Publications

In communication
❖ Mathematical Modeling of Clonazepam Microemulsions.
❖ Determination of Clonazepam in rat plasma and brain by liquid chromatography electrospray ionization ion-trap tandem mass spectroscopy.
❖ Intranasal Mucoadhesive Microemulsions of Clonazepam: Preliminary Studies on Brain Targeting

In Manuscript
❖ Nose-to-Brain Delivery of Triptans: Studies on Brain-Targeting efficiency.
❖ Radiolabeling of microemulsions

Patents
Received documents purporting to be an application for a patent by "AMBIKANANDAN MISRA, & TUSHAR K VYAS, Vadodara" relating to "DRUGS LOADED NASOADHESIVE MICROEMULSIONS FOR BRAIN "TARGETED BRISK DELIVERY IN ACUTE EPILEPSY" together with Complete Specification and fee(s) of Rs. 750 (Rupees Seven Hundred & Fifty only).

The application has been numbered as below:


To

PROF. AMBIKANANDAN MISRA, (Head), Pharmacy Department, Faculty of Technology & Engineering, MS Unive

Note:-

As per the Patents (Amendment) Act 2002 and Patents Rules, 2003, which has come in to force w.e.f. 20.5.2003, the Term of the Patent has been increased to 20 Years from the Date of Filling the Application. You are therefore requested to pay the renewal fees as per fee Schedule.
New Application Receipt

GOVERNMENT OF INDIA
PATENT OFFICE BRANCH
Todi Estate, 3rd floor, Sun Mill Compound
Lower Parel(West), MUMBAI - 400013.
Tel No. (091)(022) 24925092, 24924058, 24903684 Fax No. 24950622
E-mail : patmum@vsnl.net
Web Site : http://www.ipindia.gov.in

Application Type: Ordinary
Priority
Divisional No:
CASE: NEW
Date/Time: 20/10/2004 4:50:08 PM

Receipt No: 1128
CBR NO : 10832

Received documents purporting to be an application for a patent by “AMBIKANANDAN MISRA, & TUSHAR K VYAS, Vadodara” relating to “SEDATIVES LOADED INTRANASAL NASOADHESIVE MICROEMULSIONS FOR BRAIN TARGETED DELIVERY IN INSOMNIA” together with Complete Specification and fee(s) of Rs. 750 (Rupees Seven Hundred & Fifty only )

The application has been numbered as below :

To
PROF. AMBIKANANDAN MISRA, (Head), Pharmacy Department, Faculty of Technology & Engineering, MS Unive

Note:-
As per the Patents (Amendment) Act 2002 and Patents Rules,2003, which has come in to force w.e.f. 20.5.2003, The Term of The Patent has Been Increased to 20 Years From the Date of Filling The Application. You are Therefore requested to pay the renewal fees as per fee Schedule.
Received documents purporting to be an application for a patent by "AMBIKANANDAN MISRA, & TUSHAR K VYAS, Vadodara" relating to "DRUGS LOADED INTRANASAL NASOADHESIVE MICROEMULSIONS FOR BRAIN TRAGETED DELIVERY IN MIGRAINE" together with Complete Specification and fee(s) of Rs. 750 (Rupees Seven Hundred & Fifty only).

The application has been numbered as below:

To

PROF. AMBIKANANDAN MISRA, (Head), Pharmacy Department, Faculty of Technology & Engineering, MS University

Note:-

As per the Patents (Amendment) Act 2002 and Patents Rules, 2003, which has come in to force w.e.f. 20.5.2003, The Term of The Patent has Been Increased to 20 Years From the Date of Filling The Application. You are There for requested to pay the renewal fees as per fee Schedule.
Intranasal Drug Delivery for Brain Targeting

Tushar K. Vyas¹, Aliasgar Shahiwala¹, Sudhanva Marathe² and Ambikanandan Misra³*

¹Pharmacy Department, Faculty of Technology and Engineering, The M S University of Baroda, Post Box No. 51, Kalabhavan, Vadodara. 390 001, India; ²Hoffmann-La Roche Inc., 340, Kings land street, Nutley, NJ, 07110, U.S.A.; ³Professor and Head, Pharmacy Department, Faculty of Technology and Engineering, The M S University of Baroda, Post Box No. 51, Kalabhavan, Vadodara. 390 001, India

Abstract: Many drugs are not being effectively and efficiently delivered using conventional drug delivery approach to brain or central nervous system (CNS) due to its complexity. The brain and the central nervous system both have limited accessibility to blood compartment due to a number of barriers. Many advanced and effective approaches to brain delivery of drugs have emerged in recent years. Intranasal drug delivery is one of the focused delivery options for brain targeting, as the brain and nose compartments are connected to each other via the olfactory route and via peripheral circulation. Realization of nose to brain transport and the therapeutic viability of this route can be traced from the ancient times and has been investigated for rapid and effective transport in the last two decades. Various models have been designed and studied by scientists to establish the qualitative and quantitative transport through nasal mucosa to brain. The development of nasal drug products for brain targeting is still faced with enormous challenges. A better understanding in terms of properties of the drug candidate, nose to brain transport mechanism, and transport to and within the brain is of utmost importance. This review will discuss some pertinent issues to be considered and challenges to brain targeted intranasal drug delivery. A few marketed and investigational drug formulations will also be discussed.

Keywords: Central nervous system, blood brain barrier, nasal mucosa, brain targeting.

1. INTRODUCTION

The central nervous system is one of the complex systems in human body. The blood brain barrier (BBB) is the major bottleneck in drug delivery to the brain. Drugs used against CNS diseases should reach the brain via the BBB. The function of the BBB is dynamically regulated by various cells present at the level of BBB [1]. The tight junctions between endothelial cells in brain results in a very high trans-endothelial electric resistance of 1500-2000 Ω cm² compared to 3-33 Ω cm² of other tissues like skin, bladder, colon, lung etc. which significantly affects uptake of drugs by brain [2,3,4]. However, certain classes of drugs like benzodiazepines such as diazepam, due to its high lipophilicity, readily cross the BBB. The other barrier that a systemically administered drug encounters before entering the CNS is the blood-cerebrospinal fluid barrier (BCB). The brain is covered by a double-layered structure called the arachnoid membrane, which acts as a barrier between blood and CSF. It usually restricts passage of hydrophilic substances from the blood brain due to tight junctions [5-7]. Thus, the BBB is a predominant rate-limiting barrier in brain targeted drug delivery systems. The transport mechanisms through the BBB and physiochemical properties of the drug molecules are major factors to be considered in designing of drug delivery system for brain targeting.

Various scientific approaches [8], BBB disruption, receptor mediated transport, cell penetrating peptides and targeted delivery using produgs, have been reviewed for brain targeting. Other drug delivery systems [8] cited in literature are intranasal, intracerebral and intracerebroventricular. An area of ongoing research is discovering ways of improving the delivery of drug directly to the Central Nervous System (CNS) through nasal administration and by manipulating tight junctions at the blood-brain barrier. A great deal of interest has recently been focused on the exploration of the intranasal route for the delivery of drugs to the brain via the olfactory mucosa, although there are some studies that are contrary [9-21].

2. BRAIN TARGETING THROUGH NASAL ROUTE

For some time the BBB has impeded the development of many potentially interesting CNS drug candidates due to their poor distribution into the CNS. Owing to the unique connection of the nose and the CNS, the intranasal route can deliver therapeutic agents to the brain bypassing the BBB [22]. Absorption of drug across the olfactory region of the nose provides a unique feature and superior option to target drugs to brain [23]. When administered nasally to the rat, some drugs resulted in CSF and olfactory bulb drug levels considerably higher than those following intravenous administration [24-28]. Evidence of nose to brain transport has been reported by many scientists [29-36]. Table 1 gives an overview of some of the latest studies performed on humans. Many previously abandoned potent CNS drug candidates promise to become successful CNS therapeutic drugs via intranasal delivery. Recently, several nasal formulations,
Table 1. Studies Indicatives of Nose to Brain Transport in Man

<table>
<thead>
<tr>
<th>No.</th>
<th>Drugs</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arginine-Vasopressin (n=15)</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Cholecystokinin-8 (n=20)</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>Angiotensin II (n=12)</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>Insulin (n=18)</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Adrenocorticotropin 4-10 (n=54)</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Insulin (n=12)</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>99mTc-DPTA-hyaluronidase</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>Insulin (n=8)</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>Apomorphine (n=5)</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>Melatonin/hydroxycobalamin (n=2)</td>
<td>59</td>
</tr>
</tbody>
</table>

Functional evidence of facilitated transport to the brain

Direct evidence of nose to brain uptake

Direct evidence of nose to CSF uptake


such as ergotamine (Novartis), sumatriptan (Glaxo Smith-Kline), and zolmitriptan (Astra Zeneca) have been marketed to treat migraine [1]. Scientists have also focused their research toward intranasal administration for drug delivery to the brain, especially for the treatment of diseases, such as, epilepsy, migraine, emesis, depression and erectile dysfunction.

The investigations till date have attracted researchers to place the intranasal drug delivery option under the microscope. Nevertheless, it is imperative to understand the uptake of drug across the nasal mucosa. From a kinetic point of view, nose is a complex organ since three different processes, such as disposition, clearance, and absorption of drugs, simultaneously occur inside nasal cavity. For effective absorption of drugs across nasal mucosa, it is essential to comprehend the nasal anatomy and related physiological features of the nose.

2.1 Nasal Anatomy and Physiology of the Nose

The human nasal cavity has a total volume of about 16 to 19 mL, and a total surface area of about 180 cm², and is divided into two nasal cavities via the septum [37]. The volume of each cavity is approximately 7.5 mL, having a surface area around 75 cm² [37-38]. Post drug administration into the nasal cavity, a solute can be deposited at one or more of three anatomically distinct regions, the vestibular, the respiratory or the olfactory region.

The vestibular region is located at the opening of nasal passages [38-40], and is responsible for filtering out the airborne particles. It is considered to be the least important of the three regions with regard to drug absorption [41]. The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for drug absorption. The olfactory region is of about 10 cm² in surface area, and it plays a vital role in transportation of drugs to the brain and the CSF. The three distinct anatomical regions present in the nasal cavity and its cross sectional sketch is shown in (Fig. 1).

![Fig. (1). Anatomy of nose: cross sectional sketch illustrating (A) vestibular, (B) respiratory, and (C) olfactory region.](image-url)
The paracellular transport mechanism/route is slow and passive. It mainly uses an aqueous mode of transport. Usually, the drug passes through the tight junctions and the open clefts of the epithelial cells in the nasal mucosa. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Compounds, which are highly hydrophilic in nature and/or low molecular weight are most appropriate for paracellular transport. A sharp reduction in absorption and poor bioavailability were observed for the drugs having molecular weight greater than 1000 Daltons [57]. Moreover, drugs can also cross cell membranes by a carrier-mediated active transport route. For example, chitosan, a natural biopolymer from shellfish, stretches and opens up the tight junctions between epithelial cells to facilitate drug transport.

The transcellular transport mechanism/pathway [58-59] mainly encompasses transport via a lipoidal route. The drug can be transported across the nasal mucosa/epithelium by either receptor-mediated endocytosis or passive diffusion or fluid phase endocytosis. Small lipophilic compounds or larger molecules are usually transported by a transcellular route. The transport across nasal mucosa is mainly a function of the lipophilic nature of a drug compound. Highly lipophilic drugs are expected to have rapid/complete transnasal uptake.

The neuronal transport of drug can take place via intercellular axonal transport. The olfactory neuron cells facilitate the drug transport principally to the olfactory bulb.

Potential pathways followed by several drug molecules are recorded in Table 2 and possible transport routes are depicted in (Fig. 2).

### Table 2. Nose to Brain Transport of Drug Molecules and Possible Pathways

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal mucosa→sensory nerve cells of olfactory epithelium→subarachnoid space→blood stream</td>
<td>Albumin</td>
</tr>
<tr>
<td>Nasal mucosa→olfactory nerve fiber</td>
<td>Amino acids</td>
</tr>
<tr>
<td>Nasopharyngeal epithelium→lymphatic→cervical lymphatic vessel→blood vessel</td>
<td>Rabbit virulent type III pneumococci</td>
</tr>
<tr>
<td>Nasal mucosa→cerebrospinal fluid and serum</td>
<td>Dopamine, Estradiol</td>
</tr>
<tr>
<td>Nasal mucosa→olfactory neurons→brain and CSF</td>
<td>Estradiol, Neutropoic virus and poliomyelitis virus.</td>
</tr>
<tr>
<td>Nasal membrane→olfactory dendrites→nervous system→supporting cells in the olfactory mucosa→sub mucosal blood vascular system</td>
<td>Norethisterone, Progesterone</td>
</tr>
<tr>
<td>Nasal membrane→peripheral circulation and CSF→CNS</td>
<td>Norethisterone</td>
</tr>
<tr>
<td>Nasal mucosa→peripheral and cranial nerves→CNS</td>
<td>Herpes virus encephalitis</td>
</tr>
<tr>
<td>Nasal mucosa→cranial nerve→CNS</td>
<td>Herpes virus simplex</td>
</tr>
<tr>
<td>Nasal mucosa→trigeminal and olfactory pathways→CNS</td>
<td>Mouse passage strain of herpes virus</td>
</tr>
<tr>
<td>Nasal mucosa→sub mucous lymphatic→cervical lymphatic pathway→CNS</td>
<td>Vaccina virus</td>
</tr>
<tr>
<td>Nasopharynx→cervical lymph</td>
<td>Water</td>
</tr>
</tbody>
</table>
2.3 Intranasal Drug Delivery - Merits/Demerits [42, 44, 60-61]

The difficulties that have to be overcome include active degradation or alteration by enzyme, low pH of nasal epithelium, the possibility of mucosal irritation or the possibility of large variability caused by nasal pathology, such as common cold. An obvious advantage of intranasal route is that it is noninvasive relative to other routes of administration. Intranasal drug delivery delivers the drug directly to the brain by circumventing BBB and reduces drug delivery to non-targeted sites. Direct transport of drugs to the brain may lead to the administration of lower doses and in turn can reduce toxicity. Systemic dilution effect and first pass metabolism are also avoided. Direct transport could result rapid and/or higher uptake in brain, which provides an alternative option of self-medication in management of emergencies [62]. However, the few limitations of intranasal delivery are low dose/volume especially when compounds have less aqueous solubility are difficult to formulate. High lipophilicity and preferably low molecular weight of drug are the prerequisites as it could influence the uptake across nasal mucosa. Drug compounds devoid of offensive/pungent odor/aroma and non-irritant nature are highly desirable to facilitate dosage form design for intranasal drug delivery systems.

3. FACTORS AFFECTING BRAIN-TARGETED NASAL DELIVERY SYSTEMS

In addition, dosage form design also plays a key role in altering pharmacokinetics and bioavailability following intranasal administration. As illustrated in (Fig. 3), different delivery systems and devices which can be used to deliver various dosage forms via intranasal drug delivery. Some of the physico-chemical, formulation and physiological factors are imperative and must be considered prior to designing intranasal delivery for brain targeting. As shown in (Fig. 4), some of the physico-chemical factors are Chemical form [63], polymorphism, particle size, solubility and most importantly molecular weight [55-56, 64-65]. Moreover, several other factors like formulation factors [29-33, 38, 66-67] in addition to physiological factors [40, 68-71] are also having decisive repercussion on the in vivo result/performance of the product and in turn influence the uptake of drug at targeted site. Novel upcoming approaches are being explored by scientists in order to improve the in vivo performance of product.

Due to the typical anatomy and physiology of the nasal cavity, the distribution and deposition [72] are mainly a function of the delivery system and delivery device. Many factors [73] such as mode of administration, particle size of the formulation, velocity of the delivered particles, spray angle, plume design and spray cone influence the uptake across olfactory epithelium.

Results of studies conducted in animal models and in humans have shown the direct uptake of drugs into cerebrospinal fluid and the brain, which mainly depends on the molecular weight and lipophilicity [38, 29-32, 66]. Brain uptake can be positively correlated with lipid solubility or negatively correlated with hydrogen bonding. The higher hydrogen bonding potential results in the lower uptake by the brain. By reducing the hydrogen bonding potential for a congeneric series of steroid hormone congeners, there was a log increase in uptake with removal of each hydrogen bond pairs [1,8].

Formulation factors are also to be considered while designing brain targeted nasal drug delivery systems. Various
Intranasal Drug Delivery for Brain Targeting

**Fig. (3).** Nasal delivery devices and dosage forms.

**Fig. (4).** Critical physico-chemical factors needs to be considered prior to designing nasal drug delivery systems.

dosage forms available for nasal delivery are solutions, suspensions, emulsions and dry powders. The liquid formulations are usually water based but may also contain alcohol, oils or other organic solvents. Liquid spray and drops are the most widely used preparations for intranasal drug delivery. The nasal spray deposits anteriorly in the nasal atrium, while the drops are dispersed throughout the length of the nasal cavity. Nasal sprays deposit [74] more anteriorly, having more potential for brain delivery. Mucoadhesive agents like chitosan, carbomer derivatives and modified cellulose derivatitives are expected to substantially increase residence time of the formulation in the nasal cavity which could result in better transnasal transport/bioavailability [75-77]. In addition, penetration enhancers such as surfactants, betacyclodextrins, bile salts, phospholipids and lysophospholipids can significantly increase the permeability [78] across nasal mucosa and in turn uptake at the targeted site.

Absorption of drugs from the nasal cavity requires passage through the mucus [79]. Small, uncharged particles...
easily pass through mucus layer. However, larger or charged particles may not transverse easily. Mucin, the principal protein in the mucus, binds with solutes, which in turn hinders diffusion. Additionally, structural changes in the mucus layer are expected as a result of environmental changes (for example: pH, temperature, etc) [80].

4. DELIVERY OF PROTEINS/PEPTIDES TO CNS THROUGH THE NOSE

Investigational studies in human have provided evidence of direct delivery of macromolecules to the CNS following nasal administration. CNS effects of intranasal corticotropin-releasing hormone (CRH) without altering plasma cortisol or CRH levels has been demonstrated [81]. Perras et al. [66] have reported that intranasal delivery of growth hormone-releasing hormone (GHRH) not only increased rapid eye movement sleep and slow wave sleep in humans, but also decreased growth hormone.

The efficacy of peptide/protein following nasal administration is highly dependent on the molecular structure and size of the drugs. Respiratory epithelial cells are capable of absorbing peptide/protein by a vesicular transport mechanism, which is then transferred to the extracellular spaces, and subsequently taken up by the submucosal vascular network [82]. In recent studies, intranasal administration of wheat germ agglutinin horseradish peroxidase resulted in a mean olfactory bulb concentration in the nanomolar range. Vajdy et al. [83] reported that after nasal administration of DNA plasmids, the level of plasmid in the brain was 3.9 to 4.8 times higher than the plasmid concentration in the lungs and spleen. It was also found that the plasmid DNA reached the brain within 15 min following intranasal administration [84]. The higher distribution of plasmid to the brain after intranasal administration indicates that nasal administration might be a promising route for the delivery of therapeutic genes to the brain with reduced side effects in the other organs. Recent evidence of direct nose-to-brain transport [85] and direct access to CSF of three neuropeptides bypassing the bloodstream has been demonstrated in human trials, despite the inherent difficulties in delivery [54].

Lamia et al. [46] have studied the enhanced mucosal immunoglobulin response of intranasal adenovirus vector human immunodeficiency virus vaccine and its localization in CNS. Biodistribution of recombinant adenovirus (rAdV) vectors administered through intranasal route revealed infection of CNS, specifically in the olfactory bulb, possibly via retrograde transport by olfactory neurons in nasal epithelium. Drachia et al. [87] has demonstrated gene delivery in rat CNS via nasal instillation. It was noticed that mitral cells from olfactory bulb, locus coeruleus and area postrema expressed beta-galactosidase for 12 days and could be useful for gene therapy of disease affecting different CNS structures.

Liu et al. [88] has investigated intranasal administration of insulin like growth factor-1 (IGF-I) circumvent the blood-brain barrier and protects against focal cerebral ischemic damage. The study confirmed that IGF-I does not cross blood-brain barrier efficiently however, can be delivered to brain directly by intranasal administration.

5. DELIVERY OF NON-PEPTIDE MOLECULES TO THE CNS

Many small molecules have been shown to be transported directly to the brain and/or CSF from the nasal cavity. The properties of small molecules, including size and lipophilicity affect delivery to the CNS following intranasal delivery [40, 72-73]. Small molecular drugs, such as cocaine and benzoylcegonine [85], local anesthetics [9], dihydroergotamine [113] and dopamine [98] have been shown to reach the CNS via the olfactory pathway in animals. This has been reviewed by Illum [38] and Mathison et al. [40]. Dorman et al. [89] have investigated the olfactory transport of inhaled manganese phosphate into rat brain. The study concluded that olfactory route contributes to manganese delivery to the rat olfactory bulb and tubercle. Anand kumar et al. [90] and David et al. [91] have demonstrated intranasal delivery of estrogen and progesterone respectively, to the CSF. Considerable efforts have been made by the scientists in exploring the prospects for brain targeting following intranasal administration. Sakane T et al. [92] have investigated the transportation of 5-fluorouracil (5-FU) following intranasal, nasal perfusion and intravenous drug delivery. The results revealed that the concentration of 5-FU was significantly higher in cerebral cortex following intranasal administration in cerebral cortex. A significant amount of 5-fluorouracil was transported across nasal cavity to the brain via CSF. It was also concluded that intranasal delivery of hydrophilic drug to brain is practical. Char et al. [93] has evaluated the potential of intranasal delivery of [14C] dexamethasphor hydrochloride (DM) in rat brain. The study revealed uptake of DM in brain following intranasal route was 65.9% when compared to intravenous route. It was documented that the nasal route is a viable alternative to the parenteral route for DM administration.

In mice it is recently shown that dopamine reached the right olfactory bulb after nasal administration into the right nostril and after 4 hours, the concentration in the right olfactory bulb was 27 times higher than the left olfactory bulb [67]. Following intravenous administration, the uptake into brain was low. Moreover, micro radiography of the olfactory region of the rat showed the presence of drug molecules along the olfactory neuron bundles. This can either indicate transneural transport or transport via CSF surrounding the bundles. However, transneural transport is a slow process. Hence, the drug might be crossing the olfactory region by means of one and/or multiple transport mechanisms to reach into the CSF and the olfactory bulb.

In another study [94], methotrexate has shown preferential transfer into parts of the CNS directly from the nasal cavity compared to intravenous administration. The author concluded that the olfactory epithelium and the olfactory bulb were the essential gateways for this direct pathway and that the methotrexate after a single intranasal administration has a promising and durable therapeutic effect against certain CNS tumors.

Bergstrom et al. [95] have also reported the transport of picolinic acid along the olfactory pathways after administration via intranasal and intravenous routes in mice. Autoradiography demonstrated rapid uptake of radioactivity in the olfactory nerve layer and in the ipsilateral olfactory bulb.
following intranasal administration. The study also suggested that intact neuroepithelium is a prerequisite for uptake of picolinic acid in olfactory bulb. Picolinic acid meets the structural requirement and transfers along the olfactory pathways to brain. Increased interest in brain targeting of drugs having limited ability to pass through the blood brain barrier was also documented. A study carried out by Jansson B et al. [96], in vivo olfactory uptake and transfer using fluorescein-dextran (FD3) was demonstrated and visualized. The study showed transcellular absorption across olfactory epithelium after the intranasal administration of 3kDa FD3. Significant uptake by olfactory bulb was also noticed within 15 minutes. FD3 transfer in connective tissue surrounding the olfactory nerve bundles to the olfactory bulb of brain was also evidenced. The study concluded higher amounts were found in turbinates as compared to nasal septum. Studies have also shown that drugs such as L-NAME [97] and cocaine (at the lower end of the lipophilicity scale) [25] have a higher CSP and olfactory bulb concentration after nasal administration than that obtained after parenteral administration. Sakane et al. [28] reported that following intranasal administration of the antibiotic cephalixin to rats, higher CSF concentration was reached at 15 min., but it declined to approximately half that concentration at 30 min. Because cephalixin does not cross the BBB well and because CSF concentration was 166-fold higher after intranasal administration than after systemic administration in spite of similar blood levels, it was concluded that cephalixin entered the CSF directly from the nasal cavity. Using a series of fluorescein isothiocyanate-labeled dextrans (FITC-dextrans) with increasing molecular weights, it was found that dextrans with molecular weights of up to 20,000 daltons could be transported directly from the nasal cavity of rats into the CSF [99]. The concentration of the FITC-dextrans in the CSF increased with decreasing molecular weight. These FITC-dextrans were not found in the CSF after intravenous administration. Similarly, a comparison of the brain olfactory bulb concentrations achieved 30 min after intranasal administration of 7.4 n mol dopamine (153 daltons) [98] with those obtained after intranasal administration of 7.4 n mol nerve growth factor (NGF) (26,500 daltons) [46,47] to rats, revealed a five-fold higher delivery of the lower molecular weight dopamine. Comparing the percentages of the original dose remaining in the brain 30 to 45 min after intranasal administration of dopamine (0.12%) [54] and NGF (0.023%) [99] in rodents revealed a similar difference. In addition, with most small molecules, a significantly higher molar dose can be delivered intranasally than with larger protein or DNA therapeutic agents.

Ishikawa et al. [100] reported that powder formulation of elcatonin utilizing CaCO3 improves the nasal bioavailability by increasing residence time in the nasal cavity and thus enhances the systemic bioavailability. Recently Bergstrom et al. [95] studied the uptake of picolinic acid (PA) in the brain. [3HJPA was administered via unilateral nasal instillation or i.v. injection to mice. Autoradiography demonstrated rapid uptake of radioactivity in the olfactory nerve layer and in the ipsilateral olfactory bulb following nasal instillation, which was maintained at a high level even after 4 h. On the other hand, i.v. injection of [3HJPA demonstrated selective uptake and retention of radioactivity in the olfactory bulb. Hussain et al. [101] have found that intranasal administration of folic acid effectively results in complete and rapid absorption into the CNS. This provides a method of rapidly and reliably delivering folic acid, alone or in combination with other compounds, to the systemic circulation to produce a beneficial effect in the treatment or prevention of Alzheimer’s disease and stroke.

6. APPROACHES USED FOR IMPROVED CNS DELIVERY THROUGH NOSE

Various approaches have been tried to achieve higher CNS delivery through nasal route. A study by Gwak HS et al. [102] has shown that the analgesic effect of intranasal enkephalins is significantly higher when administered with aid of absorption enhancers. Al-Ghananeem AM et al. [103] have reported targeted brain delivery of 17-beta-estradiol via administration of water soluble produgs and absorption was fast following intranasal delivery of these produgs. These drugs are capable of producing high concentration of estradiol in CSF and have a significant value in treatment of Alzheimer's disease. Similarly, Kao HD et al. [104] have investigated during their study that water soluble produgs of L-dopa can be delivered specifically to CNS via intranasal administration. Absorption was rapid following intranasal delivery and bio availability was approximately 90%. Olfactory bulb and CSF concentration of L-dopa was significantly high. It was concluded that produgs of L-dopa can be successfully used for Parkinson's disease with many advantages such as improved bioavailability, reduced side effects and potentially enhanced CNS drug delivery. Lian Li et al. [62] reported rapid onset intranasal delivery of diazepam using ethyl-laurate-based microemulsion. At a 2 mg/kg dose, the maximum drug plasma concentration was arrived within 2-3 min, and the bioavailability (0-2 h) after nasal spray compared with i.v. injection was about 50%. The results suggest that this approach may be helpful during emergency treatment of status epilepticus. Illum et al. [105] have studied the effect of chitosan-morphine nasal formulation vis-a-vis slow i.v. infusion of morphine in healthy volunteers who reported sedation at the earliest time point after nasal administration compared with i.v. administration. This suggests that after nasal administration morphine may be able to reach CNS more rapidly than after i.v. administration.

7. MARKETED AND INVESTIGATIONAL PRODUCTS

Many products are already on the market and many more drugs are under investigation for intranasal delivery. Biopharmaceutical data and some of the marketed and investigational pharmaceuticals are summarized in Table 3, Table 4 and Table 5.

8. CONCLUSIONS

Many sophisticated and effective approaches to CNS drug delivery have emerged in recent years. Direct transport of drugs through the olfactory pathway to the CNS has generated immense interest in devising strategies and methodologies to exploit this approach as a portico for CNS drug delivery. However, numerous factors work in tandem which determines the efficiency of drug delivery. The problems
Table 3. Pharmacokinetic Data of Potential Brain-Targeted Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Animal Model</th>
<th>T_max in minutes</th>
<th>% Relative Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Rat</td>
<td>2-5</td>
<td>95</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Human</td>
<td>15-60</td>
<td>-</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Rhesus monkey</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Humans</td>
<td>60</td>
<td>72-84</td>
</tr>
<tr>
<td>Ergotamine tartrate</td>
<td>Rat</td>
<td>20</td>
<td>62-65.4</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Rat</td>
<td>10-30</td>
<td>83-127</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Humans</td>
<td>30-240</td>
<td>51</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Rat</td>
<td>20</td>
<td>101</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Rat</td>
<td>&lt;2</td>
<td>100</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Human</td>
<td>&lt;2</td>
<td>109</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Dog</td>
<td>&lt;2</td>
<td>103</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Dog</td>
<td>5</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 4. List of Marketed Nasal Products for Brain Targeting

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Indication</th>
<th>Approval Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadol NS®</td>
<td>Butorphanol tartrate (10mg/mL, 1 mg/spray)</td>
<td>Management of pain and migraine</td>
<td>08/08/2001, 12/03/2002</td>
<td>ESI Lederle, Roxane Labs.</td>
</tr>
<tr>
<td>Stimato NS</td>
<td>Desmopressin acetate (0.01%)</td>
<td>Hemophilia A</td>
<td>-</td>
<td>Rhine Poulenc Rorer</td>
</tr>
<tr>
<td>Syneral® Nasal Solution</td>
<td>Nafarelin acetate</td>
<td>Central precocious puberty</td>
<td>-</td>
<td>Roche Laboratories</td>
</tr>
<tr>
<td>Migranal</td>
<td>DHE-45 Dihydroergotamine</td>
<td>Migraine</td>
<td>31/07/2002</td>
<td>Xcel Pharm.</td>
</tr>
<tr>
<td>Zomig Nasal Spray</td>
<td>Zolmitriptan (2.5 and 5 mg/spray)</td>
<td>Migraine</td>
<td>30/09/2003</td>
<td>Astra Zeneca</td>
</tr>
</tbody>
</table>

Table 5. List of Investigational Drug Substances for Brain Targeting

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>Status</th>
<th>Indication</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Scopolamine hydrobromide</td>
<td>Human studies</td>
<td>Prevention of nausea and vomiting by motion sickness</td>
<td>106</td>
</tr>
<tr>
<td>2</td>
<td>Buprenorphine hydrochloride</td>
<td>Human studies</td>
<td>Relief of moderate to severe pain</td>
<td>107</td>
</tr>
<tr>
<td>3</td>
<td>Chlorpheniramine maleate</td>
<td>Human studies</td>
<td>Antihistaminic agent</td>
<td>108</td>
</tr>
<tr>
<td>4</td>
<td>Chlorphenylpyridamine maleate</td>
<td>Human studies</td>
<td>Antihistaminic agent</td>
<td>109</td>
</tr>
<tr>
<td>5</td>
<td>Prophenpyridamine maleate</td>
<td>Human studies</td>
<td>Antihistaminic agent</td>
<td>109</td>
</tr>
<tr>
<td>6</td>
<td>Clonazepam</td>
<td>Human studies</td>
<td>Treatment of petit mal, akinetic and myoclonic seizures</td>
<td>110</td>
</tr>
</tbody>
</table>
arise due to the physiological status in terms of nasal function and accompanying pathologies and pharmaceutical challenges with respect to CNS drug delivery, i.e., low bioavailability, local irritation and toxicity upon long-term usage. Synthesis of more lipophilic analogues, enzyme inhibitors, permeation enhancers, colloidal and bio-adhesive novel drug delivery modalities could help to eliminate few of the problems to some extent. Few formulations have already been successfully marketed and many are under phase I/II/III clinical stages. The emergence of peptide and protein moieties in the therapeutic scene has certainly heightened the scientific and industrial attention to rediscover the potential of this route of drug delivery. It is needless to say that the nasal route with all its inherent advantages has been heralded as the most promising means for the delivery of drugs to the CNS in the near future.

ACKNOWLEDGEMENTS

Mr. Baldev A Patel (Applied Arts) is acknowledged and greatly appreciated for preparing figures and its electronic transformation.

REFERENCES


<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>Status</th>
<th>Indication</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Diphenhydramine hydrochloride</td>
<td>Human studies</td>
<td>Antihistaminic and antihistive agent</td>
<td>111</td>
</tr>
<tr>
<td>8</td>
<td>Doxylamine succinate</td>
<td>Human studies</td>
<td>Antidepressant</td>
<td>112</td>
</tr>
<tr>
<td>9</td>
<td>Ergotamine tartarate</td>
<td>Human studies</td>
<td>Treatment of migraine</td>
<td>113</td>
</tr>
<tr>
<td>10</td>
<td>Metoclopramide hydrochloride</td>
<td>Human studies</td>
<td>Antiemetic</td>
<td>114</td>
</tr>
<tr>
<td>11</td>
<td>Midazolam</td>
<td>Human studies</td>
<td>Preoperative sedation, General anesthetic</td>
<td>115</td>
</tr>
<tr>
<td>12</td>
<td>Nootigmine bromide</td>
<td>Human studies</td>
<td>Myasthenia gravis</td>
<td>116</td>
</tr>
<tr>
<td>13</td>
<td>Nicotine</td>
<td>Product recently approved in USA and UK.</td>
<td>Management of smoking cessation</td>
<td>117</td>
</tr>
<tr>
<td>14</td>
<td>Propanol hydrochloride</td>
<td>Human studies</td>
<td>Management of hypertension and angina pectoris</td>
<td>118</td>
</tr>
<tr>
<td>15</td>
<td>Sufentil citrate</td>
<td>Human studies</td>
<td>Analgesic agent</td>
<td>119</td>
</tr>
<tr>
<td>16</td>
<td>Vasopressin</td>
<td>Human studies</td>
<td>Polydipsia, polyurea and dehydration with diabetes insipid</td>
<td>120</td>
</tr>
</tbody>
</table>
[74] Wermeling, D.P.; Miller, R.J.; Rudy, A.C. Drug Delivery Technol. 2003
Received: October 05, 2004  Accepted: December 10, 2004
Intranasal Mucoadhesive Microemulsions of Zolmitriptan: Preliminary Studies on Brain-targeting

Tushar K Vyas 1, A K Babbar 2, R K Sharma 2, Ambikanandan Misra 1,*

1. Tushar K Vyas, Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Post Box No.51, Vadodara. 390 001, Gujarat, India.
   Phone No.: +91-265-2434187. Fax No.: +91-265-2423898, 2418927
   E-mail: tushardnd2326@hotmail.com

   Phone No.: +91-11-23911712, 23984480. Fax No.: +91-11-23919509
   E-mail: akbabbar@hotmail.com

   Phone No.: +91-11-23911712, 23984480. Fax No.: +91-11-23919509
   E-mail: rks@inmas.org

* Correspondence Author
Ambikanandan Misra,
Professor and Head,
Pharmacy Department,
Faculty of Technology and Engineering,
The Maharaja Sayajirao University of Baroda,
Post box No. 51, Kalabhavan,
Vadodara 390 001. Gujarat, India.
Phone No.: +91-265-2434187
Fax No.: +91-265-2423898, 2418927
E-mail: misraan@hotmail.com & misraan@satyam.net.in

- 1 -