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Brain Targeting Via-Intranasal Routr of Migraine for Effective Management of Migraine

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ABSTRACT: Migraine is a disabling condition characterized by severe, painful headaches. Patients need urgent help from this pain. The presence of the blood-brain barrier does not allow the drug to enter the brain effectively. Oral administration of conventional antimigraine medications may result in decreased absorption. Slow digestion is also the reason why the drug is not absorbed well. Nausea and vomiting caused by migraine further restrict the patient's compliance with oral medications. Other limitations associated with the oral route include excessive initial metabolism, slow onset of action, inability to cross the blood-brain barrier, need for high dosage/dose injections, and frequent dosing. Antimigraine drugs, such as triptans used in migraine treatment, are effective but have low oral bioavailability. Additionally, these drugs are associated with many cardiovascular diseases. We need to create a dosage form that will allow the drug to be delivered directly to the brain, thus reducing the dosage. Invasive techniques are available to deliver treatments to the brain. But they are painful, require professional help, and are not the cost of migraine treatment. These limitations require the creation of new non-invasive methods that are safe, effective and patient-friendly. Intranasal administration via the olfactory and trigeminal nerves has been reported for brain tissue. This method is noninvasive, prevents primary metabolism, eliminates nausea and vomiting, helps reduce dosage, and helps improve patient compliance. Many factors, such as drug solubility, lipophilicity, mucociliary clearance, and enzymatic degradation, affect the nasal bioavailability of the drug. Therefore, it is necessary to develop new nasal drugs with long nasal residence time that can change pharmacokinetics to achieve adequate clinical response and provide a target This article also discusses nanocarrier-based delivery systems such as in situ gels, microemulsions, nasal spray microspheres for nose-to-brain delivery of migraine medications.

Keyword: Novel drug delivery, Nasal drug delivery, Microsphere, migraine.

I. INTRODUCTION:

Nasal administration has been a successful method of drug administration since ancient times. It enables the brain to have a better effect on many medications and is considered an important component in the treatment of many brain diseases. The olfactory region of the nose is particularly important as it has special ciliary nerves for smell perception, receives the ophthalmic and palatine branches of the trigeminal nerve, and has direct access to the cerebrospinal fluid. [1,2]

Migraine is a syndrome characterised by means of severe headache and nausea that arise at abnormal intervals and ultimate for several hours. according to the worldwide Burden of disorder (GBD) look at, migraine is the second maximum common reason of disability and the main purpose amongst girls below 50 [3] traditional migraine is normally heralded by means of an “air of secrecy” accompanied by using spreading homonymous visual view defects with coloured sharp edges, referred to as “fortification” spectra [4].Migraine sufferers may also have difficulty focusing on certain objects, have an aversion certain food, and have sensitivity to smells(nausea) orlight (photophobia).The exact cause of these symptoms is unknown, but may be related to cranial blood disruption.

In addition to genetics, factors such as mental illnes ses, insomnia and certain foods can also cause attac ks.

The most commonly used route of administration for systemic effect is oral administration. But for some drug the systemic effect was not in desirable condition due to oral bioavailability and promoted for the search of more effective route for systemic delivery [5]. Usually, the

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nasal cavity is used for the treatment of local diseases they are rhinitis, migraine, cold, pain and nasal congestion. In recent years it has been proved that many drugs achieved better systemic bioavailability through nasal route [6].

The various formulations used by nasal route are nasal gel, spray, powders, etc.The Oral mucosal (e.g., sub- or supralingual or buccal) administration of drugs is often the route of administration of choice when the nasal mucosa is the main pathway to achieve faster and higher absorption of the drug [7]. This is due to the anatomical reason that the physiological characteristics of the nose are a porous endothelial membrane with large surface area and high total blood flow, preventing first-pass metabolism and easy to access [8] [9]. In-situ is a Latin word meaning 'in place' or 'in place'. In-situ gel is a dosage form in which the drug enters the body as a solution before application and gels to form a gel after application [9].

Due to its accessibility, nasal drug administration is considered as an alternative route for systemic circulation instead of intravenous administration[10] Nasal drug delivery also provides a way to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly [11] .The nasal route is an attractive not only for delivery of vaccines due to large surface area and low proteolytic activity but also it improves the patient compliance and decrease the production cost compared to parenteral production[12].Due to their high permeability the nasal route show only smaller molecular weight drugs the absorption will be more. For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane so the drugs cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier [13].

Antibiotics such as surfactants, bile salts, and phospholipids can increase the penetration of drugs, but toxicological tests at clinical sites have proven that antibiotics have some limitations due to their irreversible damage [14,15]. Although there are many challenges facing researchers, including overcoming some of the shortcomings of nasal materials, efforts are being made to develop new nasal models.

The nasal route is an important mode of drug delivery, with a growing number of products available for administration through the route for systemic and local administration. In-situ gel is a new dosage form which has been applied in nasal drug delivery recently.[16]

Polymer network that swells from the solv ent, consisting of a physical network of long polym er particles. In situ gelation of the system prior to application is an aqueous solution that turns into a gel under physiological conditions.

There are many methods for in situ gel delivery; for example, oral, eye, genital, rectal, urinary, intraperitoneal, etc. Gelation results from the linking of polymer chains, which can be achieved by covalent bonds (chemical bonds) or non-covalent bonds (physical bonds). There are different processes that can lead to in situ gel formation; for example, those based on physical stimuli (e.g., temperature changes, pH triggering systems), physical changes in biomaterials (such as weight change and inflammation) as well as reactions based on chemical reactions (such as UV radiation, ionic cross-linking and ionic activation systems). In this way, there is no need for organic solvents, co-polymerizers or direct gelation. The insitu gel formulation is delivered through the genitals and the anus together with the nasal mucosa, bypassing the first pass metabolism of the liver which still pays attention to protein distribution and also Peptide control. They are administered intravenously because they are sensitive to gastrointestinal proteases [17].

A few years ago, most drugs were used parenterally and orally [18]. Although the oral route is simple and cheap, it is not effective in cases such as the low solubility of the drug and the first effect (the drug absorbed by the liver is transported to the body and metabolized there)[19], may cause this situation, its bioavailability is not good (like griseofulvin)[20]. The greater the initial effect of the drug (the amount of drug and where it reaches the systemic circulation), the lower its bioavailability. This approach is also not suitable for unconscious patients [21].

To solve this problem, a correct, immediate-acting parenteral route with 100% bioavailability is recommended, but this drug cannot be used if requested for the treatment of chronic diseases because this method also has disadvantages. The risk of embolism and rapidly reaching these concentrations increases the risk of adverse effects. For this reason, different methods are preferred [22]. In addition, the transdermal method is used to control drug delivery (stable blood) and is not affected by metabolism in the first place, but its use is limited due to the low permeability of the skin for many drugs [23]Non-

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parenteral routes are used to manage these problems, including nasal, buccal, pulmonary, rectal, and genital routes, also known as transmucosal routes. This approach has some benefits or advantages, such as the ability to self-regulate. The nasal mucosal application method provides faster and higher absorption of the drug. This method has great application in drug delivery of various drugs [24].

- NOSE-TO-BRAIN DELIVERY:
- Pathway for nose-to-brain delivery: Drug transport through the olfactory mucosa has been studied to deliver therapeutic substances to the brain to treat CNS diseases. As described earlier, it has the significant advantage of bypassing BBB and reducing systemic exposure. The pathways for N2B delivery have not been fully understood, but many recent studies have suggested some major possible pathways. One way is the direct transport of drugs to the brain through neuronal pathways such as olfactory or trigeminal nerves. The other way is the indirect transport of drugs through the vasculature and lymphatic system, leading to the brain crossing BBB [70]. Drug absorption from nose to brain may not be limited by one single mechanism, but may involve several pathways.
- Olfactory Pathway: Major routes of drug transport from the olfactory pathway subdivided into four different categories: intra-and extra-neuronal pathways and paracellular and transcellular pathways.

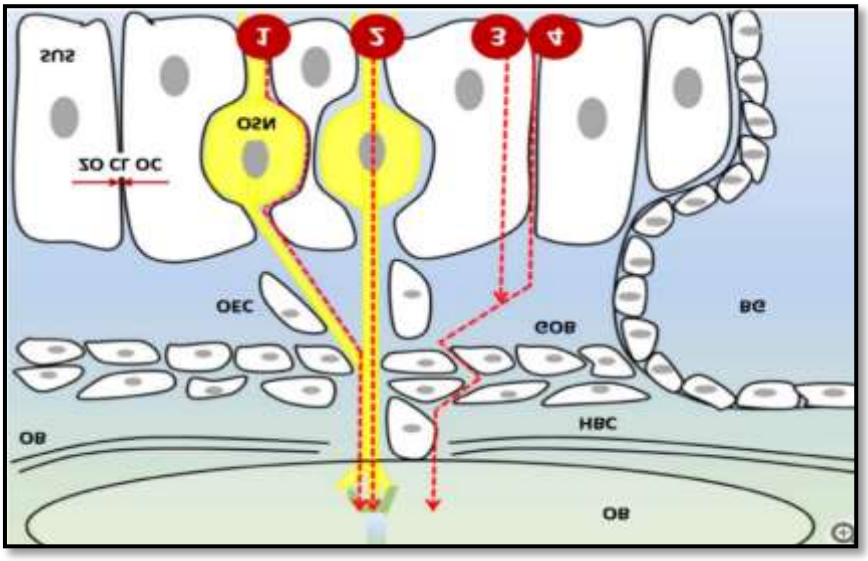

Fig 1: Four different routes of nose-to-brain drug delivery through olfactory mucosa. (1) Extra-neuronal pathway (2). Intra-neuronal pathway (3). Transcellular pathway (4). Paracellular pathway. The drug has to pass tight junctions (marked with red arrows) such as ZO, CL, and OC to travel through the intercellular space. N2B delivery is a mixture of these different pathways. Abbreviations: ZO: zonula occludens; CL: claudin; OC occludin; SUS: sustentacular cells; OSN: olfactory sensory neuron; OEC: olfactory ensheathing cell; GOB: globose basal cells; HBC: basal cells; BG: Bowman's gland; CP: cribriform plate; OB: olfactory bulb.Modified form[71].

Olfactory neurons play a major role in the N2B delivery system. Therapeutic moieties can undergo endocytosis by OSN and form vesicles, leading to the intracellular axonal transport along the neurons, cross the cribriform plate, and to the olfactory bulb. Once they reach the brain, they will undergo exocytosis and will be distributed in the CNS [72]. The diameter of the human olfactory axon is between 0.1–0.7 µm, which makes it one of the smallest axons in the CNS [73]. This small diameter suggests that only small molecules within this range can be transferred through this intracellular axonal transport. Another limitation of intracellular axonal transport is the delayed-release. The mean speed of axonal transport is 25mm per day, which means that it may take hours and days for active moieties to be delivered to the brain [74]. Since many studies showed a rapid delivery of molecules through intranasal administration, it suggests that this pathway may not be the predominant one [75].
An extra-neuronal pathway of molecules occurs by crossing the gap between the OSN and the SUS in

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the epithelial layer. Then they reach the lamina propria, and are incorporated in the cleft between the axons and the OECs [76]. The active substances need to cross a tight epithelial junction to reach the cleft, but there is some gap due to the neuronal turnover in the olfactory epithelium, which allows the drug transport to occur, even for larger moieties [77].

A paracellular pathway occurs by crossing the olfactory epithelium through the gap along the SUS and crossing the basement membrane. Instead of incorporating in the cleft, the therapeutic molecules can reach the subarachnoid space and get delivered to the brain by crossing the blood-CSF barrier. This route does not require drugs to bind to receptors, and it is particularly suitable for hydrophilic and small molecules [78]. A transcellular pathway occurs by receptor-mediated endocytosis or passive diffusion of inhaled molecules through the membrane of the SUS [79]. This pathway is suitable for hydrophobic molecules.

- Potenital challenges for nose-to-brain delivery: Nose-to-brain delivery has many advantages, including bypassing BBB, less systematic side effects, and increasing patient compliance using a non-invasive approach. However, there are a few challenges, such as optimizing mucus penetration and mucociliary clearance (MCC).
- Cilia and Nasal Mucus Transport: There are motile and non-motile cilia in the nasal cavity. Motile cilia are mostly present in the respiratory epithelium, whereas non-motile cilia are prevalent in the olfactory epithelium. Motile cilia have a motor protein called dynein, which generates motion, and non-motile cilia play roles in sensory function and transportation. A small portion of respiratory mucosa is present in the olfactory region, allowing mucus transport in the olfactory region [80].

Nasal mucus consists of about 95% water, 2~3% mucin, 1% salts, and other cellular debris such as DNA, albumin, immunoglobulins, and lipids [81]. As described earlier, mucus is secreted by goblet cells and Bowman's glands in the respiratory and olfactory epithelium, respectively, at the rate of 1.5~2 L daily. It is known to have antimicrobial and humidifying effects as wells as providing surface electrical activity. Mucus has a mesh-like structure that allows the penetration of particles less than 1 µm in diameter [82]. Therefore, therapeutic moieties need to be small enough to penetrate the mucus. Mucus can also perform interaction filtering, regardless of the size of particles. These interactions include electrostatic forces, hydrophobic, and Van der Waal's bonds [83]. Due to these interactions, lipophilic drugs have more difficulty penetrating the mucus layer than hydrophilic drugs.

- Mucociliary Clearance: Mucociliary clearance (MCC) is an interaction between the cilia and mucus layers, which helps inhaled toxic substances to adhere and transport toward the nasopharynx and gastrointestinal tract [84,85]. There is an inter-individual difference in MCC, but the speed is estimated to be 6 mm/min on average. MCC is one of the major factors to consider for N2B delivery since it can affect drug bioavailability. Drug formulation should be able to stay long enough to penetrate the mucus and adhere to the local nasal epithelium before being washed away. Once the inhaled molecules cross the mucus, they have good permeability to the nasal epithelium [86]. MCC can vary based on environmental and pathological factors. Decreased mucus viscosity, increased mucus production, and increased ciliary beat frequency will increase MCC. In contrast, the inhalation of sulfur dioxide, smoking, reduced temperature in the nasal cavity, and thickened mucus will decrease MCC. Asthma, rhinitis, allergy, and sinusitis can change MCC by affecting ciliary beat frequency or mucus production [87]. MCC can also be influenced by drugs that affect ciliary beat frequency. Anesthetics, cholinergic inhibitors, alpha-adrenergic receptor agonists, corticosteroids, and anti-histamine drugs inhibit MCC, whereas beta-adrenergic agonists and cholinergic agonists increase the ciliary beat frequency and stimulate MCC. Therefore, N2B delivery may have variable bioavailability in the brain, depending on patients' physiological conditions and medications.

➢ Advantages of nasal drug delivery system[25,26,27]

- Do it quick
- It is non-invasive and easy to manage.
- Cross the blood-brain barrier.
- Do not use chemical degradation in the digesti ve system.
- There is no hepatic first pass metabolism. Nasa l bioavailability of small doses is good.

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- The bioavailability of large drug molecules can be increased by better absorption.
- Drug candidates who are allergic to the oral ro ute can achieve nasal administration.
- Other parenteral methods, especially for protei ns and peptides.
- Provides long-term treatment convenience to patients.
- Improve bioavailability.
- Since it is consumed less, side effects are reduc ed.
- Improve patient comfort and compliance.
- Self-management skills.
- It can be sent directly to the organs in the body and the central nervous system. Reduce the risk of overdose.

➢ Limitations of nasal delivery system [28]

- It is affected by pathological diseases.
- This is how big changes are seen.
- Medicines such as budesonide and azylatine can cause nasal irritation.
- AT this intranasal distribution volume is limited to 25-20 uL.
- Smaller area for absorption compared to the intestine.

➢ Pharmacokinetics of nose-to-brain delivery:

Drug absorption through N2B delivery, as distinct from a conventional pathway for brain delivery (oral, parenteral, and transdermal), requires specific pharmacokinetic indexes to measure its effectiveness.

Drug targeting efficiency (DTE) is a parameter that represents the efficiency of the drug to reach the brain via the intranasal route relative to that obtained via the systemic route (1). AUC is the area under the curve representing drug concentration over time for the duration of the study [88]. Values can range from 0 to + ∞, and the values above 100% indicate better efficient brain targeting through IN than IV. DTE does not describe which pathway contributed to the drug concentration in the brain. Instead, it implies that intranasal administration leads to higher brain bioavailability than intravenous. To calculate whether intranasal delivery directly leads drugs to reach the brain or not, we can use direct transport percentage (DTP). DTP is a percentage of the dose reach to the brain via IN compared to the overall delivery of the drug to the brain (2). It represents the drug fraction from direct transport to the brain administration.To calculate whether intranasal delivery directly leads drugs to reach the brain or not, we can use direct transport percentage (DTP). DTP is a percentage of the dose reach to the brain via IN compared to the overall delivery of the drug to the brain (2). It represents the drug fraction from direct transport to the brain.

$$DTP(\%)_{(IN)} = \frac{AUC_{BrainIN} - F}{AUC_{BrainIN}} \times 100$$

F is the brain AUC fraction from the systemic circulation (indirect pathway) (3)

$$F = \frac{AUC_{BrainIV}}{AUC_{BloodIV}} \times AUC_{BloodIN}$$

The values of DTP can range from -∞ to 100%. A positive DTP value indicates a contribution of the direct N2B pathway to the drug levels, whereas 0 or negative values indicate the drug prefers to be delivered to the brain through systemic circulation after IV administration. These quantitative data help build advanced PK-PD models to predict CNS concentration for N2B delivery [89]. One limitation of DTE and DTP is that poorly permeable drugs to BBB will lead to high values, so it does not always correlate to high bioavailability in the brain.

$B\%_{Brain\ IN/IV}$ is used to measure the drug accumulation in the brain from IN compared to that of IV (4). Values above 100% indicate a better brain drug accumulation through IN administration.

$$B\%_{Brain\ IN/IV} = \frac{AUC_{BrainIN}}{AUC_{BrainIV}} \times 100$$

Relative bioavailability $_{Brain}$ is a measure of brain drug accumulation with nano system IN compared to drug solution IN (5). Since many N2B delivery systems use nanocarriers to deliver drugs, it may be necessary to calculate the effectiveness of the nano system compared to that of free drug solution.

$$Relative\ bioavailability_{Brain} = \frac{(AUC_{BrainIN})_{nanosystem}}{(AUC_{BrainIN})_{solution}} \times 100$$

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Values above 100 will indicate a better drug accumulation with the nano system than the drug solution. Using this relative bioavailability concept, we can also compare the relative DTE and DTP of the nano system and drug solution using the following equations:

$$RDTE\% = \frac{DTE\%_{INnanosystem}}{DTE\%_{INsolution}} \times 100$$

$$RDTP\% = \frac{DTP\%_{INnanosystem}}{DTP\%_{INsolution}} \times 100$$

➢ The potential role of nanotechnology for nose-to-brain-delivery:

Pharmaceutical nanotechnology has been widely used to deliver therapeutic molecules to the targeted area. The size of the particles is in the nano range (1–1000 nm), and these particles typically form a colloidal dispersion [90]. The use of nanotechnology in N2B delivery is very promising. It can increase the residence time of the drug at the site of absorption, promote its mucosal permeation and cellular internalization, increase drug solubility, control the release of the encapsulated drug, and reduce systemic side effects by decreasing the drug distribution to the non-targeted area. All these characteristics favor the use of nanoparticles (NPs) for N2B delivery [91].

Although nanotechnology has been widely used in drug delivery for its favorable characteristics, the effect and accumulation in the human body should not be neglected. Once nanocarriers enter the biological system, proteins, lipids, and other biological molecules in the body will be adsorbed on the surface of nanocarriers and form the so-called "biocorona" [92]. The biocorona can alter physicochemical properties such as size, shape, and hydrophilicity of original nanocarriers through nanoparticle-biomolecule interactions [93]. Also, the pharmacokinetic profile, such as cellular uptake, half-life, and distribution can be modified [94]. The biocorona can be recognized by complement receptors on macrophages and undergo increased cellular uptake and accumulated in the liver and spleen [95]. Some studies showed that metal-based nanoparticles may cause negative effects on the cardiovascular system and the nervous system. Increased inflammatory cytokines, arrhythmia, as well as increased oxidative stress and neurotoxicity could occur after the administration of titanium dioxide and silica nanoparticles, which are a commonly used nano-formulation in the industry [96]. Since peptides and lipids are present in the nasal mucus, there is a high chance that the inhaled nanoparticles will form the biocorona and may alter their physicochemical properties and cellular uptake.[97]

➢ Physicochemical Properties That Can Affect Nose-To-Brain Delivery:

1. Particle size:Particle size is one of the most crucial factors in the N2B delivery system. As stated above, the diameter of the OSN is between 0.1–0.7 µm, which limits the particle size to the nano range. Also, smaller particles have less resistance to the mucous membrane penetration, as mucus forms a mesh-like structure. There are several studies that show that particle size can be a limiting factor for N2B delivery. Mistry et al. formulated chitosan or polysorbate 80 coated polystyrene NPs with a 100 and 200 nm particle size [98]. The study showed that nonmodified polystyrene NPs and polysorbate 80 coated NPs with the particle size of 100 nm were more suitable for olfactory epithelial cells than those with 200 nm diameter. However, none of the formulations were found in the olfactory bulb. Based on this study, the authors concluded that the optimal nanoparticle diameter faxonal transport is less than 100 nm.

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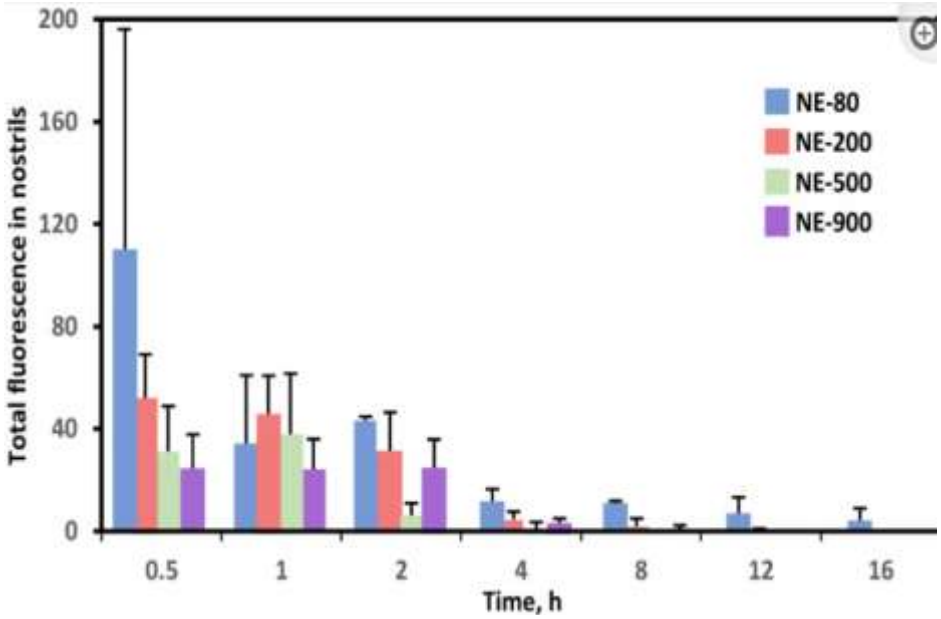

Fig 3 Quantification of total fluorescence of nano emulsions (NE) with different sizes (80, 200, 500, 900 nm) in nostrils. Replotted using data from [99].

2.Surface charge: The nasal mucosa membranes are negatively charged in general, so positively charged particles are more likely to interact with nasal mucosa through electrostatic force [100].This will lead to increased residence time and bioadhesion to the nasal epithelium. Due to this characteristic, many researchers have used positively charged carriers such as chitosan and its derivatives to increase drug bioavailability for N2B delivery. Mistry et al. showed that chitosan-coated carriers caused nanoparticles to interact with extracellular mucus for an extended period of time, allowing nanoparticles to cross the nasal epithelium paracellularly. In a study by Gabal et al., cationic nanostructured lipid carriers (NLCs) with similar absolute ZP (+33 mV) had higher absolute bioavailability than anionic NLCs after intranasal administration (77.3% vs. 44%), but slightly lower drug targeting efficiency (128.6% vs. 158.5%) [101].

Not only can the charge of NPs increase the residence time, but it can also impact its delivery pathway. Bonaccorso et al. formulated rhodamine B labeled polymeric nanoparticles with an opposite surface charge to evaluate the bioavailability after intranasal administration in mice. The study used poly-lactide-co-glycolic acid (PLGA) NPs to make negatively charged nanoparticles, and used chitosan to make them positively charged. The mean size of both types of NPs was smaller than 250 nm. The negatively charged NPs arrived at the rostral subregions after 8 h of IN administration and were further transported to the caudal region in 24 h. However, positively charged NPs arrived in caudal sub-regions after 24 h of IN administration and were transported to the rostral area (Figure 6). Since the fluorescent signal from negatively charged NPs appeared in early time points, it is suggested that they were delivered via the olfactory pathway with both intra and extra-neuronal pathways. On the other hand, positively charged NPs transported through the trigeminalnerve as the fluorescent signalstrong after 48 h in the posterior brain. The suggethat the surface charge influences the delivery pathway and the time to reach the brain [102].

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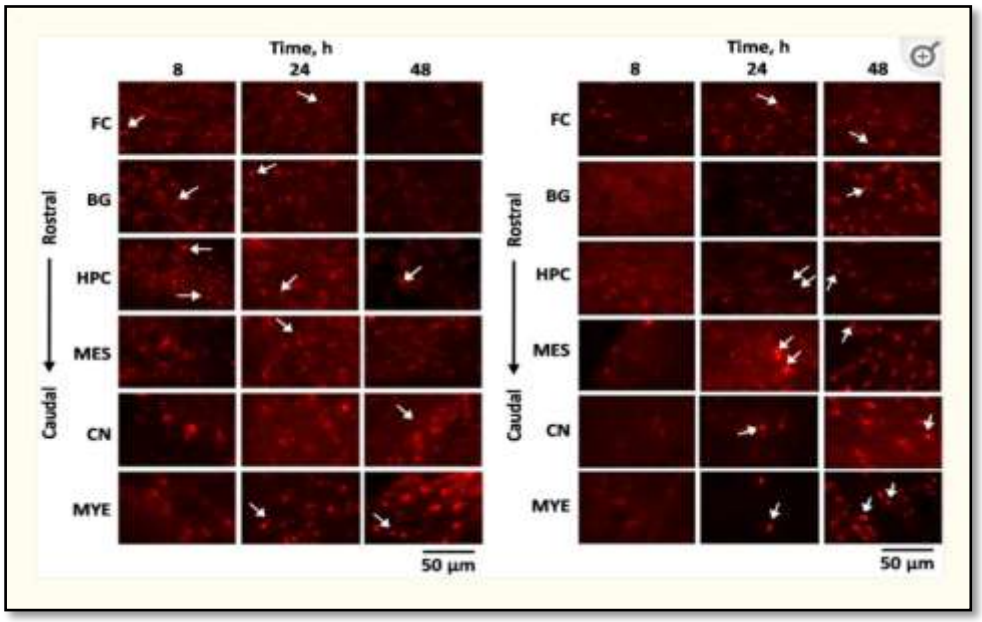

Fig 4 Localization of the negatively charged NPs (left panel) and positively charged NPs

2.Lipophilicity: Hydrophobic carriers are more likely to increase mucoadhesion as they form hydrophobic bonding with mucin's hydrophobic domains and thus increasing the residence time. However, if the carrier is too hydrophobic, it will not penetrate the mucus due to hydrophobic interaction with mucin and will be cleared by MCC [103]. Therefore, it would be essential to have a fine balance between increasing the residence time and mucus penetration. Not only can hydrophobicity affect mucoadhesion, but it also may determine the pathway of N2B delivery and distribution in the brain, just like the charge of the nanoparticle. Kanazawa et al. designed an arginine-based peptide and conjugated it either with hydrophobic stearate (STR) or hydrophilic PEG-PCL copolymer to obtain stable micellar formulations. The study used Alexa-dextran for fluorescent imaging. The fluorescent images showed that both formulations had higher fluorescent activity in the nasal mucosa and the brain than the control (Alexa-dextran). The nanoparticle complexed with hydrophilic peptide had higher intensity in the trigeminal nerve and more fluorescence spreading, which implies that it was transferred via multiple pathways. Also, its fluorescence was widely spread to the brain over time, suggesting the involvement of CSF in its delivery. On the other hand, the nanoparticle with hydrophobic peptide was highly focused on the olfactory bulb in the forebrain, and there was no drug movement to the hindbrain. These results suggest that the hydrophobic peptide increased the adhesiveness with the nasal epithelium and increased the residence time in the olfactory bulb [104]. The study supports the hypothesis that the lipophilicity of the nanoparticles may control the drug delivery pathway.

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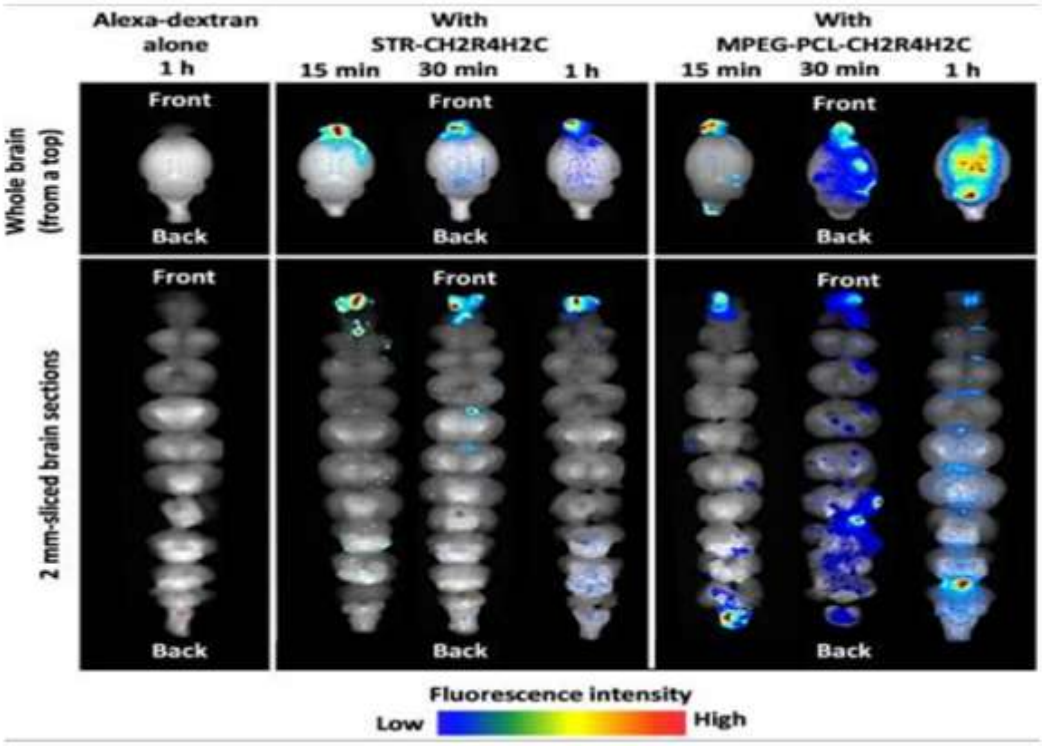

Fig 5 Dynamics of Alexa-dextran in brain tissue[104]

➢ MIGRAINE:

Migraine is usually treated with medicatio n, but some patients cannot tolerate severe pain and /or medication due to side effects or contraindicatio ns due to comorbidities such as cardiomyopathy or asthma. Some patients want to avoid taking medica tions for other reasons. Thereforenonpharmacologi cal treatments such as massage, physical therapy, a nd chiropractic care may be alternative treatments. Massage therapy in Western culture uses classical massage, massage points, myofascial release, and o ther muscle relaxation techniques, as well as other t reatments that work on weak muscles. While moder n physical therapy focuses on rehabilitation and exe rcise, manual therapy focuses on physical theraputi c work, stretching, strengthening and strengthening **,** and management strategies**.** Activity is generally defined as physical movement of a joint.[29]

The two most common chiropractic metho ds are Diversity Chiropractic and Gonstead Chiropr acticused by 91% and 59% of chiropractors, respec tively.[30] Spinal manipulation (SM) a non-invasive method that uses directional high-velocity, low amplitude impulses applied directly to specific joints over and above the body reflexes, but not beyond the anatomical limit. [29]

Migraine is a common and common condition that affects 28 million Americans, including approximately 18% of American women and 6% of American men. [31,32] Migraine is a cause of absenteeism and poor work performance and reduces quality of life. 3-6 This situation costs US employers approximately13 billion dollars a year.[33]

Although they are common and associated with serious disability, migraines have historically been underdiagnosed and undertreated. In the 1989 US Migraine Survey, only 16% of survey-identified migraine patients had seen a doctor about headaches in the past year, and only 38% of people reported being diagnosed. with migraine from the doctor. [34-35] Although 96% of migraine sufferers use medications to treat their headaches, the majority (59%) use only over-the-counter medications rather than prescription medications (37%).[36] Severe pain and disability in migraine patients whose doctor has not diagnosed migraine is an indication that they have a health problem.[37]

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➢ Neurobiology of migraine headache:

We will discuss recent advances in migraine neurobiology based on established guidelines, which are briefly summarized and described here [38,39]. Pain sensitivity in the skull is usually limited to the meningeal nerve, which is densely innervated by the nociceptive afferent fibers of the eye of the trigeminal nerve. It is generally believed that the onset of migraine is due to the activation of afferent nerves.

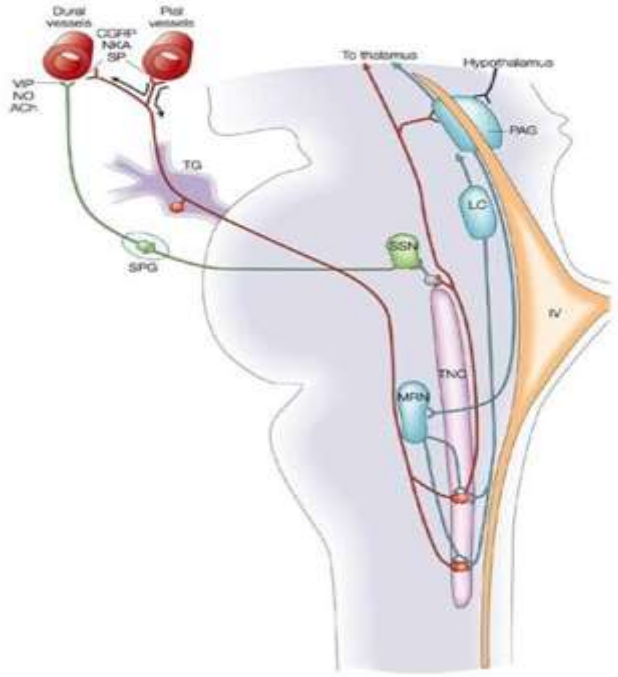

Fig 6: Neuronal pathways involved in tri-gemino vascular activation and pain processing

Activation of the meningeal trigeminal nerve in different animal models, including nonhuman primates.Afferent nerves give rise to second-order dorsal horn neurons in the caudal trigeminal nucleus (TNC) and the two uppermost parts of the cervical spinal cord. Impulses then travel to brain structures involved in visual perception, including various thalamic nuclei and the ventrolateral region of the caudal periaqueductal gray area (PAG). PAG participates in pain in the heart not by increasing projections towards the thalamus, but also by descending modulation (mainly inhibition)5 of nociceptive afferent information. Activation of the TGVS also causes the release of vasoactive neuropeptides present in its peripheral nerves, specifically calcitonin gene-related peptide (CGRP). In animal research, the neuropeptides released from the trigeminal ganglion stimulate meningeal vasodilation (due to CGRP only), plasma extravasation and degranulate mast cells, and secrete other pro-inflammatory substances in the dura mater Neurogenic Trigeminal activation at the level of the salivary nucleus It can cause meningeal vasodilation by activating the parasympathetic sensory reflex (Figure). Increased CGRP levels are observed in peripheral and intracervical blood during migraine attacks. They return to normal after treatment with [40,41] and>sumatriptan level sand then they reduce the headache [42]. > two issues are opened in the neurobiology of migraine the first is the main cause of migraine, that is, the mechanism of tgvs activation - the second is the mechanism of pain that occurs after tags activation.

➢ Primary cause of the migraine headache:

According to the once accepted "vascular theory of migraine", the symptoms of migraine aura are caused by alternation of ischemia by vasoconstriction, while headache is caused by abnormality and vasodilation of intracranial nerve blood vessels. There is mechanical activation of perivascular sensory fibers. However, brain activity during an ma attack shows that the spread of

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cortical hyperemia is followed by hypoemia, which exceeds the aura symptoms and extends to the 9th stage of the headache. There is also no clear evidence that the diameter of the central nervous system increases during migraine. Blood vessels.[43] These findings make the vascular theory impossible for most migraine patients.[44] it is now generally accepted that the primary cause of migraine is in the brain, but the cellular and molecular mechanisms are still unknown. Recent findings point to two main mechanisms: csd and brainstem generators.

- Neurobiology of migraine aura and csd:

In1941, neuropsychologist Karl Lashley studied the development of his own blindness, which was limited to slow flashing movements across the visual field (figure 2). It is believed that scotomas arise from a weak visual cortex, whereas tremors arise from a strong limbic region of the cortex. Neural effects are thought to spread slowly (about 3 mm min-1) in the Scortex.[45] a few years later, Leao reported the electrophysiological correlation of rabbit cerebral cortex [46] and named it csd. In animals, csd can be induced by local stimulation (electrical, mechanical, or high k+) of the cerebral cortex, with the occipital region being larger than other regions. It is characterized by a delay (in seconds) that promotes strong neuronal depolarization of slowly propagating waves (2-6 mmmin-1).

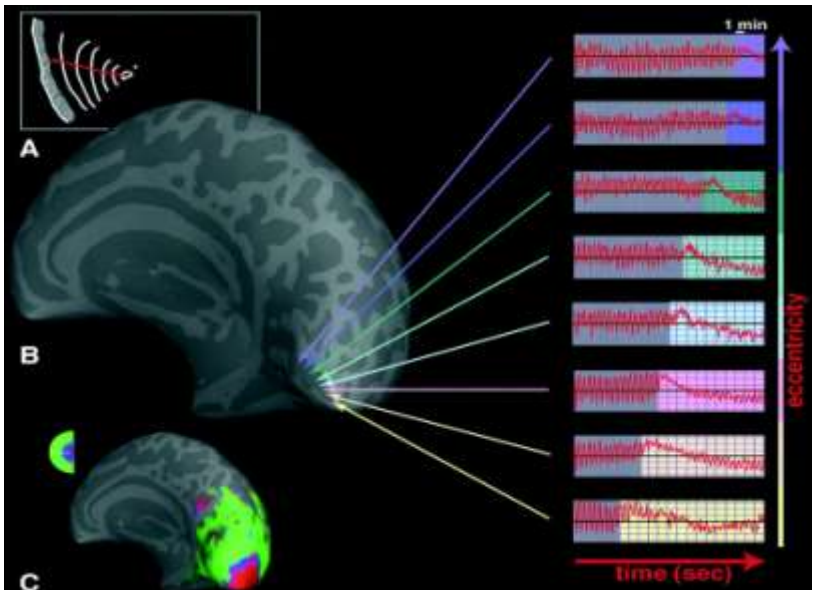

Fig 7: Spreading suppression of cortical activation during migraine aura.

Intense spike activity as it progresses into the tissue, followed by neural suppression that can last for minutes [47]. The depolarization phase is associated with an increase in regional cerebral blood flow (CBF), whereas the phase of reduced neural activity is associated with a reduction in rCBF. The similarities between migraine visual aura and CSD led to the hypothesis that CSD was responsible for the aura. This hypothesis was questioned because electroencephalographic recordings during surgery did not show CSD in humans. Whereas it is clear that CSD is more difficult to elicit in human than in rodent cortex changes in several parameters that are similar to those typical of CSD in animals were measured in the brain of a patient with head trauma [48]. Moreover, transient electrocorticogram suppressions that are consistent with CSD were recently measured in the injured neocortex of several patients [49]. CSD was induced in nonhuman primates and direct current (DC) excursions were measured, but prolonged hypoperfusion after local hyperemia was not observed [50].

Accompanied by motor or other mental disorders may also result from CSD-like events [53,54] in Fig3 CSD is measured during spontaneous or visually triggered visual auras in patients. DC MEG changes were similar to those previously measured when moving the grooves in the CSD20 animal model. Demonstration of cerebral vascular

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and magnetic field correlations in CSD in migraineurs supports the conclusion that the aura is from the prison. Auras accompanied by motor or other mental disorders may also result from CSD-like events in the primary motor or sensory cortex. Recently, blood oxygenation level-dependent functional magnetic resonance imaging (BOLD fMRI) demonstrated CSD neural changes in the cortex of migraine patients when they saw auras [51,52]. A physical correlation was established between the first sign of aura perception (tremor starting in the left paracentral visual field) and the first increase in the mean BOLD signal (sensation of cortical hyperemia). Lateral decreases in were temporally associated with darkness after light exposure. BOLD signal changes first appeared in the extrastriate cortex (area V3A) and were opposite to the visual changes. It then gradually moves to different parts of the visual cortex and represents the peripheral field, such as the development of tremors and scotomas from central vision to peripheral vision (Figure 2). More direct evidence that CSD is visual perception comes from magnetoencephalography (MEG). Neuronal depolarization in CSD is measured during spontaneous or visually triggered visual auras in patients. DC MEG changes were similar to those previously measured when moving the grooves in the CSD20 animal model.[55,56] Demonstration of cerebral vascular and magnetic field correlations in KSD in migraineurs supports the determination of aura as a result of treatment programs.

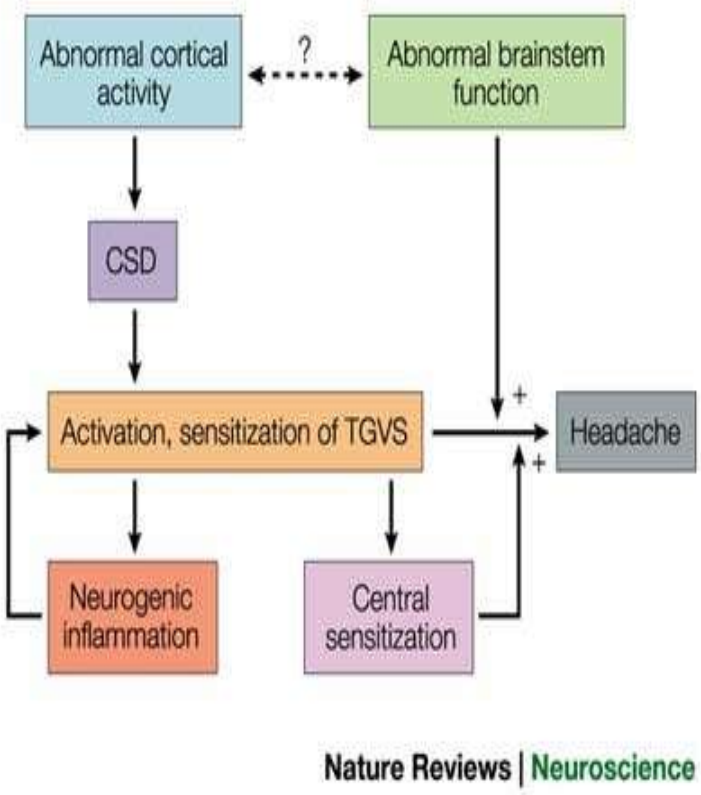

Fig8 pathophysiological mechanisms in the generation of migraine headache.

The pathogenesis of migraine is generally thought to involve peripheral and central activation of the trigeminal vascular system and cortical transmission. The underlying neurophysiological basis of migraine is thought to be depression. aura However, much is still unknown about the specific course of the disease and there are currently few legal treatments.

Migraine treatment includes intensive and preventive medications as well as a variety of non-drug treatments.[60] Despite these treatment options and extensive diagnostic procedures, treatment

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remains optimal; Misdiagnosis and undertreatment of migraine is a public health problem.[61] Population-based data from Europe show that only 2-14% of eligible people receive migraine medication,[62] a finding that is alarming and needs to be done around the world. answer. A good method must be made to facilitate diagnosis and evidence to manage.

➢ NASAL DRUG DELIVERY SYSTEM:

Intranasal delivery often provides an effective method of administering a variety of medications. Suitable for local and distribution of various chemical compounds. Therefore, there are many studies showings that the nasal cavity is a valid place for the administration of various drugs. It is effective in local treatment, diseases and the central nervous system.

- Local: Intranasal administration of medicines is the natural choice for the treatment of topical nasal Disorders. Among the most common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In these cases, the intranasal route is the primary option for drug delivery because it allows a rapid symptom relief with less side-effect.

- Systemic: Intranasal drug delivery is an effective drug delivery method that can replace oral and intravascular routes. As a result, the number of drugs designed to act via nasal formulations has increased significantly. Some of the best examples are analgesics [morphine], heart drugs propranolol and carvedilol, hormones levonorgestrel, progesterone and insulin, antibiotics Indomethacin and ketorolac, and Antiviral drug.

➢ Various formulations that can be given by nasal route for nose to brain delivery:

Medication use, prescribing information, p atient demographics, and market preferences all inf luence dosage form selection:

A. Nasalliquidformulations:

The most popular nasal forms are liquid medications. They rely mostly on water samples. Its moisturizing effects are very simple and beneficial, as many allergies and chronic conditions are often associated with inflammation and dryness of the mucous membranes. The main disadvantages of water-based food materials are lack of microbial stability, irritation and allergic rhinitis due to necessary preservatives affecting mucociliary function[105]

I. Rhinylecatheterandinstillation:

The drops are delivered to only certain areas of the nose using a catheter. Put the medicine into the tube, put one end into your nose and blow the other end with your mouth to ensure that the medicine passes into your nose.

II. Nebulizersthatusecompressedair:

Atomizers using compressed air refer to atomizers containing compressed air. All nebulizers share a similar principle in that they use oxygen, compressed air, or ultrasonic energy to disperse the medication or suspension into small aerosol droplets to be inhaled directly through the mouth of the device.

III. Asqueezedbottle:

Bottles that are squeezed into the nose are often used to deliver decongestant. These include bright plastic containers with direct spray. When the plastic bottle is pushed, the air is squeezed through the small nozzle, atomizing a certain amount of air in the plastic bottle. By applying more pressure, a vacuum is created in the bottle. When using this technique, the nasal passages are often aspirated and the fluid becomes infected.

IV. Metered-dosepumpsprays:

Metering pumps are used to administer most nasal medications on the market, including solutions, emulsions or suspensions. For more information about nasal sprays, see Nasal Sprays and Nasal Sprays. Nasal sprays and nasal sprays are used to deliver medication through the nose and can be used or given as a medication to treat allergy symptoms such as colds and nasal congestion. Although there are many delivery methods, most nasal sprays are injected well into the nose using a pump. Antihistamines, corticosteroids, and topical medications constitute the three main groups of local effects. The metered spray is equipped with a container, a pump with valve and an actuator.

B. PowderDosageForms:

V. Drypowder inhaler:

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are

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bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales · These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are many types of such devices. The dose that can be administered in a single breath is usually less than a few tens of milligrams because larger powders can cause coughing.

C. PressurizedMDIs:

VI. Ametered-doseinhaler(MDI):

Dry powder is used less frequently for nasal control. The absence of preservatives and improved formulation stability are two advantages of this form. Application of the powder will result in a more prolonged interaction with the nasal mucosa compared to the solution.

1. Insufflators:

Insufflators are devices used to inhale medications; It can be done using a tube or pipette that carries chemicals, and sometimes a syringe. Due to insufficient particle dispersion, the particle size obtained with these machines is usually higher than the powder, which has a different size in the initial deposition area. Many insufflator devices use prefilled powders in capsules. Asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases are often treated with it. Medications in metered-dose inhalers to treat asthma and COPD are usually bronchodilators, corticosteroids, or both. Other medications, such as mast cell stabilizers, are used less frequently but are still available through MDI (cromolyn or nedocromil). Advantages of MDI include its portability, size, availability of multiple dosages in a single procedure, stable dose, accurate dose, content preservation, and rapid use. More than 99% of MDI doses usually cause a reaction. The formulation contains the drug dissolved or suspended in a propellant that is released in a metered dose when activating the device. When heat does not translate into droplets, an aerosol containing small amounts of chemicals is formed and the droplets evaporate rapidly.

D. NasalGel:

This method did not gain traction until the recent invention of precision pipettes. Advantages of nasal gels include reduced postnasal drip due to higher viscosity, reduced taste due to reduced swallowing, reduced formulation leakage, reduced irritation due to the use of soothing/emollient excipients, and mucosal targeting for better results. Because the dosage and viscosity of the preparation are limited, the location of the gel in the nasal cavity depends on the method of application. It is only possible to distribute it within the nasal cavity and apply it directly without using a special application method. Recently, the first nasal gel containing vitamin B12 was released. Drug solutions are available in the form of metered-dose nebulizers, nasal sprays, and eye drops for oral inhalation. The volume and concentration of drug in the dosage form affect the amount of active ingredient released. After dissolving nitroglycerin in saline and administering it intranasally at a dose of 0.8 mg/ml, the therapeutic concentration of nitroglycerin reaches 3 ng/ml in central venous blood, 1.7 ng/ml in arterial blood, and 1.7 ng/ml in peripheral venous blood. . 10 minutes. Up to 0.4ng/ml. 2 minutes. Many researchers have reported the influence of the design of nasal inhalation, including the dose of the active ingredient, pH, and osmolarity of the drug. The Latin word “in situ,” which can be translated as “in place,” is also used to refer to the transition phase. In situ gelling is a method of delivering drugs in solution before they are distributed throughout the body. However, after application, gelation occurs in situ and a gel is formed. There are several ways to deliver the gel in the field, including oral, urinary, rectal, vaginal, topical, and nasal.

➢ APPLICATIONS:

1. Treatment of Alzheimer’s Disease:

AD is characterized by cognitive degeneration and is an incurable chronic, progressive disease of old age. In AD, plaques form in the hippocampus, a structure deep in the brain that helps encode memories, and in other areas of the cerebral cortex used for thinking and decision-making. Approximately 5.8 million peopl age 65 and older in the United States have Alzheimer's disease. 80% of them are aged 75 and over. There are approximately 50 million people living with dementia worldwide, and approximately 60% to 70% of them have Alzheimer's disease. This disease is the sixth leading cause of death in the US overall and the fifth leading cause of death for

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those aged65 years and older [106].

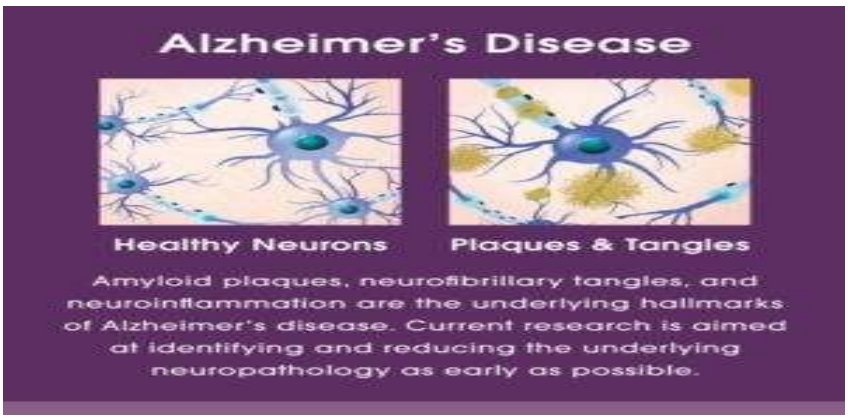

Figure 8. Comparison between Normal Healthy

Brain and Alzheimer's Disease brain.

Reported histopathological characteristics of AD are extracellular aggregates of amyloid-β (Aβ) plagues and intracellular aggregation neurofibrillary tangles (NFTs). Aβ plagues develop initially in basal, temporal, and orbito frontal neocortex regions of the brain and in later stages progress throughout the neocortex, hippocampus, amygdale, diencephalon, and basal ganglia. In critical cases, Aβ is found throughout the mesencephalon, lower brain stem, and cerebellar cortex as well. The deposition of Aβ is increased in patient with AD when there are mutations in the amyloid precursor protein (APP) and presenilin (PS). When the concentration of Aβ is high, insoluble amyloid fibers are formed in the brain.

2. Treatment of Parkinson's Disease:

The arm will not swing while walking. Your speech may be soft or slurred. Although there is no cure for Parkinson's disease, medications can improve your symptoms. In some cases, your doctor may recommend surgery to control certain areas of the brain and improve your symptoms. Worldwide, disability and death from Parkinson's disease are increasing faster than any other neurological disease. Despite the huge impact, there is disparity in resources to control the disease. This brief introduction to Parkinson's disease is intended for policy makers, healthcare managers and planners, physicians, researchers, and people living with the disease. Parkinson's disease and studies will support interdepartmental implementation of new guidelines on epilepsy and other neurological diseases. projects. Parkinson's disease is often associated with enlargement of cells in the substantia nigra of the brain. This area is responsible for dopamine production [107].

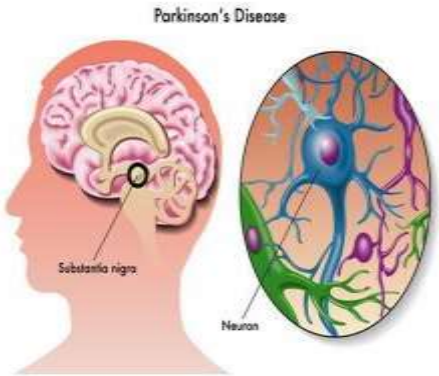

Figure 9.Parkinson's Disease

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3. Treatment of migraine:

It has been proven by many experiments and studies that the nasal application method gives the best results in migraine treatment, has better drugs in the brain and provides better bioavailability in the brain. This process may have an impact on limiting the side effects of drug therapy. Although migraine is usually a vascular dysfunction or neurological dysfunction, there are different opinions about the treatment of migraine. Sumatriptan is an oral medication that is rapidly absorbed but not completely absorbed and is the first to enter metabolism, resulting in a 14% lower BA. Transport of Sumatriptan across the BBB is poor. Therefore, the intranasal administration method provides an effective, non-invasive, alternative and effective way of delivering drugs to the brain [108].

4. Treatment of Amnesia:

Mice were trained to improve memory and recall memories faster. Microemulsions and mucoadhesive microemulsions of tacrine were evaluated for their pharmacokinetic-pharmacodynamic effects on the brain and improvement of memory in rats with scopolamine-induced amnesia. The results showed that tacrine entered the brains of mice to a greater extent, and mice with scopolamine-induced amnesia recovered from memory loss more quickly. Microemulsions are used intranasally.

5. Treatment of epilepsy:

Various types of researches have been done to provide drug delivery through nose in these diseases. Intranasal administration allows transport of the drug to the brain circumventing the BBB, thus providing the better option to target drug to the brain with quick onset of action in case of emergency epilepsy[36]. Mucoadhesive microemulsion for the antiepileptic drug clonazepam has been formulated[37]. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to 8 hours following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2-fold higher, indicating larger extent of distribution of the drug in the brain. Microemulsion containing valproic acid resulted in fractional diffusion efficiency and better brain bioavailability efficiency[109]. Hence microemulsions are the promising approach for delivery of valproic acid for treatment of epilepsy. This study showed high brain targeting efficiency of prepared clobazam microemulsion and delayed onset of seizures induced by pentylene tetrazole in mice after intranasal administration of developed formulation. Further clinical evaluation of the developed formulation may result in a product suitable for the treatment of acute seizures due to status epileptics and patients suffering from drug tolerance and hepatic impairment on chronic use in the treatment of epileptics, schizophrenia and anxiety.

6. Treatment of antidepressant:

Eucalyptus oil microemulsion was developed for intranasal administration. Eucalyptus oil microemulsion has been proven to provide rapid health, happiness and stress relief. It is also cost effective [110].

7. Treatment of angina pectoris and Neurological deficit: In order to increase the water solubility of nimodipine and facilitate brain stimulation, microemulsions suitable for intranasal application were prepared. The uptake of nimodipine into the olfactory eye by nasal administration is three times higher than that of intravenous administration. After nasal administration, the ratio of AUC in brain tissue and cerebrospinal fluid to AUC in plasma is higher than after injection. Therefore, microemulsion systems are an effective method of delivering nimodipine in the treatment and prevention of neurodegenerative diseases [111].

8. Delivery of proteins and peptides:

Oral administration of the peptide is not possible due to gastrointestinal enzyme degradation and hepatic first-pass interaction. There is growing evidence that the intranasal route of administration may be an attractive and convenient option for delivering certain compounds to the brain. In fact, many peptides are routinely used intranasally in therapy, including luteinizing hormone-releasing hormone, oxytocin, calcitonin, and vasopressin, while others such as insulin, glucagon, growth hormone, growth hormone-releasing hormone, and somatostatin are also available. to be in search.

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