enters the bloodstream immediately through the nasal route, it is a non-invasive, often utilized local treatment method that can also be employed for systemic therapy. Small chemicals are better absorbed through the nasal route than large molecules, which can be enhanced by absorption promoters. This article provides an overview of intranasal medication delivery, covering its numerous features such as preparation procedures, evaluation techniques, efforts to improve bioavailability, and ingredients used to improve nasal absorption.

KEYWORDS: Intra nasal drug delivery, vaccine delivery, polymers, penetration enhancer, absorption, bioavailability.

INTRODUCTION

Nasal drug delivery has a long history that begins with the topical administration of medications meant for localized effects. In Indian Ayurvedic medicine system, nasal therapy, also known as "Nasya karma," is a recognized kind of treatment.[1] The nasal route was introduced as a potential systemic delivery option in the early 1980s, competing with other traditional medication delivery methods.[2] Because of its highly vascularized epithelium and porous endothelium membrane, which allow for quick absorption of chemicals into the systemic circulation and prevent hepatic first pass elimination, the nasal route is a dependable, convenient, and easy route to use.

Furthermore, nasal administration enables non-invasiveness, self-administration, patient comfort and patient compliance as well as minimizing the lag time when compared to oral drug delivery. These factors also make nasal delivery, a promising alternate drug delivery system in comparison with parenteral drug therapy.[3] Lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles that are often identical to those obtained after an intravenous injection with a bioavailability approaching 100%, while hydrophilic drugs can have their absorption enhanced by absorption enhancers. Through the nasal passage, medications ranging in size from tiny compounds to macromolecules, such as hormones, vaccines, and peptide/protein therapies can also be administered.[4] For bypassing the blood-brain barrier (BBB) and delivering drugs directly into the biophase that are active in the central nervous system (CNS), nasal administration appears to be a promising approach. Additionally, the administration of vaccines has been taken into consideration because of ease of administration.[5-6] Nasal administration of several peptides, including desmopressin, calcitonin, insulin, luteinizing hormone releasing hormone, growth hormone, and adreno-corticotrophic hormone, antihypertensives (nifedipine, nitroglycerine, propranolol, hydralazine, and so forth), analgesics, and steroids (corticosteroids, estrogen, progesterone, testosterone etc.) has been effective.[7,8]

Advantages of nasal drug delivery system[9]

- Absorption of drugs is rapid via highly vascularised mucosa.
- Bypass the BBB.
- Easy to administer and non-invasive.
- Drug degradation seen in the GIT is prevented.
- There is no first-pass hepatic metabolism.
- Nasal bioavailability of tiny medicinal compounds is satisfactory.

- Absorption enhancers can raise the bioavailability of big medicinal molecules.
- Ineffective medication candidates can be administered effectively through the nasal route.
- An easy way for the patient to receive long-term therapy.
- Better bioavailability.
- The smaller dosage results in fewer side effects.
- Convenience and compliance for patients are enhanced.
- Self-management is achievable.
- Direct transfer into the central nervous system and systemic circulation is feasible.
- Reduces the chance of overdosing.

Disadvantages of nasal drug delivery system[10]

- The nasal cavity has a limited delivery capacity of 25–200 µL.
- This is not a viable route for delivering very high molecular weight drugs (mass cut off ~1kDa).
- Pathological conditions have an adverse effect.
- This route exhibits a high degree of interspecies diversity.
- Pharmacokinetic permeability is impacted by regular defensive mechanisms such as ciliary beating and mucociliary clearance.
- Irritation of the nasal mucosa with some drugs.
- Limited understanding of mechanism and less developed models at this stage.
- Systemic toxicity occurring due to absorption enhancers is yet not established.
- The nasal route is more inconvenient than the oral route due to its smaller absorption surface compared to the GIT.

Knowledge on anatomy and physiology of nose, plays a key role with respect to volume and site specificity in drug delivery thorough nasal route.

ANATOMY & PHYSIOLOGY OF THE NOSE

Anatomy & functions of nose

Breathing and olfaction are the prime functions of the nasal cavity in humans and animals.[11] This cavity's structure and function are also physiologically connected to the resonance of sounds produced, particle filtration, mucociliary clearance, immunological processes, and the heating and humidification of inspired air prior to it entering the lungs. The median septum splits the human nose in two symmetrical halves, each of which extends posteriorly to the nasopharynx and opens to the face through the nostrils.[12] The nasal vestibule, located next to the atrium, the intermediate zone, is the most anterior portion of the nasal cavity. The majority of the nasal cavity, including its turbinates, is occupied by the respiratory region the surface area is significantly increased by its turbinates or conchae. While many species have a more complicated arrangement, humans have the inferior, middle, and superior turbinate linked to the lateral wall. Sagittal section of the human nasal cavity with approximately spaced subparts are depicted in Fig. 1.

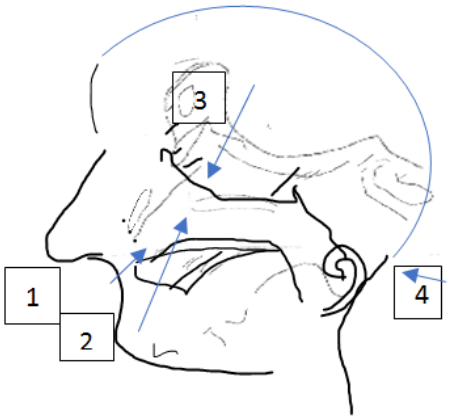

Fig. 1: **Sagittal section of the human nasal cavity, showing the nasal vestibule (1), atrium (2), olfactory region (3), and nasopharynx (4).**[13]

The nasal cavity of an adult human has a total capacity of 15-20 ml and a surface area of around 150 cm2, of which roughly 85% is occupied by the respiratory region. About 2–10 cm2 on the roof of the respiratory region in humans is occupied by the olfactory region.

The mucosa: In humans, the respiratory epithelium is highly vascular and primarily ciliated, columnar, and stratified. The anterior nasal cavity is lined with stratified squamous and transitional epithelium.[14] The skin covers the nostrils. The respiratory epithelium is made up of five primary cell types: basal cells, goblet cells, ciliated and non-ciliated 12-columnar cells, and a small number of neurosecretory cells in the basement membrane. Fig. 2 envisages the structure respiratory epithelium with different cell types.

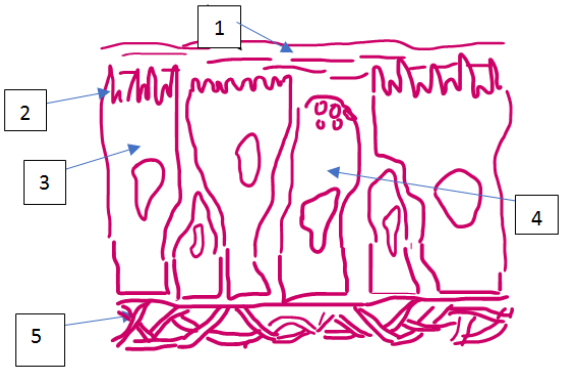

Fig. 2: The respiratory epithelium: mucus layer (1), cilia and microvilli (2), columnar cell (3), goblet cell (4), basement membrane (5).[15]

Mucus is transported into the nasopharynx by ciliated cells, which make up about 20% of all the cells in the lower turbinate area. Each ciliated cell has approximately 100 tiny projections, or cilia, on its apical surface.[16] About 300 microvilli cover every columnar cell, ciliated

or non-ciliated, helping to increase the surface area. Around 60–70% of the respiratory mucosa is lined by non-ciliated cells, which have a high metabolic activity and are involved in the movement of fluid into and out of the cells.[17] Many secretory granules can be seen in the goblet cells, which make up around 10% of the mucosa in the turbinate region. The poorly differentiated basal cells do not reach the apical side of the mucosa; instead, they serve as progenitors to the poorly differentiated columnar and goblet cells. They may be able to take the place of diverse cell types after differentiating.

The superior region of the human nasal cavity is covered by the pseudostratified columnar epithelium known as the olfactory mucosa. It is made up of basal cells, microvillar cells, supporting cells, and the typical receptor cells, also known as olfactory cells.[18]

The basement membrane, also known as the basal lamina, present between the lamina propria and the epithelium. Adjacent to the underlying skeletal bones, the lamina propria is a loose kind of connective tissue that contains glands, subepithelial cells, and vascular and nerve tissue.[19,20] Squamous, ciliated secretory and olfactory epithelia are found in the rat nasal cavity.

Although the olfactory epithelium only covers a small portion of the nasal cavity in humans, it occupies over half of the nasal cavity's surface in rats.[21] Rat nasal canals have non-ciliated cells; however, rats have also shown to contain cuboidal and brush cells, two cell types not found in human respiratory epithelium. Brush cells have apical microvilli and are columnar cells.[22] Brush cells are columnar cells that lack cilia and secretory fibres, featuring apical microvilli.

In the pig respiratory epithelium, five morphologically different cell types have been identified.[23] Similar to people, there are basal and ciliated cells, but very few, if any, non-ciliated cells. Brush cells, five goblet cell subtypes, and a unique secretory cell type not found in human tissue are also present in the porcine respiratory epithelium.

There seem to be significant interspecies differences in both function and sensitivity to toxin-induced injury.[24]

Nasal secretion

Goblet cells and plasma transudate also contribute to nasal secretions, which are mostly produced by submucosal glands.[25] The composition of mucus is as follows: water (95 percent), inorganic salts (1%) lipids (<1%), albumin, immunoglobulins, lysozyme, lactoferrin, and other proteins (1%), and glycoproteins (2%). Glycoproteins, although their small amounts, are responsible for mucus' distinctive viscoelastic characteristics.[26] The mucus layer is separated between an upper layer that is more viscous, measuring between 0.5 and 5 μm in thickness, and a lower, low-viscosity layer that is somewhat less than the length of the cilia, measuring between 5 and 10 μm. Human nasal pH is normally in a narrower range of 5.5-6.5 and 6.3 on average, with significant inter- and intrasubject variability. One laboratory reported a pH range of about 5 to 8.[27]

Excipients used in nasal formulations[28]

There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are shown table 1.

Table 1: Bio adhesive materials used in nasal drug delivery and their characteristics.

Polymers	Characteristics
Cellulose derivatives Water soluble: hydroxypropyl methylcellulose, hydroxypropyl cellulose (HPC), methyl cellulose (MC), carboxy methyl cellulose (CMC). Water insoluble: ethyl cellulose, microcrystalline cellulose (MCC)	-Prolong the residence time of drug in nasal cavity -sustain the release of drug due to high viscosity -act as absorption enhancer -effectively increase intranasal bioavailability
Polyacrylates -carbomers -polycarbophils	-excellent mucoadhesive and gel forming capability -capable of attaching to mucosal surface hence ensure intimate contact between the formulation and membrane surface.
Starch -maize starch -degradable starch microsphere (DSM)	-effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs. -mostly used in mucoadhesive microparticulate nasal delivery system.
Chitosan	-insoluble at neutral and alkaline PH -it can form water soluble salts with inorganic acids -low cost, biodegradable and biocompatible.

Bio adhesive materials: Bio adhesive polymers are compounds that have the ability to engage with biological material through interfacial forces and stay on it for extended periods of time. If the biological material is a mucous membrane, they are also known as mucoadhesive. Muccoadhesion can be explained at the molecular level by attractive molecular interactions

involving forces such hydrophobic interaction, hydrogen bonding, Van Der Waals, and electrostatic interactions.

Gelling agent: A study by Pennington et al. suggests that one way to extend the therapeutic benefit of nasal preparations is to increase the viscosity of the solution. Suzuki et al. demonstrated that whereas hydroxypropyl cellulose is an efficient drug carrier for low molecular weight medicines, it is ineffective for large molecular weight peptides.

It is frequently advised to utilize a combination of carriers due to safety concerns regarding nose irritation.

Penetration enhancer: Enhancer of penetration chemical penetration enhancers are frequently employed in nasal medication administration. The following are the categories of chemical penetration enhancers: 1) Adhesives, 2) Methyl sulfoxide alkyls, 3) Dichloridones 4,1 dodecyl azacycloheptan-2-one 5) Dispersants.

Buffers: The most frequent dose volume for nasal formulations is 100 µL, and they are typically provided in tiny quantities ranging from 25 to 200 µL. Therefore, nasal secretions may change the administered dose's pH, which may impact the amount of unionized medication that is available for absorption. Therefore, to maintain the pH in-situ, a sufficient formulation buffer capacity could be needed. Some frequently used buffers for the local and systemic applications through nasal route, are shown below with their compositions.

Phosphate buffer PH 7.4:[29] Disodium hydrogen phosphate 2.38gms
Potassium dihydrogen phosphate 0.19 gms
Sodium chloride 8gms
Purified water Q.S to 1000ml

Simulated nasal fluid PH6.5:[30] Sodium chloride 6.92gms
Potassium chloride 3.075gms
Calcium chloride 26.66 gms
Sodium lactate 3.100gms
Water Q.s to 1000 ml.

Solubilizer: Nasal medication administration in solution is always constrained by the drug's aqueous solubility. Drug solubility can be increased by using conventional solvents or co-solvents like glycols, tiny amounts of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides, and Labrasol (saturated polyglycolyzed C8–C10 glyceride).

Other substances can be employed, such as cyclodextrins or surfactants, like HP-ß-Cyclodextrin, which work as a biocompatible stabilizer and solubilizer when combined with lipophilic absorption enhancers. Their effect on nasal irritancy must to be taken into account in these situations.

Preservatives: preservatives are necessary in most aqueous nasal preparations in order to inhibit bacteria development. Benzalkonium chloride, benzoyl alcohol, phenyl ethyl alcohol, parabens, and EDTA are a few of the preservatives that are frequently found in nasal forms.

Antioxidants: To keep drugs from oxidizing, a tiny amount of antioxidants could be needed. Tocopherol, butylated hydroxytoluene, sodium metabisulfite, and sodium bisulfite are examples of commonly used antioxidants. Antioxidants often don't irritate the nasal passages or interfere with the absorption of drugs. It is important to take into account the chemical and physical interactions between antioxidants and preservatives and medications, excipients, production tools, and packaging materials when developing a formula.

Humectants: Chronic and allergic illnesses can induce mucous membrane dryness and crusting. When used in greater amounts, several preservatives and antioxidants have the potential to irritate the nasal passages. Preventing dehydration requires adequate moisture in the intranasal cavity. Humectants can thus be included, particularly in nasal solutions that are gel-based.

Humectants prevent rashes in the nose and have no effect on how well drugs absorb. Mannitol, sorbitol, and glycerin are typical examples.

Surfactants: Drug absorption through the nose may be aided by surfactant integration into nasal dosage forms, which alters the permeability of nasal membranes.

Different types of nasal drug delivery system

Nasal drug delivery is an age-old approach, primarily applied as conventional formulations. But with the advancement of technologies, this system is being used for with some novel formulations. Different types formulations used for nasal drug delivery with varied functions, are listed in Fig. 3.

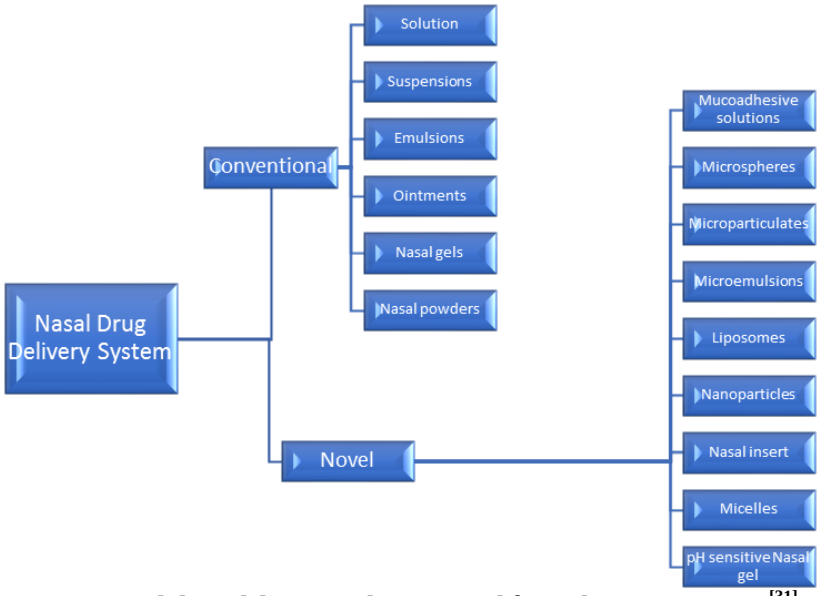

Fig. 3: Nasal drug delivery with associated formulation strategies.[31]

Nasal drops: Nasal drops are used by filling a glass dropper with liquid, sticking the dropper into the nostril, and pressing the rubber valve at the top to release the liquid.[32] Furthermore, studied the use of a nasal solution for insulin delivery. Using sterol and steryl glycoside combinations (1%), produced from soybeans, as absorption enhancers, pharmacological bio-availabilities of 6.7% and 11.3% were attained. Many products, including decongestants and regular saline, use this low-cost technology that enhances the deposition of medications in the nasal passage. The reason for patient compliance is that it necessitates a particular bodily alignment—the head cocked back and the neck stretched which causes discomfort to patients, otherwise the nasal drops get drained when lowering their heads, which impairs bioavailability.[33] With these reasons, the nasal sprays have become one of the most often utilized treatment choices, while nasal drops are used less frequently.

Nasal sprays: For the administration of measured dosages of medication to the nasal cavity, nasal sprays offer the active ingredients that are suspended or dissolved in the excipient solution or in a combination of non-pressurized dispensers. The advantages of these devices are its non-invasive nature, its ability to prevent the first-pass hepatic effect, its quick beginning of action, and its high patient compliance.[34] Spray mode, droplet size distribution, and single actuation content are essential features for nasal spray products. Certain characteristics such as position, surface area, and duration of residency in the nose, may have an impact on the medication's distribution. This can affect the drug absorption at its active site as well as its final systemic circulation.

Nasal inserts: When a nasal insert is applied, it absorbs nasal fluid from the mucosa and produces a gel consistency that sticks to the mucosa because of its bioadhesive characteristic. This gel functions as a release regulating matrix to distribute drugs continuously. Once the medicine is absorbed, there's no need to remove the insert mechanically because the gel gets dissolved and/or drained towards the nasopharynx.[35,36,37-39] Lyophilization or crosslinking are two methods that can be used to manufacture nasal inserts.[36,40-42] In short crosslinking is the process uses emulsion cross-linking agents.[40,41] However, lyophilization is a more commonly used approach for creating nasal inserts. Lyophilization is a procedure that dries the material by letting water vapor escape from the solution within the container below triple point. The resulting insert is comprised of a hydrophilic polymer matrix sponge loaded with a medication. The drug is released primarily in the following manner: inserts first come into contact with the nasal mucosa, which is highly vascularized; then the polymer in its structure takes up the mucin, which turns it into gel rapidly, and produces a regulated release profile or prolonged delivery. A lyophilized nasal insert in the shape of a bullet.

Nasal gel: A gel is a material that is soft, firm, or semi-solid-like that is made up of two or more components, at least one of which is a liquid and is present in significant amounts.[43] The type, concentration, and physical state of the polymer affect the rheological characteristics of gels. They can be very hard, brittle gels (e.g., gellan gum, pectin, and alginate) or viscous solutions (e.g., hypo cellulose, methylcellulose, xanthan gum, and chitosan). Bio adhesive polymers regulate the rate and degree of drug release and have demonstrated promising results in nasal formulations, results in reduced medication administration frequency and enhanced patient adherence.[44,46] In addition, by delaying mucociliary motility, the extended contact time provided at the absorption site can enhance drug bioavailability.[45] Gavini et al. (2011) found that roxithromycin loaded into chitosan microspheres was more soluble than the free

medication when rats intranasal drug absorption was evaluated *in vivo*.[47] There are several ideas that explain the mechanism of mucoadhesion in the nasal cavity, but most agree that the contact and consolidation stages provide the foundation of the mucoadhesive system. Thus, bio-adhesive polymer containing formulations can disseminate throughout the nasal epithelium after being injected into the nasal cavity. The polymer chains can disperse throughout the mucus as a result of the increased surface contact. This establishes enough touch to result in entanglement. This facilitates mucin molecules and polymer chains create secondary chemical connections.[48] Mucoadhesive systems have been developed using a variety of biocompatible and biodegradable polymers. Among them are starch, gellan gum, carbopol, hydroxypropyl methyl cellulose, hydroxy propyl cellulose, poly-vinyl alcohol,[49] chitosan.[50] and alginate.[52,51] Several medications have been examined for nasal administration using mucoadhesive gels, including proteins,[53,54,55] mometasone furoate,[56] carvedilol,[57] sumatriptan succinate,[58] antibiotics such roxithromycin and ciprofloxacin,[59] insulin,[60] and scopolamine hydrochloride.

In situ gel: In situ gel-forming polymeric formulations are solutions prior to being supplied to the body, but afterward, they go through an in-situ gelation process to create a gel. Gel formation is dependent upon various conditions, including changes in pH, temperature, and the presence of ions that allow for the regulated and prolonged release of medication. A viable substitute for in situ gels would be fluid gels. In essence, these fluid gels are structured liquids with a gel-forming polymer present.[61] The nasal sprays with the goal of achieving the necessary viscoelastic qualities for creation of a fluid gel formulation also reported.[62]

Suspensions: Nasal medication delivery techniques involving suspensions are not frequently employed. Senju Pharmaceuticals Inc., Osaka, Japan patented an aqueous nasal suspension of loteprednol etabonate. The nasal suspension contained microcrystalline sodium carboxy methyl cellulose for stabilization and retention in the nasal cavity. The purpose of the nasal suspension was to treat allergic rhinitis locally. A nano-suspension was employed by.[63] to target the brain through the nose. For particles ranging from 1 to 500 nm, formulation as a nanosuspension aided passage of the blood-brain barrier (BBB).

Emulsions: Emulsions have been shown by multiple authors.[64-70] to be more effective than suspensions in increasing the bioavailability of poorly soluble medicines. This pattern also holds true for nasal formulations. The solubilization of the medication and the lipophilic absorption enhancers in the mixture have been linked to absorption enhancement. Similar to this, other low-solubility substances, like testosterone.[71] and diazepam.[72] have been prepared in emulsions to boost the drug's solubility. Furthermore, researchers have just reported using nasal delivery of nano-emulsions to target specific brain regions.[73-75]

Liposomes: *In vitro* permeability experiments, absorption-enhancing effects of calcitonin and insulin in liposomes as nasal drug delivery systems have been studied.[76] Increased nasal retention of peptides was identified as the cause of the enhancing effect. Catalytic liposomes were found to adhere closely to the nasal mucosal surface, which facilitated the penetration of the encapsulated medication, and this resulted in the best carrier effect for calcitonin.[77] Comparing desmopressin-loaded cationic liposomes to anionic liposomes and solutions, it was observed that cationic liposomes produced stronger antidiuretic effects in rats than anionic liposomes.[78] Insulin nasal absorption was found to be higher for liposomes with a high membrane fluidity than for more rigid particles.[79] It is challenging to distinguish the liposomal ability to improve absorption from the additive qualities of their individual constituents, such as phosphatidylcholines and steryl glycosides. Additionally, proliposomes of propranolol and nicotine, have demonstrated promise for nasal medication administration. Proliposomes are free-flowing, dry granules made of lipids that, when in contact with water, form a liposomal dispersion which serves as a carrier. The advantages of a longer drug activity from encapsulated drug and a fast onset from surface drug, have been reported.[80,81]

Nasal powders: Typically, particulate nasal dosage forms are made by simply mixing the drug substance and excipients,[82,83] and sometimes the drug present in liquid form is freeze- or spray-dried.[84-87] The use of bio-adhesive polymers in dry-powder formulations for peptide and protein nasal delivery was initially studied.[88] Insulin was combined with water-insoluble cellulose derivatives and Carbopol® 934P, and the resulting powder was inhaled. The powder absorbed moisture, expanded, and formed a gel that stayed in the nasal cavity for a long period. When hydroxypropyl cellulose was used as the carrier in a bio-adhesive powder containing beclomethasone dipropionate for the topical treatment of allergic rhinitis, the nasal residence time was noticeably longer than the solution when administered as drops.[89] The nasal retention times of apomorphine freeze-dried with lactose, Carbopol® 971P, or sodium carboxymethylcellulose were compared. After three hours of instillation, the nasal cavity had cleared of 58%, 12%, and 27% of the formulation, respectively.[90] The powder that was administered decreased the mucociliary clearance in the nose in every instance.

Preparation of nasal formulations

Different preparation approaches are used for nasal formulations depending on their specified functions to deliver. The frequently adopted approaches are given below with general conditions.

Cold method[91] This technique entails mixing a medication with adequate distilled water and refrigerating it overnight at 4°C. The in-situ gelling polymer is then added to the solution gradually while being constantly agitated. After that, the mixture is refrigerated until it becomes a transparent solution. Finally, the volume is adjusted. This method is commonly used when gelling polymers such as poloxamer, carbopol, and chitosan are used.

Water titration method:[92] The water titration approach was used to create the drug's micro emulsion. In order to make drug-free ME, the calculated amount of drug was added to the oily phase and magnetically swirled until it was dissolved. Then, Smix in a predetermined amount of water was added and stirred.

Ether injection method:[93] The ethosomal gel was made using the injection method of ethanol. There are two mixtures utilized in this procedure. Mixture A contains phospholipid in ethanol, while donepezil hydrochloride in distilled water is called as mixture B. Mixture B was added dropwise to mixture A using a micropipette at a rate of 200 µl/min while mixture A was being stirred at a temperature of 40 °C and 700 rpm. The resultant suspension was left on the magnetic stirrer for an additional ten minutes to allow for the production of vesicles. The prepared vesicles were then chilled and subjected to sonication for later usage.

Thin layer hydration methanol:[94] A homogenous solution was prepared by dissolving phosphatidylcholine and cholesterol in 45 millilitres of dichloromethane and stirring the mixture. Furthermore, 5 mL of methanol was used to dissolve the drug. The mixture of medication, phosphatidylcholine, and cholesterol was evaporated using a rotary evaporator set at 40°C rotated at a starting speed of 50 revolutions per minute (rpm), increasing by 25 rpm every 30 minutes to reach 150 rpm. This procedure was carried out repeatedly until the film coating on the round bottom flask wall developed and all organic phases disappeared. The flask was purged with nitrogen gas and left to stand for twenty-four hours for complete removal of solvent. In order to facilitate peeling, glass beads were used to hydrate the dried film layer with a 50-mL water phase containing phosphate buffer (pH 7.4). The hydration process was done without the use of vacuum conditions. The temperature was set at 40 ºC, and the speed was started at 50 rpm and raised by 25 rpm every five minutes to 250 rpm. This dispersion after hydration was allowed to create liposomes. Lastly, the suspension of multilamellar liposomes was bath-sonicated for 30 minutes to reduce size and then kept at 4º C for a full day. Drug-containing liposomes were employed for additional research after being separated from the unentrapped drug using the centrifugation procedure for 30 minutes at 17,500 rpm and twice-washed with buffer. The filter membrane is positioned in the center of the tiny extruder, which is used to carry out the size reduction operation. The circuit is put on a heating plate, which serves as a temperature control for the system during the extrusion process, once the micro extruder has been mounted on the holder. Liposomes were injected via a 0.45 µm pore-sized polycarbonate membrane for 8 cycles (non-sterile stage) of the extrusion process. The membrane was then re-extruded for 5 cycles using a sterile 0.22 µm pore-sized polycarbonate membrane.

Drug lipid hydration method:[95] The drug-lipid hydration approach was partially modified to create the liposomes. The molar ratio of dipalmitoylphosphocholine (DPPC): Cholesterol (CH) was 1.6:1, respectively. A thin film was formed by mixing and drying 163 mg of total lipid, 124 mg of DPPC, 39 mg of CH dissolved in chloroform, and 7 mg of acyclovir dissolved in 10 ml of methanol. After that, 10 milliliters of phosphate buffer saline containing acyclovir was added to hydrate it. This process produced unilamellar liposomes can be for nasal application.

Evaluation of nasal drug formulations

General evaluation test for all nasal formulations

Visual description

The formulation state and colour were visually determined and noted.

Assay for drug content[96]

Approximately100 mg or 1 ml of formulations were mixed with 10 ml of methanol or suitable solvent and the mixture was shaken periodically for 2-3 minutes. The resultant mixture was suitably diluted with simulated nasal fluid and filtered using 0.45µm filter paper. Using spectrophotometry at corresponding wavelength maxima of drug, the amount of drug in the formulation was calculated by taking dilution factor into account.

Invitro drug release[97]

Using dialysis tubing, an *in vitro* drug release study including polymeric nanoparticles was conducted. The nasal powders, polymeric nanoparticles or nasal suspension which equated to 5 mg of medication, were suspended in 100 ml of simulated nasal fluid at 37 ± 0.5 C, while being continuously stirred at 100 rpm in a dialysis bag with a 10,000–12,000 Mw cutoff. At prearranged intervals, 2 ml aliquots of sample were taken out from the receptor compartment, and the same volume was refilled with fresh buffer. Six independent observations of the experiment were conducted again. The drug release data were processed using a variety of kinetic models, including zero order, first-order, Higuchi, and the Korsmeyer–Peppas models, in order to discover potential drug release mechanisms from nasal formulations.

***In vitro and ex vivo* studies**[98,99]

Using vertical Franz diffusion cells with a diffusion area of approximately 0.636 cm2, *in vitro* drug release and ex vivo permeation studies were conducted. The artificial membrane used for the membranes was either a dialysis

cellulose membrane (MWCO ~ 14,000, average flat width 33 mm, D9652, Sigma-Aldrich) or the nasal mucosa of pigs. The fresh mucosa is collected from a nearby slaughter house. On the day of the experiment, pig ventral nasal turbinates were carefully used to collect nasal tissue, which was then submerged in saline solution (0.9% w/v NaCl in MilliQ Water). In order to evaluate membrane integrity and appropriate arrangement on the cell surface, the donor chamber was filled with simulated nasal fluid (SNF) prior to the tests, and leakage to the empty receptor chamber was tracked.

The receptor compartment contained 5 Millilitre of SNF, which was agitated at 600 revolutions per minute and kept at 37 ºC ± 0.5 ºC (ensuring 32 ºC at the membrane surface) using a thermostatic water pump to replicate the physiological conditions of the nasal mucosa. To encourage powder wetting, powder formulations (approximately 5 mg) were placed straight to the donor compartment and then 50 µl of SNF was added. The 400 µL receptor compartment samples were taken at 10, 15, 20, 30, 60 mins and 1.5, 2, 3, 4, 6 and 8hrs.

The same volume was replaced with preheated SNF following each collection. Prior to HPLC analysis, collected samples were centrifuged for 5 minutes at 12,100 g.

The samples were examined using HPLC with diode array detector.

Accelerated stability studies[98,99]

The nasal formulation stability investigations were conducted in compliance with guidelines from the International Conference on Harmonization. A desiccator (Sabar Scientific, India) with a saturated sodium chloride solution (relative humidity (RH) of 75 ± 5%) was used to hold a suitable amount of nasal formulation in bottles. The samples were taken out of the desiccator after 1, 2, 3, 5, and 6 months of being kept in a hot air oven at 40 ± 2 °C. Investigations were conducted to study the alterations in the preserved formulation's appearance, drug content, and in vitro drug release. The three replicate mean values were noted.

Specific evaluation test for different nasal formulations

The general evaluation methods are not suitable for some specific formulations with different states of matter. Some formulations require specific evaluations testes based on their functions. The evaluations tests of some nasal delivery systems are shown below

Nasal Gels

Gelling temperature[100]

The term "gelling temperature" describes the point at which, at a test tube slanted at 90 degrees, the formulation's meniscus would no longer move. This method was applied to ascertain the gelation investigations. By setting a test tube full enough of the produced solutions in a water bath at 4 °C, the gelling temperature was ascertained. Every two minutes, the temperature of the water bath was gradually raised by 1 °C.

Gelling time[101]

The methods outlined were used to calculate the gelling time of formulations. Before they are administered, the delivery systems are in the sol form; but, afterward, they go through gelation to become a gel. The time of the initial gelation detection was noted as the gelling time. By adding 2 milliliters of the prepared formulation to a 10-milliliter test tube with a 1.0-centimeter diameter, the sol-gel transition temperature (Tsol-gel) of the prepared in situ gel formulations was measured. The tube was placed in a water bath that was circulated at 37 °C and sealed with parafilm. There was a 10-minute equilibration period after every temperature setting. When the test tube was finally positioned horizontally, the sample's condition was examined for gelation and noted.

Viscosity of solution[102]

The viscosity of the gel systems was assessed using an S-94 spindle and the Brookfield viscometer. The gel formulations that were ready were moved to the beaker. At a speed of 1.000 rpm, the spindle was dropped perpendicularly into the gel while the temperature was kept at 37 ± 0.5 °C. When the system was cooling, the viscosity was measured. Three duplicates of each measurement were made.

Gel strength[103]

A 100 ml graduated cylinder was used to hold the sample (50 g). The formulations were put in a thermostat set at 37 °C to facilitate gelation. By timing how long it took a 35 g weight to sink 5 cm in the gel, the strength of the gel was ascertained.

Spread ability[104]

A glass slide that measured 10 by 4 cm was used to assess spread ability. Using a thread, the serosal side of the sheep's nasal mucosa was secured to the slide surface. A drop of gel was applied to the mucosa of the slide at an angle of 120 degrees while it was held in a hot air oven at 37 °C. Before the gelation process, the spread ability of a liquid gel drop was measured in relation to its travel distance. An average of three readings were taken.

Mucoadhesive strength[105]

The lower surface of the right pan was covered with a thin layer of gel (1 g). The beaker from the left pan was taken out and the gel was spread onto the right pan. To guarantee optimal contact between the gel and the nasal mucosa, the pan was kept undisturbed for two minutes. After that, the nasal mucosa was gradually detached from the gel film by adding water to the left pan with a burette. By calculating the weight necessary to separate the mucosa, the mucoadhesive force was computed.

Dynes per square centimeter, or dyne/cm2, was used to express the force.

Liposomes[106]

Determining Particle Size and Morphology

Tthe particle size of freshly manufactured liposomes was determined using Laser particle analysis. A scanning electron microscope was used to perform morphology analysis of the vesicles.

Entrapment efficiency

A sample of the liposome suspension was centrifuged for 10 minutes at 6000 rpm. The dru present supernatant solution was removed to find the entrapped drug.

PDI, surface charge

Zetasizer was utilized to determine the surface charge and polydispersity Index (PDI) of the powder formulations. Prior to examination, the specimens underwent diluting with PBS. Three replications were performed.

Electron Scanning Microscopy

The morphology was ascertained by the use of scanning electron microscopy (SEM). After diluting the nano-size formulations in an appropriate solvent, a drop was placed on gold-coated metal stubs kept under vacuum, and subjected to SEM analysis.

Nasal Powders[107]

Particle size, size distribution, zeta potential

Using Zetasizer, the particle size distribution, polydispersity index, and zeta potential of NPs were calculated. At 25°C, the dynamic light scattering technique was used to quantify the average particle size and polydispersity index at a scattering angle of 90 degrees.

The electrophoretic mobility of the NPs in the U-shaped tube was used to calculate the zeta potential. Prior to the measurements, NPs were diluted in an excess of water in a calibrated vial.

Determination of particulate surface morphology

The surface morphology was examined using a scanning electron microscope. running at 15 kV. A tightly focused electron beam (probe) was employed to non-destructively blast nanoparticles (NPs) inside the electron microscope. The NPs' secondary electrons were utilized to describe the shape of the particles. After that, the samples were randomly scanned, and SEM photomicrographs were taken.

Nasal deposition studies

The nasal deposition was assessed by manually loading nasal powders (20 mg) in equipment made by combining the Next Generation Impactor (NGI) and the Alberta Idealized Nasal Inlet (AINI). In order to replicate human nasal deposition, an idealized nasal airway geometry in aluminum was created using computational fluid dynamics simulations carried out in a collection of realistic nasal geometries.

The four areas of interest such as the vestibule (nostril), the turbinates, the olfactory region, and the nasopharynx were used to quantify the medication. Brij solution (0.15 g/ml Brij in ethanol) in glycerol (1 mL Brij solution for 5 g glycerol) was applied to the AINI and NGI stages to reduce particle bounce. Based on prior experience with this device, the device was operated in three 2 sec bursts at a 45º angle between the vestibule's inlet plane and the device tip. The inhalation flow rate was set at 15 L/min. HPLC analysis was used to quantify drug in the AINI regions, NGI stages, and device following fixed quantities of methanol washing.

Mass balance (%) = m reversed /m filled x 100

Where m filled is the drug mass filled in the device prior to actuation and m recovered is the drug mass quantified in all AINI regions, NGI stages, and device after actuation. Data are reported as the fraction of recovered dose on AINI areas and NGI stages, without taking into account of dose retention in the device or loss in the equipment, in order to standardize the results.

***In vitro* nasal permeation studies:[108]** The nasal diffusion cell is made of glass, containing a donor tube chamber, water-jacketed recipient chamber which has a 60 ml total capacity, a thermometer, and a lid. The donor tube chamber also has a total capacity of 60 ml with 10 cm in length and 1.13 cm in diameter. The lid features three apertures, one for a thermometer and one for sampling. A small amount of distilled water containing genatamycin was injected into the sheep's nasal mucosa after it had been removed from the sublayer of bone structures. The donor chamber tube is connected once all blood has been completely removed from the muscosal surface. The donor chamber tube with sheep's mucosa is positioned in such a way that the recipient chamber's diffusion medium is barely touched. Samples (0.5 ml) are drawn from the recipient chamber at prearranged intervals and put into ampoules having an amber tint. The removed samples are appropriately replaced. The drug content of the samples is estimated using an appropriate analytical method. The experiment is conducted with the temperature maintained at 37 °C.

***In vivo* nasal absorption studies**

There are two kinds of animal models used in nasal absorption research: entire animals, or in vivo models, and isolated organ perfusion models. These models are performed using different experimental animals.

Rat model[109] Rats are surgically prepared for an *in vivo* nasal absorption investigation in the following manner

An intraperitoneal injection of sodium pentobarbital is used to anesthetize the rat. A polyethylene tube is used to cannulate the trachea after a neck incision. Another tube

is introduced through the oesophagus into the nasal cavity's posterior area. In order to prevent the medication solution from being drained from the nasal cavity through the mouth, the nasopalatine tract channel is blocked. Either the cannulation tubing or a nostril is used to deliver the medication solution to the nasal cavity. Blood samples are taken via the femoral vein. The only way the medication can be absorbed and moved into the systemic circulation is by diffusion or penetration through the nasal mucosa, as all other likely drainage outlets are closed.

Rabbit model:[110] Rabbits have a number of following benefits when used as an animal model for nasal absorption research.

1. It is easily maintained in laboratory settings, readily available, and reasonably priced.
2. There is enough blood (about 300 ml) for sampling, hence it is possible to fully characterize a drug's absorption and determine its pharmacokinetic profile.
3. It allows to extend pharmacokinetic research with large animals, such as monkeys.

To permit frequent l-2 ml blood sampling, 3 kilogram rabbits are either kept conscious or put under anaesthesia.

A mixture of ketamine and xylazine is injected intramuscularly to the anesthetize rabbit. A nasal spray of medication solution is sprayed into each nostril by holding the rabbit's head upright.

Ex vivo nasal perfusion models[111]

The following surgical setup is identical to that of the *in vivo* rat model. A funnel is positioned between the reservoir and the nose during the perfusion experiments to reduce the amount of medication solution lost. Using a peristaltic pump, the medication solution is pumped through the rat's nasal cavity and the reservoir is maintained 37°C. The perfusion solution flows back into the reservoir after exiting the nose (via the funnel). The reservoir's medication solution is constantly agitated. The remaining drug concentration in the perfusing fluid is used to estimate the amount of drug absorbed.

For rabbit, parenteral uretliane-acepromazine is used for anaesthesia. The trachea is cannulated with a polyethylene neonatal endotracheal tube, the oesophagus is isolated and ligated, the distal end of the oesophagus is closed with suture, and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract, which connects the nasal cavity to the mouth, is closed with adhesive to prevent drug solution from draining from the nasal cavity, and the drug is recirculated using a peristaltic pump.

***In vivo* bioavailability**[112] A study on *in vivo* bioavailability is carried out on male rabbits in good health. Three groups, each with six rabbits, participated in the study and fasted for twenty-four hours. One group received standard traditional preparation, a control group was also maintained, a third group used for test formulation. In the fasting period, no water is provided throughout the experiment and. The rabbits' marginal ear veins were used to draw blood, with a sample of roughly 2 ml taken in heparinized centrifuge tubes at 0.5,1,2,3,4,5,6,7, 8 hours after the medication was administered. After the blood samples are centrifuged at 3000 × g for 15 minutes, the plasma is extracted and kept at -20°C for further examination.

The drug extracted from plasma is used for HPLC analysis.

Pharmacokinetic analysis: The semilogarithmic plot of plasma concentration vs. time yields the elimination rate constant (Kel), which is then calculated from the elimination half-life (t1/2) using the formula t1/2 = 0.693/Kel. The plot of plasma concentration vs. time also yields the area under the curve (AUC), the peak plasma concentration (Cmax), and the time to attain peak concentration (Tmax).

Applications of nasal drug delivery system

Epilepsy and schizophrenia

Better brain bioavailability and rational diffusion efficiency were demonstrated,[113] and produced micro emulsion containing valproic acid.

Lorazepam microemulsions which is sedative, muscle relaxant, tranquilizer, antiepileptic, and inducer of sleep. Lorazepam is a weakly water-soluble medication in microemulsion via nasal route showed very little hemolytic potential and good chemical and physical stability, making them a suitable substitute for the lorazepam formulations that are currently on the market.[114]

Cosolvent-based parenteral formulations have a number of drawbacks, including discomfort and tissue damage at the injection site as well as the drug's tendency to precipitate upon dilution in certain situations makes nasal delivery a better option.

Antidepressant

To be administered intravenously to the brain, created a microemulsion of eucalyptus oil[115] and proven that the eucalyptus oil microemulsion is an economical and effective formulation that offers a quick start to its calming stimulant and antidepressant effects.

Migraine

Migraines are largely belongs to vascular or neurological conditions. Migraine treatments for neural impairment have developed by the scientific community. Once, sumatriptan taken o908rally, is rapidly but incompletely absorbed and goes through first-pass metabolism, which results in poor absolute bioavailability of 14% in

humans. Blood-brain barrier (BBB) transport of sumatriptan is incredibly inadequate. Intranasal administration has been shown to produce positive outcomes.[116]

Angina pectoris and deflect neurological diseases

In order to increase nimodipine's (NM) solubility and brain uptake, microemulsion that was appropriate for intranasal administration. When NM was administered by nasal route, it was three times more absorbed in the olfactory bulb than when it was administered intravenously (IV). The ratios of area under the curve (AUC) between plasma and brain tissues and cerebrospinal fluid obtained following nasal injection were significantly larger than those obtained following intravenous administration. A very promising method for treating and preventing neurodegenerative disorders, is using intranasal administration of NM.[117]

Analgesics

It is evident that nasal medication delivery and pain treatment work together to satisfy the demands of an expanding but neglected market. The combination of nasal medication delivery with pain management could be extremely advantageous for people experiencing break through moderate-to-severe, or acute pain. Analgesics delivered by nasal spray will provide a quick-acting, safe, and effective way to reduce the pain. When it comes to managing cancer pain, nasal route is crucial. For instance, in case of modern opioids for cancer pain control, they must be used when the pain is moderate to severe.

The above-mentioned applications are the tip of iceberg in total usage. Different drugs loaded in various nasal formulations using wide variety of excipients were marketed and patented. Table 2 shows different drugs used in nasal delivery system. Different nasal formulation made from various API and excipients was elaborated Table 3. Some Marketed products of nasal drug delivery system with their manufacturers were listed in Table 4. Finally, Table 5 depicts a few critical Patents filed on intra nasal delivery system.

Table 2: Different drugs used in nasal delivery system.

Drug	Category	Formulation	References
Mirtazapine	Antidepressant	In situ gel	[118]
Rizatriptan	Antimigraine agent	In situ gel	[119]
Levodopa	Anti Parkinson effect	In situ gel	[120]
Zolmitriptan	selective serotonin receptor agonists.	Insert	[121]
Valproic acid	Anti epilepsy	Liposome	[122]
Donepezil	anti-alzhemier	Liposome	[123]
Acyclovir	Antiviral	Liposome	[124]
Rivastigamine	Anti-alzhemier	Liposome	[125]
Glime pride	Anti diabetic	Liposome	[126]
Olanzapine	Antipsychotic	Micro emulsion	[127]
Glioblastoma	Antitumor	Micro emulsion	[128]
Risperidone	Antipsychotic	Nanoparticles	[129]
Azelastine	Antihistamine	Nanosuspension	[130]
Amantadine	Anti Parkinson	Nasal spray	[131]
Sumatriptan	Acute treatment of migraine	In situ gel	[132]
Huperzine	Anti-alzheimer	In situ gel	[133]
Almotriptan	Acute treatment of migraine	In situ gel	[134]
Geniposide	Anti inflammation	In situ gel	[135]
Rivastigmine hydrogen tartrate	Used to treat mild to moderate Alzheimer's dementia	In situ gel	[136]
Mometasone furoate	treatment of asthma	In situ gel	[137]
Montelukast sodium	treatment of milssd asthma	In situ gel	[138]
Hydrocortisone	Anti inflammation	In situ gel	[139]
Pramipexole dihydrochloride	Anti Parkinson	Nano particle	[140]
Efavirenz	Treatment of HIV	Nano particle	[141]

Table 3: Different nasal formulation made from various API and excipients.

Nasal dosage form	API	Excipients	Reference
In situ gel	Huperzine A	Poloxamer (407,188) castor oil, ringer solution	[142]
In situ gel	Almotriptan	Poloxamer (407,188), Na-CMC, precirol	[143]
In situ gel	Sumatriptan	Poloxamer (407,188), carrageenan, soyabean	[144]
In situ gel	Ziprasidone	Poloxamer (407,188), HPMC E5, PEG 6000,4000	[145]
In situ gel	Geniposide	Poloxamer (407,188), HPMC, borneol, NaCl	[146]
In situ gel	Rivastigmine hydrogen	Poloxamer 407, polymer NPs	[147]

	tartrate		
In situ gel	Mometasone furoate	Poloxamer 407, Carbopol 974 NF, PEG 400, NaCl	[148]
In situ gel	Montelukast sodium	Poloxamer 407, HPMC, PEG 400	[149]
In situ gel	Hydrocortisone	Poloxamer 188, Carbopol 934, PG, isopropyl alcohol.	[150]
Nano particle	Pramipexole dihydrochloride	CS, sodium triphosphate	[151]
Nano particle	Efavirenz	CS chloral hydrate, tween80, HP-β-CD	[152]
Nano particle	Efavirenz	Chloral hydrate, tween 80, HP-β-CD	[153]

Table 4: Marketed products of nasal drug delivery system with their manufacturers.

Brand name	Drug	Manufacturer	References
Allegro-Comod	Cromolyn sodium	Ursapharm	[154]
Lomusal	Cromolyn sodium	Sanofi Aventis	[155]
Vividrin	Cromolyn sodium	Bausch and Lomb	[156]
Astelin	Azelastine	Meda Pharm	[157]
Bactroban	Mupirocin	Glaxo Smith Kline	[158]
Beconase	Beclomethasone dipropionate	Glaxo Smith Kline	[159]
Decadron	Dexamethasone	Merck and co, Inc	[160]
Flixonase	Fluticasone propionate	Glaxo Smith Kline	[161]
Livocab	Levocabastine	Janssen	[162]
Nasalcrom	Sodium cromoglicate	Mc Neil Consumer Healthcare	[163]
Nasivin	Oxymetazoline	Braco	[164]
Nasonex	Mometasone furoate	Merck and co., Inc	[165]
Otrivin	Xylometazoline	Novartis	[166]
Patanase	Olapatadine	Alcon laboratories	[167]

Table 5: Patents filed on intra nasal delivery system.

Delivery system type	Drug studied	Patent	References
Nasoadhesive micro emulsion	Benzodiazepine	A Misra, TK Vyas 1061/MUM/2004	[168]
Nasal spray	Epinephrine	Nigel Ten Fleming US20150005356 A1(2015)	[169]
Nasal sprays and inhalers	Ketamine	Dennis S. Charney, Sanjay j. Mathew Husseini K. Manji, Carles A. Zarate, John H. Krystal US20170181966A1(2017)	[170]
Drops/spray	Ketorolac	Giancarlo Santus, Giuseppe Botton, Ettore Bilato US9211253 B2(2001)	[171]
Nasal sprays	Naloxone	Roger Crystal, Michael Brenner Weiss. US9211253 B2 (2015)	[172]
Nano emulsion	Proteasomes Glatiramer	D Frenkel, R maron, D Burt, HL Weiner. US20060229233 A1(2006)	[173]
Gel formulation	Noseafix	Claudia Mattern US20170189414 A1(2017)	[174]
Nasoadhesive microemulsions	Triptans, Caffeine	A Mistra, TK Vyas 1125/MUM/(2004)	[175]

CONCLUSION

Nasal drug delivery is a cutting-edge delivery system that shows promise as a substitute for injection drug delivery. Various factors impact the bioavailability of a drug from nasal products It is anticipated that new nasal products would be introduced for the treatment of chronic conditions like diabetes, osteoporosis, and infertility. More medications in the form of nasal formulations meant for systemic treatment may be introduced to the market in the near future.

Due to the increased demand for nasal medicine products in the global pharmaceutical market, pharmaceutical companies are investing a significant amount of money in the development of nasal products especially for vaccine delivery. Hence focus on fundamental research is a need of hour in nasal medicine delivery to reduce adverse effects and increase the efficacy of nasal products.

REFERENCE

1. Hicke A.J., Pharmaceutical Inhalation Aerosol Technology, 2nd ed Marcel Dekker, Inc: NewYork, 2004.
2. Illum L. Nasal drug delivery-possibilities, problems and solutions. J Control Release, 2003; 87: 187–198.
3. Ugwoke M.I., Verbek N., and Kinget R. The biopharmaceutical aspects of nasal mucoadhesion drug delivery. J Pharm Pharmacol, 2001; 59: 3–22.

4. Arora P., Sharma., Gary S. Permeability issues in nasal drug delivery. Drug Discovery Today, 2002; 7: 967–975.
5. Marttin E., Nicolaas G.M., Schipper J., Coos V., Frans WH. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Del Rev., 1997; 29:13- 38.
6. Choi H.G., Jung J.H., Ryu J.M. Int J of pharm, 1998; 165: 33-44.
7. CIllum L. Nasal drug delivery: new developments and strategies. Drug Discov Today, 2002; 7: 1184- 1189.
8. Graff L.C., Pollock G.M. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci., 2005; 94: 1187-1195.
9. Lipworth B. J., and Jackson C.M. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf, 2000; 23: 11–33.
10. Wiseman J.W. Steroid hormone enhancement of gene delivery to a human airway epithelial cell line in vitro and mouse airways in vivo. Gene The, 2001; 8: 1562–1571.
11. Chien, Y.W., Chang, S.-F., Intranasal drug delivery for systemic medications. Crit Rev Ther Drug Carrier Syst, 1987; 4(2): 67-194.
12. Chien, Y.W., Su, K.S.E., Chang, S.-F., Anatomy and physiology of the nose, *in* Y. W. Chen, K. S. E. Su, and S.-F. Chang, eds., Nasal systemic drug delivery: Drugs and the pharmaceutical sciences, 1989; 39: 1-19.
13. Chiou, W.I., Chung, S.M., Wu, T.C., Mu, C., A comprehensive account on the role of efflux transporters in the gastrointestinal absorption of 13 commonly used substrate drugs in humans. Int J Clin Pharmacol Ther, 2001; 39(3): 93-101.
14. Mygind, N., Pedersen, M., Nielsen, M.H., Morphology of the upper airway epithelium., *in* D. F. P. A. I. Andersen, ed., the Nose: Upper airway physiology SSand the atmosphere environment: Amsterdam, Elsevier, 1982; 71-97.
15. Mathison, S., Nagilla, R., Kompella, U.B., Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug Target, 1998; 5(6): 415-441.
16. Petruson, B., Hansson, H.-A., Karlsson, G., Structural and functional aspects of cells in the nasal mucociliary system. Arch. Otolaryngol, 1984; 110: 576-581.
17. Mygind, N., Pedersen, M., Nielsen, M.H., Morphology of the upper airway epithelium., *in* Andersen, D. F. P. A. I. ed., The Nose: Upper airway physiology and the atmosphere environment: Amsterdam, Elsevier, 1982; 71-97.
18. Morrison, E.E., Constanzo, R.M., Morphology of the human olfactory epithelium. J Comp Neurol, 1990; 297: 1-13.
19. Petruson, B., Hansson, H.A., Function and structure of the nasal mucosa after 6 weeks' use of nose-drops. Acta Otolaryngol, 1982; 94: 563-569.
20. Petruson, B., Hansson, H.A., Karlsson, G., Structural and functional aspects of cells in the nasal mucociliary system. Arch. Otolaryngol, 1984; 110: 576-581.
21. Gross, E.A., Swenberg, J.A., Fields, S., Popp, J.A., Comparative morphometry of the nasal cavity in rats and mice. J Anat, 1982; 135: 83-88.
22. Monteiro-Riviere, N.A., Popp, J. A., Ultrastructural characterization of the nasal respiratory epithelium in the rat. The American Journal of Anatomy, 1984; 169: 31-34.
23. Monteiro-Riviere, N.A., Popp, J.A., Ultrastructural characterization of the nasal respiratory epithelium in the rat. The American Journal of Anatomy, 1984; 169: 35-43.
24. Harkema, J.R., Comparative pathology of the nasal mucosa in laboratory animals exposed to inhaled irritants. Environ. Health Prospect, 1990; 85: 231-238.
25. Chien, Y.W., SU, K.S.E., Chang, S. F., Anatomy and physiology of the nose, *in* Y. W. Chen, K. S. E. SU, and S.-F. Chang, eds., Nasal systemic drug delivery: Drugs and the pharmaceutical sciences, New York, Marcel Dekker Inc, 1989; 39: 1-19.
26. Luppi B, Bigucci F, Cerchiara T, Zecchi V. Chitosanbased hydrogels for nasal drug delivery: from inserts to nanoparticles. Expert Opin Drug Deliv, 2010; 7(7): 811-828.
27. Chajed S., Sangle S., and Barhate S. Advantagious nasal drug delivery system; A review, International journal of pharmaceutical science and research, 2011; 2(6): 1322-1336.
28. Al Asmari AK, Ullah Z, Tariq M, Fatani A. Preparation, characterization, and in vivo evaluation of intranasally administered liposomal formulation of donepezil. Drug design, development and therapy, 2016 Jan 12; 205-15.
29. Nagare SA, Rajguru JR, Rajurkar VG, Shirsat MK. Development and Evaluation of Nasal Mucoadhesive in Situ Gel Formulations of Carbamazepine Using In Vitro, Ex-Vivo and In-Vivo Methods. International Research Journal of Pharmacy and Medical Sciences ISSN 2581-3277
30. Lalan M, Tandel H, Lalani R, Patel V, Misra A. Inhalation drug therapy: Emerging trends in nasal and pulmonary drug delivery. Novel Drug Delivery Technologies: Innovative Strategies for Drug Re-positioning, 2019; 291-333.
31. Shah, S.A.; Berger, R.L.; McDermott, J.; Gupta, P.; Monteith, D.; Connor, A.; Lin,W. Regional deposition of mometasone furoate nasal spray suspension in humans. Allergy Asthma Proc, 2015; 36: 48–57.
32. Ranade, S.; Bajaj, A.; Londhe, V.; Babul, N.; Kao, D. Fabrication of topical metered dose film forming sprays for pain management. Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci., 2017; 100: 132–141.
33. Habib, A.R.; Thamboo, A.; Manji, J.; Dar Santos, R.C.; Gan, E.C.; Anstead, A.; Javer, A.R. The effect of head position on the distribution of topical

nasal medication using the Mucosal Atomization Device: A cadaver study. Int. Forum Allergy Rhinol, 2013; 3: 958–962.
34. Li, B.V.; Jin, F.; Lee, S.L.; Bai, T.; Chowdhury, B.; Caramenico, H.T.; Conner, D.P. Bioequivalence for locally acting nasal spray and nasal aerosol products: Standard development and generic approval. AAPS J., 2013; 15: 875–883. Pharmaceutics, 2022; 14:1073 16-19.
35. Tong, X.; Dong, J.; Shang, Y.; Inthavong, K.; Tu, J. Effects of nasal drug delivery device and its orientation on sprayed particle deposition in a realistic human nasal cavity. Comput. Biol. Med, 2016; 77: 40–48.
36. Basu S, Bandyopadhyay AK. Nasal drug delivery: An overview. Int J Pharm Sci Tech, 2010; 4(1): 20.
37. Karmarkar AB, Gonjari ID, Hosmani AH, Dhabale PN, Thite RD. Preparation and in vitro evaluation of lyophilized nasal inserts of tramadol hydrochloride. Asian J PharmSci., 2008; 3(6): 276- 28.
38. Merkus FWHM, Verhoef JC. Nasal drug delivery: trends and perspectives. In: Boyian JC. [Ed.], Encyclopedia of Pharmaceutical Technology, New York, 1994; 191-220.
39. Bertram U, Bodmeier R. Parameters affecting the drug release from in situ gelling nasal inserts. Eur J Pharm Biopharm, 2006; 63: 310-319.
40. Thapa P, Baillie AJ, Stevens HNE. Lyophilization of unit dose pharmaceutical dosage forms. Drug Dev Ind Pharm, 2003; 29(5): 595- 602.
41. Mitra A, Dey B. Chitosan microspheres in novel drug delivery systems. Indian J Pharm Sci., 2011; 73(4): 355–366.
42. Mishra RK, Banthia AK, Majeed ABA. Pectin based formulations for biomedical applications: A review. Asian J Pharm Clin Res., 2012; 5(4): 1-7.
43. McInnes F, Thapa P, Stevens HNE. Enhanced Nasal Delivery with Lyophilized Inserts. In: Williams RO, Taft DR, McConville JT. [Eds.], Advanced Drug Formulation Design to Optimize Therapeutic Outcomes, CRC Press, Florida, 2007; 281-301.
44. Chaturedi M., Kumar M., & Pathak, A review on mucoadhesive polymer used in nasal drug delivery system. Journal of Advanced Pharmaceutical Technology and Research, 2011; 4: 215-222.
45. Rathbone, M. J., Hadcraft, J., & Roberts, M. S. (Eds.). Modified-release drug delivery technology. CRC Press.
46. Nakamura, K., Tanaka, Y., & Sakurai, M. Dynamic mechanical properties of aqueous gellan solutions in the sol–gel transition region Carbohydrate Polymers, 1996; 30: 101–108.
47. Patil, S. B., & Sawant, K. K.Mucoadhesive microspheres: a promising tool in drug delivery. Current drug delivery, 2008; 5(4): 312-318.
48. Gavini, E., Rassu G., Ferraro L., Generosi A., Rau, J. V., Brunetti, A., & Dalpiaz, A. Influence of chitosan glutamate on the in vivo intranasal absorption of rokitamycin from microspheres. Journal of Pharmaceutical Sciences, 2011; 100(4): 1488-1502.
49. Swamy, N. G. N., & Abbas, Z. Preparation and in vitro characterization of mucoadhesive polyvinyl alcohol microspheres containing amlodipine besylate for nasal administration. Indian Journal of Pharmaceutical Education and Research, 2012; 46(1): 55.
50. Casettari, l., & illum, l. Chitosan in nasal delivery systems for therapeutic drugs. Journal of Controlled Release, 2014; 190: 189-200.
51. Rathananand, M., kumar, D. S., shirwaikar, A., kumar, R., sampath kumar, D., & prasad, R. S. Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Indian journal of pharmaceutical sciences, 2017; 69(5): 651.
52. Cao, S. L., Zhang, Q. Z., & Jiang, X. G. Preparation of ion-activated in situ gel systems of scopolamine hydrobromide and evaluation of its antimotion sickness efficacy. Acta pharmacological sinica, 2007; 28(4): 584-590.
53. Zitt, M., kosoglou, T., & hubbell, J.Mometasone furoate nasal spray. Drug Safety, 2007; 30(4): 317-326.
54. Nilesh, S. Nanosuspension based in situ gelling nasal spray of carvedilol: development, in vitro and in vivo characterization. AAPS PharmSciTech, 2013; 14(1): 189-199.
55. Galgatte, U. C., kumbhar, A. B., & chaudhari, P. D. Development of in situ gel for nasal delivery: design, optimization, in vitro and in vivo evaluation. Drug Delivery, 2014; 21(1): 62 73.
56. Mahdi, M. H., conway, B. R., & smith, A. M. Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 2015; 488(1): 12-19.
57. Mahdi, M. H., conway, B. R., & smith, A. M. Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 2015; 488(1): 12-19.
58. Sworn, g., sanderson, G. R., & gibson, W. Gellan gum fluid gels. Food Hydrocolloids, 1995; 9(4): 265-271.
59. Swamy, N. G. N., & abbas, Z. Preparation and in vitro characterization of mucoadhesive polyvinyl alcohol microspheres containing amlodipine besylate for nasal administration. Indian Journal of Pharmaceutical Education and Research, 2012; 46(1): 55.
60. Klang, V., Schwarz, J. C., & valenta, C. Nanoemulsions in Dermal Drug Delivery. In Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement, 2015; 255-266.
61. Casettari, L., & illum, L.Chitosan in nasal delivery systems for therapeutic drugs. Journal of Controlled Release, 2014; 190: 189-200.
62. Rathananand, M., kumar, D. S., Shirwaikar, A., Kumar, R., Sampath kumar, D., & Prasad, R. S. Preparation of mucoadhesive microspheres for

nasal delivery by spray drying. Indian Journal of Pharmaceutical Sciences, 2007; 69(5): 651.
63. Galgatte, U. C., kumbhar, A. B., & chaudhari, P. D. Development of in situ gel for nasal delivery: design, optimization, in vitro and in vivo evaluation. Drug Delivery, 2014; 21(1): 62 73.
64. Mahdi, M. H., conway, B. R., & smith, A. M. Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 2015; 488(1): 12-19.
65. Mahdi, M. H., conway, B. R., & smith, A. M. Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 2015; 488(1): 12-19.
66. Sworn, G., sanderson, G. R., & gibson, W.Gellan gum fluid gels. Food Hydrocolloids, 1995; 9(4): 265-271.
67. Kararli, T. T., needham, T. E., griffin, M., schoenhard, G., ferro, L. J., & alcorn, L.Oral delivery of a renin inhibitor compound using emulsion formulations. Pharmaceutical Research, 1992; 9(7): 888-893.
68. Kararli, T. T., Needham, T. E., Schoenhard, G., Baron, D. A., Schmidt, R. E., Katz, B., & Belonio, B. Enhancement of nasal delivery of a renin inhibitor in the rat using emulsion formulations. Pharmaceutical Research, 1992; 9(8): 1024-1028.
69. Li, l., Nandi, i., & kim, K. H. Development of an ethyl laurate-based microemulsion for rapid-onset intranasal delivery of diazepam. International Journal of Pharmaceutics, 2002; 237(1): 77-85.
70. Ko, k. T., Needham, T. E., & Zia, H.Emulsion formulations of testosterone for nasal administration. Journal of Microencapsulation, 1998; 15(2): 197-205.
71. Klang, V., Schwarz, J. C., & valenta, C. Nanoemulsions in Dermal Drug Delivery. In Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement, 2015; 255-266.
72. Zhang, X., & WU, B. Submicron lipid emulsions: a versatile platform for drug delivery. Current Drug Metabolism, 2015; 16(3): 211-220.
73. Shinde, R. L., Bharkad, G. P., & Devarajan, P. V. Intranasal microemulsion for targeted nose to brain delivery in neurocysticercosis: role of docosahexaenoic acid. European Journal of Pharmaceutics and Biopharmaceutics, 2015; 96: 363-379.
74. Yadav, S., Gattacceca, F., Panicucci, R., & Amiji, M. M. Comparative biodistribution and pharmacokinetic analysis of cyclosporine-a in the brain upon intranasal or intravenous administration in an oil-in-water nanoemulsion formulation. Molecular Pharmaceutics, 2015; 12(5): 1523-1533.
75. Law, S. L., & Shih, C. L. Characterization of calcitonin containing liposome formulations for intranasal delivery. Journal of Microencapsulation, 2001; 18(2): 211-221.
76. Law, S. L., Huang, K. J., & Chou, H. Y. Preparation of desmopressin-containing liposomes for intranasal delivery. Journal of Controlled Release, 2001; 70(3): 375-382.
77. Muramatsu, KS., Maitani, Y., Takayama, k., & Nagai, T. The relationship between the rigidity of the liposomal membrane and the absorption of insulin after nasal administration of liposomes modified with an enhancer containing insulin in rabbits. Drug Development & Industrial Pharmacy, 1999; 25(10): 1099-1105.
78. Jung, B. H., Chung, B. C., Chung, S. J., lee, M. H., & Shim, C. K. Prolonged delivery of nicotine in rats via nasal administration of proliposomes. Journal of Controlled Release, 2000; 66(1): 73-79.
79. Jung, B. H., Chung, S. J., & Shim, C. K. Proliposomes as prolonged intranasal drug delivery systems. STP Pharma sciences, 2002; 12(1): 33-38.
80. Takenaga, S., Serizawa, Y., Azechi, Y., Ochiai, A., Kosaka, Y., igarashi, R, & mizushima, Y.Microparticle resins as a potential nasal drug delivery system for insulin. Journal of Controlled Release, 1998; 52(1): 81-87.
81. Ishikawa, E., Yanaka, K., Sugimoto, K., Ayuzawa, S., & Nose, T. Reversible dementia in patients with chronic subdural hematomas. Journal of Neurosurgery, 2002; 96(4): 680- 683.
82. Illum, L., farraj, N. F., & davis, S. S.Chitosan as a novel nasal delivery system for peptide drugs. Pharmaceutical Research, 1994; 11(8): 1186-1189.
83. Ugwoke, M. I., agu, R. U., Vanbilloen, H., Baetens, J., Augustijns, P., Verbeke, N., & Bormans, G. Scintigraphic evaluation in rabbits of nasal drug delivery systems based on carbopol 971P® and carboxymethylcellulose. Journal of Controlled Release, 2000; 68(2): 207-214.
84. Callens, C., & Remon, J. P. Evaluation of starch–maltodextrin-Carbopol® 974 P mixtures for the nasal delivery of insulin in rabbits. Journal of Controlled Release, 2000; 66(2): 215-220.
85. Hasçiçek, C., Gönül, N., & Erk, N. Mucoadhesive microspheres containing gentamicin sulfate for nasal administration: preparation and *in vitro* characterization. Il Farmaco, 2003; 58(1): 11-16.
86. Fernandez-urrusuno, R., Calvo, P., Remuñánlópez, C., Vila-Jato, J. L., & Alonso, M. J. Enhancement of nasal absorption of insulin using chitosan nanoparticles. Pharmaceutical Research, 1999; 16(10): 1576-1581.
87. Nagai, k., & Thøgersen, H. C. Generation of β-globin by sequence-specific proteolysis of a hybrid protein produced in *Escherichia coli*. Nature, 1984; 309(5971): 810-812.
88. Ugwoke, M. I., Sam, E., Van den mooter, G., Verbeke, N., & Kinget, R.Nasal mucoadhesive delivery systems of the anti-parkinsonian drug, apomorphine: influence of drug-loading on *in vitro* and *in vivo* release in rabbits. International Journal of Pharmaceutics, 1999; 181(1): 125-138.

89. Schmolka IR 1972. Artificial skin. I. Preparation and properties of pluronic F-127 gels for treatment of burns. J Biomed Mater Res, 6(6): 571-582.
90. Klang V, Schwarz JC, Valenta C. Nanoemulsions in dermal drug delivery. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Drug Manipulation Strategies and Vehicle Effects, 2015; 255-66.
91. Development and Evaluation of Thermoreversible Ethosomal Gel of Donepezil Hydrochloride for Intranasal Delivery Arka Gangopadhyay1 · Panchaxari M. Dandagi1 Kishori P. Sutar1
92. Yuwanda A, Surini S, Harahap Y, Jufri M. Study of valproic acid liposomes for delivery into the brain through an intranasal route. Heliyon, 2022 Mar 1; 8(3).
93. Law, S. L., and Hung, H.Y. Preparation of acyclovir-containing liposomes for potential ocular delivery. *J. Control. Rel*., 1998; 161: 253–259.
94. Achim M, Precup C, Nitu GD, Barbu-Tudoran L, Porfire AS, Scurtu R, *et al.* Thermosensitive liposomes containing Doxorubicin. Preparation and *in vitro* evaluation. Farmacia, 2009; 57(6): 703-10.
95. Nasr M, Ghorab MK, Abdelazem A. *In vitro* and *in vivo* evaluation of cubosomes containing 5-fluorouracil for liver targeting. Acta Pharm Sin B, 2015; 5(1): 79-88.
96. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci., 1961; 50: 874–875.
97. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of potassium chloride release from compressed, hydrophilic, polymeric matrices: Effect of entrapped air. J Pharm Sci., 1983; 72:1189-1191.
98. Miller SC, Donovan MD. Effect of poloxamer 407 gels on the miotic activity of pilocarpine nitrate in rabbits. Int J Pharm, 1982; 12: 142-152.
99. Miller SC, Donovan MD. Effect of poloxamer 407 gels on the miotic activity of pilocarpine nitrate in rabbits. Int J Pharm, 1982; 12: 142-152.
100. Shinde JS, Mali KK, Dias RJ, Havaldar VD, Mahajan NS. *In situ* mucoadhesive nasal gels of metoclopramide hydrochloride: preformulation and formulation studies. J Pharm Res., 2008; 1: 88-96.
101. Choi HG, Shim CK, Kim DD. Development of *in situ* gelling and mucoadhesive acetaminophen liquid suppository. Int J Pharm, 1998; 165: 33-44.
102. Choi HG, Shim CK, Kim DD. Development of *in situ* gelling and mucoadhesive acetaminophen liquid suppository. Int J Pharm, 1998; 165: 33-44.
103. Singh RM, Kumar A, Pathak K. Thermally triggered mucoadhesive *in situ* gel of loratadine: β-cyclodextrin complex for nasal delivery. AAPS. Pharm Sci Tech, 2013; 14: 412-424.
104. Alsarra IA, Hamed AY, Alanazi FK. Acyclovir liposomes for intranasal systemic delivery: development and pharmacokinetics evaluation. Drug delivery, 2008 Jan 1; 15(5): 313-21.
105. Henriques P, Bicker J, Carona A, Miranda M, Vitorino C, Doktorovová S, Fortuna A. Amorphous nasal powder advanced performance: in vitro/ex vivo studies and correlation with in vivo pharmacokinetics. Journal of Pharmaceutical Investigation, 2023 Sep; 53(5): 723-42.
106. Charlton ST, Davis SS, Illum L. Evaluation of bioadhesive polymers as delivery systems for nose to brain delivery: *In vitro* characterisation studies. J Control Release, 2007; 118: 225-34.
107. Giuliani A, Balducci AG, Zironi E, Colombo G, Bortolotti F, Lorenzini L, *et al. In vivo* nose to brain delivery of the hydrophilic antiviral ribavirin by microparticle agglomerates. Drug Deliv, 2018; 25: 376-87.
108. Mustafa E, Shaimaa NM, Al A. Design zolmitriptan liquisolid orodispersible tablets and their *in vitr*o evaluation. Int J Pharm Pharm Sci., 2016; 9: 297-303.
109. Achim M, Precup C, Nitu GD, Barbu-Tudoran L, Porfire AS, Scurtu R, *et al.* Thermosensitive liposomes containing Doxorubicin. Preparation and *in vitro* evaluation. Farmacia, 2009; 57(6): 703-10.
110. Nasr M, Ghorab MK, Abdelazem A. *In vitro* and *in vivo* evaluation of cubosomes containing 5-fluorouracil for liver targeting. Acta Pharm Sin B., 2015; 5(1): 79-88.
111. Jalwal P, Singh B, Kumar A. A comprehensive review on dissolution testing.
112. Thakur D, Kaur G, Puri A, Nanda R. Therapeutic potential of essential oil-based microemulsions: reviewing state-of-the-art. Current Drug Delivery, 2021 Nov 1; 18(9): 1218-33.
113. Amit et al. prepared lorazepam microemulsions, 2010; 1: 21-26.
114. Zhang Q, Jiang X, Jiang W, Lu W, Su L, Shi Z. Preparation of nimodipine-loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain. International journal of pharmaceutics, 2004 May 4; 275(1-2): 85-96.
115. Mujawar N, Ghatage S, Navale S, Sankpal B, Patil S, Patil S. Nasal drug delivery: Problem solution and its application. Journal of Current Pharma Research, 2014 Apr 1; 4(3): 1231.
116. M. Vispute, S. Nazim, T.Khan and Siraj Shaikh. International Journal of Pharmaceutical Science and Research, 2013; 4(4): 1294-1311.
117. Ghazwani M, Vasudevan R, Kandasamy G, Manusri N, Devanandan P, Puvvada RC, Veeramani VP, Paulsamy P, Venkatesan K, Chidmabaram K, Dhurke R. Formulation of intranasal mucoadhesive thermotriggered in situ gel containing mirtazapine as an antidepressant drug. Gels, 2023 Jun 2; 9(6): 457.
118. Suhagiya K, Borkhataria CH, Gohil S, Manek RA, Patel KA, Patel NK, Patel DV. Development of mucoadhesive in-situ nasal gel formulation for enhanced bioavailability and efficacy of rizatriptan

in migraine treatment. Results in Chemistry, 2023 Dec 1; 6: 101010.
119. Sharma A, Saxena R, Dubey A, Yadav R, Yadav SK. Development and characterization of in-situ gel system for nasal delivery of levodopa. Rhinology and Otology, 2015; 18-20.
120. 121.Kaur K, Kaur G. Formulation and evaluation of chitosan-chondroitin sulphate based nasal inserts for zolmitriptan. BioMed Research International, 2013 Jan 1.
121. 122.Yuwanda A, Surini S, Harahap Y, Jufri M. Study of valproic acid liposomes for delivery into the brain through an intranasal route. Heliyon, 2022 Mar 1; 8(3).
122. 123.Al Asmari AK, Ullah Z, Tariq M, Fatani A. Preparation, characterization, and in vivo evaluation of intranasally administered liposomal formulation of donepezil. Drug design, development and therapy, 2016 Jan 12; 205-15.
123. Alsarra IA, Hamed AY, Alanazi FK. Acyclovir liposomes for intranasal systemic delivery: development and pharmacokinetics evaluation. Drug delivery, 2008 Jan 1; 15(5): 313-21.
124. Yang Z. Preparation and Evaluation of Rivastigmine Liposomes for Intranasal Delivery. Liposome-Based Drug Delivery Systems, 2021; 325-44.
125. Vp P. Formulation and evaluation of glimepiride-loaded liposomes by ethanolinjection method. Asian Journal of Pharmaceutical and Clinical Research, 2016 Jul 1; 192-s.
126. Patel RB, Patel MR, Bhatt KK, Patel BG. Formulation and evaluation of Microemulsion based Drug Delivery system for intra nasal administration of Olanzapine. Int J Biomed Pharm Sci., 2013; 7(1): 20-7.
127. Preparation and Evaluation of Mebendazole Microemulsion for Intranasal Delivery: an Alternative Approach for Glioblastoma Treatment Julio Mena-Hernández,1,2 Helgi Jung-Cook,2,3,8 Monserrat Llaguno-Munive,4 Patricia García-López,4Adriana Ganem-Rondero,5 Simón López-Ramírez,6 Fernando Barragán-Aroche,6 Marisol Rivera-Huerta,7 and Lourdes Mayet-Cruz2.
128. Rukmangathen R, Yallamalli IM, Yalavarthi PR. Formulation and biopharmaceutical evaluation of risperidone-loaded chitosan nanoparticles for intranasal delivery. Drug Development and Industrial Pharmacy, 2019 Jun 3.
129. Mehmood Y, Shahid H, Abbas M, Farooq U, Alshehri S, Alam P, Shakeel F, Ghoneim MM. Developing Nanosuspension Loaded with Azelastine for Potential Nasal Drug Delivery: Determination of Proinflammatory Interleukin IL-4 MRNA Expression and Industrial Scale-Up Strategy. ACS omega, 2023 Jun 21; 8(26): 23812-24.
130. Lungare S, Bowen J, Badhan R. Development and evaluation of a novel intranasal spray for the delivery of amantadine. Journal of Pharmaceutical Sciences, 2016 Mar 1; 105(3): 1209-20.
131. Omar, M.M.; Eleraky, N.E.; El Sisi, A.M.; Ali Hasan, O. Development and Evaluation of in-situ Nasal Gel Formulations of Nanosized Transferosomal Sumatriptan: Design, Optimization, in vitro and in vivo Evaluation. Drug Des. Dev. Ther, 2019; 13: 4413–4430. Materials, 2022; 15: 6547 14 of 15.
132. Omar, M.M.; Eleraky, N.E.; El Sisi, A.M.; Ali Hasan, O. Development and Evaluation of in-situ Nasal Gel Formulations of Nanosized Transferosomal Sumatriptan: Design, Optimization, in vitro and in vivo Evaluation. Drug Des. Dev. Ther, 2019; 13: 4413–4430. Materials, 2022; 15: 6547 14 of 15.
133. Londhe, V.; Krishnan, S. Formulation, Evaluation, and Pharmacodynamic Investigation of Ziprasidone-b-cyclodextrin In Situ Nasal Gel. Proceedings, 2020, 78, 42.
134. Wang, Y.; Jiang, S.;Wang, H.; Bie, H. A mucoadhesive, thermoreversible in situ nasal gel of geniposide for neurodegenerative diseases. PLoS ONE, 2017; 12: e0189478.
135. Salatin, S.; Barar, J.; Barzegar-Jalali, M.; Adibkia, K.; Jelvehgari, M. Thermosensitive in situ nanocomposite of rivastigmine hydrogen tartrate as an intranasal delivery system: Development, characterization, ex vivo permeation and cellular studies. Colloids Surf. B Biointerfaces, 2017; 159: 629–638. [PubMed]
136. Altunta¸s, E.; Yener, G. Formulation and Evaluation of Thermoreversible In Situ Nasal Gels Containing Mometasone Furoate for Allergic Rhinitis. AAPS PharmSciTech, 2017; 18: 2673–2682. [PubMed]
137. Durgapal, S.; Rana, M.; Mukhopadhyay, S.; Rana, A.J.; Goswami, L.; Joshi, S. Formulation and Evaluation of in-Situ Nasal Gel of Montelukast Sodium for the Effective Treatment of Asthma. Int. J. Pharm. Sci. Res., 2018; 9; 2792.
138. Khandagale, P.M.; Rokade, M.M.; Phadtare, D.G. Formulation Development and Evaluation of Nasal In- Situ Gel of Hydrocortisone. Asian J. Pharm. Technol, 2018; 8: 92–102.
139. Raj, R.;Wairkar, S.; Sridhar, V.; Gaud, R. Pramipexole dihydrochloride loaded chitosan nanoparticles for nose to brain delivery: Development, characterization and in vivo anti-Parkinson activity. Int. J. Biol. Macromol, 2018; 109: 27–35. [PubMed]
140. Belgamwar, A.; Khan, S.; Yeole, P. Intranasal chitosan-g-HP_CD nanoparticles of efavirenz for the CNS targeting. Artif. Cells Nanomed. Biotechnol, 2018; 46: 374–386. [PubMed]
141. Chen, Y.; Cheng, G.; Hu, R.; Chen, S.; Lu, W.; Gao, S.; Xia, H.; Wang, B.; Sun, C.; Nie, X.; et al. A Nasal Temperature and pH Dual-Responsive In Situ Gel Delivery System Based on Microemulsion of Huperzine A: Formulation, Evaluation, and In

Vivo Pharmacokinetic Study. AAPS PharmSciTech, 2019; 20: 1–12. [PubMed]
142. Youssef, N.A.H.A.; Kassem, A.A.; Farid, R.M.; Ismail, F.A.; EL-Massik, M.A.E.; Boraie, N.A. A novel nasal almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: Preparation, characterization and in vivo evaluation. Int. J. Pharm, 2018; 548: 609–624.
143. Omar, M.M.; Eleraky, N.E.; El Sisi, A.M.; Ali Hasan, O. Development and Evaluation of in-situ Nasal Gel Formulations of Nanosized Transferosomal Sumatriptan: Design, Optimization, in vitro and in vivo Evaluation. DrugDes. Dev. Ther, 2019; 13: 4413–4430. Materials 2022, 15, 6547 14 of 15
144. Londhe, V.; Krishnan, S. Formulation, Evaluation, and Pharmacodynamic Investigation of Ziprasidone-b-cyclodextrin In Situ Nasal Gel. Proceedings, 2020; 78: 42.
145. Wang, Y.; Jiang, S.;Wang, H.; Bie, H. A mucoadhesive, thermoreversible in situ nasal gel of geniposide for neurodegenerative diseases. PLoS ONE, 2017; 12: e0189478.
146. Salatin, S.; Barar, J.; Barzegar-Jalali, M.; Adibkia, K.; Jelvehgari, M. Thermosensitive in situ nanocomposite of rivastigmine hydrogen tartrate as an intranasal delivery system: Development, characterization, ex vivo permeation and cellular studies. Colloids Surf. B Biointerfaces, 2017; 159: 629–638. [PubMed]
147. Altunta¸ S, E.; Yener, G. Formulation and Evaluation of Thermoreversible In Situ Nasal Gels Containing Mometasone Furoate for Allergic Rhinitis. AAPS PharmSciTech, 2017; 18: 2673–2682. [PubMed]
148. Durgapal, S.; Rana, M.; Mukhopadhyay, S.; Rana, A.J.; Goswami, L.; Joshi, S. Formulation and Evaluation of in-Situ Nasal Gel of Montelukast Sodium for the Effective Treatment of Asthma. Int. J. Pharm. Sci. Res., 2018; 9: 2792.
149. Khandagale, P.M.; Rokade, M.M.; Phadtare, D.G. Formulation Development and Evaluation of Nasal In- Situ Gel of Hydrocortisone. Asian J. Pharm. Technol, 2018; 8: 92–102.
150. Raj, R.;Wairkar, S.; Sridhar, V.; Gaud, R. Pramipexole dihydrochloride loaded chitosan nanoparticles for nose to brain delivery: Development, characterization and in vivo anti-Parkinson activity. Int. J. Biol. Macromol, 2018; 109: 27–35. [PubMed]
151. Belgamwar, A.; Khan, S.; Yeole, P. Intranasal chitosan-g-HP_CD nanoparticles of efavirenz for the CNS targeting. Artif. Cells Nanomed. Biotechnol, 2018; 46: 374–386. [PubMed]
152. Wilson, B.; Mohamed Alobaid, B.N.; Geetha, K.M.; Jenita, J.L. Chitosan nanoparticles to enhance nasal absorption and brain targeting of sitagliptin to treat Alzheimer's disease. J. Drug Deliv. Sci. Technol, 2021: 61; 102176.
153. Ursapharm. Allergo-Comod Nasal. http://www.pharmaturca.com/marka/ursapharm.aspx?tabId=123, (Accessed on 14.08.17).
154. Drugs.com. https://www.drugs.com/international/cromoglicic-acid.html, (Accessed on 14.08.17).
155. https://www.drugs.com/uk/pdf/leaflet/928905.pdf, (Accessed on 14.08.17).
156. https://www.accessdata.fda.gov/drugsatfda_docs/l glucagon and human calcitonin to healthy subjects: abel/2012/020114s023lbl.pdf, (Accessed on 14.08.17). a comparison of powders and spray solutions and of different enhancing agents. Eur. J. Clin Pharmacol., 37: 427-430.
157. https://au.gsk.com/media/222812/bactroban_nasal_ointment_cmi_au_004_approved.pdf, (Accessed on 14.08.17).
158. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Beconase_AQ/pdf/BECONASE-PI-PIL.PDF, (Accessed on 14.08.17).
159. Decadron. https://online.epocrates.com/drugs/151910/Decadron/Monograph, 14.08.17).
160. https://au.gsk.com/en-au/products/our-consumer-healthcare products/respiratory/flixonase/, (Accessed on 14.08.17).
161. http://www.janssen.com/netherlands/sites/www_janssen_com_netherlands/files/livocabneus_b_0.pdf, (Accessed on 14.08.17).
162. http://www.clinicaladvisor.com/nasalcrom/drug/309 5/, (Accessed on 14.08.17).
163. https://www.google.co.in/search?q=nasivin+nasal+spray+Braco&tbm=isch&tbo=u&source=univ&sa=X&ved=0ahUKEwjjn47tvtHVAhVLqI8KHY0VA50Q7AkINw&biw=1383&bih=645#imgrc=kJ_8f2Mv7 XjjtM: (Accessed on 14.08.17).
164. https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM463501.pdf, (Accessed on 14.08.17).
165. http://www.thehindubusinessline.com/todays-paper/tp-economy/now-novartis-otrivin-spray-will-be-available-over-the-counter/article1065586.ece, (Accessed on 14.08.17).
166. https://www.patanase.com/, (Accessed on 14.08.17).
167. Misra, A. and T.K. Vyas, 2005. Drugs Loaded Nasoadhesive Microemulsions For Brain Targeted Brosk Delivery In Acute Epilepsy. (h1n1) (Intranasal). http://www.seruminstitute.com/product_influenza_vaccines.php, 2017 (Accessed on 17.08.17).
168. Fleming, N.T., Intranasal Formulation of Epinephrine for the Treatment of Anaphylaxis. US 20150005356 A1. https: / / medikamio.com/de-2015;
169. Charney, D.S., S.J. Mathew, H.K. Manji, C.A. Zarate at/medikamente/calcitonin-novartis-100-ie- and J.H. Krystal, Intranasal administration of nasalspray/pil, (Accessed on 17.08.17), 2017.

170. Santus, G.,G .Bottoni and E. Bilato, 2001. https://clinicaltrials.gov/ct2/results?cond =&term=TherapeuticAS01%E2%84%A2&cntry1= &state1=&Search=Se compositions for intranasal administration which include KETOROLAC®. US arch, (Accessed on 17.08.17)
171. Crystal, R. and M.B. Weiss, 2015. Nasal drug https://clinicaltrials.gov/ct2/results?cond=&term= products and methods of their use. US 9211253 B2. AS02%E2%84%A2&cntry1=&state1=&recrs=, (Accessed on 17.08.17).
172. Frenkel, D., R. Maron, D. Burt and H. Weiner, Compositions and methods for treating neurological disorders, 2006. US 20060229233 A1.
173. Mattern, C., Controlled release delivery system for nasal applications and method of treatment., 2017. US 20170189414 A1.
174. Misra, A. and T.K. Vyas, Drugs Loaded Intranasal Nasoadhesive Microemulsions for Brain Targeted Delivery In Migrane.2015; 1125/MUM/2004 /MUM/2004.