ABSTRACT
Different barriers like a blood-brain barrier in the brain restrict the transport of potential therapeutic elements for direct entry into the brain. For delivery of a wide range of therapeutic drugs directly to the brain can be achieved by direct targeting the brain via an olfactory and trigeminal neural pathway which bypasses the blood-brain barrier hence has gained more importance and considered as an accurate route of drug targeting to brain. Intranasal route transports the drug by delivering it directly to the brain and avoiding the systemic absorption which also avoids the side effect of enhancing the efficacy of nano therapeutics. As these types of drug delivery commonly targeted drug delivery to the brain via nose are complex. Different strategies applied for overcoming these challenges has been covered. Drugs to be transported through this system are usually carried out through nano particulate system known as nanotechnology which helps in transportation of drug particles directly to the central nervous system and participates in drug release through a carrier-mediated system called nano particulate system have been extensively covered within the article. Parallel to this recent advancement in brain targeted drug delivery has been thoroughly explained and characterized. Although direct drug delivery to the brain is a vital challenge for researchers which can be overcome by using different types of strategies that have been covered under this article.

Key words: Nanostructured lipid carriers, Targeting, Intranasal, Brain, Delivery.

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INTRODUCTION
Based on recent scenario changes in lifestyle, work stress, irregular schedule and other factors such as pollution, environmental free radicals and higher exposure of toxic chemicals lead to several neurological disorders and disease.1,2 There are various neurological diseases, among that promptly growing case of dementia touched threatening level. It is estimated that the population suffering from this disease will be doubled in the next 20 years.3 Due to which it has drawn a lot of attentiveness and concern from the scientific community, where they have labeled this worldwide (25% of cases from Europe followed by 49% and 18% from India and America).4 Neurodegenerative disorder (ND) is a term usually used for conditions that primarily affect the nervous system. Neurodegenerative disorder results in continuous damage to nerve cells which are the building block of the nervous system. The degradation may cause chronic, progressive loss of neurons which decreases the cognitive abilities of the brain such as the mental functioning of the brain (dementia) or movement problem (ataxia). It is a challenge to traditional drug delivery approaches for the effective delivery of drugs to the brain and central nervous system (CNS) because of the protective anatomy of the brain. Clinical potency of the therapeutic agent is not only depending on its bioavailability but also on its ability to penetrate the protective layer, i.e., blood-brain barrier (BBB) and cerebrospinal fluid (CSF).

There are several invasive techniques like intravenous, intrathecal, intraparenchymal and non-invasive techniques like chemical modification, produg approach, sublingual delivery and conjugation of drugs with ligands and antibody have been used to target the drug to the central nervous system (CNS).5 The olfactory route and peripheral circulation is a linkage between the brain and nose. The intranasal drug delivery route has achieved the interest of researchers as it’s a potential delivery route for targeting the brain.6 Intranasal drug delivery is not a novel approach; it has been used traditionally for the administration of psychotherapeutic and another compound in the name of “Nasya Rasayana.”7 During intranasal drug delivery, the drug molecule is absorbed through the nasal mucosa and reaches olfactory which eases the non-invasive entry of molecule into the brain to achieve the therapeutic effect.8

DIFFERENT STRATEGIES ADOPTED FOR BRAIN TARGETING DRUG DELIVERY
There are various types of drug delivery systems adopted for targeting drugs directly into the brain by overcoming BBB and enhancing the transportation of drug molecules through this barrier (as shown in Figure 1). These strategies are mainly divided into three categories according to their function and characteristic: 1) Invasive technique. 2) Non-invasive. 3) Recent techniques for BBB disruption.

INVASIVE TECHNIQUE
Chemical disruption of blood brain barrier
There are several invasive techniques which are commonly used to disrupt BBB and enhance the delivery of the drug into the brain. Osmotic disruption of BBB is one of the invasive technique in which temporary shrinkage of endothelial cells occurs which leads to the opening of tight junction and causing leakage of the drug to the CNS.9 According to mechanism BBB opening effects of bradykinin are due to activation of B1 receptor and leakage of endothelial cells which are

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It is used to overcome the disadvantage of the intracerebral delivery system. This system employs a continuous infusion method and pressure gradient to administered a large volume of drugs at target tissues via an intracranial catheter. CED has some limitation drug exposure to neighbouring tissue, the problem in designing the optimal formulations and sub-therapeutic level of drug in the targeted area. Combinations of CED with liposome enhance the efficiency of CED for brain tumor targeting.16

**Polymeric wafers and microchip technology**

Improvement in polymer technology led to the expansion of polymeric devices for controlled and targeted delivery of therapeutic moieties. Bypassing the BBB and achieving the control release delivery of drug at the intracranial tumour with the help of polymer device is a big accomplishment in the field of polymeric nanotechnology. Poly anhydride based wafers were inserted into the tumour resection area, crosses the BBB and gradually release the drug and distribute it into the brain and targeted site. Clinically polymeric wafers used local strategy for crossing BBB and providing the sustained release of antineoplastic drugs at the tumour-targeted site. Now According to clinical trials, local drug delivery based on polymeric anhydride polymer gave an efficacious result in animals without major organ toxicity.17

Programmed microchips knew as intracranial devices which are implanted to control the release of drug at the targeted site. There are two different types of chips – a) microelectromechanical system. b) Passive chip. Through these technologies single or multiple doses, delivery can be accomplished. Active microchips are based on microelectromechanical system which comprises a drug-filled reservoir on a silicon chip. It provides a high release of drug at the targeted site.18 Active chip technology allows the development of multiple reservoirs that contain separate drugs to be released at the time or at different time intervals. Passive chip release drug on moderate degradation of polymeric film enclosing reservoir. On-demand of the therapy, these chips also deliver multiple drugs.19

**NON-INVASIVE STRATEGY**

Non-invasive strategy utilizes the endogenous mechanism for the transport of the drug across BBB. It includes the prodrug approach, efflux pump inhibition and chemical modulation of BBB, the alternative route of administration and nano carrier-based drug delivery to the brain.

**Prodrug approach**

In this approach by increasing the lipophilicity character of drug BBB permeation ability can be accelerated. Basically prodrug approach is a process of chemical modification of active pharmaceutical ingredients to modify the lipophilic behaviour and increasing the permeation ability with its water solubility. A targeted prodrug is a combination of chemical constituent and parent drug which is designed to offer an enzyme and transport system at the targeted site for converting it to an active moiety. This approach follows redox chemical delivery for saving the chemotherapeutic potential of mustard alkylating agents. As redox derivative of alkylating agents cross the BBB and stay in the brain for a longer time.20

**Efflux pump inhibition**

Another barrier for constructive drug delivery to the brain is due to the presence of the efflux pump in BBB. Efflux is due to the active p-glycoprotein (p-GP) present on the apical membrane of endothelial cells of BBB which results in poor drug accessibility at the targeted brain tissue. More likely p-GP has a close association with lipophilicity and cationic drugs. Drugs with low molecular weight are the substrate of p-GP and are prohibited to enter the brain. So, inhibition of p-GP efflux is a helpful approach to retain the therapeutic efficacy of the potent drug.21 It was seen that the administration of first-generation p-GP efflux associated

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**Figure 1:** Depicting different strategy used in nasal drug delivery for brain targeting.
with cytochrome P<sub>450</sub> 3A (CYP3A) enzyme inhibitor was toxic. While the second-generation strong P-GP inhibitor showed less toxicity related to issues and the third generation inhibitor which has proved safety and not having any effect on CYP3A enzyme inhibitions. For avoiding the serious adverse effect which was associated with efflux inhibitor, dual therapy of efflux inhibitor is combined with nanoparticles was explored. Combinations of p-GP and multidrug resistance-associated protein (MRP) families are located on the endothelial cell which is responsible for the efflux of the cationic molecule. As the prime function of p-GP and MRP is to protect the brain from entering the harmful chemical substrate which inhibits the entry of drugs to the brain.  

**Cell-based therapy**

Cell-based therapy has retained most attention due to its capability of delivering a variety of drug effectiveness and treating a neurological disorder and brain tumours. In this therapy macrophages and different type of stem cells are used as a carrier for delivery of the drug to the brain. As macrophages can travel through the brain by paracellular and transcellular mechanisms. In the case of brain tumour and some inflammatory conditions, macrophages are engaged and infiltrated towards the brain. However, macrophages are an appropriate candidate for targeted drug delivery of nano particles with some of their special features like diagnosis and imaging of agents to the brain tumors and neurodegenerative diseases. Stem cells can be used as a vector for delivery of cytokines, oncolytic viruses and some suicides genes to the brain.  

**Nanocarrier as a drug delivery system**

In today's scenario nano carrier has got more attention and is the area of interest for researchers due to their capability as the permeation enhancement nano vehicle of a therapeutic molecule across BBB. Based on the study it was found that nanocarrier was having the capability of targeted site-specific delivery of different drug-like anticancer, anti-Alzheimer, anti-Parkinson and protease inhibitor which made them more suitable candidate for the carrier of neurological disorder and brain tumor-targeted delivery. A combination of polymeric nanoparticles and SLN<sub>i</sub> are also effective nano vehicles for increasing the brain targeting efficiency of the drug.  

**Intranasal drug delivery**

It was found that drugs administered through the nasal route of administration were absorbed into the systemic circulation. While the drug absorption within nasal respiratory epithelium follows transcellular and paracellular absorption with carrier-mediated transport and absorption of the drug through transcytosis mechanism. However, it was a big challenge of delivering the drug through the nasal cavity to the brain due to the presence of BBB mediated restriction. But the administration of drug deep into the nasal cavity which approached nasal mucosa led to direct transportation of drug into the brain via specific olfactory pathways which consist of olfactory neuron carrying drug from olfactory mucosa to the brain which is a slow process of drug transportation. On the other hand, the olfactory epithelium pathway is a more confined and faster way of drug transportation. In this drug is directly passed through olfactory epithelium by paracellular mechanism into parenchymal space and is directly transferred into the brain.  

**RECENT ADVANCEMENT IN BRAIN TARGETED DRUG DELIVERY**

Antibodies mediated drug delivery

Antibodies based therapy become most prominent over the last decade. But the restriction created by BBB and low permeability of antibodies in the brain limit the potential of antibodies mediated therapy used for neurological diseases. However monoclonal antibodies (mAb) are much larger so they are not able to cross BBB as small molecules do and move towards the targeted site in the brain. Till the date, mAb has been approved for brain targeting strategies but several mAb are under clinical trials generally for the treatment of Alzheimer's diseases. A bispecific antibody (bsAb) is recently and newly developed Ab having two binding specificities. bsAb is incorporated for chemotherapy with a single binding specific target to the tumour cell and other targets the antigen present on the immune cell. The application of bsAb is targeted delivery across BBB. Many of the bsAb which crosses were formulated and evolved for achieving brain targeted delivery like bsAb with transferrin receptor (TFR) binding domain for crossing BBB and single-chain variable region fragments specific against amyloid beta-peptide. Major Facilitator Super family Domain containing 2A (Mfsd2a) based drug delivery strategy. This is a novel approach for brain targeted drug delivery as Mfsd2a present over the surface of endothelial cells present in BBB, which prohibit the transportation of molecule through transcytosis and facilitate the transport of specific lysophosphatidylcholine (LPC) derivative. Mfsd2a works on two principles one of which is inhibition of Mfsd2a which promotes transcytosis in endothelium and which results in the enhancement of BBB permeation. Whereas LPC acts as a carrier for small molecule and is transported by Mfsd2a across BBB. The second approach involves LPC mediated delivery which resembles parallely to glucose transporter and I. type amino acid transporter based transport.  

**Facial intradermal injection**

Facial intradermal injection crosses the BBB through trigeminal neuronal connection. Trigeminal pathway contains vasculature; perineurium and epineurium interlink facial skin with the brain. The trigeminal pathway is used in facial intradermal targeting of the brain.  

**CONCLUSION**

According to literature it has been declared that brain targeting via nasal drug delivery is a fascinating approach. However, some of the alterations like surface modification of nanocarriers and the introduction of some specific ligand have provided some useful information and progress in the field. Modification of carriers by nano particles, micelles, liposome has led to a new era of drug delivery system commonly delivery of peptide and protein-based therapeutic agents to the brain. Nasal drug delivery serves some limitations like only specified and small quantity can be administered with its increasing molecular weight. Some effective non-invasive treatments of nasal delivery have some limitations because of the presence of dynamic barriers like BBB and CSF. However, there is a commanding challenge to increase the potency of effective drug targeting to the brain which can be achieved by a non-invasive and...
effective approach like intranasal drug delivery through which obstacle offered by BBB can be controlled.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ABBREVIATIONS

BBB: blood brain barrier; CNS: Central Nervous System; CSF: Cerebro Spinal Fluid; ND: Neurodegenerative Disease; SLN: Solid Lipid Nano Particles; TFR: Transferrin Receptor; mAb: Monoclonal Antibody; bsAb: Bispecific Antibody; CED: Convection Enhanced Delivery; p-GP: P Glycoprotein; CYP3A: Cytochrome P 450; LPC: lysophosphatidylcholine; Mfsd2a: Major Facilitator Superfamily Domain containing 2A.

REFERENCES