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# An Overview on: Intranasal Drug Delivery System

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**ABSTRACT:** The practice of intranasal drug delivery, which dates back thousands of years, has been given a fresh start. It's a great delivery technique for pharmaceuticals like proteins and peptides that are active at low dosages and have no minimal oral bioavailability. The nasal cavity's high permeability, high vasculature, low enzymatic environment, and avoidance of hepatic first pass metabolism make it ideal for systemic medication distribution by nose. Because most acute CNS disorders (e.g., Parkinson's disease, Alzheimer's disease) require rapid and/or selective targeting of medications to the brain, many drug delivery systems for nasal application of liquid, semisolid, and solid formulations are being studied. peptides, hormones, and DNA plasmids for DNA vaccines This study will also look at some of the factors that affect nasal absorption, as well as bioavailability barriers, nasal absorption strategies, new developments in nasal dosage form design, and nasal drug delivery system applications.

**KEYWORDS:** Intranasal administration Drug delivery CNS indication Delivery enhancer techniques Transporter interactions.

## I. INTRODUCTION

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption Because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus, and less dilution by gastrointestinal contents, nasal mucosa has been considered as a potential administration route to achieve faster and higher levels of drug absorption (Krishnamoorthy and Mitra, 1998). Many medications have been demonstrated to have improved systemic bioavailability when administered via nasal route rather than oral administration in recent years. Nasal therapy, also known as "NASAYA KARMA" in the Ayurvedic schools of Indian medicine, is a recognized kind of treatment (Chien and Chang, 1987). The practice of intranasal drug delivery, which dates back thousands of years, has been given a new lease on life. It's a good delivery technique for pharmaceuticals like proteins and peptides that are active at low dosages and have no minimal oral bioavailability. One of the reasons for the limited absorption of peptides and proteins via the nasal route is the mucociliary clearance mechanism's quick movement away from the absorption location in the nasal cavity. The nasal route avoids the hepatic first-pass elimination that occurs with oral distribution, and it is simple to use and self-administer. Pharmaceutical scientists and physicians have been increasingly interested in the viability of drug delivery via the nasal route over the last several decades. Various animal models have been used to assess drug candidates ranging from tiny metal ions to big macromolecular proteins (Chien YW et al., 1989). Nasal administration of some hormones and steroids has been shown to result in a more thorough absorption (Hussain AA. et al., 1979; Hussain AA et al., 1981). This demonstrates the nasal route's potential value for systemic pharmaceutical administration as well as using it for local effects.) Given these benefits, in administration should be considered while creating new therapies or extending the life or changing the profile of an existing medicine. A number of questions about the medication and its use were asked to determine the appropriateness and viability of such a strategy, and many questions must be addressed.

## II. RELATED WORK

**Advantages:**(Aulton M.E et al., 2002, Krishnamoorthy R et al., 1998

- 1) There is no evidence of drug breakdown in the gastrointestinal tract.
- 2) First-pass hepatic metabolism is avoided.
- 3) It is possible to obtain rapid medication absorption and action.
- 4) Using an absorption enhancer or another method, the bioavailability of large medication molecules can be enhanced.
- 5) Smaller drug molecules have good nasal bioavailability.
- 6) Nasal medication administration can deliver drugs that are not absorbed orally to the systemic circulation.



- 7) Preliminary research suggests that the nasal route is a viable alternative to the parenteral route, particularly for protein and peptide medicines.
- 8) When compared to parenteral medication, it is more convenient for patients, especially those on long-term therapy.
- 9) Nasal administration is used for drugs with low g.i.t. fluid stability. Polar chemicals with low oral absorption may be particularly well suited to this delivery method.

Limitations: (Hirai S *et al.*, 1993; Kadam SS *et al.*, 1981)

- 1) The histopathological toxicity of absorption enhancers utilised in nasal medication delivery systems is still unknown.
- 2) Patients find it inconvenient when compared to oral administration systems since nasal discomfort is a potential.
- 3) When compared to the GIT, the nasal cavity has a smaller absorption surface area.
- 4) Both the substance and the ingredients added to the dosage form provide a risk of local side effects and irreversible damage to the cilia on the nasal mucosa.
- 5) In high concentrations, certain surfactants employed as chemical enhancers can damage and even dissolve membranes.
- 6) An inappropriate manner of administration could result in mechanical loss of the dose form into other areas of the respiratory tract, such as the lungs.

### III. EXPERIMENTAL RESULTS

**ANATOMY & PHYSIOLOGY OF NASAL CAVITY:** The nasal septum divides the nasal cavity into two parts and extends posterior to the nasopharynx, while the nasal vestibule, which is the most anterior region of the nasal cavity, opens to the face through the nostril. Nose vestibule, olfactory area, and respiratory region are the three primary regions of the nasal cavity. The lateral walls of the nasal cavity, which have a folded structure, can increase the surface area of the nose by roughly 150cm, making it a very large surface area compared to its small volume. There are three turbinates in this folded structure: superior, medium, and inferior (Michael *et al.*, 2005). The main nasal airway has thin channels, which are usually 1-3mm broad, and these narrow structures let the nose perform its primary activities. The mucous membrane that covers the nasal cavity is divided into two areas: non-olfactory and olfactory epithelium. The non-olfactory area includes the nasal vestibule, which is covered with skin-like stratified squamous epithelium cells, and the respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport (Sarkar 1992). The mucus layer is driven in a path from the front to the back of the nasal cavity in this manner. The mucus membrane that covers the nasal turbinates and atrium contains goblet cells, which release mucus as mucus granules that swell in the nasal fluid and contribute to the mucus layer. The mucus secretion is made up of 95% water, 2% mucin, 1% salts, 1% additional proteins like al-bumin, immunoglobulin s, lysozyme, and lactoferrin, and 1% lipids (Kaliner *et al.*, 1984). Immune protection against inhaled germs and viruses is provided by mucus production. . It also serves a variety of physiological purposes. (1) It covers the mucosa and protects it both physically and enzymatically. (2) Mucus has the ability to hold water. (3) It has electrical activity on the surface. (4) It allows for effective heat transfer. (5) It serves as an adhesive and transports particle to the nasopharynx.

**MECHANISM OF NASAL ABSORPTION:** The initial step in absorption is for absorbed medicines from the nasal cavity to pass through the mucus layer. Small, inert medications get through this layer readily, but large, charged substances find it harder to get past. Mucin is the mucus' main protein, and it tends to adhere to solutes, preventing diffusion. Environmental changes (such as pH, temperature, and so on) can also cause structural changes in the mucus layer (Illum L *et al.*, 1999). Although several absorption processes have been discovered in the past, only two have been widely used.

**First mechanism:** It involves an aqueous transport channel, commonly known as the paracellular route, but which is slow and inactive. Intranasal absorption and the molecular weight of water-soluble substances have an inverse log-log relationship. Drugs with a molecular weight larger than 1000 Daltons have limited bioavailability (Aurora J *et al.*, 2002).

**Second mechanism:** It is also known as the transcellular process since it requires transport via a lipoidal pathway. It is in charge of transporting lipophilic medicines with a rate dependence on their lipophilicity. Drug also cross cell membranes through an active transport route via carrier-mediated mechanisms or transfer by the opening of tight junctions (Aurora J *et al.*, 2002).



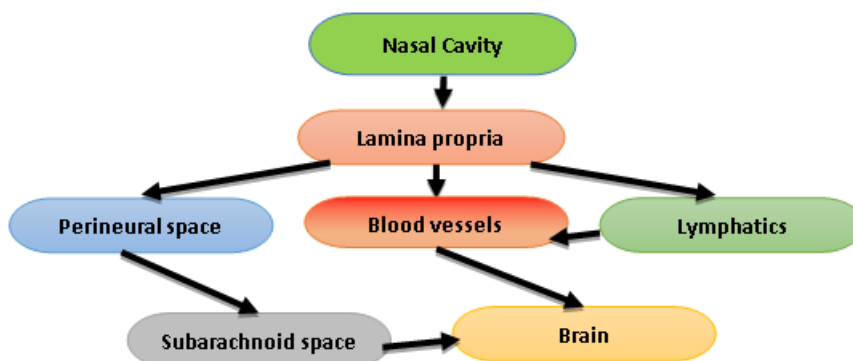


Fig.1 Modified from Crowe, Life Sciences, 2018 (Crowe et al., 2018).

**MODELS FOR TESTING DIRECT NOSE-TO-BRAIN DELIVERY:** Drug delivery into CNS via nasal pathway has been testified in humans and animal models of AD (Jogani et al., 2008), brain tumors (Hashizume et al., 2008), epilepsy (Barakat et al., 2006), pain (Westin et al., 2005) etc. The nasal cavity-to-brain route by olfactory and respiratory epithelium may involve paracellular, transcellular and neuronal transport (Illum, 2003, 2000). Models of IN drug delivery can be used for detecting and testing nasal drug absorption and permeation enhancement, for PK/PD studies, toxicological and electrophysiological studies, it can also use for assessment of drug transporter interaction and the nasal barrier. Models frequently used in nasal drug delivery experiments are *in vitro*, *in vivo* and *ex vivo* models. The different models can be used for several studies. *in vitro* techniques authorized permeation and diffusion studies, while *in vivo* models are preferable for characterization of nasal absorption as well as for pharmacokinetic profile determination of a drug and finally, *ex vivo* technique could be performed to study the nasal perfusion (Chhajed et al., 2011). All these models are conversed below.

### In vivo models

For resourcefully studying the IN-delivery systems, adequate *in vivo* models are crucial. before selecting suitable animal model for an *in-vivo* nasal absorption studies, it's very important to study the anatomy of the nasal cavity of that particular animal. The rat model was the first animal model and was presented in the late 1970s, and after that, with the progress in the nasal absorption studies the rabbit, dog, sheep, mouse, and monkey were also used. Demonstrative reports on various species/strains of experimental animals used for IN drug administration studies are presented in **Table 1**.

Mouse and rat models are very useful in preliminary studies of the absorption of drugs from the nose to the brain route, while rabbits, dogs and sheep model widely used in pharmacokinetic studies. however, outcomes of studies received from animal models do not constantly correlate well with those of humans, because of the anatomical and physiological differences in their nasal cavities (Cho et al., 2010). The direct transfer of medication from the olfactory mucosa to the CNS is usually divided into switch inside the nerve axon, or outside the nerve. both pathways provide potential for bypassing the blood-brain barrier (BBB). The solubility and the potency of the drug is commonly the limiting element, because the absorption ability is restricted. it's far important to observe that direct nostril-to-brain absorption avoids preabsorption metabolism, first pass effect, as well as dilution resulting from distribution and protein binding. The dosage to be introduced to the olfactory region or to be absorbed neuronally may easily be as low as zero.01–1% of oral dosage. It is also important that the drug is soluble in those few microliters that could be administered intranasally. The clearance within the nasal cavity is so fast that if the drug needs to be dissolved before being absorbed, the time is normally not enough for the dissolution method, before being absorbed.



Animal	Strain	Tools for administration	Volume administered per nostril ( $\mu$ l)	Subject of the study	References
Dogs	Labrador Retriever	Mucosal atomizer device	2400	Analgesic treatment	Micieli et al. (2017)
Guinea pigs	Hartley	Syringe/pipette	10	Induction of rhinitis	Mizutani et al. (2003)
Mice	CD-1	Micropipette	10	Delivery of insulin to brain	Salameh et al. (2015)
Sheeps	Sprague-Dawley	Syringe/pipette	50	Administration of morphin	Westin et al. (2005)
	Karaman	Cannula	2000	Administration of diverse nasal formulations	Karasulu et al. (2008)
	Suffolk	Syringes	1000	Intranasal inoculation with prion for comparison of different scrapie strains	Moore et al. (2016)
Rabbits	New Zealand	Spray	200	Insulin absorption	Najafabadi et al. (2004)
	Japanese White	Nasal actuator	100	Corticosteroid treatment for new-generation	Sato et al. (2007)
Monkeys	Rhesus monkey	Modified nasal atomizer	50-200	Opioid administration	Saccone et al. (2016)
Rats	Wistar	Intranasal cannula	40	Minimal-stress model for intranasal administration in freely moving rats	Stevens et al. (2009)

### In vitro models

However in vivo studies are most significant for any nasal drug absorption and permeation tests, mechanistic features of nasal absorption and the drug transport can be more evidently studied and controlled by in vitro studies. Primarily two cell lines (RPMI 2650 and CaCo-2) are used to evaluate absorption and permeability of nasal cavity. It should be noted that these cellular models provide information regarding transport across the cells or paracellular, along with concurrent factors such as physiological and anatomical factors, mucus, mucins and clearance involved in regulating the nose functional and may also affect the absorption. Furthermore, the cellular models consist of receiving lumen which does not wholly reflect the essential transport from the mucosa to the receiving nerves.

### RPMI 2650 a cell culture model of the nasal barrier

RPMI 2650 is derived from the human nasal epithelial tissue, a human nasal squamous cell carcinoma (a spontaneously formed tumor) of the nasal septum. A cell culture model based totally on human RPMI 2650 cell line does not form monolayers, best grows to multilayer, for that reason it is commonly used for nasal metabolism studies and also for toxicity assays (okayürti et al., 2013; Wengst and Reichl, 2010). although RPMI 2650 cellular line is not suitable for drug delivery study, its application for drug permeation research has been stated (Bai et al., 2008). The serially passaged RPMI 2650 cells form confluent cell monolayer underneath controlled situations. those conditions consist of cultivating medium for cells and the components for the cellular differentiations. each monolayer creates tight junctions with a transepithelial electric resistance (TEER) value permitting transportation of drugs. Werner and coworker studied the transportation of drugs in vitro using transwell insert, that is a permeable support device that provide independent access to both sides of a monolayer (Schmidt et al., 1998; Werner and Kissel, 1995). even though the contamination of epithelial cells with pathogens can be a problem, this technique is convenient for comparing the transport and metabolism of peptides (Hoang et al., 2002).

There are two types of culture conditions of these passaged monolayers, the air-liquid interface (ALI) and the liquid-covered culture (LCC) (Dolberg and Reichl, 2016). In LCC model each apical and basolateral sides are filled with cellular culture medium. Morphologically is characterized with denuded and flattened ciliated cells with distinctly susceptible mucin expression and TEER value peak on the second day and then decrease swiftly. In ALI model each apical and basolateral sides are packed with cellular culture medium, and then apical side is exposed to the air, after which the medium in basolateral side is changed every 2nd days. Morphological appearance is a whole lot close to the nasal tissue in vivo with number of ciliated cells and more potent mucin gene expression. maximum TEER value is appeared on day five, and high TEER value is maintained over 10 days. these variations between LCC and ALI models display that ALI condition compared to LCC could provide extra adequate surroundings for drug transport studies.



RPMI 2650 cells in ALI culture could be used as first screening device for cytotoxicity and permeability in the preclinical evaluation and comparison of solid formulations for intranasal transport of drugs (Gonçalves et al., 2016).

#### **CaCo-2 cell line**

Another common cell culture model is CaCo-2 cell line that has been used for three decades and is suitable to evaluate the nasal absorption of the formulations. The cell line is derived from human colon carcinoma and differentiates to various monolayers slowly. CaCo-2 cell culture is the most suitable model to assess the drug absorption and permeability through the intestinal epithelia (Dolberg and Reichl, 2016; Dyer et al., 2002; Qian et al., 2018; Tan et al., 2018). Reconstructed human nasal mucosa (the 3-dimensional reconstructed human nasal mucosa model of permeation barriers) Reconstructed three-dimensional model makes use of reseeded human nasal fibroblasts in collagen matrix included by RPMI 2650 epithelial cells. A collagen matrix containing fibroblasts is used as a growth support for the epithelial cells. The 3-dimensional reconstructed nasal mucosa model shows comparable permeation barrier properties and 4 –to 5- times faster paracellular permeation than in the epithelial cell model. even though the drawback of this 3-dimensional model is the more complex handling of the constructs it is promising model to evaluate passive permeation of substances through the nasal mucosa (Wengst and Reichl, 2010).

#### **IV. CURRENT STATUS OF APPROVED DRUGS FOR NASAL APPLICATION**

The IN-delivery route has gained significant interest in the delivery of various drugs and treatments. In the previous decade, the amount of interposing IN studies, including patients of different age groups, all sex and comprehensive clinical phases increased around three multiples compared with the time period from 2000 to 2010 (ClinicalTrial.gov). This increase in number of clinical trials is further higher than for other administration routes studies. There are near about 18 times more completed intravenous interventional studies included in the ClinicalTrial.gov from 2000 to 2020, as compared to completed intranasal interventional studies; even so, the number of published interventional intravenous studies, by using the same filters, only increased two multiples in the previous decade.

nonetheless IN delivery is generally associated with locally acting drugs as well as systemic effects and treatment of CNS disorders are upsurgedly focused upon by preclinical research and the pharmaceutical industry. The nasal route put forward many advantages over ordinary

routes such as the oral route, as it is non-invasive and easily approachable for the administration of drugs. Furthermore, IN administered systemically acting drugs shows rapid absorption

and exhibit a fast onset of action. The rapid absorption follows due to the abundant vasculature in the submucosa. The avoidance of the metabolic first pass effect can lead to a higher bioavailability.

nasal drug delivery leads to a lower systemic exposure and a more efficient targeting to the brain so the side effects are in many cases reduced. One of the most remarkable arguments supporting the increasing interest in IN drug delivery system is the possibility to bypass the BBB. The BBB is a limitation factor in the treatment of neurological CNS disorders.

There are many further limitations and aspects which have to be considered for the nasal application of drugs and biopharmaceutical products. While smaller, lipophilic drugs (MW < 1 kDa) are well absorbed; the nasal mucosa shows poor permeability for larger hydrophilic drugs (MW > 1 kDa) such as peptides and proteins. Along with that, processes such as the enzymatic degradation, mucociliary clearance and a low drug retention time limit the efficiency of drug delivery via IN delivery systems. Various technologies and approaches which aim to reduce these limiting effects are still under investigation. Nasal device technologies are under optimization for precise targeting of the location of action and therapeutic effect by IN drug delivery system.

#### **NASAL DRUG DELIVERY DEVICES**

It should be highlighted that efficient and novel nasal drug delivery devices used for direct transport of drugs from nasal cavity to brain is another important strategy for the improvement of treatment effects and diagnosis of diseases. which help drugs to be transported to the brain across the olfactory/trigeminal pathway. Some devices, such as syringes, pressurized meter dose inhalers, droppers, Breathe Powered Bi-directional nasal devices, and pressurized olfactory delivery devices, were accepted and adopted fully in clinical treatment and were also categorized into devices with powder, liquid and semisolid formulations (Djupestrand, 2013; Erdő et al., 2018). The suitable drug delivery system depended on the type of drug formulation. Powder formulations with high stability most likely to stick to the nasal mucosa before it is cleared. Liquid formulations are the simplest, oldest, cheapest method. Popular nasal sprays spread easily also convenient to use and deposit in the olfactory region. The spray would distribute in the

nasal cavity via nasal mucociliary clearance. But the limitation of nasal drops or spray devices completely depends on the self-administration technique.

### **Powder based devices**

As Compared to liquid (solution or suspension) and gel formulations of drugs, powder particles are more stable and not generally dissolved so they can last in the nasal mucosa for a very long time. Furthermore, because of presence of free preservatives, powder dosages could be administrated in a large dose quantity and can prevent microbial contamination. Deposition and absorption of a powder formulation of drugs intended for nasal delivery depend upon many factors such as size as well as shape of a powder particles, flow characteristics of powder, and solubility. An insufflator composition includes straw or tube with drugs, could directly transfer drugs to the olfactory region, though usually local anesthetics or decongestants are needed to deliver before insufflation delivery. Direct Haler device, originally developed by Danish company used for delivery of fine particles into the nasal cavity with pulmonary exposure. As Compared to pressurized metered dose inhalers (pMDI) with poor patient acceptability, insufflators provide the exhalation force of patients with normal temperatures and was favoured by patients. The Direct Haler device exhibited exceptional advantages such as being free from contamination and preservatives, priming, and cleaning. As the Direct Haler's route of drug delivery starts from nose to the brain, targeting the nasal valve is necessary. Smaller powder particles below 5  $\mu$  are used for olfactory absorption to increase the deposition of drug in the lungs. Bi-Directional technology uses the normal breathing process of the body to deliver drugs available in liquid or powder form on the nasal epithelium (Djupesland, 2013). The nasal valve acts as a barrier for delivery of drugs because the space in the nasal cavity is narrow. Optinose is a biopharmaceutical company, proposed closed-palate Bi-Directional™ Breath Powered® DDSs, in which an exhale device is used to target the drug beyond this valve (Djupesland, 2013; Djupesland et al., 2014). As we know, for the treatment of patients of autism spectrum, oxytocin has been already used, yet a higher dose would lead to adverse effects. Quintana et al. (2015) proposed a randomized four-way crossover trial where they used a breath powered optinose device to study the relationship between the effect of oxytocin on social cognition with dose. Through this device, a lower dose was monitored with a breath powered optinose device to deliver oxytocin across the nasal mucosa to the brain and determined that lower doses are found to be more efficacious than higher dose in producing a cognitive response. Bepak developed Unidose-DP™, approximates Flit Lizer technology, which was composed of a sealed container used for delivering a single shot of a drug. Through this technique near about 95% of the drug was delivered to the nasal cavity and about 60–70% reached the nasal vestibular region (Kaye et al., 2009). SoluVent™ is a powder delivery device which forces the powder to the nasal cavity. Few Vaccines have been delivered through this device (Huang et al., 2004).  $\mu$ co™ System was developed by Shin Nippon Biomedical Laboratories for better drug absorption and decreased dose requirement. Powder carriers with systemic drug delivery, low molecular weight, and high molecular weight enhanced safety in clinical treatment (Bell et al., 1971; Ugwoke et al., 1999). The  $\mu$ co™ carrier technology was developed on basis of a mucoadhesive powder drug carrier, which decreased doses of drug and increased absorption of drug. also provided a high activity and long contact time (Djupesland, 2013).

### **Liquid Based Devices**

Catheter-delivered drugs are the easiest method to deliver the drug into the nasal cavity through the insertion of a catheter in the nose cavity. This technique is usually assisted with sedative or an anesthesia to deliver the liquid dose. Mucosa found to be sensitive to the deposition site so it is a major issue with this method of drug delivery. By blowing with the help of mouth, solution filled in the catheter enters into the nostril by the other end of the catheter in the nose cavity (Trangsrud et al., 2002; Berger et al., 2007; Djupesland, 2013). Drops are another significant method of IN drug delivery for liquid formulations and have been used for decades because of their cost effectiveness and easy manufacturing. However, this method has some risks such as microbial contamination and chemical instability. Glass droppers are a typical single dose drug delivery, and spray pumps would most likely be used for multidose administration. However, spray pumps are expensive and are frequently replaced by cheap disposable pipettes in clinical treatment. Pipettes, especially in treatment for irrigation purposes and nasal decongestion, regularly replace the drop or spray pump in the European market (Penttilä et al., 2000). The olfactory epithelium is located in the upper part of the nasal cavity and acquires about 3–10% of the surface area of the nasal cavity between the nose and brain. It is a challenge to deliver therapeutic molecules through the nasal cavity due to its turbinate restriction (Morrison and Costanzo, 1990; Fonseca-Santos et al., 2015; Brozzetti et al., 2020). The pressurized olfactory device (POD) of Impel NeuroPharma (Seattle, Washington), composed of a suitable tank, compressed air or nitrogen, hydrofluoroalkane (HFA), or chlorofluorocarbon (CFC) used as a propellant and air chamber, was utilized to target the drug to the olfactory part of the nasal cavity. POD used to transport both liquid and powder formulations through the nasal epithelium. Impel NeuroPharma deliver liquid and powder forms of cholinergic



reactivator (pralidoxime, 2-PAM) by POD with a higher concentration of 2-PAM in the brain (Brunelle et al., 2012; Bachurin et al., 2018).

### **Nanogels**

IN drug delivery, is captivating alternative method, has been used in the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorders, and panic disorder. However, less residence time of drugs in the nasal cavity would affect absorption of that particular dose and in turn bioavailability of the drug, which has been a crucial problem occurred in clinical treatment. That is, the anatomic and physiologic characteristics of nasal mucosa must be taken under consideration for development of nasal dosage forms used for solving the rapid mucociliary clearance (MCC) (Grinberg et al., 2017; Patel and Patel, 2017; Li S. et al., 2018; Jiang et al., 2019; Qiu et al., 2020). Gel as a nasal mucoadhesive has been very prominent due to its fluid-like qualities prior to nasal administration and it can be easily administered by drops which allows accurate drug dosing. Moreover, gelation can be constructed by using thermos-sensitive smart polymers which can be elect sensing with nasal temperature (Dias et al., 2010; Singh et al., 2013; Naik and Nair, 2014; Gholizadeh et al., 2019; Zhang Y. et al., 2019). Bhandwalkar and Avachat (2013) developed an in situ mucoadhesive thermoreversible gel used to improve bioavailability of the antidepressant drug, venlafaxine hydrochloride, composed of Lutrol F127 (18%). Mucoadhesive thermoreversible in situ nasal gel enhanced nasal residence time as well as absorption of venlafaxine hydrochloride across the nasal mucosal membrane to improve bioavailability of the drug as compared with the other routes such as oral route and administration of an equivalent dose. A thermoreversible biogel system based on chitosan and glycerophosphate used for delivery of doxepin to the brain through IN administration was also reported (Naik and Nair, 2014). The antidepressant doxepin hydrochloride was loaded into the mixture of chitosan and glycerophosphate with polyethylene glycol. The mixture gelled rapidly at 37°C, and upon cooling it returned to sol state. The gels exhibit potential and effective drug delivery methods to the brain via the nose. Furthermore, an intranasal chitosan nanoparticles (NPs)-loaded in situ gel, Tramadol HCl, against depression was developed (Kaur et al., 2014). Chitosan nanoparticles (NPs) were formulated by ionic gelation method followed by the addition of developed NPs within the Pluronic and HPMC-based mucoadhesive thermo-reversible gel. Depression induction of forced swim test and various biochemical and behavioral parameters demonstrated that intranasal TRM HCl NP-loaded in situ gels found to be a promising formulation for the treatment of depression.

### **Nanostructured lipid**

Nanostructured lipid carriers (NLCs), these are the nanostructured particles formulated from the two-phased blend of solid and liquid lipids, have gained increasing attention during the last years. controlled “imperfections” nanostructure is characteristic feature of NLC, which is developed by lipid particle matrix as imperfectly as possible by spatial arrangement of very different molecules being mixed into them. The imperfections in NLC tends to increase drug loading capacity and minimize or avoid drug loss obtained from light, oxidation and hydrolysis. NLC has been used as a delivery carrier of therapeutic dosage form to the brain (Muchow et al., 2008).

Duloxetine (DLX) is the first class of anti-depressant agents which ensures rapid and sustained efficacy in treatment of both physical and emotional symptoms of depression. DLX undergoes hepatic first pass metabolism on oral administration, its bioavailability, kept about 50% (Martin et al., 2003). Moreover, as we know, the efficacy of antidepressants depends on their continued presence at the site of action (brain), although, as DLX is an oral as well as intravenous administration, the BBB would restrict the entry of antidepressant drugs to the brain, leading to the reduction in dose and side effects (Laffleur and Keckeis, 2020).

Alam et al (2014) stated that a nanostructured lipid carrier system of IN administration in which the antidepressant drug, duloxetine (DLX), was contained to bypass the BBB and maintain prolonged release at the site. DLX-NLC was formulated by mixing melted solid lipid (glyceryl monostearate) and liquid lipid (capryol PGMC), after mixing both of them were homogenized with hot surfactants aqueous solution (80°C pluronic F-68, 1.5%; sodium taurocholate, 0.5%) and lyophilized. The biodistribution studies proposed that DLX-NLC formulation had a better brain targeting efficiency and higher concentration of DLX delivered in the brain by intranasal administration compared with the intravenous administration in the treatment of depression.

### **Liposomes**

Till this date, two of the most popular ways to delivery drugs via nasal administration that are also highly lipid-soluble compounds are hydrophilic and semi lipophilic substances. moreover, highly lipid-soluble compounds usually require several steps and are generally slow. Hydrophilic and semi lipophilic substances provide a relatively faster absorption into the cerebrospinal fluid (CSF). Now liposomes have been used as an effective drug delivery system to the brain, due to particles being entrapped into the compounds which prevents the rapid degradation through the BBB and





distribution in the brain tissue (Talegaonkar and Mishra, 2004; Krauze et al., 2006; Ding et al., 2019b). Liposomes could be developed into nanosize vesicles (20–100 nm) by phospholipids and similar amphipathic lipids. As the drug is entrapped in liposomes, a decreased dose of a compound is usually expected (Sharma and Sharma, 1997; Druliskawa and Dorotkiewiczjach, 2010; Loirapastoriza et al., 2014).

CNS disorders have limitations such as its poor absorption and very low distribution to the brain after oral administration (Dandrea, 2015; Wang et al., 2016) for rapid metabolism and bypassing of the BBB. The nasal route of CNS acting drugs can serve as a potential pathway for systemic drug delivery because of the high degree of vascularization and permeability of the nasal mucosa.

Priprem et al. (2008) developed intranasal quercetin liposomes and evaluated the anxiolytic and cognitive effects on rats

### **Nanoparticles (nanosuspensions, nanoformulations)**

The formation of nanosuspensions of drugs encapsulated in polymeric carriers is a popular formulation method for many routes of administration. These carriers may provide advantageous characteristics to the drug dose like enhanced absorption, mucoadhesion and increased stability. Bhavna et al. (2014) formulated a nanosuspension formulation of donepezil, a cholinesterase inhibitor, for enhancing brain exposure to treat AD. In another paper, the researchers tested chitosan nanoparticles loaded with bromocriptine (Md et al., 2014) and found that bromocriptine-loaded nanoparticles given by IN route produced two-fold greater brain AUCs than that were in case of intravenous administration of the nanoparticles. Other studies also testified Nano formulation-induced enhanced drug delivery to the brain (wheat germ agglutinin (Gao et al., 2007), olanzapine (Seju et al., 2011), lorazepam (Sharma et al., 2014), rivastigmin (Fazil et al., 2012; Mistry et al., 2015). Pegylation (Kamiya et al., 2018) and dendrimers are also likely nanotechnological solutions to improve CNS drug delivery (Lu et al.,

2014) by IN drug administration. Pegylation may well increases the retentivity in the nasal cavity according to Kamiya et al. (2018).

For a inclusive review about the development and testing of nanocarriers for nose to brain delivery see the recent article of Sonvico et al. (2018). there are some marketed drugs listed in the same article for nasal administration and CNS targeting (nicotine, Nicotrol® NS,

Pfizer, New York City, NY, USA, pain management: fentanyl, Intstanyl®, Takeda, Japan and Pecfent/Lazanda®, Archimedes Pharma Ltd., Reading, UK; butorphanol tartrate spray, Mylan Inc., Canonsburg, PA, USA, the treatment of migraine: zolmitriptan, Zomig®, AstraZeneca,

Cambridge, UK; sumatriptan, Imigran, GSK, Brentford, UK and Onzetra™ Xsail™, Avanir Pharmaceuticals, Aliso Viejo, CA, USA).

### **V. CONCLUSION**

Nasal drug delivery is a viable alternate mode of administration for a variety of systemically active medicines with low bioavailability, and it has advantages over parenteral drug administration in terms of patient acceptability and compliance Because it requires rapid and/or specific targeting of drugs to the brain, this delivery system is beneficial in conditions such as Parkinson's disease, Alzheimer's disease, or pain, and it is a suitable route to produce immune response against various diseases such as anthrax, influenza, and other diseases by delivering vaccines through the nasal mucosa. We anticipate that intranasal medications will be used to treat erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks, and Parkinson's disease in the near future, as well as novel nasal therapies for the treatment of long-term disorders like diabetes, It will also be sold for growth deficiency, osteoporosis, reproductive treatment, and endometriosis. The proper application of these traits necessitates careful consideration of both medication formulation and delivery factors device, and a clear understanding of the ways in which they impact on each other.

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