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Review Article

NOSE-TO-BRAIN DRUG DELIVERY: AN UPDATE TO THE ALTERNATIVE PATH TO SUCCESSFUL TARGETED ANTI-MIGRAINE DRUGS

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ABSTRACT

The Blood-Brain Barrier (BBB) limits transportation to the brain of possible treatment moieties. Specific stimulation of the brain through olfactory and trigeminal neural pathways by BBB has been taken into consideration for the development of a wide spectrum of brain therapeutics. The intranasal delivery path delivers the drugs through the brain, eliminating any side effects and increasing neurotherapeutics performance. Diverse drug delivery systems (DDDss) for reaching the brain via the nasal route have been researched over the past few decades. Large-scale molecular biologics, such as Deoxyribonucleic acid (DNA), gene vectors, and stem cells, can be administered intranasally, as a method for the management of a range of CNS illnesses, including stroke, Parkinson's diseases, multiple sclerosis, Migraine, Alzheimer's diseases, epilepsy, and mental disorders. New DDSs, including nanoparticles, liposomes, and polymeric micelles, have acquired potentials in the nasal mucosa and central nervous system (CNS), as effective means of concentrating the brain without toxicity. Differential nasal cavity structures posed a significant obstacle in ineffective drugs beyond the nasal valve. Pharmaceutical firms have increasingly used emerging techniques for the production of new nasal pharmaceutical drugs to overcome these obstacles. This review aims to identify the new advances in the nasal administration of brain-based DDSs for Migraines.

Keywords: Drug delivery system, Brain targeting, Nasal route, Latest approaches, Migraine

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INTRODUCTION

Central nervous system (CNS) dysfunction means the victims, their families, and the community as a tremendous mental, financial and social pressure. Despite intense study activities, the numerous "diseases of the mind" also have significant deep-rooted issues for improved therapeutic strategies, and CNS therapy can also be effective for other disorders [1]. The complex pathophysiology of neurological disorders, trouble reaching the brain with large as well as small molecular drugs, and risk, uncertainty, and massive costs of controlled clinical trials present major obstacles in the research and production of novel drugs for brain disorders [2]. These issues have caused a drop in the pharmaceutical sector in recent years, with decreased funding in pharmaceutical production for many CNS conditions being identified. Neural disabilities are the world's second leading cause of death (16.8 percent of the world's deaths) and the primary cause of Disability-Adjusted Life Years(DALY) [3]. Oral drug administration is the most appropriate path if clinical consequences are envisaged [4]. Because of numerous disadvantages including a sluggish action and poor bioavailability(40–45%), oral therapeutic methods cannot effectively convey a variety of therapeutic agents into the brain along with nausea and inadequate treatment for pain of headaches recurring. Oral preparations also have a short half-of 1–2 h, with the drug-exposed to hepatic first-pass metabolism and renal functions easily cleared away [5].

According to a new World Health Organization (WHO) study, central nervous system (CNS) conditions such as brain cancers, migraine, autism, neurodegenerative disorders (e. g., diseases of Alzheimer's and Parkinson's), and dementia are among the key triggers of human population impairment [6]. Nevertheless, the production of drug therapies for the treatment of brain neurological disorders relies heavily on the capacity of medicinal agents to successfully permeate the blood-brain barrier (BBB) and have a major effect on the brain [7, 8]. The brain consists of two major barriers stopping external materials: BBB and BCSF. The brain has two major barriers that prohibit the entrance of external materials. When intravenous or oral drugs are used, the BBB must first travel to transfer into the brain [9]. In the last couple of decades, researchers have continued to look at new solutions to the introduction of medications into the brain [7]. The provision of nose-to-brain supplies the immediate supply of medicines to the brain without the need to permeate the BBB which can also avoid adverse effects that may arise as medicines are routinely ingested. The intranasal administration is non-invasive, eliminates the first-pass metabolism, and may maximize the amount of drugs that enter the brain in contrast with other routes of administration [10]. Talinolol, for example, has demonstrated better transmission to rat brain and cerebrospinal fluid with intranasal perfusion than with intravenous (IV) infusion [11].

In recent years, the efficacy of intranasal administration to transmit a large variety of molecules to the brain has been evaluated including insulin, mRNA, siRNA, peptides, liposomes, nanoparticles, and also stem cells [11, 16]. For example, in various regions of the mouse brain, albumin that can not cross the BBB was found to be present 5 min after intranasal administration [17]. Although the BBB may be circumvented, the nose-to-brain administration has additional obstacles. The drug's capacity to enter the upper and back of the nose, including the olfactory area, is a key element in nose-to-brain medication transmission [10]. The volume of medication that can enter the brain when administered nasally can be very low (sometimes, relative to the nasal level of the medication, just 0,1-<1 percent bioavailability in the brain) [18, 19]. Migraine headache is the most common headache neurological condition that induces pulsating and throbbing pain in the brain. This typically requires an irregular artery sensitivity in the brain, which also results in rapid alterations of the diameter of the artery. It leads to severe headaches affecting certain nerves in the brain and scalp [20]. Antimigraine drug treatment intranasally has multiple benefits over administration through oral, injectable, or rectal routes [21]. A medication delivered intranasally is consumed by the nose's highly porous mucous membranes, which allows the fast transfer of non-metabolized drugs to the central nervous system [22, 23]. The onset of action therefore requires gastrointestinal absorption considerably faster than in the case of oral administration.

The intranasal path also provides some clinical advantages, such as greater patient acceptability due to the non-invasive method of delivery, the ability to administer medication when extreme nausea or vomiting happens, and a clearer record of adverse effects [24]

Dihydroergotamine, sumatriptan and zolmitriptan constitute first-line therapies for intranasal medications approved by the FDA for the treatment of headache migraine. Originally marketed in Canada and Europe, intranasal dihydroergotamine, which was approved by the FDA in 1997. Sumatriptan and zolmitriptan nasal spray formulations were approved by the FDA respectively in 1997 and 2003. Clinical trials clearly indicate that triptans administered intranasally provide quicker relief than their oral counterparts. It, along with their stronger acceptability for patients with intermittent nausea and vomiting, provides clear explanations for their daily use [24, 25].

Nose to brain drug transmission mechanism

Different drug delivery pathways have been identified, such as the systemic pathway by which the drug is absorbed directly into the systemic bloodstream via the nasal cavity and then through the BBB into the brain; the olfactory pathway through which the drug passes through the olfactory epithelium through the olfactory bulb and deeper into the brain tissue or the cerebrospinal fluid (CSF); and the pathway through which it passes through the olfactory epithelium [26]. The neuronal Olfactory pathway is further split into two intraneuronal routes. In the intraneuronal cascade olfactory neurons in the olfactory epithelium consume the molecules by mechanisms such as endocytosis, and then axonally enter the olfactory bulb. In the extraneuronal pathway, drugs delivered intranasally first cross the distances between the olfactory nerves in the olfactory epithelium and are then transferred to the olfactory bulb. The substances can invade other brain regions by diffusion after entering the olfactory bulb, which may also be facilitated by a "perivascular pump" which is powered by arterial pulsation [27]. There is a distinction between medication transmission by olfactory or trigeminal nervous systems and permeation of the nasal mucosa. Upon administration of the drug by the nasal cavity, the drug permeates to the systemic circulation through the highly vascularized nasal mucosa and may or may not cross BBB and enter the brain. Olfactory epithelium, olfactory cortex, or trigeminal nerves, however, play a major role in delivering drugs into the brain.

Nose-to-brain transmission of drug has been attempted by many researchers who have explored the benefits of this path such as ease of medication administration and needle-free substance usage without the need for skilled professionals, promoting self-medication, non-invasiveness, virtually painless, avoidance of first-pass hepatic metabolism and hence dose control capacity relative to oral dosage. Fast ingestion, fast onset of action due to relatively broad ingestion surface, strong vascularisation, avoidance of chemical and enzymatic drug degradation in gastrointestinal (g. i. t) fluid, increased permeability of lipophilic, low molecular weight drugs via nasal mucosa allow this path for drug administration such as peptides or protein [28]. The transmission of nose-to-brain is possible via the olfactory zone on the nasal cavity roof and the neuroepithelium is the only part of the CNS that is open to the external atmosphere [29]. The olfactory area of nasal mucosa providing a clear link between nose and brain is used to target drug molecules that function on CNS used in disorders such as Alzheimer's disease, epilepsy, migraine, schizophrenia, etc [30]. Although humans were not commonly studied on the olfactory route because of problems in absolute CSF or brain tissue measurements, numerous animal tests have been reported for medicines such as olanzapine, risperidone, buspirone, ropinorole, didanosin, zolmitriptan, sumatriptane, rivastigmine, venlafaxine, and clonazepine.

For testing such schemes, statistical parameters such as drug targeting index (DTI), direct transport percentage (DTP percentage), drug targeting efficiency (DTE percent), and their visualization techniques such as gamma scintigraphy are used. The degree to which the drug affects the brain after i. n. DTI, which can be defined as the ratio of the value of the AUC brain/AUC blood following i. n. subsequent administration to i. v. control. The higher the DTI is, the more it can be predicted that the drug will reach the brain after the i. n. management [31].

The brain targeting efficiency is measured as follows: DTE percent and DTP percent which reflects the time-average partitioning ratio.

1. The efficiency of drug targeting (DTE percent) reflecting the time-average partitioning ratio is determined as follows:

$$DTE\% = \left(\frac{(AUC_{brain}/AUC_{blood})\,i.n.}{(AUC_{brain}/AUC_{blood})\,i.v.}\right) \times 100$$

2. The percentage of direct nose-to-brain transport (DTP percent) is calculated as follows:

$$DTP\% = \left(\frac{B_{i.n.} - B_x}{B_{i.n.}}\right) \times 100$$

Where B_x 1/4 $P_{i.\,n.}$ ($B_{i.\,v.}$/$P_{\,i.\,v.}$) Bx is the brain AUC fraction that is contributed after intranasal administration by systemic circulation by BBB

$B_{i.\,v.}$ is the AUC0–240 (brain) following intravenous administration.

$P_{i.\,v.}$ is the AUC0–240 (blood) following intravenous administration.

$B_{i.\,n.}$ is the AUC0–240 (brain) following intranasal administration.

$P_{i.\,n.}$ is the AUC0–240 (blood) following intranasal administration [32]

Imaging of gamma scintigraphy is conducted on the brain of animals following i. v. and I. n. Administration to determine the location of the medication in the brain and other tissues such as heart, kidney, esophagus, stomach, and intestine. Imaging is achieved using Computerized Tomography Single Photon Emission (SPECT, LC 75-005, Diagram, Siemens AG, Erlanger, Germany) gamma cameras [33].

Conventionally, many dosage formulations have been used for intranasal delivery such as liquid drop, liquid spray/nebulizer, aerosol, gel, and suspension spray. There are many barriers in the nasal cavity such as the physical removal of mucociliary clearance, enzymatic degradation, and nasal epithelial permeability. Several methods for enhancing medication permeation through the nasal mucosa, including the use of mucoadhesive polymers and absorption enhancers, were studied for the prolongation and improvement of the drug's contact time with the nasal mucosa.

Nanoparticles, nanosuspension, nanostructured frames, microemulsion, and solid lipid (SLN) nanoformulations are the different investigated nanoformulations. Different nanoformulations are investigated. These formulations could be used as an effective carrier for the delivery of therapeutic agents through the nose-to-brain route for the therapy of CNS disorders based on the reports on nanoformulations.

Strategies for nose-to-brain transmission

Improving permeation

Permeation boosters are widely used in the provision of drugs for increased membrane permeation. While most lipophilic drugs can permeate the nasal mucosa themselves, it is typically difficult to permeate small hydrophilic compounds, peptides, and macromolecules, and therefore it would be of considerable benefit to enhance permeation [34]

Surfactants are typically used to improve the permeation of substances through the nasal mucous membrane, but their process can include nasal barrier disruption, which can lead to discomfort or nasal mucous toxicity[35,36]. Types of surfactants used to improve nose-to-brain transmission are non-ionic surfactants, such as Cremophor EL, Cremophor RH40, Poloxamer 188, and laurate sucrose ester [37].

The permeation of medicines across the nasal mucosa is also improved by cyclodextrins, lipids, and even polymers [4, 35, 36]. For instance, β-cyclodextrin and chitosan microparticles were used by Rassu *et al.* to improve the nose-to-brain distribution of deferoxamines [38].

Chitosan can loosen tight joints in the nasal epithelium and increases drug permeability. Chitosan's mucoadhesive characteristics also increase drug holding time in the nasal mucosa and result in increased drug permeation[39]. Horvát *et al.* used sodium hyaluronate and Cremophor RH40 to effectively improve the

permeation of dextran, a hydrophilic molecule with 4.4 kDa molecular weight. Hyaluronate has clotting properties which increase the time the formulation is in contact with the nasal mucosa and Cremophor RH40 helps to increase permeation as a surfactant. While surfactants can cause irritation or tissue toxicity, in this particular case no irritation and ciliotoxicity have been observed by either Cremophor RH40 or Hyaluronate [37].

Inhibitors of enzymes

The nasal cavity has many proteins, such as CYP450 isoforms, transfers, carboxylesterases, and other drug-metabolizing factors. Inhibition of these enzymes can improve in situ stability and avoid biotransformation, and thus increase the amount of active drug that can be ingested into the brain to create an

Effect [36, 40, 41]. After fluvoxamine, a competitive CYP450 inhibitor, Dhamankar and Donovan have recently demonstrated an improvement in melatonin permeation through the respiratory nasal olfactory mucosa [42]. In addition, the saturation of the enzyme at a high melatonin concentration also increased the permeation of melatonin without metabolic activity [42]. Hussain *et al.* also showed that α-aminoboronic acid derivatives inhibit protease degradation in the nasal mucosa, even though no research on enhanced nasal absorption and nose-to-brain transmission was conducted to understand the effect on [43].

Inhibitors of P-glycoprotein

P-glycoproteins (Pgp) are membrane conveyor proteins that are found in the BBB, nasal mucosa, olfactory epithelium, and the olfactory bulb that are responsible for the efflux of the brain drugs. Fortunately, Pgp substrates aren't all drugs. Pgp substrates may be lost by the nose-to-brain supply and released with a negligible effect from the brain to the blood circulation. Verapamil is one such example [44-46] To resolve this effect, Shingaki *et al.* use cyclosporin A as a Pgp inhibitor and show that the permeability of verapamil following nasal or intravenous infusion has increased by cyclosporin A [11]. In the absence of Pgp, diazepam, verapamil, and antipyrine, graff *et al.* used Pgp-deficient mouse and Pgp-competent mice to show that they improved their brain transfer compared with Pgp-competent mouse [46]. In another study, the use of rifampin, which is a Pgp inhibitor, in Pgp-competent and Pgp-deficient mice increased the use of verapamil in the brain [44, 45]. Coadministration of two Pgp inhibitors pantoprazole and elacridar with imatinib mesylate also raised the later brain concentration [47].

Mucociliary clearance antagonists

The nasal mucosal cilia act as a barrier to particle penetration from the outside. They are found in the respiratory area and part of the olfactory region. In the olfactory zone, though, those are not motile. In the respiratory area, cilia are responsible for transferring mucus from the nose to the oropharynx. Every 10–15 min the mucus is cleansed through this mechanism. This method is called mucociliary clearance [48]. Once medications enter the nasal cavity and become caught in the secretions of cilia and mucus, they appear to be removed in minutes. Approaches to suppress cilia improve the processing time in the nasal mucosa and, thus, can be used to increase the amount of medication that can be absorbed into the brain via the respiratory epithelium or olfactory epithelium. Because the olfactory epithelium doesn't have flexible cilia it arises if it can influence the absorption of the drug through the olfactory epithelium into the brain or either via trigeminal nerve pathways and/or the respiratory epithelium into the brain by inhibiting the mucociliary clarification in the respiratory area. Or in other words, if inhibiting motile cilia in the respiratory region will improve drug absorption in the olfactory epithelium region above? The dimension in the current literature does not seem to have been widely explored. For improved nose-to-brain transmission, sodium hyaluronate and cremophore RH 40 have been used in the study by Horvát *et al.* As a permeation enhancer and as a mucosal polymer, cremophor RH40 was used as a mucosal hyaluronate. When used alone, except for the olfactory bulb and frontal cortex the excipients did not increase the supply of dextrane to the brain. But, besides, they increased the amount of drug in the olfactory bulb and intravenous cortex [49]. This study demonstrates that dextran was directly taken to the brain and stopped blood and BBB from going through it, but it does not reveal the direction of entry into the brain of the molecule. Therefore, the authors hypothesized that it may be linked to sodium hyaluronate's mucoadhesive features and possible increased residence times as well as increased surfactant permeation [37]. Mucociliary clearance strategies include the use of chitosan (see above), hyaluronan, poloxamer, carbopol, gellane-gum, polycarbophil, and other polymers which increase viscosity, stick to the mucus, and delay mucociliary clearance [49, 50]. Those polymers are thermo-responsive materials, liquid when stored and applied, and starting to gel only when in contact with the nasal mucosa [51, 52]. The use of agonistic α-adrenergic receptors including ephedrine was also studied to decrease the amplitude of cilia beat and postpone the mucociliary clearance [53, 54]. Nevertheless, not many studies have been carried out to relate directly to their effect on the clearance and transportation of drugs to the brain. Section 4.9 addresses vasoconstrictors.

Concept of prodrug

Prodrugs are chemically modified compounds, which improve the permeation of certain tissues or prevent degradation of chemical substances. Medicines are usually inactive medicines that are activated only after the activation of the enzyme. When drugs come to the body, the enzymes (for example, esterase) are converted, the active drug is released from the intended place of delivery [41, 55]. The approach was used in the treatment of nausea, vomiting, and Parkinson's disease to improve the permeation for delta-9-tetrahydrocannabinol and L-dopa via nasal mucosa [41, 56, 57].

Nanoparticles

Nanoparticles are commonly used for transmission from nose to brain.

Several authors covered the surface of nanoparticles with additives with a certain similarity to the sugar molecules of the cavity and thus increased the molecular transport from the nose to the brain (e. g. lectin-coated nanoparticles). Nanoparticles may have a high molecular weight and low lipophilicity as well as a major impact on the supply of medicinal products prone to metabolism in the nasal cavity. The nanoparticles are encapsulated to keep the drugs intact with the nasal mucous membrane, as is seen in the vasoactive intestinal peptide (VIP) delivery below [58].

The nasal permeability of polar and high molecular weight compounds is small. However, this challenge has been solved by the use of micro-particles and nanomaterials [59]. One of the drawbacks of nanoparticles is their significantly larger size, as nanoparticles>100 nm surpass the diameter in the olfactory filia, resulting in at least less transportation through the olfactory tract[60].

If nanoparticles are transported intact to the brain through the olfactory epithelium or whether nanoparticles release drugs and then are transported or distributed to the brain is still not clear.

Lectins are proteins or agglutinins that bind directly to sugar molecules or components of a glycosylated membrane. The nasal mucosa comprises certain components. Consequently, lectins have been commonly used to cover the surface of nanoparticles or other carriers to improve their binding to the nasal mucosa to increase their absorption into the brain [58]. For example, nanoparticles were used to improve the supply of vasoactive intestinal peptide (VIP) and Fluorescent samples by Gao *et al.* in poly(ethylene glycol)-poly (lactic acid) (PEGPLA) surfaces [58, 61].

VIP-WGA-coated PEG-PLA nanoparticles in rats were administered on an intranasal basis and led to brain levels 5-7 times higher than VIP solution control intranasal. The nanoparticles without WGA also produced a 3-to 4 times more brain levels of VIP than the intranasal VIP solution. This showed that nanoparticles enhance drug delivery in the olfactory zone [58]. The drawbacks of this method are related to the inability to pick the lectins for an olfactory epithelium and to dispersion into other regions of the nasal mucosa, such as the olfactory and respiratory regions in general [58, 61, 62].

Peptides for cell penetration

Cell-Penetrating Peptides (CPP) are small sequences of amino acids that cross the cell membranes and aid the internalization of material into the cells. protein transduction domain [63]. Kamei *et al.* effectively increased the insulin release in the brain after penetratin coadministration. The team found that insulin did not enter the brain effectively relative to IV administration following intranasal administration. Intranasal administration took 10 times the dosage for IV to reach the same amounts of the medication in the brain [12]. L-or D-penetratin as a CPP was then used in combination with insulin and the amount of insulin in the brain, mainly by the olfactory bulb, was increased, both by L-and D-penetratines. The hippocampus, which is known to have insulin sensors, was also transported by insulin. In comparison, D-penetratin improved the delivery of insulin to the brain with the least systemic absorption and helped contribute to a greater amount of insulin in the plasma [12]. The latest research on visualization and quantification of insulin delivery in the brain confirmed this once again [64].

Eutectic mixtures

To treat migraine exacerbations, Khan *et al.* produced a dry eutectic zolmitriptan powder. The findings showed that, compared with intranasal instillation of zolmitriptan powder or IV zolmitriptan injection of a solution of zolmitriptan, the intranasal administration of zolmitriptan eutectic mixture led to higher rates in the brain [65]. Borneol/menthol eutectic mixtures were also used as cobrotoxin enhancers. When the eutectic mixture was used cobrotoxin permeated the olfactory epithelium, but in the absence of the eutectic mix, it was not observed. Conspicuously improved brain delivery of cobrotoxin intranasally relative to intravenous administration of Borneol/Menthol [66].

Vasoconstrictors

Dhuria *et al.* have used vasoconstrictors to increase drug supplies from the nose to the brain by decreasing drug absorption into the systemic circulation and increasing nasal mucosal retention time. In conjunction with hypocretin 1 (HC) and L-Tyr-D-Arg (DKTP), for example, when 1 percent was used in phenylephrine hydrochloride, blood plasma content was decreased by 65 percent, and 56 percent respectively, compared to the drug alone 30 min after intranasal administration. More specifically, when the vasoconstrictor was used the sum of HC and D-KTP entered the olfactory bulbs in the brain. Besides, when phenylephrine concentration was raised from 1% to 5% and administered nasally, in conjunction with D-KTP, a substantial increase in medication was observed not only in the smelling bulbs but also in other areas of the CNS [67]. Illum *et al.* co-administered Ephedrine in rats previously, but no decrease in systemic absorption was observed with angiotensin antagonist GR138059 solution.

Besides, both systemic and brain absorption was increased by the combination of 1% ephedrine with a drug solution. The medicinal concentration within the brain was significantly higher compared with blood plasma levels when comparing ephedrine effects in systemic absorption and brain absorption. The authors conclude that ephedrine may have affected the tests, contrary to previous research on other mucosal surfaces, when used in the drug solution instead of administering the vasoconstrictor [53]. This, however, may not be the case as more recently intranasally and systemic absorption was decreased during the increase in nose-to-brain supply, Dhuria *et al.* reported coadministration of phenyl and neuropeptides [67].

Physical methods

The localization of the drug until it penetrates the olfactory epithelium and reaches the brain is another disadvantage of nose-to-brain delivery. Physical methods are effective at position monitoring.

Magnetophoresis

The poor transmission capacity in the olfactory area is one of the drawbacks of nose-to-brain transmission. Magnetophoresis consists of applying a magnetic force in a particular region of the corps to attract magnetic particles. In order to improve the delivery of drug output in the olfactory region and thus the amount of drug that can be directly transferred to the brain, Xi *et al.* used magnetophoresis[68]. Researchers estimated that ferromagnetic microspheres will be delivered to the brain 64 times higher than their ability [68]. The key advantages are the ability to identify and target those regions, especially the most difficult to reach olfactory epithelium using standard methods. The main drawback of this approach is that the magnet intensity (90 percent) decreases by only 5 mm from the magnet; a magnet strength which has to be used in order to balance gravity and enable particles to be moved in a given region and the need for a magnetic gradient. The drawbacks make this approach very difficult for nose-to-brain delivery, but this article also demonstrates that this method is feasible for medicinal supply purposes.

The distribution efficiency to the olfactory area was 45 percent compared to the traditional approaches based on the right particle size and magnet configuration (in this case 15 μm)

Ultrasound

In order to evaluate its effect on transportation to the brain of a brain-derived neurotrophic factor (BDNF), Chen *et al.* used mouse-based ultrasound sonication (FUS). This approach was previously used by the same community to slowly open and locate BBB to IV-injected drugs in a particular focus in the brain (millimeter range) [69, 70]. Chen *et al.* suggested a similar effect to combining FUS with intravenous administration with the application of centered ultrasounds with intranasally-administered BDNF. Further, the combination of the FUS and the intranasal administration of the BDNF alone improves the location of the BDFN in a specific area of the brain [71].

Devices

The limited surface size of the olfactory system (1–5 cm^2) and its position on the nasal mucus prevents drugs from entering and building up in the region and from being prepared for absorption [72]. Different devices have been designed to enhance the direct interaction with the olfactory region of the nasal cavity for drug formulations.

A breathing system is used to manufacture sumatriptan in the olfactory area of the nasal cavity in one of the items currently on the market. The system was first invented by Optinose ®, named OptPowder, so when the patient exhales the palate closes, the lung is not deposited and drug deposition is enhanced [73]. ONZETRA ® XSail ® is the first on the market to use the system technique for sumatriptan supply and migraine care. The substance has shown drug deposition in the back and top regions of the nasal cavity, but no evidence of drug transfer to the brain has been identified via the olfactory region or trigeminal nerve pathway. The absorption of sumatriptan mainly through the nasal cavity seems to be systemical [74, 75]. Another example is ViaNase™ which is an atomizer based on the vortical flow of fluid gout in the vortex chamber and even when the system exits the nasal cavity, providing successful saturation and preventing pulmonary and stomach deposition [76, 77]. This device, by Kurve Technologies™, has demonstrated evidence of insulin delivery intranasally to patients with mild Alzheimer's disease and mild amnestic cognitive impairment [78, 79]

Challenges

The intra-nasal drug delivery route is also regarded as an enticing way to rapidly enter the brain. Their rapid response has various advantages, such as their ability to avoid BBB, more accurate targeting of medicinal products, faster action, avoiding first-pass metabolism of drugs at the liver, more important areas of medicine absorption, reduced systemic side effects, non-invasive, convenient and patient-friendly route to administration [80, 81]. In addition, the clinical use of IN formulations for the delivery of brain pharmaceutical products must go further. Some of the common limitations to the delivery of IN drugs include poor nasal mucosal permeability, mucociliary clearance, drug degradation, low drug retention times, and nasomucosal toxicity [82]. Various enhancers of permeation [83], guided supply structures, colloidal drug carriers, and other new methods were used to increase drug permeability

and absorption [84]. By using an effective mucoadhesive method, such as viscous solution, mucoadhesive polymers, hydrogel, in situ gelations, durability is increased and mucociliary clearance is reduced [85]. In addition, other protective measures (such as encapsulation in the nanocarrier system) are required to protect the drug against enzymatic degradation. The IN-drug delivery should be supported by these formulating strategies. However, since the sometimes and high dose of the formulation irritates the nasal mucosa, the clinical effectiveness of IN insulin therapy is minimal. In addition, nasal mucosa protective barriers restrict the effects of IN therapy as only 1% or<1% of the drug enters the brain following IN. Work will therefore focus on creating an appropriate formulation to resolve these barriers [86].

The essence of the medication, the excipients, and the drug's potency should also be considered together with this. Compared to the other pathways, the volume of the nasal cavity is comparatively low (25 cm^3), allowing only a limited amount of formulation (100–200 µl) at a time. A strong agent is therefore ideal for the delivery of drugs to the brain in IN. The excipients must also be biocompatible and contain no offensive odour [87]. In fact, the formulation's pH (5.0–6.5), tonicity, and viscosity also serve a significant role in the shaping of formulations[86-88]. The expertise to administer the drug into the brain plays one of the main parameters of drug absorption. The mucociliary clearance of the drug is obvious if the formulation is dumped to the basal area of the nasal cavity. The movement of the drug towards the blood flow is possible by the frontal section and the drug captivation to the olfactory area or brain is done by the posterior and upper region of the nasal void. Specific delivery equipment like a needleless syringe, spray, nasal dropper, etc. is used to put the medication into a suitable section in the cavity of the nose [89]. OptiMist™ (a breath actuator) [90] and ViaNasa™ (electronic atomizer) [79] are the most popular equipment for aiming to the brain [86].

Various scientific studies prerogative straightforward as well as active drug migration from the nasal cavity to the brain. But various other research works just deny this matter of direct transport. The researchers working at Leiden University haven't seen any proof of nose-to-brain delivery with estradiol, vitamin $B_{12,}$ and melatonin [91] whereas, several other scientists claimed a significant amount of those compounds in the brain [92]. This incident shows the alteration of methods, aspects regarding formulations as well as the condition of the whole study. So, a profound understanding of formulation factors is recommended for effective medical application of the approach [91]. Though there are so many positive results as well as obstacles regarding the application of drug through nasal route but more study and research is needed for successful marketing of those products.

Migraine: an overview

Migraine can be considered as an incapacitating and ubiquitous neurovascular ailment [93], commonly categorized with a headache with ≥2 features of pulsation, one -sided position, moderate to unembellished strength and deteriorating by the scheduled physical bustle, associated with ≥1 indication of nausea and/vomiting, photophobia and phonophobia [94]. But all the symptoms are subjective as well as different. Moreover, one out of three subjects of migraine are sufferers of a special type of focal neurologic visual syndrome called aura [95, 96]. Throughout the spell, the blood vessels in the brain expand and then assemble by triggering nerve culminations near the exaggerated blood vessels. There lies the main reason for pain or discomfort [97]. The duration of the pain varies from 2 h and even up to 3 d and it may move from one half to another [98]. Several hereditary and environmental influences are considered as two main reasons behind migraine. As a preliminary statistics hereditary cases lead to two-third of migraine cases. Variability in gender also causes an alteration in the disease population. Females are more susceptible to the migraine than the males especially the difference rises after adolescence. The research revealed 3 out of 4 patients with migraine are females [99].

Migraines became well recognized in ancient human culture. In the Old World (7000 BCE) Trepanation (drilling a hole in a hole in the skull) has been recommended for migraine care. The people believed this practice back then let certain evil spirits escape the mind. In the position, William Harvey suggested trepanation as an effective migraine treatment even in the 17th century. That was 1868 when the "ergot" fungus was first used in migraine medication. Ergotamine was eventually successfully isolated from ergot in 1918 and used for migraine treatment. Then methysergide was synthesized in 1959 and sumatriptan(the first triptan) was developed in 1988 [100].

Migraine is typically separated into two types: (1) aura migraine and (2) non-aura migraine. Migraine disorder pathophysiology is not well established; some experts theorize that the CNS bears sole responsibility for the pain. Others assume the peripheral one sensory neuron and including blood supplying vessels play a significant function in the initiation of disease. Standard analgesics such as paracetamol, headache ibuprofen, and popular nausea prescription items are used for primary treatment. If these are unsuccessful, the prescription is for triptans and ergotamines. Caffeine can also sometimes be used to treat serious pain. Analysis Present Calcitonin-based gene peptides (CGRP) such as telcagepant and olcegepant claiming to be pathophysiologically working on migraine medication focused on the use of pain associated genes. Unfortunately, in 2011 Merck failed to perform a Phase III clinical trial on telcagepant. CGRP monoclonal antibodies are now also being tested for competent migraine therapy [101].

Recent developments in the nasal sector for migraine therapy at a glance

Mucoadhesive nanoemulsion of zolmitriptan

Abdou *et al.* claimed that Zolmitriptan Nanoemulsion Mucoadhesive was thriving formulated and defined for intranasal delivery to be appropriate for use. The nanoemulsion primed showed a small average globule size, longer retention time, and increased drug propagation through the nasal mucosa. *In vivo* research of the formula in mice resulted in improved direct delivery of drugs to the brain, with a greater proportion of drugs and quicker onset of action than the intravenous or nasal solution. The formula showed high DTP percentage and DTE percentage resulting in the drug being extremely bioavailable in the brain. Additionally, it revealed no abnormality in mice's nasal mucosa after application for 14 d. From the results, it appears that zolmitriptan formulation as mucoadhesive nanoemulsion is a potential drug delivery method to improve its bioavailability and effective treatments [102].

Transnasal zolmitriptan novasomes

Radwa *et al.* produced free fatty acid-enriched vesicles, termed as novasomes were successfully prepared and filled with a high percentage of a nano-sized hydrophilic product (Zolmitriptan or ZT). Especially in comparison to the I. V 99mTc-ZT approach, 99mTc-ZT-loaded novasomes showed enhanced nose to brain targeting. Therefore, ZT-loaded novasomes administered through the nasal route can be an advance in the management of acute migraine attacks [103].

Almotriptan loaded solid lipid nanoparticles in mucoadhesive in-situ gel preparation

In this study by Yossef *et al.*, the intranasal drug delivery method for ALM brain targeting was developed. SLNs were prepared using the double emulsion solvent evaporation technique w/o/w, specifically selected to trap hydrophilic drugs in SLNs. Studies of optimization of; the forms and quantities of lipid and external stabilizers were done. After comprehensive trials, air-dried and dispersed into an engineered, thermo-sensitive mucoadhesive in situ gel, the selected solid lipid nanoparticles formula had the highest percentage of entrapment efficiency and small particle sizes, which increases nasal time and thus bioavailability. Evaluation of pharmacokinetics and bio-distribution revealed that intranasal in-situ gel-based formulae, Nasal Formulation (SLN-based) is a good candidate for brain targeting of Almotriptan from the nose, as it showed obvious rapid ALM brain delivery; Tmax/brain was 10 min, Cmax/brain was twice as high ND (Free ALM-based) and IV. The measured targeted indices (DTE percent and DTP percent) confirmed both NF and ND capabilities for ALM nose targeted brain. The evaluation of

biomarkers and the results of histopathological exams indicated the higher NF (in-situ gel-based SLNs) health profile for nasal administration; It has shown no signs of cell necrosis, damage to the mucosa, or loss of cilia, with a healthy biomarker.

Lastly, their NF Pr-SLNALM in C4 in-situ gel combined a well-known vector which preferably targets olfactory receptors, enhances ALM absorption and targets the brain, bypasses the BBB, and uses a secure delivery system which starts even faster than in an intravenous course, preferably with more. Further clinical trials of the developed method in humans in future studies are reinforcing the results achieved [104].

Sumatriptan nasal powder

Al-Salama *et al.* reported that Sumatriptan nasal powder was successful in treating acute migraine with or without aura in well-designed phase 3 trials in adults. Sumatriptan nasal powder has been substantially better than placebo for primary care after a single procedure and with these advantages, most secondary endpoints persisted at 24 and 48 h. Sumatriptan nasal powder was significantly more effective than oral sumatriptan during the first 30 min of treatment during the multi-treatment study; Relief, pain relief, and full freedom of migraine at all times 15 to 90 min after the dose and the reduction of photophobia-, Phonophobia-and-nausea symptoms associated with migraine (but not vomiting) at different times during this period. Sumatriptan nasal powder was significantly more effective than oral sumatriptan during the first 30 min of treatment during the multi-treatment study; pain relief and full freedom of migraine at all times 15 to 90 min after the dose and the reduction of photophobia-, Phonophobia-and-nausea symptoms associated with migraine (but not vomiting) at different times during this period.

No significant intergroup exists from 1.5 h after dosing Nasal powder and oral formulations differ in ineffectiveness. The fast beginning of the action can be attributed to Delivery mechanics resulting in fine powder propulsion to the mucosa of the back Nasal cavity, a rich mucosa region permitting the medicine into the systemic circulation is absorbed directly. The majority of the adverse events related to administration site and of moderate or mild severity were tolerated in clinical trials with sumatriptan nasal powder. The atypical sensations of Triptan were slightly lower with the lower mean average plasma levels found with Sumatriptan Nasal Powder in patients receiving nasal sumatriptan powder than in those receiving oral sumatriptan. Sumatriptan was an inexpensive and effective nasal powder tolerated generally well-designed migraine treatment test of phase 3. With a new breath, nasal delivery powered. This leads to a faster action start than oral sumatriptan, nasal powder Sumatriptan offers a new useful possibility for acute migraine treatment in adults with and without aura [105].

Chitosan nanoparticles

Gulati *et al.* described the ionotropic gelation process using Taguchi design to optimize sumatriptan succinate-loaded chitosan nanoparticles have been successfully formulated. The nanoparticles obtained can easily penetrate through particle size into the nasal mucosa. The formulation showed a continuous release of up to 24 h, with several daily doses reduced to once a day [106].

Zolmitriptan nasal spray

Tepper *et al.* formulated Zolmitriptan NS has therapeutic benefits for migraine patients. alt can be summarized as "5-10-15-30" for the pharmacokinetics and efficacy of the plasma within 5 min. The headache action is essential as early as 10 min, major painless reactions as early as 15 min and total relief happened as early as 30 min [21].

Almotriptan microsphere

Abbas *et al.* prepared GG microspheres filled with Mucoadhesive and biodegradable ALM were successfully developed by cross-linking w/o emulsification technique employing 23 total factory construction. The findings of their present study demonstrated the promising potential of GG microspheres for intranasal drug delivery. Upon contact with the nasal mucosa, the microspheres form a viscous gel by removing water, and interaction with cations present in nasal secretions, which eventually leads to a reduction in the rate of ciliary clearance and consequently prolongs the residence time for the formulation. Besides, mucoadhesive microspheres could be utilized at desired times for burst release to influence any necessary modulation in the plasma level of drugs. ALM's controlled release profile from the microsphere can help to decrease the dosing frequency and potentially maximize the therapeutic profit, ensuring healthy, patient-friendly, reliable, and cost-effective distribution of drugs.

Even so, for these formulations to be adequate in clinical practice, extensive animal studies of diverse species followed by extension clinical trials and toxicology assessment need to be carried out [107].

Randomized trial between AVP-85 sumatriptan nasal powder vs 100 mg oral sumatriptan

COMPASS is a rigorous, comparative design in which the efficacy study shows that the bi-directional intranasal delivery system of the investigational AVP-825 provides an earlier reduction in the intensity of migraine pain statistically and clinically essential and pain relief levels higher without the lack of suffering and dignity within 30 min. Maintained efficacy as the most effective oral dose given slightly lower sumatriptan (100 mg) exposure to medications. Furthermore, AVP-825 statistically conferred significantly fewer adverse effects associated with triptan than 100 mg of oral sumatriptan. Since oral sumatriptan is the triptan used most commonly for acute migraine treatment, the findings of this trial will provocate the current model of migraine treatment [108].

CONCLUSION

The Blood-Brain Barrier (BBB) limits the transportation to the brain of possible treatment moieties. Intranasal delivery path delivers the drugs through the brain, eliminating any side effects and increasing neurotherapeutics performance. New DDSs, including nanoparticles, liposomes, and polymeric micelles, have acquired potentials in the nasal mucosa and central nervous system (CNS), as effective means of concentrating the brain without toxicity. Differential nasal cavity structures posed a significant obstacle in ineffective drugs beyond the nasal valve. Pharmaceutical firms have increasingly used emerging techniques for the production of new nasal pharmaceutical drugs. So, in the case of effective therapy for CNS diseases especially Migraine, the nasal route can be a torch-bearer.

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CONFLICTS OF INTERESTS

The authors declared that they have no conflicts of interest.

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