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NANOSPANLASTICS AS PROMISING CARRIERS FOR NOSE-TO-BRAIN DRUG DELIVERY

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ABSTRACT

Drug delivery to the brain remains the biggest hurdle in central nervous system (CNS) disorders due to the protective nature of the blood-brain barrier (BBB) obstructs most of the drugs from reaching their target site. Intranasal drug delivery has gained attention as a non-invasive and direct nose-to-brain targeting to bypass the BBB. However, conventional nasal formulations often struggle with rapid clearance and poor absorption. This review article focuses on nanospanlastics, a highly flexible, surfactant-based nanovesicle, as a novel and promising approach for nose-to-brain drug delivery. In this review article, we will discuss methods of nanospanlastics formulation, their mechanism of drug release, ability to carry a wide range of drugs, protect them from degradation, and release them in a controlled manner, making them useful for treating chronic CNS disorders. The review also covers recent research showing their potential in managing various chronic CNS disorders like Alzheimer's, Parkinson's, epilepsy, brain tumors, and more. Growing interest and encouraging preclinical results show that nanospanlastics offer a powerful new tool in the fight against neurological and psychiatric disorders. Looking ahead, further clinical studies and scalable production methods will be significant to bringing this innovative technology from the lab to the clinic.

Key words: Nanospanlastics, Nose-to-brain delivery, Intranasal drug delivery, Blood-brain barrier (BBB), Central nervous system (CNS) disorders, Brain targeting, Nanocarriers.

1 INTRODUCTION

CNS disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, brain tumors, stroke, depression, and schizophrenia are among the many neurological, neurodegenerative, and psychiatric conditions that affect the brain and spinal cord. As the world's population ages and life expectancy rises, the frequency of CNS disorders is rising, posing important socioeconomic and health challenges.[1] CNS disorders are responsible for a considerable proportion of disability-adjusted life years (DALYs) and premature deaths. For example, Alzheimer's disease and other dementias are leading causes of disability in the elderly, while epilepsy and depression affect individuals across all age groups.[2] Many of these conditions are chronic, progressive, and currently incurable, requiring long-term therapeutic administration. The pathogenesis of CNS disorders is often multifactorial, involving complex interactions among genetic, environmental, and biochemical factors. This heterogeneity obscures drug development and therapeutic targeting.[3]

2 CHALLENGES WITH CONVENTIONAL THERAPIES

2.1 Blood–Brain Barrier (BBB)

One of the most significant obstacles in CNS pharmacotherapy is the BBB, a highly selective physiological barrier formed by endothelial cells of the brain capillaries.[4] As a result, over 98% of small molecule drugs and nearly all large biologics are unable to cross the BBB in therapeutic concentrations.[5]

2.2 Systemic Side Effects

The BBB restricts the entry of most therapeutic agents particularly large, hydrophilic, or charged molecules into the brain parenchyma. As a result, over 98% of small-molecule drugs and nearly all large biologics are unable to cross the BBB in therapeutic concentrations.[6]

2.3 Poor Patient Compliance

Oral and parenteral method control CNS drug delivery but express more difficulties like first-pass metabolism (oral route), invasiveness (injections), and poor bioavailability.[7]

2.4 Delayed Onset and Limited Brain Targeting

CNS drugs have an overdue onset of action due to slow absorption, extensive metabolism, and limited brain distribution. Moreover, systemic administration often results in extensive drug distribution, leaving a smaller portion of the dose that reaches the CNS.[8]

3 ADVANTAGES OF INTRANASAL DELIVERY

3.1 Direct Access to the Brain

The unique structural and physiological characteristics of the nasal cavity facilitate the intranasal administration of medications, enabling them to circumvent the blood-brain barrier and directly access the brain.[9]

3.2 Non-Invasiveness and Enhanced Patient Compliance

Intranasal administration is devoid of needles, painless, and readily self-administered, rendering it especially suitable for chronic treatment in juvenile and geriatric populations. In contrast to intrathecal or intracerebral injections, which are invasive and associated with significant risk and patient concern, intranasal administration offers a non-invasive, safer, and more cost-effective alternative.[10]

3.3 Rapid Onset of Action

Drugs delivered via the nasal route show a rapid onset of pharmacological action, as they bypass first-pass metabolism and reach the brain within minutes. This feature is mainly helpful in acute CNS disorders such as seizures, migraines, and neurotrauma, where direct therapeutic effect is dangerous.[11]

3.4 Avoidance of First-Pass Hepatic Metabolism

The oral drugs frequently experience extensive metabolism in the gastrointestinal tract and liver, causing reduced bioavailability**.** Intranasal delivery circumvents this metabolic barrier, allowing for higher bioavailability at lower effective doses. These reduce systemic toxicity and improve the therapeutic index.[12]

3.5 Targeted and Sustained Drug Delivery

The nasal drug delivery systems, including nanovesicles included in mucoadhesive gels**,** in situ form systems**, or** thermo-sensitive formulations**,** enable targeted, protracted residence time in the nasal cavity. This enhances drug incorporation and allows for sustained release**,** which is beneficial in maintaining consistent beneficial levels in chronic CNS conditions.[13]

4 NOSE-TO-BRAIN DELIVERY PATHWAYS

Considering these anatomical and physiological routes is crucial for designing effective nose-to-brain drug delivery systems, such as **nanospanlastics**, which rely on these mechanisms for enhanced brain target (fig 1).[14]

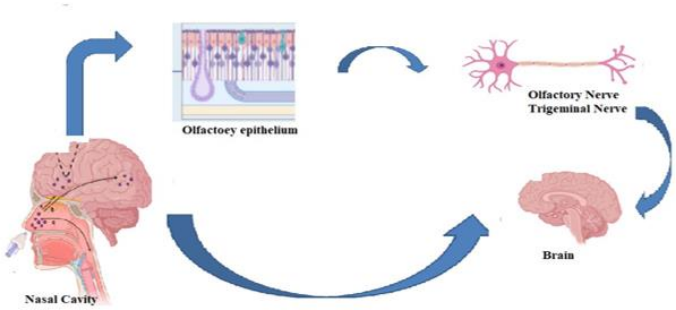

Figure 1: Schematic Representation of the Nose-to-Brain Transport Pathways.[15]

4.1 Olfactory Nerve Pathway

This is the most direct route for drug transport into the brain. Drugs deposited in the olfactory region are taken up by olfactory sensory neurons**.** They are then transported intracellularly via axonal transport to the olfactory bulb**,** a part of the forebrain.[16]

4.2 Trigeminal Nerve Pathway

The trigeminal nerve (cranial nerve V) innervates both the respiratory and olfactory regions. It contains sensory neurons whose branches (ophthalmic and maxillary) extend from the nasal

mucosa to the brainstem and spinal cord. Drugs can utilize this pathway via neuronal or extracellular diffusion to reach deeper brain regions like the brainstem**,** pons**,** thalamus**,** and even the spinal cord.[17]

4.3 Lymphatic and Vascular Pathways

Although the primary advantage of nasal delivery lies in bypassing the BBB, a portion of the drug may be absorbed into the nasal vasculature or lymphatic system**,** reaching the brain via systemic circulation. However, this route is less efficient due to first-pass metabolism and limited BBB penetration.[18]

5 CHARACTERISTICS OF NANOSPANLASTICS

Nanotechnology has revolutionized drug delivery systems in a significant manner in recent years, mainly for targeting hard-to-reach sites like the CNS.[19] Nanospanlastics are customized non-ionic surfactant vesicles**,** typically derived from **niosomes**, that are rendered ultra-flexible by incorporating an edge activator (EA) such as Tween 80, sodium cholate, or Span 80 into the formulation. These edge activators destabilize the lipid bilayer, increasing its elasticity and allowing the vesicles to deform and squeeze through the narrow intercellular spaces of the nasal mucosa and epithelial layers.[20]

5.1 Nanospanlastics: Structure and Properties

Nanospanlastics are a novel class of ultra-deformable, surfactant-based nanovesicles**,** developed to defeat the limitations of the conventional vesicular system, such as liposomes and niosomes (fig.2).[21]

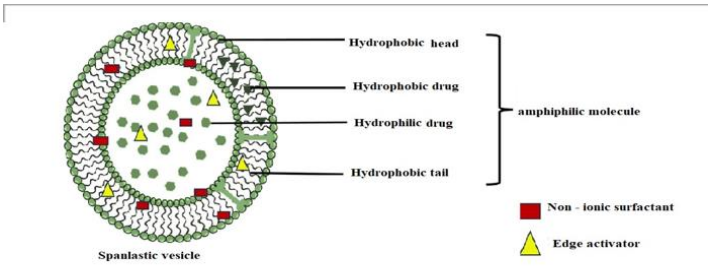

Figure 2: Structure and Composition of Nanospanlastics.[22]

5.1.1 Structural components of nanospanlastics

Nanospanlastics are composed of the following components:

5.1.1.1 Non-Ionic Surfactants

It makes the bilayer membrane of the vesicles and gives the vesicle stability, and encapsulates the drug. The common examples of non-ionic surfactants are Span 60**,** Span 80**,** Tween 60**,** and Tween 80**.** It provides the vesicle structure, controls the hydrophilicity/lipophilicity balance, and controls entrapment efficiency.[23]

5.1.1.2 Edge activators (EAs)

These are the single-chain surfactants used to make the bilayer membrane more substantial and flexible. Examples are Sodium cholate**,** Sodium deoxycholate**,** Tween 80**,** Span 20. They disrupt the prepared bilayer structure, increasing membrane elasticity, and provide the ability of nanospanlastics to squeeze into intercellular gaps without breaking.

5.1.1.3 Drug payload

Nanospanlastics can encapsulate different types of drugs successfully, including hydrophilic drugs within their aqueous core, lipophilic drugs inside the lipid bilayer, and amphiphilic drugs distributed crossways both regions of the vesicle.

5.1.1.4 Optional additives

Cholesterol sometimes added to modulate bilayer fluidity and stability. Charge inducers for the modifying zeta potential and attractive mucoadhesion or stability. Polymers (e.g., chitosan, carbopol) can be added for surface coating, increased mucoadhesion, and sustained release.[24]

5.1.2 Morphology and Size

Nanospanlastics are typically unilamellar or multilamellar spherical vesicles**.** The average particle size ranges from 50–200 nm**,** which is best for nasal absorption and neuronal transport**.** Polydispersity index (PDI) is usually low (<0.3), representing uniform size distribution. Zeta potential is often rather negative or neutral to avoid rapid authorization by mucosal defenses while maintaining stability.[25]

5.2 Advantages of Nanospanlastics for Intranasal Delivery

5.2.1 Enhanced permeability and deformability

Their ultra-flexible nature allows passage through the tight junctions of the nasal epithelium without damaging the mucosa.

5.2.2 Enhanced brain targeting efficiency

Bypassing the systemic circulation reduces drug degradation and increases drug levels in the brain .[26]

5.2.3 Defence from enzymatic degradation

Nanospanlastics give a protective environment, preventing enzymatic degradation within the nasal cavity.[27] bilayer membranes can be made to release drugs in a controlled and long-lasting way, which makes it possible to distribute drugs over a longer period while keeping therapeutic levels.

5.3 Formulation Strategies for Intranasal Nanospanlastics

5.3.1 General principles of nanospanlastics formulation

Nanospanlastics are prepared by incorporating edge activators (EAs) into non-ionic surfactant-based vesicles**,** forming ultra-flexible membranes. The general principles of formulating nanospanlastics are given below

- Selection of the right **type and ratio** of surfactant and EA
- Selection of a s**uitable technique** to control vesicle size, entrapment, and stability
- Employing **post-formulation modification** such as surface coating or gel absorption for enhanced nasal habitation.[28]

6 FORMULATION METHODS

6.1 Hand Shaking / Thin-Film Hydration Method

Nanospanlastic vesicles are prepared by dissolving the surfactant (e.g., Span 60 or Span 80) in ethanol inside a round-bottom flask and then evaporating the solvent under reduced pressure (60 °C) to form a uniform thin lipid film; this film was subsequently hydrated with a warm aqueous solution containing the drug and an edge activator (e.g., Brij 35) at around 60 °C under stirring, producing a milky vesicular dispersion, which was then sonicated to reduce vesicle size and subjected to freeze–thaw cycles (four cycles between –8 °C and 25 °C) to enhance drug entrapment and stability before final characterization(fig 3).[29]

6.2 Ethanol Injection Method

In this method the nanospanlastic vesicles are prepared by first dissolving an accurate amount of drug and surfactant (e.g., Span 60) in approximately 3- 5 mL of absolute ethanol to form a uniform organic phase, which was then slowly injected (around 0.2–1.0 mL/min) into a preheated aqueous solution (60–70 °C) containing an edge activator (e.g., Tween 80) under vigrous stirring; as the ethanol diffused, elastic nanovesicles self-assembled into a milky dispersion, which was stirred for an additional 30–60 minutes to evaporate residual ethanol, followed by brief sonication (typically 3–10 minutes) to reduce particle size and polydispersity, then cooled (usually overnight at 4 °C) to allow vesicle maturation (fig.4).[31]

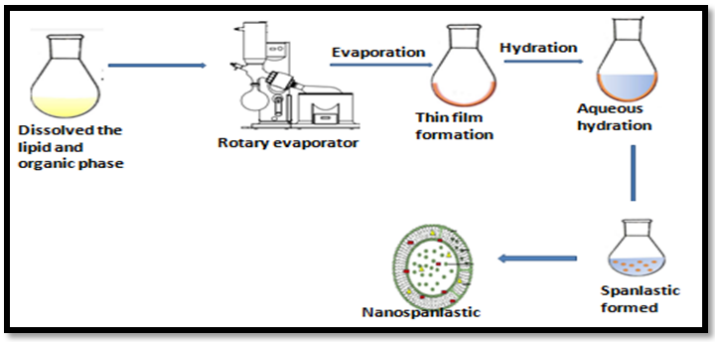

Figure 3: Thin film hydration method.[30]

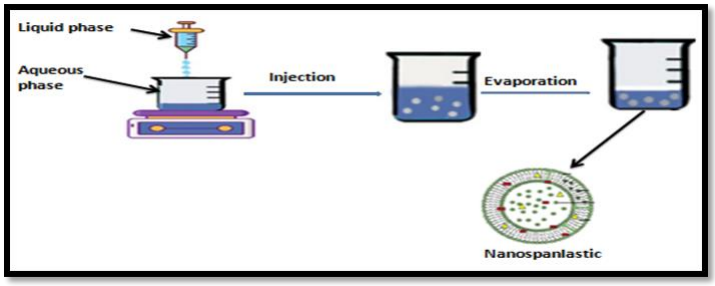

Figure 4: Ethanol injection method.[32]

6.3 Sonication Method

In this method the nanospanlastic vesicles are prepared by first dissolving the drug, non-ionic surfactant (e.g., Span 60), and an edge activator (e.g., Tween 80) in an aqueous medium or after thin-film hydration, forming a coarse vesicular suspension; then subjected this suspension to ultrasonic energy typically via a probe or bath sonicator for a specified duration (3-5 minutes) which reduces particle size and narrows the size distribution, with the sonication time critical to balance vesicle refinement against entrapment efficiency losses, as longer exposure (e.g., 5 minutes) tended to lower drug entrapment due to vesicle disruption and drug discharge into the aqueous phase.[33]

6.4 Microfluidization / Submerged-Jet Principle

The Microfluidization / Submerged-Jet (High-Pressure Homogenization) method to produce nanospanlastic vesicles by feeding the surfactant and frequently drug and edge activator mixture into a microfluidizer, where two high-velocity liquid

streams collide within precisely engineered microchannels under intense pressure (~500–20,000 psi or up to ~200 MPa). This high-shear impingement generates uniform, unilamellar elastic vesicles that form within size distributions and improve reproducibility compared to conventional delivery.[34]

7 APPLICATIONS OF NANOSPANLASTICS IN CNS DISORDERS

Nanospanlastics deformable, elastic vesicular carriers have emerged as a talented platform for overcoming these limits due to their enhanced penetration capability, targeted delivery potential, and biocompatibility (fig 5).[35]

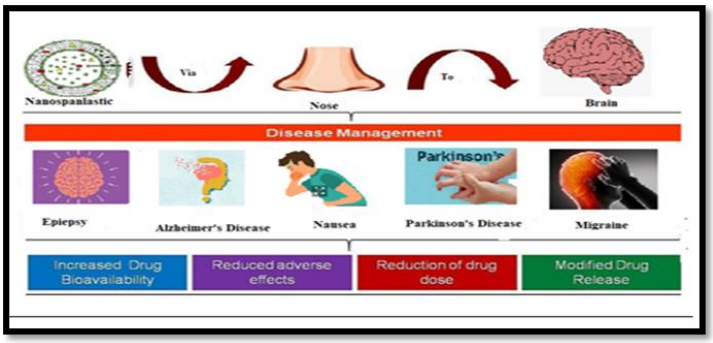

Figure 5. Applications of Nanospanlastics in Central Nervous System (CNS) Disorders.[36]

7.1 Neuroinflammation and Neurodegeneration

7.1.1 Rheumatoid arthritis (RA)

Nanospanlastics encapsulating **anti-inflammatory agents** (e.g., dexamethasone, methotrexate, curcumin) have shown promise in delivering these compounds directly to inflamed neural tissues. Their surface modifiability allows targeted delivery to activate microglia or irritated endothelium, potentially reducing CNS inflammation and associated symptoms in RA.[37]

7.1.2 Alzheimer's disease (AD)

Encapsulation of anti-amyloid agents like curcumin, resveratrol, or galantamine in nanosponges has improved brain bioavailability and continued drug release. Fictionalization with transferrin or apolipoprotein Emimetics can enhance BBB translocation and targeting to the amyloid-prone region.[38]

7.1.3 Parkinson's disease (PD)

PD treatment requires sustained dopaminergic stimulation and neuroprotection. However, most dopaminergic drugs are rapidly metabolized and do not cross the BBB. Encapsulation of levodopa, ropinirole, or selegiline in nanospanlastics prolongs plasma half-life and enhances BBB permeability.[39]

7.1.4 Epilepsy

Many antiepileptic drugs (AEDs) include poor brain bioavailability, require frequent dosing, and exhibit systemic side effects. Nanospanlastics have been used to deliver AEDs like carbamazepine, valproic acid, and lamotrigine, attractive their brain uptake and reducing systemic toxicity.[40]

7.1.5 Depression and anxiety disorders

Most antidepressants and anxiolytics exhibit low CNS bioavailability, slow onset of action, and adverse effects. Drugs such as fluoxetine, sertraline, or diazepam encapsulated in nanospanlastics show enhanced brain delivery and earlier onset of action.[41]

7.1.6 Stroke and cerebral ischemia

After ischemic injury, fast and targeted delivery of neuroprotectants and anti-inflammatory agents is critical. Nanospanlastics transport neuroprotective agents (e.g., edaravone, nimodipine, or antioxidants) and have exposed improved targeting to ischemic tissues.[42]

8 CONCLUSIONS

The management of CNS disorders remains a significant clinical challenge due to the complexity associated with delivering therapeutic agents across the highly discriminating and protective BBB. Despite the availability of a broad array of pharmacological treatments, many drugs fail to attain effective concentration in the brain when administered during conventional systemic routes, resulting in reduced therapeutic efficacy and increased systemic side effects. This underlines the critical need for alternative, targeted, and efficient drug delivery strategies to the brain. Intranasal drug delivery has emerged as a non-invasive, patient-compliant, and promising route that facilitates direct drug transport to the brain by bypassing the BBB via the olfactory and trigeminal neural pathway. However, conventional nasal formulations are limited by rapid mucociliary clearance, enzymatic degradation, and poor penetration across the nasal epithelium. These limitations can be overcome by the incorporation of advanced nanocarrier systems, among which nanospanlastics have shown considerable promise. Nanospanlastics are ultra-deformable, non-ionic surfactant-based nanovesicles customized with edge activators that endow them with better flexibility and membrane-disruptive properties. These structural facial appearances allow them to go

through biological barriers more effectively than conventional vesicular systems. Moreover, their ability to summarize both hydrophilic and lipophilic drugs, along with their biocompatibility and capacity for surface alteration, makes them an ideal candidate for intranasal delivery. Nanospanlastics show estimable mucoadhesion, improved nasal absorption time, and enhanced permeation through the nasal mucosa, all of which contribute to considerably improved brain targeting and therapeutic outcomes.

Pharmacokinetic and pharmacodynamic studies have recognized that intranasal nanospanlastic formulations exhibit higher drug concentrations in the brain, reduced systemic exposure, faster onset of action, and extensive therapeutic effects. The use of mucoadhesive polymers and in situ thermo-responsive gels further optimizes their presentation by minimizing nasal clearance and facilitating sustained release. These qualities position nanospanlastics as a transformative technology in the field of CNS drug delivery. Despite the promising *in-vitro* and *in-vivo* results, the translation of nanospanlastic-based intranasal therapy into clinical use is still in its infancy. Challenges such as large-scale production, long-term safety, regulatory approval, and patient suitability must be carefully addressed. Additionally, consistent protocols for evaluating brain targeting competence, long-term toxicity, and neuropharmacological outcome are necessary for advancing clinical development. In conclusion, nanospanlastics offer a powerful and original platform for nose-to-brain drug delivery. Their ability to overcome the limitations of conventional therapies, coupled with their high competence in targeting the brain, holds major potential for civilizing the treatment of a wide range of CNS disorders. Future studies, heading towards clinical translation and addressing rigid and manufacturing challenges, will be crucial in realizing the full possible of nanospanlastics in CNS therapeutics.

9 CONFLICT OF INTEREST

The authors declare no conflict of interest

REFERENCES

1. Slikker W, Wu L, Xu J, Shafer T J. In pursuit of precision medicine for brain injury and neurotoxicity, and improved protection of human health. In: Comprehensive Precision Medicine. 2024; 495–510.
2. Cui Y, Yang W, Shuai J, Ma Y, Yan Y. Lifestyle and Socioeconomic Transition and Health Consequences of Alzheimer's Disease and Other Dementias in Global, from 1990 to 2019. J Prev Alzheimer's. 2024 Jan 1; 11(1): 88–96.
3. Pangalos MN and Gallen CC. Drug discovery for disorders of the central nervous system. Neurorx. 2005; 2(4): 539–40.
4. Daneman R, Prat A. The blood-brain barrier Cold Spring Harb Perspect Biol. 2015 Jan 5; 7(1): a020412.
5. Gabathuler R. Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. Neurobiol Dis. 2010 Jan 1; 37(1): 48–57.
6. Abbott NJ. Blood–brain barrier structure and function and the challenges for CNS drug delivery. J Inherit Metab Dis. 2013 May 23; 36(3): 437–49.
7. Price G, Patel DA. Drug Bioavailability. StatPearls Elsevier. 2025; 1–2.
8. Devadasu VR, Deb PK, Maheshwari R, Sharma P, Tekade RK. Physicochemical, Pharmaceutical, and Biological Considerations in GIT Absorption of Drugs. In: Dosage Form Design Considerations. Elsevier 2018; 149–78.
9. Huang Q, Chen X, Yu S, Gong G, Shu H. Research progress in brain-targeted nasal drug delivery. Front Aging Neurosci. 2023 Jan 17; 15: 1341295.
10. Parida S, Senthilnathan M. Administration of paediatric intranasal sedation: Need for appropriate formulation & equipment for dispensation. Indian Journal of Medical Research. Wolters Kluwer Medknow Publications. 2023; 157: 96–99.
11. Slikker W, Wu L, Xu J, Shafer TJ. In pursuit of precision medicine for brain injury and neurotoxicity and improved protection of human health. In: Comprehensive Precision Medicine. Elsevier. 2024; 495–510.
12. Ahmed R. First-Pass Metabolism and Its Effect on Bioavailability. OSF. 2025.
13. Salamah M, Budai-Szűcs M, Sipos B, Volk B, Katona G, Balogh GT. Development and Characterization of In Situ Gelling Nasal Cilostazol Spanlastics Gels. MDPI. 2025 Jan 22; 11(2) :82.
14. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. Signal Transduct Target Ther. 2023 May 25; 8(1): 217.
15. Boyuklieva R and Pilicheva B. Micro-and Nanosized Carriers for Nose-to-Brain Drug Delivery in Neurodegenerative Disorders. Biomedicines. 200; 10: 1706.
16. Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: An approach to bypass the blood brain barrier. Pharmaceutics MDPI. 2021; 13: 2049.

17. Nur Husna SM, Tan HTT, Md Shukri N, Mohd Ashari NS, Wong KK. Nasal Epithelial Barrier Integrity and Tight Junctions Disruption in Allergic Rhinitis: Overview and Pathogenic Insights. Front Immunol. 2021 May 21; 12: 663-626.
18. Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. Drug Deliv Transl Res. 2022 Apr 25; 12(4): 735–57.
19. Zhang S, Gan L, Cao F, Wang H, Gong P, Ma C, et al. The barrier and interface mechanisms of the brain barrier, and brain drug delivery. Brain Res Bull. 2022 Nov 1; 190: 69–83.
20. Almohamady HI, Mortagi Y, Gad S, Zaitone S, Alshaman R, Alattar A. Spanlastic Nano-Vesicles: A Novel Approach to Improve the Dissolution, Bioavailability, and Pharmacokinetic Behavior of Famotidine. Pharmaceuticals. 2024 Dec 1; 17(12): 1614.
21. Annisa R. Spanlastic as a Transdermal Drug Delivery System: A Systematic Review. Biomed Pharmacol J. 2025 Mar 31; 18(1): 447–57.
22. Sahin S, Sarma S, and Das A. Spanlastics ocular delivery: a comprehensive review of formulation and therapeutic potential. Discov. Pharm. Sci. 2025; 1: 9.
23. Kumar GP, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery—an overview. Acta Pharm Sin B. 2011 Dec 1; 1(4): 208–19.
24. Amin MK, Boateng JS. Enhancing Stability and Mucoadhesive Properties of Chitosan Nanoparticles by Surface Modification with Sodium Alginate and Polyethylene Glycol for Potential Oral Mucosa Vaccine Delivery. Mar Drugs. 2022 Mar 1; 20(3): 156.
25. Almohamady HI, Mortagi Y, Gad S, Zaitone S, Alshaman R, Alattar A. Spanlastic Nano-Vesicles: A Novel Approach to Improve the Dissolution, Bioavailability, and Pharmacokinetic Behavior of Famotidine. Pharmaceuticals. 2024 Nov 29; 17(12): 1614.
26. Bahadur S, Jha MK. Emerging nanoformulations for drug targeting to brain through intranasal delivery: A comprehensive review. J Drug Deliv Sci Technol. 2022 Dec 1; 78: 103-132.
27. Ansari MD, Saifi Z, Pandit J, Khan I, Solanki P, Sultana Y. Spanlastics a Novel Nanovesicular Carrier: Its Potential Application and Emerging Trends in Therapeutic Delivery. AAPS PharmSciTech. 2022 May 11 ; 23(4): 112.
28. Engelhardt B, Sorokin L. The blood-brain and the blood-cerebrospinal fluid barriers: Function and dysfunction. Semin Immunopathol. 2009 Nov; 31(4): 497–511.
29. Abdelbari MA, El-Mancy SS, Elshafeey AH, Abdelbary AA. Implementing Spanlastics for Improving the Ocular Delivery of Clotrimazole: In vitro Characterization, Ex vivo Permeability, Microbiological Assessment and In vivo Safety Study. Int J Nanomedicine. 2021 Sep; 16: 6249–6261.
30. Lamprou A D, Meziane A, Weaver E and Jaradat E. Microfluidics Technology for the Design and Formulation of Nanomedicines. Nanomaterials. 2021 Dec; 11(12): 3440.
31. Mall J, Naseem N, Haider MF, Rahman MA, Khan S, Siddiqui SN. Nanostructured lipid carriers as a drug delivery system: A comprehensive review with therapeutic applications. Intell Pharm. 2025; 3(4): 243-255.
32. Gharib Riham, Greige-Gerges Helene, Fourmentin Sophie, Charcosset Catherine and Auezova Lizette. Liposomes incorporating cyclodextrin–drug inclusion complexes: Current state of knowledge. Elsevier. 2015; 129: 175-186.
33. Mazyed EA, Helal DA, Elkhoudary MM, Abd Elhameed AG, Yasser M. Formulation and optimization of nanospanlastics for improving the bioavailability of green tea epigallocatechin gallate. Pharmaceuticals. 2021 Jan 1; 14(1): 1–30.
34. Zhang S, Gan L, Cao F, Wang H, Gong P, Ma C. The barrier and interface mechanisms of the brain barrier, and brain drug delivery. Brain Res Bull. 2022 Nov 1; 190: 69–83.
35. Niazi SK. Non-Invasive Drug Delivery across the Blood–Brain Barrier: A Prospective Analysis. Pharmaceutics. 2023 Nov 1; 15(11): 2599.
36. Nadim N, Khan AA, Khan S, Parveen R, Ali J. A narrative review on potential applications of spanlastics for nose-to-brain delivery of therapeutically active agents, Advances in Colloid and Interface Science. Elsevier. 2025; 335: 103341.
37. Mazyed EA, Helal DA, Elkhoudary MM, Abd Elhameed AG, Yasser M. Formulation and Optimization of Nanospanlastics for Improving the

Bioavailability of Green Tea Epigallocatechin Gallate. Pharmaceuticals. 2021 Jan 15; 14(1): 68.

38. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics. Eur J Pharm Biopharm. 2018 Jul 1; 128: 337–362.
39. Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008; 79(4): 368–376.
40. Zahoor I, Shafi A, Haq E. Pharmacological Treatment of Parkinson's Disease. Park Dis Pathog Clin Asp. 2018 Dec 21; 129–144.
41. Garakani A, Murrough JW, Freire RC, Thom RP, Larkin K, Buono FD. Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. Front psychiatry. 2020 Dec 23; 11: 595-584.
42. Saleh A, Khalifa M, Shawky S, Bani-Ali A, Eassa H. Zolmitriptan Intranasal Spanlastics for Enhanced Migraine Treatment; Formulation Parameters Optimized via Quality by Design Approach. Sci Pharm. 2021 May 27; 89(2): 24.