Nano formulation: A novel approach for nose to brain drug delivery

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ABSTRACT

Nano technology plays a unique and pivotal role in the development of brain specific drug delivery, imaging and diagnosis. Targeted drug delivery is a means of concentrating drugs at a specific site relative to other parts of the body. It spares the rest of the body from toxic effects of the drug and is also a potential means of improving therapeutic index. The delivery of drugs to the CNS is of prime importance for treating specific neurological disorders and various diseases such as Meningitis, Encephalitis, degenerative diseases such as Alzheimer, Parkinson’s and tumors such as Glioblastoma. The major problem in treating such CNS disorders is due to their inability to surpass the natural CNS protective barriers, mainly the Blood Brain Barrier and the Blood cerebrospinal fluid Barrier. Nanoparticle systems in CNS targeted drug therapy provide better penetration of therapeutic and diagnostic agents, and a reduced risk in comparison to conventional treatments. By using nanotechnology it is possible to deliver the drug to the targeted tissue across the BBB, release the drug at a controlled rate, and avoid degradation processes. Different types of nanoparticles used for CNS targeted drug delivery like inorganic nanoparticles, Polymeric Nanoparticles, Solid Lipid Nanoparticles, Nano crystals, Carbon nanotubes, Dendrimers, Gold Nanoparticles and Magnetic Nanoparticles.

Key words: Nanoparticles, Central nervous system, blood brain barrier, nanotechnology

INTRODUCTION

1.1 BLOOD BRAIN BARRIER
The blood brain barrier (BBB) represents one of the strictest barriers of in vivo therapeutic drug delivery. The barrier allows restricted exchange of hydrophilic compounds, small proteins and charged molecules between the plasma and central nervous system (CNS). For decades, the BBB has prevented the use of many therapeutic agents for treating Alzheimer’s disease, Parkinson’s, brain tumour, stroke, head injury, depression, anxiety and other CNS disorders etc. [1]. Various techniques and attempts were made to deliver the drug across the BBB such as modification of therapeutic agents, altering the barrier integrity, carrier-mediated transport, invasive techniques, etc. [2]. Describe number of possibilities that could explain the mechanism of the delivery of nanoparticulate formulations across the BBB. As compared to the pure drugs, there is an increased retention of the nano formulations in the brain blood capillaries combined with more adsorption to the capillary walls. These retention and adsorption create a higher concentration gradient that would enhance the transport across the endothelial cell layer and result in better delivery to the brain.

1.2 NASAL ANATOMY AND PHYSIOLOGY
In humans the functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. The nasal cavity is a space situated above the oral cavity and hard palate and
below the skull base and intracranial compartment. The nasal septum consists of cartilage in its front end and bone towards the back of the nose. The perpendicular plate of the ethmoid bone, vomer bone, and maxilla bone these three gives nasal septum. The nasal septum is sometimes crooked or off-midline, which leads to narrowing of one or both sides of the nasal cavity. The left and right nasal cavities become continuous in the back of the nose via the opening to the nasopharynx are called as the choana. In this area, the nasal cavity transitions into the nasopharynx. The nasopharynx contains a collection of centrally located lymphoid tissue called the adenoids. The human nasal cavity has a total volume of 15-20mL and a total surface area of 150 cm$^2$. It is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics.

1.2.1 RESPIRATORY REGION
The respiratory epithelium is made of with four types of cells are non-ciliated and ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia and also to prevent drying of the mucosa by trapping moisture in order to facilitate mucociliary clearance. A viscous gel layer, the mucus blanket floats on the serous fluid layer. The viscous gel layer is moved along by the hook shaped cilia termini during the energy dependent „effective stroke” phase of the ciliary motion Cilia are up to 7mm in length when fully extended but can fold to half this length during the recovery stroke where the hook terminus detaches from the gel layer and moves immersed in the sol layer in the opposite direction to the gel layer movement. The cilia beat with a frequency of 1000 strokes per min. Hence the mucus moves only in one direction from the anterior to the posterior part of the nasal cavity to the nasopharynx.

1.2.2 OLFACTORY REGION
Smell allows humans and animals with olfactory receptors to identify food, mates, predators, and provides both sensual pleasure as well as warnings of danger. The olfactory region of the two nasal passages in humans is an area of about 2.5 square centimeters containing in total of about 50 million primary sensory receptor cells. The olfactory region consists of cilia projecting down out of the olfactory epithelium into a layer of mucous which is about 60 microns thick. This mucous layer is a lipid-rich secretion that bathes the surface of the receptors at the epithelium surface. The mucous layer is produced by the Bowman’s glands which reside in the olfactory epithelium. The mucous lipids assist in transporting the odorant molecules as only volatile materials that are soluble in the mucous can interact with the olfactory receptors and produce the signals that our brain interprets as odor. [3]

2. NANOFORMULATIONS INVESTIGATED
Numerous nanoformulations have been investigated successfully for better brain delivery which includes nanoparticulate systems (polymeric/solid lipid), liposomes, dendrimers, nanoemulsions, nanosuspensions, and ligand mediated nanosystems.

2.1 POLYMERIC NANOPARTICLES
Nanoparticles (NPs) are colloidal particles, less than 1000 nm, that can be used for better drug delivery and prepared either by encapsulating the drug within a vesicle and or by dispersing them drug molecules within a matrix [4]. Nanoparticulate drug delivery systems have been extensively studied in recent years for spatial and temporal delivery, especially in tumour and brain targeting.

2.2 SOLID LIPID NANOPARTICLES (SLN)
Solid lipid nanoparticles (SLN) are colloidal particles composed of biocompatible/biodegradable lipid matrix that is solid at body [5]. Temperature and exhibit size in a range of 100 to 400 nm. SLN offer several advantages such as controlled drug release, targeted delivery, increased drug stability, high drug payload, least biotoxicity, large scale production and ease of sterilization [6].

2.3 LIPOSOMES
Nanoformulations such as liposomes consists of bilayer phospholipid systems in which water-soluble drugs could reside in the aqueous phase enveloped by phospholipid bilayer and the lipophilic drugs, could directly integrate into the membrane [7]. Targeted brain delivery using liposomal systems resulted in considerable increase of drug concentration in brain/in vitro cell lines [8].

2.4 MICROSPHERE
Microsphere technology is one of the specialized systems becoming popular for designing nasal products, as it provide prolonged contact with the nasal mucosa and thus enhances absorption and bioavailability. In the presence of microspheres, the nasal mucosa is dehydrated due to moisture uptake by the microspheres. This result in reversible shrinkage of the cells, providing a temporary physical separation of the tight (intracellular) junctions that
increases the absorption of the drugs. Microsphere used in nasal drug delivery is water insoluble but absorb water into matrix resulting swelling of the spheres to form a gel. The materials used in formulation of microspheres are starch, dextran, albumin, and hyaluronic acid. Starch and dextran microspheres administered repeatedly. Bioavailability of protein and peptides has been improved in different animal by microsphere formulation. Some low molecular weight drugs also successfully delivered in microsphere formulation. Microspheres have been reported to be present up to 3-5 h in the nasal cavity depending upon the bio adhesive material used for formulation. The ideal microsphere particle size requirement for nasal delivery should range from 10 to 50 µm as smaller particles than this will enter the lungs.

2.5 MICELLES
Polymeric micelles obtained from block copolymers as colloidal carriers for drug and gene targeting have been receiving much attention in the field of drug delivery and targeting because of the high drug-loading capacity [9]. A variety of drugs with diverse characteristics, including genes and proteins, can be incorporated into the core. Researchers have demonstrated effective targeting of micelles systems to the brain by intravenous as well as intra nasal route [10].

2.6 CHITOSAN NANO PARTICLES
Currently, NPs prepared from cationic polysaccharide chitosan (CS) have shown promising results in nose to brain drug delivery because of its excellent intrinsic properties like low toxicity, excellent biocompatibility, high loading and entrapment efficiency and ability of delivering hydrophilic molecules.

Bromocriptine loaded chitosan nanoparticles (BRC-CS NPs) by an ionic gelation with tri-polyphosphate (TPP; 0.175% w/v) as anion. The chitosan used was of medium Mw and with degree of deacetylation of about 85%, prepared in acetic acid (2% v/v; pH 3.5). The concentration of chitosan used was 0.175% w/v. Bio-distribution and pharmacokinetic studies revealed the higher brain/blood ratios of intranasal BRC-CS NPs compared to intranasal BRC solution and intravenous BRC-CS NPs ,indicating the direct nose to brain transport of BRC along olfactory or trigeminal nerve pathways bypassing the BBB. This was further confirmed by higher drug targeting index (DTI), drug targeting efficiency (DTE) and drug transport percentage (DTP) [11].

The enhanced direct nose to brain drug delivery effect of chitosan formulations is suggested to be attributable to a combination of:
1) The passive targeting ability of chitosan by mucoadhesion resulting in increased residence time of formulation over the olfactory region and
2) The increased permeability of nasal epithelia to drug due to tight junction opening between apical cells.

2.7 NANOEMULSIONS AND MUCOADHESIVE NANOEMULSIONS
Nanoemulsions (NEs), by virtue of their lipophilic nature and low globule size, are widely explored as a delivery system to enhance uptake across the nasal mucosa. The addition of mucoadhesive agents such as polyelectrolyte polymers help in the retention of formulation on the nasal mucosa, thereby providing an extended delivery of the drug to the olfactory region and henceforth to the brain. The NEs modified with mucoadhesive agents are referred to as Mucoadhesive nanoemulsions (MNEs).

The formulation and development of ropiniroleloaded NE and MNE for i.n. administration as a better management option for the treatment of PD. The formulation was characterized, primarily, by physico-chemical investigations like particle size (58.61 ± 5.18), Polydispersity index (0.201), viscosity (31.42 ± 6.97), stability, dilution capability and ability to improve i.n. flux. The ex-vivo studies showed a significant higher drug translocation in different parts of the Wistar rat brain. From the in vitro, ex-vivo and in vivo evaluation, the authors have concluded that the NEs and MNEs could be a promising approach for the IN delivery of ropinirole hydrochloride and utilized as a better treatment option for PD (Table: 1) [12].

<table>
<thead>
<tr>
<th>THERAPEUTIC DRUG</th>
<th>NANOCARRIERS</th>
<th>FORMULATION TECHNIQUE</th>
<th>THERAPEUTIC OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>CS NPs</td>
<td>Ionic gelation</td>
<td>High brain uptake</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>CS NPs</td>
<td>Ionic gelation</td>
<td>Enhanced brain uptake, increased brain bioavailability</td>
</tr>
<tr>
<td>Ropinirole HCl</td>
<td>SLN</td>
<td>Emulsification-solvent diffusion</td>
<td>Enhanced stability, reduced dosing frequency</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>NE and MNE</td>
<td>-</td>
<td>Enhanced brain translocation</td>
</tr>
</tbody>
</table>

CS NPs: Chitosan nanoparticles; PEG: Poly (ethylene glycol); HCl: Hydrochloride; SLN: Solid lipid nanoparticles; NE: nanoemulsion; MNE: Mucoadhesive nanoemulsion;

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3. INTRANASAL ROUTE OF ADMINISTRATION FOR THE BRAIN DELIVERY

Enormous progress has been made regarding the pathogenic mechanism of neurological diseases; there are only few drugs for treating the illness. A key obstacle for developing effective drugs for treating neurological diseases is the blockage of drug entrance into CNS by BBB [13]. Less than 2% of small molecule drugs and virtually no large molecules or drugs can cross the BBB. Therefore, it is of critical significance to search for drug-delivery strategies that can effectively deliver drugs into the CNS. An increasing number of studies on both animals and human subjects have suggested that intranasal drug delivery could be used to deliver both small and large sized drugs into the CNS by bypassing the BBB. In the 1970s and 1980s there were multiple studies suggesting the intranasal administration may enable substances to directly enter into the brain by pathways involving the olfactory epithelium and olfactory bulb [14]. Reports were made for the first quantitative study indicating that intranasal administration could deliver large size molecules into the brain by bypassing the BBB [15]. A number of studies using animal models of neurological diseases have demonstrated that intranasal delivery of large sized molecules can produce beneficial effects. For example, intranasal nerve growth factor (NGF) administration can attenuate memory deficits and neurodegeneration in transgenic models of Alzheimer’s disease (AD) administration of erythropoietin [16] or IGF-I [17] by the intranasal approach can significantly decrease ischemic brain damages and intranasal delivery of growth factors can also increase neurogenesis in rat brain [18].

There has been growing interest and focus on the use of nasal route for systemic delivery & Brain targeting. Drug which undergoes first pass metabolism to avoid this and increases there bioavailability of drug nasal route is preferred [19]. It is useful for the drug which are active at low doses & show very less oral bioavailability such as Protein and peptide, central nervous system diseases such as Epilepsies, meningitis, migraine, Parkinson diseases, Alzheimer diseases has difficulty in targeting because of the transport through Blood Brain Barrier [20]. From literature it shows that such diseases can be treated by transporting exogenous material to brain by nose or it’s an effective route by passing BBB [21]. The result of concentration time Profile of intranasal administration drug is similar to the Intravenous route [22]. The pathway employed for the delivery of particular drug from the nose to brain is highly dependent on various factors, such as existence of specific receptor on the olfactory neurons, the lipophilicity and molecular, weight of the drug [23]. Intra nasal delivery is non-invasive & painless delivery and it does not required sterile preparation & it is easy method of drug administration for patient or physician. The nasal route offers improve delivery for “non-Lipinski” drug [24]. Lipophilic drug can easy cross BBB by travelling throw transcellular pathway. Hydrophilic drug transport throw paracellular pathway so they have very less chance to pass BBB. Polar molecule have very less chance to pass from respiratory region to blood stream so they have some chances to reach brain by passing or travelling throw olfactory mucosa in nose [25]. Many novel nasal products for systemic delivery on various diseases are launched in market but still no drug exploiting the nasal route to treat CNS diseases. Development of drug delivery throw nose to enable rapid & effective concentration in Brain challenges for Researchers.

4. MECHANISM OF DRUG DELIVERY FROM NOSE TO BRAIN

There are three mechanisms underlying the direct nose to brain drug delivery, one is intracellular transport mediated route and two extracellular transport mediated routes. The intracellular transport mediated route is a relatively slow process, taking hours for intra nasally administered substances to reach the olfactory bulb. The two extracellular transport mediated routes could underlie the rapid entrance of drug into the brain which can occur within minutes of intranasal drug administration. In the first extracellular transport based route intranasally administered substances could first cross the gas between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb. In the second extracellular transport based route, intranasal administered substances may be transported along trigeminal nerve to bypass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter in to other regions of brain by diffusion, which may also be facilitated by perivascular pump that is driven by arterial pulsation. Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of therapeutic agents for central targets due to the impenetrable nature of the drug through blood-brain barrier (BBB). The BBB obstruct the substrate penetration based on several characteristics, including lipophilicity, molecular size and specificity for a variety of ATP-dependent transport systems. Injection of dyes in the ventricles of rabbits and monkeys showed that the cerebrospinal fluid (CSF) is drained via the olfactory neurons into the olfactory neurons, originating from the olfactory bulb; connect the brain with the nasal cavity by penetrating the cribriform plate, which brings the neurons into the nasal mucosa. This coined the idea that this transport route could also exist in the opposite direction, which would imply direct access from the nasal cavity to the brain, thus circumventing the BBB [26]. It has been a promising approach for the rapid-onset intranasal delivery and the optimized nasal formulation showed effective absorption in terms of in-vitro release through excised goat nasal mucosa [27]. Brain drug level following the nasal administration are the results of double absorption pathway that is direct transfer through olfactory region and absorption into the systemic circulation and then transport across the blood brain barrier (BBB) [28].

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The selection of delivery system depends upon the drug being used, proposed second extracellular transport based route, and intranasal administered substances may be transported along trigeminal nerve to bypass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter in to other regions of brain by diffusion, which may also be facilitated by perivascular pump that is driven by arterial pulsation. Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of therapeutic agents for central targets due to the impenetrable nature of the drug through blood-brain barrier (BBB). The BBB obstruct the substrate penetration based on several characteristics, including lipophilicity, molecular size and specificity for a variety of ATP-dependent transport systems. Injection of dyes in the ventricles of rabbits and monkeys showed that the cerebrospinal fluid (CSF) is drained via the olfactory neurons into the olfactory neurons, originating from the olfactory bulb; connect the brain with the nasal cavity by penetrating the cribriform plate, which brings the neurons into the nasal mucosa. This coined the idea that this transport route could also exist in the opposite direction, which would imply direct access from the nasal cavity to the brain, thus circumventing the BBB [26]. It has been a promising approach for the rapid-onset intranasal delivery and the optimized nasal formulation showed effective absorption in terms of in-vitro release through excised goat nasal mucosa [27]. Brain drug level following the nasal administration are the results of double absorption pathway that is direct transfer through olfactory region and absorption into the systemic circulation and then transport across the blood brain barrier (BBB) [28].

### TABLE 2: BARRIERS TO NASAL ABSORPTION

<table>
<thead>
<tr>
<th>Category</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physiological Barrier</td>
<td>- Nasal Mucus&lt;br&gt;- Nasal Epithelial Barrier&lt;br&gt;- Mucociliary Clearance&lt;br&gt;- Pathophysiological factor&lt;br&gt;- Nasal Metabolism&lt;br&gt;- Efflux Transport System</td>
</tr>
<tr>
<td>2. Physiochemical Barrier</td>
<td>- Drug Solubility and Dissolution&lt;br&gt;- Molecular Weight and Size&lt;br&gt;- Compound Lipophilicity&lt;br&gt;- pH and pKa</td>
</tr>
<tr>
<td>3. Formulation Factor</td>
<td>- Drug Concentration, Dose and Volume&lt;br&gt;- Osmolarity&lt;br&gt;- Site of Disposition</td>
</tr>
</tbody>
</table>

### 5. ADVANTAGES OF INTRANASAL DRUG DELIVERY

- Rapid drug absorption via highly vascularized mucosa.
- Ease of administration, non-invasive.
- Improved bioavailability.
- Improved convenience and compliance.
- Self-administration.
Large nasal mucosal surface area for dose absorption.
Avoidance of the gastrointestinal tract and first-pass metabolism.
Rapid onset of action.
Lower side effects.
Drugs which cannot be absorbed orally may be delivered to the Systemic circulation through nasal drug delivery system.
Convenient route when compared with parenteral route for long term therapy.
Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

6. DISADVANTAGES OF INTRANASAL DRUG DELIVERY
- Some drugs may cause irritation to the nasal mucosa.
- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Drug delivery is expected to decrease with increasing molecular weight.
- Frequent use of this route leads to mucosal damage.
- The amount of drug reaches to different regions of the brain and spinal cord varies with each agent.

7. LIMITATIONS OF INTRANASAL DRUG DELIVERY
- The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
- Absorption surface area is less when compared to GIT.
- Once the drug administered cannot be removed.

Table 3: Review of research on nose-to-brain drug delivery

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>CATEGORY</th>
<th>DRUGS</th>
<th>DRUG DELIVERY SYSTEM</th>
<th>REFERENCE NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luppi et al 2011</td>
<td>Anti-Parkinsonism</td>
<td>Tacrine</td>
<td>Nanoparticles</td>
<td>29</td>
</tr>
<tr>
<td>Wang et al 2008</td>
<td>Anti-alzheimer</td>
<td>Estradiol</td>
<td>Nanoparticles</td>
<td>30</td>
</tr>
<tr>
<td>Patel et al 2011</td>
<td>Antipsychotics</td>
<td>Risperidone</td>
<td>Nanoparticles</td>
<td>31</td>
</tr>
<tr>
<td>Lai et al 2011</td>
<td>Anti-Parkinsonism</td>
<td>Odorranalectin</td>
<td>Nanoparticles</td>
<td>32</td>
</tr>
<tr>
<td>Fazil et al 2012</td>
<td>Anti-alzheimer</td>
<td>Rivastigmine</td>
<td>Nanoparticles</td>
<td>33</td>
</tr>
<tr>
<td>Desai et al 2010</td>
<td>Anticonvulsant</td>
<td>Midazolam</td>
<td>Microspheres</td>
<td>34</td>
</tr>
<tr>
<td>Vyas et al 2006</td>
<td>Hypnotic’s, Sedative</td>
<td>Clonazepam</td>
<td>Microemulsion</td>
<td>35</td>
</tr>
<tr>
<td>Rasil et al 2010</td>
<td>Anti-Migraine</td>
<td>Sumatriptan</td>
<td>Microemulsion</td>
<td>36</td>
</tr>
<tr>
<td>Misra et al 2009</td>
<td>Antipsychotics</td>
<td>Olanzapine</td>
<td>Nanoemulsion</td>
<td>37</td>
</tr>
<tr>
<td>Sharma et al 2012</td>
<td>Antiepileptic</td>
<td>Gabapentin</td>
<td>Microspheres</td>
<td>38</td>
</tr>
<tr>
<td>Bhanshah et al 2009</td>
<td>Anti-migraine</td>
<td>Rizatriptan benzoate</td>
<td>Nanoemulsion</td>
<td>39</td>
</tr>
<tr>
<td>Kumar et al 2008</td>
<td>Antipsychotics</td>
<td>Risperidone</td>
<td>Nanoemulsion</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 4: Drug molecules and drug carrier systems being delivered by direct nose to brain drug delivery route

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CARRIER SYSTEM</th>
<th>PROBLEM</th>
<th>OUTCOME</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxin</td>
<td>Polymeric nanoparticles</td>
<td>Slow onset of action, poor oral bioavailability</td>
<td>Quick onset of action, enhanced brain uptake</td>
<td>41</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Polymeric nanoparticles</td>
<td>Nasal mucociliary clearance, low permeability</td>
<td>Enhanced retention, high brain uptake</td>
<td>42</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Microemulsion</td>
<td>High hepatic first-pass metabolism, limited uptake across BBB</td>
<td>High bioavailability, high brain uptake</td>
<td>43</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Polymeric nanoparticles</td>
<td>Poor oral bioavailability, non-targeted delivery</td>
<td>High bioavailability, high brain uptake</td>
<td>44</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Nanoemulsion</td>
<td>High hepatic metabolism, high P-glycoprotein efflux</td>
<td>High bioavailability, high therapeutic efficiency</td>
<td>45</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Polymeric micelle</td>
<td>Slow onset, low oral bioavailability</td>
<td>Quick onset, high distribution in brain tissues, high bioavailability</td>
<td>46</td>
</tr>
</tbody>
</table>

Table 5: Patents on nose to brain drug delivery systems

<table>
<thead>
<tr>
<th>DRUG</th>
<th>THERAPEUTIC APPLICATION</th>
<th>DRUG DELIVERY SYSTEM</th>
<th>PATENT</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Epilepsy</td>
<td>Nasoehesivemicroemulsion</td>
<td>Misra and Vyas 1061/MUM (2005)</td>
<td>50</td>
</tr>
<tr>
<td>Triptans, caffeine</td>
<td>Migraine</td>
<td>Nasoehesivemicroemulsion</td>
<td>Misra and Vyas 1125/MUM(2005)</td>
<td>51</td>
</tr>
</tbody>
</table>
CONCLUSION

A successful drug delivery system is one which offers commercial applicability to pharmaceutical industries for large-scale production. CNS drug delivery is complex due to limitations imposed by the BBB. Direct nose to brain drug delivery system is a potential strategy to overcome the obstacles presented by the BBB. Intranasal delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects. It is an attractive option of drug delivery due to its non-invasiveness.

A variety of neurotherapeutic agents including small drug molecules, proteins, peptides, hormones and biological cells such as stem cells can be delivered by this route, thereby yielding new insights into prevention and management of different neurological disorders. It is uncertain, however, whether the drug is being released from the carrier system in the nasal cavity and transported to CNS, or the carrier system is transported along olfactory and/or trigeminal nerve pathways into the CNS where the drug is released. Thus, more basic research is required to determine the possible transport pathway of therapeutic carrier to the CNS and their further fate into the biological system. Again, delivery of surface engineered carrier systems through passive or active targeting approach would be desirable for further progress in the field.

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