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CURRENT ADVANCES IN THE CARRIER MEDIATED NOSE TO BRAIN DRUG DELIVERY: A REVIEW

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ABSTRACT

Transmitting drug through nose to the brain is difficult. In reality there are many neurological illnesses that call for the treatments where the medicine must cross a blood brain barrier and go through the brain, Alzheimer's disease, Multiple sclerosis and other illnesses of central nervous system are becoming more and more public health concern partly due to longer life expectancies and an ageing population. Although treatments have access to the brain via these channels, the primary drawbacks of this strategy is only a few drug absorption and nasal permeability. This article will describe the routes by which drugs go from the nose to the brain and the toxicity of nanoparticles, the necessity of nanostructured lipid carriers (NLCs) in combination with an drug delivery intranasally to specifically target the brain.

Keywords: Nose to Brain Drug Delivery, Olfactory, Nanocarriers, Transport Pathways, Brain Targeting

INTRODUCTION

The most difficult challenge in delivering a medicine to the brain is because of the "anatomy and physiological barriers like blood-brain barrier (BBB)" **[1]**. "Drugs which contain lipophilic molecules and having the partition coefficient of 1.5 to 2.7 with a molecular weight of less than 600D might be able to pass across the BBB" **[2]**. Additionally the BBB has a greater number of transporters primarily P glycoprotein, Drug entrance into the Central Nervous System (CNS) is constrained by efflux transporters **[3]**. "Effective treatment optionis still lacking presumably as a result of a complexity of central nervous system and the hypothesized multifactorial pathogenic mechanisms despite significant advancements in drug delivery research and considerate the pathogenesis of neurological diseases" **[4]**. Due to these restrictions, researchers are having a tough time developing effective therapeutic treatments for many CNS disorders which includes Alzheimer's and Parkinson's diseases **[5, 6]**. Targeting the CNS has involved both surgical and noninvasive methods **[7, 8]**. The benefits of nose to brain drug delivery comprised of patient compliance, non invasiveness, safety and avoid hepatic first pass metabolism **[9, 10]**. "The current review article aim to elucidate the transport mechanism concerned with the nasal delivery of therapeutics to the brain and the current barriers impeding through drug delivery from the nose to the brain via the olfactory mucosa as well as the current strategies to improve drug transport and summarize a most recent developments in carrier development of Nose to Brain delivery".

INTRANASAL DELIVERY AND FEW CLINICAL EVIDENCES OF ITS APPLICABILITY

"Generally nasal cavity is ideally suitable for the drug administration because both small molecule medications and biopharmaceuticals can be effectively absorbed and passed through the nasal mucosa with excellent permeability" **[11]**. With reasonable patient compliance minimally invasive nose to brain delivery has the possibility for self-medication **[12]**. It is described how the drugs are delivered to the brain via trigeminal and olfactory nerves using nose to brain drug pathway **[13]**. Since peptides, proteins, stem cells, viruses, and nucleotides contain all shown to travel from the nose to the brainis not just limited to small molecule medications **[14]**.

MECHANISMS AND PATHWAYS FOR NOSE TO BRAIN DELIVERY

"Even though multiple studies have been focused on the direct delivery of various therapeutic agents to the brain via the nasal cavity only a minor portion of the initial medicine dose really makes it to the brain suggesting that the precise pathways and the underlying mechanisms are still unknown" **[15]**. In order to overcome present restrictions and raise the drug concentration in brain to levels that are able to induce a pharmacological effect, a quick summary of the mechanisms or pathways influencing the intranasal transport of medicines to the CNS is provided below **[16]**.

THE SYSTEMIC PATHWAY

The medicine is directly absorbed through the extremely high vascular nasal respiratory epithelium and lymphatic system via the systemic pathway, which is an indirect method of delivering medication from the nose to brain **[17]**. The observed bioavailabilities for highly hydrophilic compounds that go through the aqueous paracellular route vary depending on their molecular weight and range from 1 to 10 percent. In contrast to large, hydrophilic molecules, minute lipophilic molecules are able to enter the bloodstream and pass via blood brain barrier (BBB) with ease **[18]**.

OLFACTORY PATHWAY

Therapeutic methods after being inhaled, it moves into olfactory mucosa. Olfactory receptor neurons were found in olfactory mucosa and are in charge of the transduction. The therapeutic portion can enter an olfactory bulb and CSF from olfactory nerves **[19]**. Axonal transport is involved in the intra-neuronal pathway, and it can take hours or days intended for the active moiety to attain various parts of the brain. For neuronal pathways involving transport viaper neural channels active moiety can reach the brain in just a few minutes **[20, 21]**.

THE TRIGEMINAL PATHWAY

Trigeminal nerve pathway connects medulla, pons and spinal cord in the back of the brain. Drug delivery through the nose via trigeminal nerve might occur endocytosis or intracellularly (axonal transport) **[22]**. Once the compounds have passed from the nasal mucosa and reached the trigeminal nerve branches in respiratory and olfactory areas, they are then delivered to the axonal pathway via the brain stem **[23]**. Few Marketed products which are available in the market were shown in **Table 1**.

Table 1: List of the marketed Nasal products for Targeting CNS

DRUG	BRAND NAME	FORMULATION	INDICATIONS	MANUFACTURE
Dihydroergotaminemesylate	Migranal®	Nasal Spray	Migraine	Xcel Pharm
Butorphanoltaratarate	Stadol®		Migraine and Pain	ESI lederle, Roxane Labs
Zolmitriptan	Zoming®	Nasal Spray	Migraine	Astra Zeneca
Desmopressin acetate	DDAVP®	Nasal Spray	Prevention of polydipsia, polyurea and head trauma	FerringPharma, Aventis Pharma
Desmopressin acetate	Stimate®	Nasal Spray	HaemophiliaA	Rhone Poulenc Rorer
Nafarelin acetate	Syneral®	Nasal Spray	Central precocious puberty	Roche laboratories

APPROACHES TO IMPROVE DRUG ABSORPTION TO THE BRAIN

As earlier mentioned that unique properties of nasal cavity that impede effective release of pharmaceuticals to brain in therapeutically pertinent doses, Such properties include chemical modification to a drug molecule using auxiliary agents like formulation components or as co-administrative agents and also as formulation development approaches which could act as CNS targeting delivery.

CHEMICAL MODIFICATION OF THERAPEUTIC AGENTS

Chemically modifying a compound's structure to change its properties is an intriguing way to improve stability, control protease vulnerability and enhance the membrane permeability and absorption of active chemicals **[24, 25]**. In order to optimize the therapeutic agent's qualities for the intended application, chemical modifications attempt to change or inherit specific features of therapeutic agent on an individual basis **[26, 27]**. For instance, chemical alterations and surface functionalization can go on targeting-specificity, whereas lipidization, PEGylation, or amino acid substitution can modulate hydrophilicity or hydrophobicity **[28]**.

ENZYME INHIBITORS

Since it serves as the host for a numerous drug metabolizing enzymes it is very renowned that nasal cavity especially olfactory region shows the strikingly increased mucosal protease along with reductase activity. As an alternative, the enzymatic environment causes the degradation or metabolism of some drugs that uses the nasal cavity like portal for entrance into body **[29]**.

PERMEATION ENHANCERS

The most adaptable functional formulation additives for improving the penetration of therapeutic substances through the biological membranes been suggested as permeation or absorption enhancers. Fatty acids, cyclodextrins, hydrophilic polymers, bile salts and surfactants are just a few of the substances that have been found to have permeation-enhancing properties **[30]**. Permeation enhancers musteventually try to change the amount of transport over the nasal membrane for nose to brain delivery applications by focusing primarily on the olfactory epithelium, from which the drug would be additionally directed towards the olfactory bulb and CNS **[31]**.

VASOCONSTRICTORS

Nasal decongestants have traditionally been made from vasoconstrictors. Their mode of action temporarily entails the constraint or blood vessels which are dilated raises blood pressure, lowers swellingas well as alleviates symptoms of nasal congestion **[32, 33]**.

EFFLUX TRANSPORTERS

Drug delivery through the nasal mucosa has rarely mentioned Efflux transporters.

Recently, it has been demonstrated that rifampicin (a Pglycoprotein efflux inhibitor) co-administration boosted drug absorption in the brain. Though more research is required to determine whether the P glycoproteins seen in olfactory epithelium these play a important role in improving drug uptake in central nervous system **[34]**.

MUCOADHESIVE AGENTS

Mucoadhesive agents like polymers with mucoadhesive qualities as carbopol chitosan, pectin and polacrylic acid are also used as co-administration agents or formulation excipients to enhance nose to brain transport **[35]**. "Chitosan also considerably increased the brain's bioavailability of a nerve growth factor". Additionally by combining chitosan hydrochloride and hydroxypropyl cyclodextrin as mucoadhesive agents increased targeting of buspirone hydrochloride was accomplished **[36]**.

POLYMERIC CARRIERS

The effectiveness of nanoparticles basing on both naturally occurring polymer such as chitosan, alginate and synthetic polymers such as polyesters and poly (lactic acid) is examined. "An alternative method for creating PLGA NPs is by o/w emulsification and nanoprecipitation in which Chitosan the biocompatible and mucoadhesive cationic polysaccharide consists of N acetylglucosamine and D glucosamine which is characterized by its exclusive ability to assistparacellular transport of the biopharmaceuticals because of the temporary opening of the structures of the tight junctions" **[37]**.

LIPID CARRIERS

A biocompatible solid lipid core, such as triglycerides encloses the dissolve API which is stabilised by a variety of surfactants **[38]**. Solid lipid nanoparticles combine benefits of liposomes and polymers nanoparticles **[39]**. Nanostructured lipid carriers are the colloidal structure which comprise of a lipid core comprising of liquid lipids and mixed solids which are accountable for the characteristic structure of a lipid matrix **[40]**. Concentric bilayered vesicles called liposomes have an aqueous centre and one, a few or many phospholipid bilayers around them **[41]**. "A long lasting analgesic effect is seen in comparison to the administration of aerosolized medication when given intranasally to rats using a pressurized olfactory drug delivery device which preferablydeposit the aerosol to olfactory region of the nasal cavity". This could be explained by a smaller amount or sustained release of fentanyl from a liposomal formulation **[42, 43]**.

EMULSIONS

Emulsions like the nanoemulsions and microemulsions are increasingly being used by pharmaceutical industry because of their numerous beneficious properties similar to improved biocompatibility as a result of its lipid constituents resistance to enzymatic degradation, enhanced permeation via the epithelial mucosa, controlled release of APIs and etc. **[44]**. Nanoemulsions because of their typical composition of oil, a surfactant maybe a co-surfactants which are isotropic nano droplet dispersion of 20–500 nm that take more energy to produce and are thermodynamically unsteady **[45]**. "Related observations were presented by Florence and his coworkers who quickly and effectively delivered clobazam i.e., for treating complex partial or acute seizures due to status epilepticus to the brain via the intranasal administration route in the form of a mucoadhesive microemulsion" **[46]**.

NANOCARRIERS IN THERMOREVERSIBLE GELS

For topical delivery of the drugs thermoreversible gels are already applied as a formulation **[47, 48]**. Ahmad and his collogues assessed the competence of applying to the nose the thermosensitive gel which is impregnate with the nanoemulsion for nose to brain delivery in comparison with direct administration of nanoemulsion and the mucoadhesive nanoemulsion additionally **[49]**.

POTENTIAL OF THE NANOCARRIERS

Nanotechnology in modern times became highly interesting field in the particle of not more than 100nm that had a large benefit in field of pharmaceutics in addition to biomedical fields than predictable drug therapy. Different biological macromolecules which is used for the brain disorder via the BBB by using nanotechnology **[50]**.

However the polymeric nanoparticulate systems have a numerous drawbacks including infectivity from production process due to usage of toxic monomers, organic solvents, polymer aggregates, polymerization initiation, toxic degradation production method, large-scale production were not feasible, production methods that are expensive, sterilisation process, concern of toxicity and stability, and more **[58, 59]**. Because of their high lipophilic nature these penetrate into the BBB and because of its irregular structure of NLS's more of the medication can be holded **[51]**. The therapeutic moiety's nasal penetration and retention time are enhanced by the nanocarriers and they are also serving as the vehicle for the passage of encapsulated drugs across the membranes **[52]**.

LIMITATIONS OF NOSE TO BRAIN DRUG DELIVERY

Nasal cavities have a variety of anatomy due to which there will be a wide range of administration procedure and each individual anatomical feature must be taken into the account. The patient's overall health is also crucial since individuals with allergies or a cold may experience issues with the performance of intranasal delivery devices **[53]**. Although few studies claim somewhat independent transport of a hydrodynamic radius, often determines how well the epithelial barrier of endocytosis is penetrated. These compounds need to be connected to the ligand that increases bioavailability **[54]**.

CONCLUSION

Besides from rapidly reaching the brain by avoiding the BBB, Nose to Brain delivery is a non-invasive, convenient, and patient-friendly administration route with a rapid onset of action, precise drug targeting, and fewer systemic side effects. Different kinds of nanocarriers (e.g., polymer or lipid-based) have been shown to facilitate the Nose to Brain delivery of their cargo, for example by adhering to the olfactory epithelium (mucoadhesion or targeting) and allowing the paracellular or intracellular transport of the drug, whereas in rare cases direct transport of the nanocarriers (usually of average sizes ≤200 nm) could be achieved via the olfactory and trigeminal nerve pathways. According to the preceding, nanocarriers should be small in size so that they are not strongly affected by mucocilliary clearance and can be transported via the olfactory and trigeminal nerve pathways. Simultaneously, the nanocarriers should have mucoadhesive qualities to improve their residence length at the olfactory mucosa, as well as increased drug loading to ensure a lower dose form. To date, no significant data has been produced confirming nose to brain transit of intact nanocarriers, which could be regarded favourable because excipient buildup in the brain could result in unwanted side effects. The primary endpoint for successful pharmacological action is the total dosage given to the targeted area. The overall dosage is determined by the total quantity of medication transported through the olfactory mucosa, but it is also determined by the transfer and distribution inside the brain, which is known to be dynamic and very non-uniform. A systematic research of lipid and polymer-based formulations and their nasal administration applications could aid in genuinely appraising their potential for direct nose to brain transfer and revealing both their strengths and drawbacks.

REFERENCES

[1] Illum, L. Transport of drugs from the nasal cavity to the central nervous system. *European journal of pharmaceutical sciences*, 2000; *11*(1): 1-18.

[2] Pajouhesh, H., & Lenz, G. R. Medicinal chemical properties of successful central nervous system drugs. *NeuroRx*, 2005; *2*(4), 541-553.

[3] Miller, D. S. Regulation of P-glycoprotein and other ABC drug transporters at the blood–brain barrier. *Trends in pharmacological sciences*, 2010; *31*(6): 246-254.

[4] Simonato, M., Bennett, J., Boulis, N. M., Castro, M. G., Fink, D. J., Goins, W. F., & Glorioso, J. C. Progress in gene therapy for neurological disorders. *Nature Reviews Neurology*, 2013; *9*(5): 277-291.

[5] Sweeney, P., Park, H., Baumann, M., Dunlop, J., Frydman, J., Kopito, R., & Hodgson, R. Protein misfolding in neurodegenerative diseases: implications and strategies. *Translational neurodegeneration*, 2017; *6*(1): 1-13.

[6] Thorne, R. G., Emory, C. R., Ala, T. A., & Frey II, W. H. Quantitative analysis of the olfactory pathway for drug delivery to the brain. *Brain research*, 1995; *692*(1-2): 278-282.

[7] Mathison, S., Nagilla, R., &Kompella, U. B. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction?. *Journal of drug targeting*, 1998; *5*(6): 415-441.

[8] Sherry Chow, H. H., Chen, Z., & Matsuura, G. T. Direct transport of cocaine from the nasal cavity to the brain following intranasal cocaine administration in rats. *Journal of pharmaceutical sciences*, 1999; *88*(8): 754-758.

[9] Colombo, G., Lorenzini, L., Zironi, E., Galligioni, V., Sonvico, F., Balducci, A. G., & Scagliarini, A. Brain distribution of ribavirin after intranasal administration. *Antiviral research*, 2011; *92*(3): 408-414.

[10] Illum, L. Nasal drug delivery—possibilities, problems and solutions. *Journal of controlled release*, 2003; *87*(1-3): 187-198.

[11] Lochhead, J. J., & Thorne, R. G. Intranasal delivery of biologics to the central nervous system. *Advanced drug delivery reviews*, 2012; *64*(7): 614-628.

[12] Gänger, S., &Schindowski, K. Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics*, 2018; *10*(3): 116.

[13] Crowe, T. P., Greenlee, M. H. W., Kanthasamy, A. G., & Hsu, W. H. Mechanism of intranasal drug delivery directly to the brain. *Life sciences*, 2018; *195*: 44-52.

[14] Schipper, N. G., Verhoef, J., &Merkus, F. W. The nasal mucociliary clearance: relevance to nasal drug delivery. *Pharmaceutical research*, 1991; *8*(7): 807-814.

[15] Mistry, A., Stolnik, S., &Illum, L. Nose-to-brain delivery: investigation of the transport of nanoparticles with different surface characteristics and sizes in excised porcine olfactory epithelium. *Molecular pharmaceutics*, 2015; *12*(8): 2755-2766.

[16] Mittal, D., Ali, A., Md, S., Baboota, S., Sahni, J. K., & Ali, J. Insights into direct nose to brain delivery: current status and future perspective. *Drug delivery*, 2014; *21*(2): 75-86.

[17] Kozlovskaya, L., Abou-Kaoud, M., &Stepensky, D. Quantitative analysis of drug delivery to the brain via nasal route. *Journal of controlled release*, 2014; *189*: 133-140.

[18] Schaefer, M. L., Böttger, B., Silver, W. L., & Finger, T. E. Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. *Journal of Comparative Neurology*, 2002; *444*(3): 221-226.

[19] Chen, X. Q., Fawcett, J. R., Rahman, Y. E., Ala, T. A., & Frey II, W. H. Delivery of nerve growth factor to the brain via the olfactory pathway. *Journal of Alzheimer's Disease*, 1998; *1*(1): 35-44.

[20] Frey, W. H., Liu, J., Chen, X., Thorne, R. G., Fawcett, J. R., Ala, T. A., & Rahman, Y. E. Delivery of 125I-NGF to the brain via the olfactory route. *Drug Delivery*, 1997; *4*(2): 87-92.

[21] Krewson, C. E., Klarman, M. L., & Saltzman, W. M. Distribution of nerve growth factor following direct delivery to brain interstitium. *Brain research*, 1995; *680*(1-2): 196-206.

[22] Dhuria, S. V., Hanson, L. R., & Frey II, W. H. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *Journal of pharmaceutical sciences*, 2010; *99*(4): 1654-1673.

[23] Liu, X. F., Fawcett, J. R., Hanson, L. R., & Frey II, W. H. The window of opportunity for treatment of focal cerebral ischemic damage with noninvasive intranasal insulin-like growth factor-I in rats. *Journal of Stroke and Cerebrovascular Diseases*, 2004; *13*(1): 16-23.

[24] Menco, B. P. M. Ciliated and microvillous structures of rat olfactory and nasal respiratory epithelia. *Cell and tissue research*, 1984; *235*(2): 225-241.

[25] Aungst, B. J. Absorption enhancers: applications and advances. *The AAPS journal*, 2012; *14*(1): 10-18.

[26] Yi, X., &Kabanov, A. V. Brain delivery of proteins via their fatty acid and block copolymer modifications. *Journal of drug targeting*, 2013; *21*(10): 940-955.

[27] Lee, K. C., Park, M. O., Na, D. H., Youn, Y. S., Lee, S. D., Yoo, S. D., ... & DeLuca, P. P. Intranasal delivery of PEGylated salmon calcitonins: hypocalcemic effects in rats. *Calcified tissue international*, 2003; *73*(6): 545-549.

[28] Vyas, T., Tiwari, S. B., &Amiji, M. M. Formulation and physiological factors influencing CNS delivery upon intranasal administration. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, 2006; *23*(4).

[29] Huang, C. H., Kimura, R., Bawarshi-Nassar, R., & Hussain, A. Mechanism of nasal absorption of drugs II: Absorption of L-tyrosine and the effect of structural modification on its absorption. *Journal of pharmaceutical sciences*, 1985; *74*(12): 1298-1301.

[30] Ozsoy, Y., Gungor, S., &Cevher, E. Nasal delivery of high molecular weight drugs. *Molecules*, 2009; *14*(9): 3754-3779.

[31] Davis, S. S., &Illum, L. Absorption enhancers for nasal drug delivery. *Clinical pharmacokinetics*, 2003; *42*(13): 1107-1128.

[32] Wen, M. M. Olfactory targeting through intranasal delivery of biopharmaceutical drugs to the brain—current development. *Discovery medicine*, 2011; *11*(61): 497-503.

[33] Mistry, A., Stolnik, S., &Illum, L. Nanoparticles for direct nose-to-brain delivery of drugs. *International journal of pharmaceutics*, 2009; *379*(1): 146-157.

[34] Bitter, C., Suter-Zimmermann, K., &Surber, C. Nasal drug delivery in humans. *Topical Applications and the Mucosa*, 2011; *40*: 20-35.

[35] Ugwoke, M. I., Agu, R. U., Verbeke, N., &Kinget, R. mucoadhesive drug delivery: background, applications, trends and future perspectives. *Advanced drug delivery reviews*, 2005; *57*(11): 1640-1665.

[36] Asane, G. S., Nirmal, S. A., Rasal, K. B., Naik, A. A., Mahadik, M. S., & Rao, Y. M. Polymers for mucoadhesive drug delivery system: a current status. *Drug development and industrial pharmacy*, 2008; *34*(11): 1246-1266.

[37] Kammona, O., &Kiparissides, C. Recent advances in nanocarrier-based mucosal delivery of biomolecules. *Journal of controlled release*, 2012; *161*(3): 781-794.

[38] Florence, K., Manisha, L., Kumar, B. A., Ankur, K., Kumar, M. A., &Ambikanandan, M. Intranasal clobazam delivery in the treatment of status epilepticus. *Journal of pharmaceutical sciences*, 2011; *100*(2): 692-703.

[39] Sharma, S., Lohan, S., & Murthy, R. S. R. Formulation and characterization of intranasal mucoadhesive nanoparticulates and thermo-reversible gel of levodopa for brain delivery. *Drug development and industrial pharmacy*, 2014; *40*(7): 869-878.

[40] Ved, P. M., & Kim, K. Poly (ethylene oxide/propylene oxide) copolymer thermo-reversible gelling system for the enhancement of intranasal zidovudine delivery to the brain. *International journal of pharmaceutics*, 2011; *411*(1-2): 1-9.

[41] Ahmad, E., Feng, Y., Qi, J., Fan, W., Ma, Y., He, H.,& Wu, W. Evidence of nose-to-brain delivery of nanoemulsions: cargoes but not vehicles. *Nanoscale*, 2017; *9*(3): 1174-1183.

[42] Md, S., Khan, R. A., Mustafa, G., Chuttani, K., Baboota, S., Sahni, J. K., & Ali, J. Bromocriptine loaded chitosan nanoparticles intended for direct nose to brain delivery: pharmacodynamic, pharmacokinetic and scintigraphy study in mice model. *European Journal of Pharmaceutical Sciences*, 2013; *48*(3): 393-405.

[43] Haque, S., Md, S., Fazil, M., Kumar, M., Sahni, J. K., Ali, J., & Baboota, S. Venlafaxine loaded chitosan NPs for brain targeting: Pharmacokinetic and pharmacodynamic evaluation. *Carbohydrate polymers*, 2012; *89*(1): 72-79.

[44] Alam, S., Khan, Z. I., Mustafa, G., Kumar, M., Islam, F., Bhatnagar, A., & Ahmad, F. J. Development and evaluation of thymoquinone-encapsulated chitosan nanoparticles for nose-to-brain targeting: a pharmacoscintigraphic study. *International journal of nanomedicine*, 2012; *7*: 5705.

[45] Di Filippo, L. D., Duarte, J., Fonseca-Santos, B., Tavares Júnior, A. G., Araújo, V., Roque Borda, C. A.,& Chorilli, M. Mucoadhesivenanosystems for nose-to-brain drug delivery in the treatment of central nervous system diseases. *Current Medicinal Chemistry*, 2022; *29*(17): 3079-3110.

[46] Kao, Y. Y., Cheng, T. J., Yang, D. M., Wang, C. T., Chiung, Y. M., & Liu, P. S. Demonstration of an olfactory bulb–brain translocation pathway for ZnO nanoparticles in rodent cells in vitro and in vivo. *Journal of Molecular Neuroscience*, 2012; *48*(2): 464-471.

[47] Alam, M. I., Baboota, S., Ahuja, A., Ali, M., Ali, J., Sahni, J. K., & Bhatnagar, A. Pharmacoscintigraphic evaluation of potential of lipid nanocarriers for nose-to-brain delivery of antidepressant drug. *International journal of pharmaceutics*, 2014; *470*(1-2): 99-106.

[48] Mittal, D., Ali, A., Md, S., Baboota, S., Sahni, J. K., & Ali, J. Insights into direct nose to brain delivery: current status and future perspective. *Drug delivery*, 2014; *21*(2): 75-86.

[49] Ahmad, E., Feng, Y., Qi, J., Fan, W., Ma, Y., He, H.,& Wu, W. Evidence of nose-to-brain delivery of nanoemulsions: cargoes but not vehicles. *Nanoscale*, 2017; *9*(3): 1174-1183.

[50] Stützle, M., Flamm, J., Carle, S., & Schindowski, K. Nose-to-Brain delivery of insulin for Alzheimer's disease. *ADMET and DMPK*, 2015; *3*(3): 190-202.

[51] Pardeshi, C. V., &Belgamwar, V. S. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting. *Expert opinion on drug delivery*, 2013; *10*(7): 957-972.

[52] Wu, H., Hu, K., & Jiang, X. From nose to brain: understanding transport capacity and transport rate of drugs. *Expert opinion on drug delivery*, 2008; *5*(10): 1159-1168.

[53] Vyas, T. K., Shahiwala, A., Marathe, S., & Misra, A. Intranasal drug delivery for brain targeting. *Current drug delivery*, 2005; *2*(2): 165-175.

[54] Bahadur, S., & Pathak, K. Physicochemical and physiological considerations for efficient nose-to-brain targeting. *Expert opinion on drug delivery*, 2012; *9*(1): 19-31.