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Nanotechnology-Based Intranasal Drug Delivery Systems For Brain Targeting: A Comprehensive Review

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Abstract: Intranasal drug delivery has emerged as a promising non-invasive strategy for direct brain targeting by bypassing the blood–brain barrier via the olfactory and trigeminal nerve pathways. However, conventional intranasal formulations suffer from limited nasal residence time and poor mucosal absorption. Recent advances in nanotechnology have enabled the development of diverse nanocarrier systems, including polymeric nanoparticles, lipid-based carriers, micelles, dendrimers, and nanoemulsions, which significantly enhance drug solubility, stability, permeability, and brain bioavailability. Anatomical and physiological features of the nasal cavity play a crucial role in determining delivery efficiency, while biocorona formation influences nanoparticle pharmacokinetics and biodistribution. Stimuli-responsive and targeted nanocarriers offer improved spatiotemporal control of drug release and cellular uptake. Despite encouraging preclinical outcomes, challenges related to toxicity, scalability, and regulatory approval hinder clinical translation. This review summarizes recent advancements in nanotechnology-based intranasal delivery systems and highlights their potential in improving therapeutic outcomes for central nervous system disorders.

Keywords

Nanotechnology, Mucoadhesion, nose-to-brain, nanoparticles, micelles, emulsions, liposomes, SLNs, NLCs, blood–brain barrier, bioavailability.

INTRODUCTION

These days, nasal drug delivery has garnered a lot of interest since it is a reliable, practical, and promising way to provide drugs systemically, especially for injectable and inefficient oral treatments [1]. This route avoids the first-pass metabolism, is easily accessible, has a big surface area, a porous endothelium membrane, and a high total blood flow. Furthermore, the nasal mucosa is more permeable to chemicals than the gastrointestinal tract because of the absence of pancreatic and stomach enzymatic activity as well as interference from the gastrointestinal tract [2]. Lipophilic drugs are usually efficiently absorbed through the nose canal, and their pharmacokinetic profiles are frequently identical to those obtained following intravenous injection. They have about 100% bioavailability in various circumstances.[3] Through the olfactory and trigeminal pathways, the nasal canal offers a direct avenue for the delivery of drugs from the nose to the brain. Drugs must be administered and absorbed through nasal mucus. The protein mucin, which is present in mucus, has the ability to form bonds with solutes, changing the diffusion process. Numerous techniques are used for nasal delivery and absorption through the mucosa, including as paracellular and transcellular routes [4]. There has been much interest in the use of intranasal drug administration for neurological disorders. However, a number of factors, including as the drug's physicochemical properties, experimental conditions, and anatomical and structural traits, make it challenging to achieve targeted drug

delivery to certain areas of interest [5]. A viable substitute for distributing drugs via the NR, including macromolecules and even medicines that are prone to cleavage, is the creation of DDS based on nanotechnology [6]. Depending on the physicochemical characteristics of the medication and the physiological characteristics of the human nose, nanotechnology-based modified delivery has gained favor as a remedy for issues with compliance and limited bioavailability from the nasal cavity. Additionally, target-oriented delivery-specific therapy offers many benefits for the treatment of chronic human diseases. [8–11].

2.2. Pathways in the intranasal route of drug administration

The development of dependable drug delivery systems from the nose to the brain is seriously hampered by individual differences in nasal shape. The complex shape of the nasal canal, which includes variations in surface area, airflow patterns, and mucosal lining thickness, affects the reliability and efficiency of medication absorption and transport to the brain [13]. There are three probable avenues for drugs to enter the brain via the nasal cavity: (i) indirect or systemic pathways via the respiratory portion of the nasal cavity; (ii) olfactory pathway via olfactory neurons; and (iii) trigeminal pathway. The indirect pathway involves medication absorption from the pulmonary epithelial area directly into the bloodstream. From here, the medicine can be delivered to the site of action, and it may even enter the brain.

2.3. Nasal route for drug delivery

The systemic treatment of many CNS disorders, such as depression, epilepsy, schizophrenia, and migraine, is severely hampered by the restricted dispersion of therapeutic medications. Discriminatory barriers that divide the central nervous system from the circulatory system are the main cause of restricted CNS access. Peptides and proteins can cross the blood-brain barrier by entering the brain through the olfactory bulb and trigeminal pathways after nasal delivery [14, 15].

2.4. Advantages and disadvantages of nasal drug delivery

For drug delivery, the nasal cavity's respiratory and olfactory areas offer unique benefits and limitations. For non-surgical medication administration, the respiratory region provides a large, extremely porous surface area that enables quick absorption and direct brain distribution while avoiding the blood-brain barrier.[16] Limitations in this area include poor protein delivery to the brain, possible membrane disruption by high surfactant concentrations, and enzymatic inactivation of medications by nasal enzymes, requiring modest prescription amounts (less than 200 µL).

2.5. Therapeutic applications of nose to brain drug delivery

Systems for delivering drugs from the nose to the brain have demonstrated encouraging possibilities in the treatment of numerous neurological psychiatric conditions. This novel strategy has been investigated for diseases including epilepsy, where anticonvulsant efficacy can be improved by direct brain targeting. Intranasal administration of psychotropic drugs in depression and schizophrenia may provide a quick onset of action and better results from treatment. This approach offers a possible way for prompt intervention and neuroprotection in acute circumstances like stroke. Nose-to-brain delivery systems can help deliver dopaminergic drugs directly to the afflicted areas of the brain in neurodegenerative diseases like Parkinson's disease. Additionally, by providing a non-invasive way to get around the blood-brain barrier and more efficiently administer therapeutic drugs to the central nervous system, this strategy shows promise for a number of different CNS and neurological illnesses.[1,4,9]

3. Nanotechnology for nose to brain delivery

Drug delivery from the nose to the brain can be greatly enhanced by using nanocarriers, such as liposomes and nanoparticles. These carriers are excellent in precisely delivering pharmaceuticals to designated targets, encapsulating them, and maintaining stability. It is An improved delivery method can decrease the necessary dosage while increasing brain medication absorption, which will lessen systemic side effects. By increasing bioavailability and reducing systemic toxicity, nanoparticle-based formulations for nose-to-brain medication delivery systems show promise in improving treatments for neurological disorders. Table 1 displays different kinds of nanotechnology that are supplied from the nose to the brain.[17]

Table No1. Types and characteristics of nanoparticles

Sr No	Types of Nanoparticles	Characteristics
1	Liposomes	Phospholipid bilayers are the basis of liposomes, which are lipid-based nanoparticles.
2	Nanoemulsions	Surfactants stabilize oil-in-water or water-in-oil dispersions, which are known as Nanoemulsions.
3	Nanostructured Lipid Carriers (NLCs)	Lipid-based carriers, known as NLCs, consist of a liquid lipid matrix and a solid lipid core.
4	Solid Lipid Nanoparticles (SLNs)	Solid lipids make up SLNs, which stabilize medications inside their matrix.
5	Polymeric Nanoparticles	The biocompatible polymers used to make these nanoparticles include chitosan and PLGA.
6	Magnetic Nanoparticles	magnetically-active nanoparticles.
7	Dendrimers	Proteins with a tree-like branched structure.

3.1. Lipid based nanoparticles

Lipid nanoparticles are solid structures that provide an interesting substitute for other kinds of nanoparticles, such as polymeric ones, nanogels, and nanoemulsions. These lipid nanoparticles are really small as well! Their size ranges from 1 to 1000 nanometers [18] Since safe lipids and surfactants make up the surface of these solid lipid nanoparticles, human soften claim they are safe for our body. Triglycerides, diglycerides, monoglycerides, fatty acids, and waxes are examples of common lipids [19]. Like unique delivery systems, these lipid nanoparticles are really helpful! They aid in overcoming some of the problems that polymeric nanoparticle systems present. Here, we must take into account two generations! SLNs, or solid lipid nanoparticles, are the initial generation. Next, the second generation of nanostructured lipid carriers (NLC) is introduced [20].

3.2. Liposomes

Liposomes are one of the most widely used lipid-based NPs for drug delivery applications. One or more phospholipid bilayers, often in combination with other lipids like phosphatidylcholine or cholesterol, make up a liposome. Different types of lipids can be used to modify the size and surface charge of liposome membranes. As an illustration, hydrophilic(found inside the Neutral or slightly negatively charged liposomes may contain hydrophobic (found inside the lipid membrane) or watery core) active compounds. Conversely, multiplexes can be formed by positively charged liposomes and negatively charged nucleic acid [21–24].

3.3. Solid Lipid nanoparticles

Solid lipid nanoparticles (SLNs), a more modern kind of lipid-based nanocarriers, are lipid emulsions in which a solid lipid has replaced a liquid lipid. They create a solid lipid matrix and have diameters between 100 and 300 nm. They are often made up of aqueous surfactants or physiological lipids in water [25].SLNs provide a number of advantages for medication delivery, such as excellent physical stability, enhanced, regulated release of loaded medications, and the ability to be produced without the use of organic solvents. The primary drawbacks of SLNs are their rigid shape, which restricts the efficiency of drug loading (especially for hydrophilic molecules) and results in undesired particle development through agglomeration, which may cause the drug to burst [26,27].

3.4. Nanostructured lipid carriers

Nanostructured lipid carriers, or NLCs, are a more recent class of lipid-based NPs created to overcome the shortcomings of SLNs. NLCs boost drug loading and prevent the drug's burst release because they contain a combination of liquid and solid lipids [28]. NLCs are frequently made using high-pressure homogenization and the twofold emulsion method (w/o/w) [29]. Because hydrophobic chemicals are more soluble in liquid lipids than in solid lipids, they can achieve higher encapsulation efficiency. NLC's disadvantages include reduced encapsulation efficiency for a combination of two or more therapeutic agents and relatively limited drug loading capacity for hydrophilic medicines [30].

3.5. Nanoemulsions

The micelles that make up nanoemulsions are composed of three phases: an aqueous phase, an emulsifier, and an oily phase. Three different kinds of nanoemulsions exist: oil in water, water in oil (also known as "reversed" micelles), and bi-continuous (inter-dispersed water and oil domain). [31] Nanoemulsions can improve the stability of drugs, especially lipophilic ones. bioavailability while boosting medication absorption by using nanoscale droplets with a greater surface area [32]. However, because it is thermodynamically unstable, it can lead to poor stability and the release of the encapsulated molecules during storage [33].

3.6. Polymeric nanoparticles

3.6.1. Natural Polymer-Based Nanoparticles

Chitosan (CS) has been used to produce a variety of nanoparticles. The polymer known as chitosan is created when the chitin found in insects and crustaceans is deacetylated to form N-acetyl-D-glucosamine [34]. Chitosan is protonated in acidic environments due to its pKa of approximately 6.5.Since mucus has a pH between 5.5 and 6.5, chitosan is positively charged, which encourages its consistency [35,36]. Because both the respiratory and olfactory epitheliums are negatively charged, chitosan-based NPs prolong the bioavailability of the encapsulated drug for the brain by staying longer in the mucosa. Additionally, it serves as an activator of permeation, helping to open tight junctions between epithelial cells and enabling material movement between cells.

3.6.2. Synthetic Polymer-Based Nanoparticle

Synthetic polymers have been widely used in the development of drug delivery techniques. Many of these polymers are good N2B delivery carriers because they are both biocompatible and biodegradable. The most widely used polymers are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(L-lactide-co-glycolide) (PGLA). Due of their hydrophobic nature, They are used to prevent drugs from breaking down in the nasal cavity and encourage hydrophobic drug loading [37,38]. Pharmaceuticals are encapsulated in these polymer-based nanoparticles using single or double emulsion techniques [39]. PEG or poloxamers are commonly utilized to alter the surface of polymeric nanoparticles to increase their stability, drug loading, and ability to pass through nasal mucus, much as lipid-based liposomes [40].

3.7. Dendrimers

Although dendrimers are classified as polymeric nanoparticles, their modified structure distinguishes them from other polymers. These are large, three-dimensional, single-weight molecules composed of repeating units, nuclei, and various functional groups such as COONa, COOH, and NH2. [41] Several types of dendrimers, such as carbosilane, polyamidoamine (PAMAM), The chemical composition of the core and branches gives rise to poly-l-lysine (PLL) and polypropylene-imine (PPI). Because of the synthesis process, the form, size, polydispersity, and specific surface structure (hydrophilic or lipophilic, charged or neutral) may be controlled in the nanoscale range. [42] The most common kind of dendrimers, called PAMAM dendrimers, are used in gene transfer, medicines, and regenerative medicine, among many other areas. They consist of an alkyl-diamine inner core and an outer shell containing amine branches. Because dendritic patterns are so extensively controlled, dendrimers are potential carriers for biomedical applications and an effective method of delivering insoluble and hydrophobic drugs.[43,44]

Nanocarriers for Nose-to-Brain Delivery

Micelles

Micelles are nanoscale colloidal assemblies that arise from the self-assembly of amphiphilic molecules in an aqueous phase, usually block copolymers or surfactants [54]. Both hydrophilic and hydrophobic areas can be found in these compounds. When amphiphilic molecules are in water, their hydrophilic heads face outward and interact with the surrounding water, while their hydrophobic tails group together to form a nonpolar core [55]. Micelles are effective carriers for poorly soluble medications because of this arrangement, which produces a spherical structure that can contain hydrophobic materials within its center [56]. In drug delivery, micelles can improve hydrophobic medications' solubility, bioavailability, and stability [57,58]. Better medication absorption, longer circulation durations, and the possibility of targeted distribution are made possible by their nano size [55]. Micelles have been utilized in numerous trials to carry drugs from the nose to the brain. The drug's ability to penetrate a cellulose barrier was enhanced when risperidone was encapsulated in micelles [59]. Similarly, dexamethasone-loaded micelles demonstrated a rise in the solubility of the drug in water. medication [60] and increased permeability [14-fold]. Other research revealed in vivo tests that proved micelles' effectiveness in targeting the brain. For instance, after IN inhalation, baicalein was loaded into poly(ethylene glycol)-block-poly(D, L-lactide) (PEG-PLA) micelles, which showed an AUC brain that was 1.50 times higher than the oral drug powder [61]. When compared to the IV free drug solution, rotigotine-loaded micelles demonstrated an extended MRT (1.43-fold) of the drug in rat plasma following IN treatment [62]. Next, the micelles were loaded. into poloxamer gel, resulting in an additional 1.79-fold rise in MRT. The distribution of rotigotine in the olfactory bulb, cerebrum, cerebellum, and striatum rose by 276.6%, 170.5%, 166.5%, and 184.4%, respectively, in comparison to the IV group. One medication used to treat schizophrenia is clozapine. Because to its weak solubility, slow rate of dissolution, gastrointestinal tract degradation, and significant hepatic first-pass metabolism, it has a limited distribution in the brain after oral treatment. In an earlier investigation, clozapine-loaded polymeric Tetronic® 904 and 701, two hydrophobic poloxamines, and Synperonic® PE/F127, a hydrophilic poloxamer, were used to create nanomicelles [63]. The improved formulation demonstrated a five-fold increase in flux in an exvivo nasal penetration investigation when compared to the free drug suspension with no histological injury. Higher brain distribution was seen in mice with in vivo biodistribution. Polydopamine-coated surfactinmicelles were loaded with ibudilast for in administration.[64] The combination improved drug delivery to the mouse brain and showed promising results in the treatment of multiple sclerosis (anti-inflammatory and neuroprotective). Mixture loaded with luridone Using the solvent evaporation approach, Gelucire 44/14 and Poloxamer 407 micelles were created and refined using a 3^2 factorial design [65]. The micelles had a size of 175 nm and a 97.8% entrapment efficiency. Improved ex vivo permeability was exhibited by the hydrogel containing carbopol940 (79%). Histopathological investigations verified that the nasal mucosa of sheep did not exhibit nasociliary toxicity. The injection of the mixed micelles resulted in a notable increase in the concentration of the medication in the brain. Its effectiveness for nose-to-brain drug delivery was highlighted by its 19.1-hour half-life, 394% DTE, and 74% DTP. Polymeric micelles of D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), Poloxamer 407, and Pluronic P123 were loaded with olanzapine [66]. In addition to this development, some research has documented IN micelles that have not worked. Soluplus micelles loaded with meloxicam enhanced drug penetration across the nasal mucosa barrier culture model in an earlier work [67]. The drug is present in the rats' brains after IN injection, albeit the AUC brain is lower than the AUC plasma (only 0.65%). Therefore, even if the micelles' nasal administration assisted in delivering the medication to The majority of the medication entered the blood stream and went to the brain. Binary mixed micelles loaded with clozapine demonstrated decreased penetration into nasal mucosal tissues in a different research [68].

Micelle-Based Formulations (Table 1)

Drug	Components	Key Outcome	References
Risperidone	Poloxamer 407 & 188	Increased permeation across a cellulose membrane.	[45]
Dexamethasone	PCL-PVAc-PEG, TPGS	14-fold increase in aqueous solubility and enhanced permeability.	[46]
Baicalein	PEG-PLA	1.50-fold higher brain AUC compared to oral powder.	[47]
Rotigotine	mPEG-PLGA, Poloxamer	Increased drug distribution in the olfactory bulb (276.6%) and striatum (184.4%).	[48]
Clozapine	Tetronic 904/701, Synperonic	5-fold higher flux ex vivo; brain DTE of 396.5%.	[49,50]
Lurasidone	Gelucire 44/14, Poloxamer 407	1.3-fold higher nasal permeation; brain DTE of 394% and DTP of 74%.	[51,52]
Olanzapine	Poloxamer 407, Pluronic P123, TPGS	Brain DTE of 535.9% and DTP of 81.3%; improved anti-schizophrenia deficits.	[53]

CONCLUSION

Intranasal medication delivery systems based on nanotechnology present a viable way to improve brain targeting and get around the drawbacks of traditional approaches. These technologies show lower systemic adverse effects, increased bioavailability, and the possibility of precision medication delivery to the central nervous system. Although difficulties including enzymatic degradation, restricted formulation limitations and the absorption of specific compounds continue to be problems that are being investigated. More efficient therapies for neurological conditions are made possible by the development of sophisticated nanocarriers and a better knowledge of nasal physiology and medication transport mechanisms.

REFERENCES

1.Alnasser S. A review on nasal drug delivery system and its contribution to therapeutic management. Asian J Pharm Clin Res. 2019;12(1):40-45.

2.Chhajed S, Sangale S, Barhate SD. Advantageous nasal drug delivery system: A review. Int J Pharm Sci Res. 2011;2(6):1322 1336.

3.Alagusundaram M, Chengaiah B, Gnanaprakash K, Ramkanth S, Chetty CM, Dhachinamoorthi D. Nasal drug delivery system - An overview. Int J Res Pharm Sci. 2010;1(4):454-465.

4.Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of the intranasal delivery route of drug administration for brain targeting. Brain Res Bull. 2018;143:155-170.

5. Borkar SP, Raizaday A. Different Strategies for Nose-to-Brain Delivery of Small Molecules. In: Nasal Drug Delivery. Berlin/Heidelberg: Springer; 2023. p. 361-379.

6. Fortuna A, Alves G, Serralheiro A, Sousa J, Falcão A. Intranasal delivery of systemic-acting drugs: small-molecules and biomacromolecules. Eur J Pharm Biopharm. 2014;88(1):8-27.

7. Moakes RJA, Davies SP, Stamataki Z, Grover LM. Formulation of a Composite Nasal Spray Enabling Enhanced Surface Coverage and Prophylaxis of SARS-COV-2. Adv Mater. 2021;33(26):2008304.

8. Kumar A, Pandey AN, Jain SK. Nasal-nanotechnology: revolution for efficient therapeutics delivery. Drug Deliv. 2016;23(3):671-683.

9. Westin UE, Boström E, Gråsjö J, Hammarlund-Udenaes M, Björk E. Direct nose-to-brain transfer of morphine after nasal administration to rats. Pharm Res. 2006;23:565-572.

10. Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Res Bull. 2018;143:155

11. Jeong SH, Jang JH, Lee YB. Drug delivery to the brain via the nasal route of administration: exploration of key targets and major consideration factors. J Pharm Investig. 2023;53(1):119-152.

12. Bahadur S, Pathak K. Physicochemical and physiological considerations for efficient nose-to-brain targeting. Expert Opin Drug Deliv. 2012;9(1):19-31.

13. Veronesi MC, Kubek DJ, Kubek MJ. Intranasal delivery of neuropeptides. Methods Mol Biol. 2011; 789:303-312

14. Rao TS, Tirumala R, Rao PS. Quantification of tamsulosin in human plasma using LC-MS/MS. Journal of Bioanalysis & Biomedicine. 2011 Mar 3;3

15. Shen AM, Minko T. Pharmacokinetics of inhaled nanotherapeutics for pulmonary delivery. J Control Release. 2020;326:222 244.

16. Kumar A, Pandey AN, Jain SK. Nasal-nanotechnology: a revolution for efficient therapeutics delivery. Drug Deliv. 2016;23(3):671-683

17. Sarella PN, Vipparthi AK, Valluri S, Vegi S, Vendi VK. Nanorobotics: Pioneering Drug Delivery and Development in Pharmaceuticals. Research Journal of Pharmaceutical Dosage Forms and Technology. 2024 Feb 22;16(1):81-90.

18. Almeida AJ, Alpar HO. Nasal delivery of vaccines. J Drug Target. 1996;3:455-467

19. Dow S. Liposome-nucleic acid immunotherapeutics. Expert Opin Drug Deliv. 2008;5(1):11-24.

20. Garbuzenko OB, Mainelis G, Taratula O, Minko T. Inhalation treatment of lung cancer: the influence of composition, size and shape of nanocarriers on their lung accumulation and retention. Cancer Biol Med. 2014;11(1):44-55.

21. Shah V, Taratula O, Garbuzenko OB, Patil ML, Savla R, Zhang M, et al. Genotoxicity of different nanocarriers: Possible modifications for the delivery of nucleic acids. Curr Drug Discov Technol. 2013;10(1):8-15.

22. Sanchez-Purra M, Ramos V, Petrenko VA, Torchilin VP, Borros S. Double-targeted polymersomes and liposomes for multiple barrier crossing. Int J Pharm. 2016;511(2):946-956.

23. Dhaliwal HK, Fan Y, Kim J, Amiji MM. Intranasal Delivery and Transfection of mRNA Therapeutics in the Brain Using Cationic Liposomes. Mol Pharm. 2020;17(6):1996-2005.

24. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009;71(4):349-358.

25. Puri A, Loomis K, Smith B, et al. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. Crit Rev Ther Drug Carrier Syst. 2009;26(6):523-580.

26. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages. Res Pharm Sci. 2018;13(4):288-303.

27. Martins S, Sarmento B, Ferreira DC, Souto EB. Lipid-based colloidal carriers for peptide and protein delivery--liposomes versus lipid nanoparticles. Int J Nanomedicine. 2007;2(4):595-607.

28. Tapeinos C, Battaglini M, Ciofani G. Advances in the design of solid lipid nanoparticles and nanostructured lipid carriers for targeting brain diseases. J Control Release. 2017;264:306-332.

29. Gupta A, Eral HB, Hatton TA, Doyle PS. Nanoemulsions: formation, properties and applications. Soft Matter. 2016;12(11):2826-2841.

30. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: An advanced mode of drug delivery system. 3 Biotech. 2015;5(2):123-127.

31. Costa C, Moreira JN, Amaral MH, Sousa Lobo JM, Silva AC. Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. J Control Release. 2019;295:187-200.

32. Elieh-Ali-Komi D, Hamblin MR. Chitin and Chitosan: Production and Application of Versatile Biomedical Nanomaterials. Int J Adv Res. 2016;4(3):411-427.

33. Thummala UK, Vallabhareddy PS, Sarella PN. Enhancing Oral Absorption of Orlistat through Gastroretentive Mucoadhesive Pellets: Formulation and Evaluation. Journal of Clinical and Pharmaceutical Research. 2023 Apr 30:9-17.

34. England RJ, Homer JJ, Knight LC, Ell SR. Nasal pH measurement: A reliable and repeatable parameter. Clin Otolaryngol Allied Sci. 1999;24(1):67-68.

35. Sarella PN, Mangam VT. AI-Driven Natural Language Processing in Healthcare: Transforming Patient-Provider Communication. Indian Journal of Pharmacy Practice. 2024;17(1).

36. Ong WY, Shalini SM, Costantino L. Nose-to-brain drug delivery by nanoparticles in the treatment of neurological disorders. Curr Med Chem. 2014;21(37):4247-4256.

37. McCall RL, Sirianni RW. PLGA nanoparticles formed by single- or double-emulsion with vitamin E-TPGS. J Vis Exp. 2013;(82):1-8.

38. Sarella PN, Thammana PK. Potential applications of Folate-conjugated Chitosan Nanoparticles for Targeted delivery of Anticancer drugs. Research Journal of Pharmaceutical Dosage Forms and Technology. 2023 Oct 1;15(4):281-8.

39. Wong L, Ho P. Dermal and Transdermal Drug Delivery Systems: Current Trends and Approaches. J Pharm Pharmacol. 2017;70(1):59-72.

40. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, et al. Dendrimers: synthesis, applications, and properties. Nanoscale Res Lett. 2014;9(1):247.

41. Janaszewska A, Lazniewska J, Trzepiński P, Marcinkowska M, Klajnert-Maculewicz B. Cytotoxicity of Dendrimers. Biomolecules. 2019;9(8):330.

42. Karmakar S, Bhowmik M, Laha B, Manna S. Recent advancements on novel approaches of insulin delivery. Medicine in Novel Technology and Devices. 2023 Jul 14:100253.

43. Abedi-Gaballu F, Dehghan G, Ghaffari M, Yekta R, Abbaspour-Ravasjani S, Baradaran B, et al. PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. Appl Mater Today. 2018;12:177-190.

44. Dhas N, Pathak YV, Yadav HKS, editors. Biomedical Applications of Nanocarriers in Nasal Delivery. In: Nasal Drug Delivery. Cham: Springer; 2023. p. 101-126.

45. Sipos, B.; Katona, G.; Csóka, I. Risperidone-Loaded Nasal Thermosensitive Polymeric Micelles: Quality by Design-Based Formulation Study. *Pharmaceutics* 2024, 16, 703

46. Sipos, B.; Csóka, I.; Budai-Szűcs, M.; Kozma, G.; Berkesi, D.; Kónya, Z.; Balogh, G.T.; Katona, G. Development of dexamethasone-loaded mixed polymeric micelles for nasal delivery. *Eur. J. Pharm. Sci.* 2021, 166, 105960.

47. Zhang, L.; Yang, S.; Huang, L.; Ho, P.C. *Poly (ethylene glycol)-block-poly (D, L-lactide) (PEG-PLA) micelles for brain delivery of baicalein through nasal route...* Int. J. Pharm. 2020, 591, 119981.

48. Wang, F.; Yang, Z.; Liu, M.; et al. *Facile nose-to-brain delivery of rotigotine-loaded polymer micelles thermosensitive hydrogels...* Int. J. Pharm. 2020, 577, 119046.

49. Sayed, S.; Elsharkawy, F.M.; Amin, M.M.; et al. *Brain targeting efficiency of intranasal clozapine-loaded mixed micelles following radio labeling with Technetium-99m*. Drug Deliv. 2021, 28, 1524–1538

50. Fatma, M.E.; Maha, M.A.; Hesham, A.S.-D.; et al. *Self-Assembling Lecithin-Based Mixed Polymeric Micelles for Nose to Brain Delivery of Clozapine...* Int. J. Nanomed. 2023, 18, 1577–1595.

51. Sharifian, A.; Varshosaz, J.; Aliomrani, M.; Kazemi, M. *Nose to brain delivery of ibudilast micelles for treatment of multiple sclerosis...* Int. J. Pharm. 2023, 638, 122936

52. Pokharkar, V.; Suryawanshi, S.; Dhapte-Pawar, V. *Exploring micellar-based polymeric systems for effective nose-to-brain drug delivery as potential neurotherapeutics*. Drug Deliv. Transl. Res. 2020, 10, 1019–1031.

53. Abo El-Enin, H.A.; Ahmed, M.F.; Naguib, I.A.; et al. *Utilization of Polymeric Micelles as a Lucrative Platform for Efficient Brain Deposition of Olanzapine...* Pharmaceuticals 2022, 15, 249.

54. Cagel, M.; Tesan, F.C.; Bernabeu, E.; Salgueiro, M.J.; Zubillaga, M.B.; Moretton, M.A.; Chiappetta, D.A. Polymeric mixed micelles as nanomedicines: Achievements and perspectives. Eur. J. Pharm. Biopharm. 2017, 113, 211–228.

55. Hwang,D.;Ramsey, J.D.; Kabanov, A.V. Polymeric micelles for the delivery of poorly soluble drugs: From nanoformulation to clinical approval. Adv. Drug Deliv. Rev. 2020, 156, 80–118.

56. Ghezzi, M.; Pescina, S.; Padula, C.; Santi, P.; Del Favero, E.; Cantù, L.; Nicoli, S. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J. Control. Release 2021, 332, 312–336.

57. Nguyen,T.-T.-L.; Duong, V.-A.; Maeng, H.-J. Pharmaceutical Formulations with P-Glycoprotein Inhibitory Effect as Promising Approaches for Enhancing Oral Drug Absorption and Bioavailability. Pharmaceutics 2021, 13, 1103.

58. Sipos, B.; Katona, G.; Csóka, I. Risperidone-Loaded Nasal Thermosensitive Polymeric Micelles: Quality by Design-Based Formulation Study. Pharmaceutics 2024, 16, 703.

59. Sipos, B.; Csóka, I.; Budai-Sz″ucs, M.; Kozma, G.; Berkesi, D.; Kónya, Z.; Balogh, G.T.; Katona, G. Development of dexamethasone loaded mixed polymeric micelles for nasal delivery. Eur. J. Pharm. Sci. 2021, 166, 105960.

60. Zhang, L.; Yang, S.; Huang, L.; Ho, P.C. Poly (ethylene glycol)-block-poly (D, L-lactide) (PEG-PLA) micelles for brain delivery of baicalein through nasal route for potential treatment of neurodegenerative diseases due to oxidative stress and inflammation: An in vitro and in vivo study. Int. J. Pharm. 2020, 591, 119981. [

61. Wang, F.; Yang, Z.; Liu, M.; Tao, Y.; Li, Z.; Wu, Z.; Gui, S. Facile nose-to-brain delivery of rotigotine-loaded polymer micelles thermosensitive hydrogels: In vitro characterization and in vivo behavior study. Int. J. Pharm. 2020, 577, 119046.

62. Sayed, S.; Elsharkawy, F.M.; Amin, M.M.; Shamsel-Din, H.A.; Ibrahim, A.B. Brain targeting efficiency of intranasal clozapine loaded mixed micelles following radio labeling with Technetium-99m. Drug Deliv. 2021, 28, 1524–1538.

63. Sharifian, A.; Varshosaz, J.; Aliomrani, M.; Kazemi, M. Nose to brain delivery of ibudilast micelles for treatment of multiple sclerosis in an experimental autoimmune encephalomyelitis animal model. Int. J. Pharm. 2023, 638, 122936.

64. Fatma, M.E.; Maha, M.A.; Hesham, A.S.-D.; Walla, I.; Ahmed, B.I.; Sinar, S. Self-Assembling Lecithin-Based Mixed Polymeric Micelles for Nose to Brain Delivery of Clozapine: In-vivo Assessment of Drug Efficacy via Radiobiological Evaluation. Int. J. Nanomed. 2023, 18, 1577–1595.

65. Pokharkar, V.; Suryawanshi, S.; Dhapte-Pawar, V. Exploring micellar-based polymeric systems for effective nose-to-brain drug delivery as potential neurotherapeutics. Drug Deliv. Transl. Res. 2020, 10, 1019–1031.

66. Abo El-Enin, H.A.; Ahmed, M.F.; Naguib, I.A.; El-Far, S.W.; Ghoneim, M.M.; Alsalahat, I.; Abdel-Bar, H.M. Utilization of Polymeric Micelles as a Lucrative Platform for Efficient Brain Deposition of Olanzapine as an Antischizophrenic Drug via Intranasal Delivery. Pharmaceuticals 2022, 15, 249.

67. Sipos, B.; Bella, Z.; Gróf, I.; Veszelka, S.; Deli, M.A.; Sz˝ucs, K.F.; Sztojkov-Ivanov, A.; Ducza, E.; Gáspár, R.; Kecskeméti, G.; et al. Soluplus® promotes efficient transport of meloxicam to the central nervous system via nasal administration. Int. J. Pharm. 2023, 632, 122594.

68. Tan, M.S.A.; Pandey, P.; Falconer, J.R.; Siskind, D.J.; Balmanno, A.; Parekh, H.S. Clozapine-Encapsulated Binary Mixed Micelles in Thermosensitive Sol-Gels for Intranasal Administration. Gels 2022, 8, 38.