DOI: https://doi.org/10.31351/vol34iss3pp1-11

Spanlastics for Targeted CNS Drug Delivery: A Review

Rajaa A. Dahash[*,1] and Mowafaq M.Ghareeb[2]

[1]Ministry of Health, Baghdad, Iraq .
[2]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

[*]**Corresponding author**
Received 17/10/2023, Accepted 19/5/2024, Published 20/9/2025

Abstract

Numerous pharmacological compounds on the market are ineffective in treating brain disorders, and they are not getting to the brain with the concentration required to have a pharmacological effect. Since there are many barriers, including blood-brain barrier (BBB), P-glycoprotein (an active efflux transporter), and specific enzymatic activity) gamma glutamyl transpeptidase (gamma-GT) and alkaline phosphatase ALP (are some of the mechanisms that protect the brain from harmful circumstances. These systems, in particular BBB, hinder therapeutic interventions of many medications. Thus, most medications cannot give the desired effect because they cannot penetrate the brain, so they are useless in treating brain illnesses. As a result, numerous strategies could enhance drug delivery to the brain. Thus, the vesicular medication delivery devices have made essential advancements in nanotechnology. These systems are helpful in avoiding several problems with traditional dosage forms, such as liposomes, nanoparticles, and spanlastic are proving to be more effective. Spanlastics are surfactant-based elastic vesicular drug delivery system that traps the medication in the core cavity as a bilayer, they are amphiphilic and deliver both hydrophilic and hydrophobic medications. Surface active agents, edge activators, and ethanol are used to prepare the spanlastic, and many methods can be used to prepare these vesicles.
Keywords : Brain , Nanotechnology, Nanovesicles , Spanlastics, Surfactant .

Introduction

The brain is a complex and crucial organ that receives messages from the sense organs and regulates most body functions. In addition to numerous other organs, it regulates hormone secretion, memory encoding, and both voluntary and involuntary motions [(1)], and it is safeguarded both internally and outside because of its crucial function within the human body. Cerebrospinal fluid (CSF), the CSF-blood barrier, and the blood-brain barrier (BBB) shield it from external harm. It also has a cranium that protects against internal harm with multiple membrane layers. These defenses shield the brain against physical trauma, infections, endotoxins, and other adverse effects while preserving homeostasis [(2)].

Several pharmacological compounds now available in the market are ineffective in treating brain disorders. Disorders occur because the requisite concentration of the drug in the brain is not being reached to have a pharmacological effect. Hence, techniques that might enhance the transportation of medications to the brain are a significant focus [(3)].

Despite extensive research on the subject of neuroscience, patients can still be afflicted with severe, life-threatening, and incapacitating brain illnesses such as epilepsy, cerebrovascular diseases, neurodegenerative disorders (e.g., Alzheimer's, Huntington and Parkinson's disease), and various forms of brain cancer. Often, the clinical effectiveness of a therapeutic agent is not just because of its lack of potency but can also be attributed to challenges in accurately delivering the agent to its intended site of action [(4)]. Because their physiochemical characteristics do not meet the criteria for molecular entrance of some medications into the CNS [(5)]. Some drugs, known as lipophilic compounds, may be able to pass through the blood-brain barrier (BBB) if their molecular weight is less than 600 Dalton (Da) and their partition coefficient (Log P) is between 1.5 and 2.7 [(6)].

Reasons for Insufficient Access of Medications to Brain

1. The Presence of Barriers

The BBB functions as a barrier that governs and manages the passage of drug molecules from the circulation to the brain. Over 98% of medication molecules are unable to penetrate the blood-brain barrier due to this reason [(7)].

2- Mechanisms of efflux of Drug Transport to the brain

It is a further obstruction at the BBB interface. The active efflux transporters (AET) that

are present here help the BBB function by expelling the substances from the brain tissue back into the bloodstream (8), mechanisms of drug transport represented in Figure (1) [8,9]:

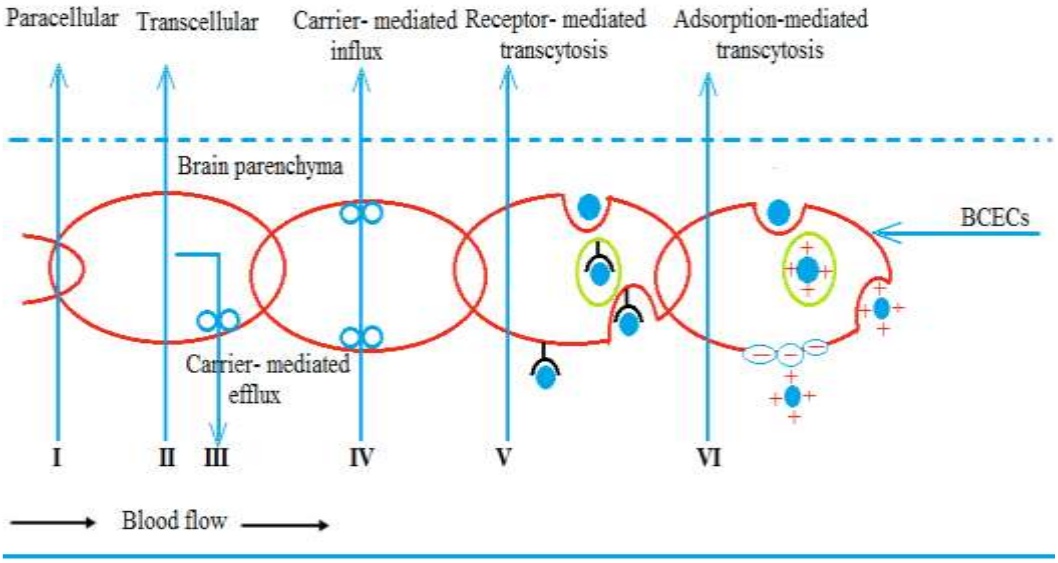

Figure 1. Transport mechanisms across the BBB.

Transportation method across the BBB

The mechanisms used for medication passage over the BBB can be illustrated as follows:

1. Paracellular (aqueous) diffusion

The transfer of medication substances between cells is a part of this process. It is an uncompetitive, untapped process. Few molecules can pass through the tight connections at the endothelial cells of the brain. This method can only transport tiny, water-soluble compounds through the BBB, such as cimetidine, ranitidine, famotidine, and furosemide [10].

2.Transcellular (lipophilic) diffusion (transcytosis)

Transcellular diffusion is a non-competitive, non-saturated process, just like paracellular diffusion. The medication ingredient must travel between cells during this procedure. By using this method, substances with low molecular weight (500 Da) and high lipophilicity (log p > 2) can be transferred so easily through BBB [11].

3. Facilitated carrier-mediated transport

Similar to passive diffusion, the mechanism of facilitated carrier-mediated transport involves the development of transient narrow pores brought about by the binding of a specific drug substrate to a specific carrier. These pores only permit the passage of that drug substrate from high to low concentration [12].

Peptides, amino acids, hexoses, organic anions and cations, neurotransmitters, and nucleosides are some of the carrier systems involved in this transport that have been observed in brain capillaries [13].

4. Receptor-mediated Transcytosis

Large endogenous proteins, certain hormones, and high molecular weight compounds can pass across the blood-brain barrier with the assistance of particular receptors found on the luminal membrane of the barrier. It has also been established that some particular receptors for insulin are insulin-like growth factors [14].

5. Transcytosis mediated by receptors

Large endogenous proteins, certain hormones, and other substances can pass through the BBB with the help of specific receptors located on the luminal membrane [15].

In pinocytosis, or adsorption mediated transcytosis, positively charged material interacts electrostatically with the negatively charged glycocalyx surface of the plasma membrane, causing pinocytosis. Pinocytosis can be used to internalize polycationic proteins like cationized albumin/immunoglobulin in the brain without the involvement of particular plasma membrane receptors. Comparatively speaking, this mechanism has a higher capacity and a lower affinity than receptor-mediated endocytosis [16].

Delivery of active compounds/nanoparticles from the nasal cavity to the brain

The current research suggests that the nose-to-brain pathway is a promising method for delivering medicinal substances or nanocarriers directly to the brain without the need to travel through the blood-brain barrier. Three distinct transport mechanisms are involved: olfactory pathway, Trigeminal nerve pathway, and systemic pathway, which can be explained as follows [17]:

Olfactory pathway

Therapeutic modalities are supplied through the nose and pass to the olfactory mucosa, also known as olfactory epithelium. The olfactory mucosa houses olfactory receptor neurons that are responsible for transduction. Olfactory transduction occurs in the cilia at the distal end of olfactory receptor neurons [18].

Trigeminal pathway

The trigeminal nerve route connects to the caudal region of the brain, including the spinal cord, medulla, and pons. Medications are delivered through the nose via the trigeminal nerve pathway. Intracellular transport occurs by axonal transport or endocytosis. The trigeminal nerve is the biggest of the cranial nerves and consists of three branches: ophthalmic, maxillary, and mandibular. The ophthalmic and maxillary branches are crucial for medication administration from the nose to the brain as their neurons pass straight through the nasal mucosa. A portion of the trigeminal nerve terminates in the olfactory bulbs [19,20].

Systemic pathway

Drugs can enter the brain from the nasal cavity via the bloodstream. The medication was absorbed into the systemic circulation more through the rich vasculature of the respiratory epithelium than the olfactory mucosa portion. The respiratory segment consists of a combination of continuous and fenestrated endothelium that permits the entry of tiny and big molecules into the bloodstream, facilitating their transit across the blood-brain barrier to the central nervous system [21].

Nasal route nanoparticulate drug delivery system for brain targeting

To get to the brain, drug compounds must cross the BBB. Due to the brain's efflux mechanism or its low penetration properties, the majority of medication molecules do not successfully cross the BBB. To overcome these challenges, several nanoparticles (NPs)-based drug delivery methods have been created by numerous researchers [22,23]. NPs are defined as particles with a diameter of less than 1000 nm. They can be made using a variety of biodegradable substances, including lipids and/or phospholipids, various natural and synthetic polymers, and even metals [24,25]. Several vesicles have appeared and been extensively developed for a variety of biomedical uses, as represented in Figure (2) [26,27]. Vesicular drug delivery systems (VDDSs) are defined as drug carriers with a vesicular structure formed of one or more concentric or continuous bilayers resulting from amphiphiles self-assembling in an aqueous medium [28]. Table (1) shows an example of different nanovesicle dosage forms.

Table 1. Examples of different types of nanovesicles

Drug	Nanosystem	Disease
Ropinirole hydrochloride [29]	bilosome	Parkinson's disease
Nisoldipine [30]	bilosome	Calcium channel blocker
Lornoxicam [31]	Cubosomes:	Nonsteroidal anti-inflammatory (NSAID)
Fenticonazole Nitrate [32]	terpesomes	antifungal agent
Zolmitriptan [33]	spanlastic	Migraine treatment
Celecoxib [34]	spanlastic	Anti-Inflammatory effect
Spironolactone hyaluronic [35]	centrosome	Hirsutism treatment
fenticonazole nitrate [36]	centrosome	antifungal agent
Diacerein [37]	Novasome	anti-inflammatory
Ondansetron [38]	Invasomes	Treatment of nausea and vomiting
Terconazole [39]	novasomes	antifungal agent
Tolmetin[40]	niosomes	Nonsteroidal anti-inflammatory (NSAID)
Nisoldipine [30]	bilosome	Calcium channel blocker
Lornoxicam [31]	Cubosomes	Nonsteroidal anti-inflammatory (NSAID)

These days, a variety of vesicles, including liposomes, niosomes, phytosomes, transfersomes, and spanlastic, are the preferred methods for delivering drugs [41]. Compared to conventional ones, VDDSs have several benefits, including superior cell membrane permeability, strong biocompatibility and degradability, self-adapting deformation, and the flexibility to incorporate both hydrophilic and lipophilic medicines [42]. Figure 2 illustrates the varying structures of nanovesicles [43] .

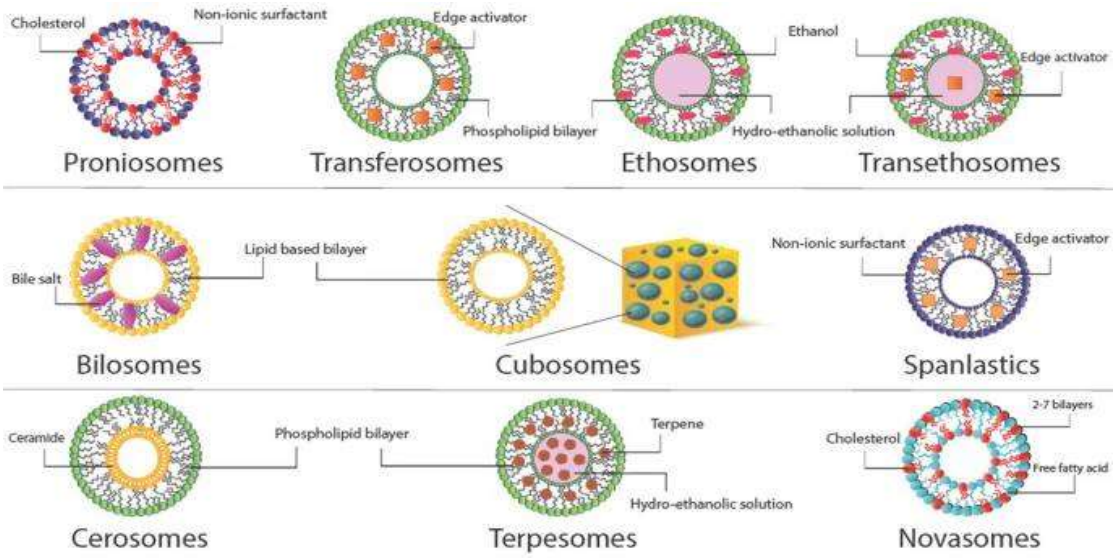

Figure 2. Schematic diagram represents the structure of different nanovesicles

Spanlastics vesicles are amphiphilic, meaning they have both hydrophobic and hydrophilic properties. They enclose medication in a vesicle formed by a non-ionic surfactant. These tiny vesicles can only be seen under a microscope [44,45].

Spanlastics belong to a unique class of nanovesicles that address the drawbacks of liposomes, such as chemical instability. Liposomes are prone to oxidative degradation and have variable phospholipid purity, which affects their chemical stability. The elastic properties of Spanlastics are due to edge activators present in their structure, such as tween80 [46,47]. Spanlastic is a distinct form of vesicular carrier that functions as a drug delivery system for the purpose of targeting drugs to specific sites in specific areas of the body, such as the eyes, mouth, skin, nose, and nails [48,49].

Advantages of Spanlastics [50]:

- Encapsulate hydrophilic and hydrophobic drugs
- Protect drugs from degradation
- Improve drug solubility and bioavailability
- Target specific tissues or cells
- Have controlled release properties

Disadvantages of Spanlastics [51,52]:

- Difficult to scale up production
- Have limited stability under certain conditions
- May have limited drug-loading capacity
- Require specialized equipment or expertise for formulation
- May induce immunogenicity or toxicity
- It may be expensive compared to other drug delivery systems
- It may be challenging to store or transport due to sensitivity to temperature and moisture

Characteristics of Spanlastics Nanovesicles [53,54]

1. Targeted drug delivery: Spanlastics serve as drug delivery systems that target specific body areas precisely.
2. **Flexibility**

These vesicular carriers are adaptable and capable of delivering hydrophilic and lipophilic drugs.

3. **Improved drug effectiveness**

By enhancing drug stability and bioavailability while reducing degradation rates, Spanlastics improve drug efficacy.

4. **Their formulation is intended for targeted action on a particular site in the eye**.

It can reach both the anterior and posterior segments of the eye, facilitating precise drug delivery to the retinal pigment epithelium, vitreous cavity, and choroid.

5. **Wide range of applications**

Spanlastics help deliver drugs to various body parts, including the eyes, mouth, skin, nose, and nails.

Classification of Spanlastics [55,56]

Spanlastics, similar to liposomes, can be categorized based on the number of layers they consist of:

- Multi-Lamellar Vesicles (MLV) are the most commonly used type of Spanlastics. They comprise several bilayers with an estimated diameter of 0.5 to 1.0 microns. MLVs are easy to manufacture and remain mechanically stable for an extended period of time when stored.
- Large Unilamellar Vesicles (LUVs) possess a high ratio of aqueous to lipid components, which allows for the entrapment of more substantial amounts of bioactive materials.
- Small Unilamellar Vesicles (SUVs) are primarily created through techniques such as sonication, French press, and extrusion, which involve preparing them from Multi-lamellar Vesicles.

Constituents of Spanlastics:

Spanlastics have a similar structure to conventional liposomes and Transfersomes, being highly elastic and deformable. Their composition primarily consists of two components: a non-ionic surfactant and an edge activator. They are called

Spanlastics because they are primarily composed of Spans, which make up their composition [57,58].

Non-ionic surfactants lower the interfacial tension between two liquids, such as water and oil. These surfactants do not have any charged group in their head region. Spanlastics primarily comprise Spans, an essential class of non-ionic surfactants known as sorbitan alkyl esters. Spans organize themselves into concentric bilayers to create the vesicular structure in Spanlastics [59, 60].

Different types of Spans, including Span 80, Span 60, Span 40, and Span 20, exhibit varying degrees of stability depending on the fatty acid linked to the polyoxyethylene sorbitan portion of the molecule. For instance, vesicles formed from Span 80 and 40 are prone to disruption, clumping, and instability. However, Span60 contains saturated alkyl chains that provide the vesicles with higher stability. The production of unilamellar or multi-lamellar matrix vesicles is facilitated by the lipophilic character of these saturated alkyl chains in Span 60. Moreover, the surfactant's surface-active characteristics enhance the edge activator's performance, causing a decrease in interfacial tension and producing fine Spanlastics [61,62].

Edge activators

A distinctive group of surfactants with high hydrophilicity, known as high HLB surfactants, possess singular characteristics. They are classified as single-chain surfactants that decrease the interfacial tension, making the vesicles unstable and improving the deformability of their bilayer structure. This characteristic makes the lipid bilayer membranes of the vesicles flexible. EAs also produce more spherical vesicles with smaller particle sizes [63].

The flexibility of the vesicles can be improved by adding an edge activator, such as Tween 80; this enables them to temporarily increase the biological membrane's whole size, allowing slightly larger vesicles to pass through. Additionally, these hydrophilic surfactants can destabilize vesicular membranes, make them more flexible, and produce systems with variable degrees of packing characteristic disturbance [64,65].

Ethanol

Ethanol has beneficial effects on the characteristics of these nano-vesicles. It enhances the ability of the vesicles to incorporate and retain drugs. Ethanol also condenses the membrane, reducing vesicle size and altering the system's net charge, giving rise to negative zeta potential and some steric stabilization [66.67].

The mechanism of Spanlastics penetration

Edge activators cause destabilization of the lipid bilayer, which enhances vesicle deformability. These vesicles have a surfactant component that induces the formation of pores in lipid structures such as membranes and can cause lysis at higher concentrations. Due to their elastic nature, the vesicles can move through intercellular regions based on the water gradient and the bending energy of the membrane, which is dependent on its composition [68,69].

There are two ways that drugs can be ingested [70,71]:

1- The elastic vesicles can act as drug-carrier systems, carrying the drug through intercellular spaces inside cells and biological membranes.

2- The intercellular lipid lamellae are altered by the elastic vesicles' interaction with the epithelial cell membrane, which they do by acting as enhancers to promote penetration.

The successful transport of these carriers can be credited to two factors: the vesicle bilayer's high stress-dependent elasticity and the presence of an osmotic gradient [72,73].

Approaches to Creating Spanlastic Nanocarriers:

1- ethanol injection method Byusing this method, spanlastics with a predetermined ratio of edge activator to non-ionic surfactant may be made. The medication to be enclosed is dissolved in span and ethanol. Sonicate the lipid solution for five minutes. This solution is now continuously fed into a heated aqueous phase that contains an edge activator (such as Tween-80), and it has been stirred on a magnetic stirrer for 30 minutes at 800-1600 rpm and 70–80°C The mixture is stirred at a cold temperature for a further thirty minutes. Ten milliliters is the final formulation after adding distilled water [74,75].

2- Thin film hydration method The thin film hydration approach creates drug-loaded nanovesicles. In summary, a specific weight of medicine is added to a mixture of span and EA in various ratios and dissolved in a specific volume of organic solvent in a round-bottom flask immersed in a water bath at 50°- 60°C. A rotary evaporator spinning at a predetermined rpm is used to gently evaporate the solvent at 50°- 60°C under negative pressure until a thin, dry film is formed inside the flask. The deposited dried film is hydrated using distilled water to verify that the film is fully hydrated and allows time to rotate the flask while maintaining a constant hydration temperature and atmospheric pressure. To get nano vesicular dispersions, the final volume should completed to the required volume at room temperature. This dispersion was maintained overnight at 4°C in the refrigerator [76,77].

Variables affect the physical and chemical properties of spanlastics

The properties of drugs, such as their molecular weight, chemical structure, hydrophilicity, lipophilicity, and HLB value, can impact drug entrapment efficiency in spanlastics. The presence of medicines in spanlastics may cause a rise in vesicle size. This results from interactions between drug particles and the surfactant head group, which can raise the polymer's charge and make the bilayer repellent, resulting in more giant vesicles [78,79].

The stability of spanlastics can be enhanced by incorporating additional compounds in the formulation with the primary surfactant and drug, known as membrane additives. The presence of additives can affect the vesicles' morphology, permeability, and ability to maintain their structure and properties over time. For example, adding tweens can increase the flexibility of the vesicles, making them more able to enter the targeted area [80,81].

To explain the effect of surfactant HLB on vesicle size, an increase in HLB causes a decrease in TC and a shift towards the liquid phase. This shift towards the liquid phase results in an increase in vesicle size due to the increase in surfactant mobility and ability to form larger bilayer structures for surfactant and lipid characterization and the effectiveness of spanlastics' trapping. The HLB value also impacts the entrapment efficiency of spanlastics, with high entrapment efficiency being seen at an HLB value of 8.6 and values between 14 and 17 being unsuitable for their formulation [82,83].

The surfactant's structure can also influence the physicochemical properties to determine the structure of vesicles formed by surfactants. The critical packing parameter (CPP) is used to predict the geometry of the vesicles formed during preparation. It is calculated based on the hydrophobic group volume, critical hydrophobic group length, and area of the hydrophilic head group. By analyzing the CPP value, one can predict the structure of vesicles as spherical micelles if CPP<1/2, bilayer micelles if 1/2<CPP<1, and inverted micelles if CPP>1. Hence, the CPP value is an essential parameter to determine the structure of vesicles formed by surfactants [84.85].

How spanlastics are prepared can notably impact their final properties, with methods like handshaking, ether injection, and sonication all playing a role. When compared to handshaking, ether injection typically results in smaller vesicles. Therefore, if handshaking is used, a potential solution to this issue is first to hydrate the mixture and then vortex it, which can help decrease the size of the vesicles produced [86].

In vivo behaviour of spanlastic

In vivo studies have demonstrated that spanlastics have comparable efficacy to nano-vesicles and exhibit a distribution pattern in the body similar to other colloidal drug delivery systems. The natural vectoring process of spanlastics produces a high distribution of the constituents in vivo [87,88].

The size of the vesicles also plays a role in drug elimination from the bloodstream. Smaller vesicles can pierce sinusoidal epithelium and have easier access to organs like the spleen, skin, nails, nose, and middle ear. However, giant vesicles are more likely to be caught in the alveolar part of the lungs due to retention or phagocytic action [89].

Conclusion

The presence of specific barriers, such as the BBB, represents a well-known obstacle in delivering medications to the brain. The development of the nose-to-brain route professes to be a promising technique to bypass the blood-brain barrier (BBB) and directly transport medicinal compounds to the brain. Nanovasicular systems like Spanlastics, surfactant-based vesicles, can be recruited for the nose to the brain drug delivery system. They prevent first-pass metabolism and address the problems associated with the limited brain bioavailability of medicines. By using these vesicular systems, lipophilic and hydrophilic medications can provide site-specific effects.

Acknowledgment

The authors express their appreciation to the College of Pharmacy - University of Baghdad for providing the necessary resources to conduct the review.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

Funding

This review paper received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Statement

Since there were no humans or animals involved, no ethical approval was needed for this project.

Author Contributions

Study conception and design: Rajaa A., and Mowafaq M.; draft manuscript preparation: Rajaa A., and Mowafaq M. All authors reviewed and approved the final version of the manuscript.

Reference

1. Battaglia L, Panciani PP, Muntoni E, Capucchio MT., Biasibetti E., de Bonis P, Mioletti S., Fontanella M., & Swaminathan S . Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery. In Expert Opinion on Drug Delivery 2018;15 (4), 4: 369–378. Taylor and Francis Ltd. https://doi.org/10.1080/17425247.2018.1429401.
2. Lee D, & Minko T. Nanotherapeutics for nose-to-brain drug delivery: An approach to bypass the blood brain barrier. In Pharmaceutics, 2021; 13(12). MDPI.
3. Assadpour S, Shiran MR, & Akhtari J. . Nose-to Brain Direct Delivery of Nanodrug Formulations in Treatment of Neurological Disorders: A Review Study. In J Mazandaran Univ Med Sci 2021; 31. Persian.
4. Hamzah M. & Kassab, HJ . Frovatriptan succinate intranasal delivery for brain targeting

–in vivo study. The Iraqi Journal of Veterinary Medicine, 2023; 47(2), 101–109. https://doi.org/10.30539/me2mm152

5. Craft S, Raman R, Chow TW, Rafii MS, Sun CK, Rissman RA, et al. Safety, efficacy, and feasibility of intranasal insulin for the treatment of mild cognitive impairment and alzheimer disease dementia: A randomized clinical trial. JAMA Neurol 2020;77(9):1099–109. [PubMed: 32568367] .
6. Taher SS, & Al-Kinan KK. In vivo Brain Pharmacokinetics of Dolutegravir Sodium-Loaded Nanostructured Lipid Carrier in situ Gel: Comparative Study with an Intravenous Drug Solution. Al-Rafidain Journal of Medical Sciences, 2025 ; 8(1):119–125.
7. Alnasser S. A review on nasal drug delivery system and its contribution in therapeutic management. Asian Journal of Pharmaceutical and Clinical Research. 2019 7;12(1):40-45.
8. Yasir M, Vir Singh Sara, U, Som I., Gaur P, Singh M, & Ameeduzzafar. Nose to Brain Drug Delivery: A Novel Approach Through Solid Lipid Nanoparticles. Current Nanomedicine, 2016 ;6(2):105–132.
9. Selvaraj K., Gowthamarajan K, & Karri VV . Nose-to-brain transport pathways an overview: the potential of nanostructured lipid carriers in the nose-to-brain targeting. In Artificial Cells, Nanomedicine and Biotechnology . 2018; 46(8) : 2088–2095.
10. Salman AH, Alkufi HK, Taher SS, Al-Mahmood S, & Haiss MA. Response surface optimization and in vitro study of nasal solusomes nanovesicles for the bioavailability improvement and brain targetting of sumatriptan. Epitheorese Klinikes Farmakologias Kai Farmakokinetikes, 2024; 42:107–117.
11. Markovic M, Zur M, Garsiani S, Porat D, Cvijić S, Amidon GL, & Dahan A. The Role of Paracellular Transport in the Intestinal Absorption and Biopharmaceutical Characterization of Minoxidil. Pharmaceutics . 2022; 14(7).
12. León G, Gómez E., Miguel B., Hidalgo AM., Gómez M, Murcia, MD, & Guzmán MA. Feasibility of Adsorption Kinetic Models to Study Carrier-Mediated Transport of Heavy Metal Ions in Emulsion Liquid Membranes. Membranes . 2022; 12(1).
13. Patharapankal EJ, Ajiboye, AL, Mattern C, & Trivedi V. Nose-to-Brain (N2B) Delivery: An Alternative Route for the Delivery of Biologics in the Management and Treatment of Central Nervous System Disorders. In Pharmaceutics . 2024 ;16 (1).
14. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics. Eur. J. Pharm. Biopharm. 2018, 128. 337–362.
15. Ainurofiq A, Prasetya A, Rahayu BG, al Qadri, M S, Kovusov M, & Laksono OEP. Recent developments in brain-targeted drug delivery systems via the intranasal route. Farmacja Polska. 2022;, 78(12): 695–708.
16. Razzak RA, Florence GJ, & Gunn-Moore FJ. Approaches to cns drug delivery with a focus on transporter-mediated transcytosis. In International Journal of Molecular Sciences . 2019; 20(12). MDPI AG.
17. Liu X, Jiang J, Meng H. Transcytosis - An effective targeting strategy that is complementary to “EPR effect” for pancreatic cancer nano drug delivery. Theranostics . 2019; 9 (26) : 8018-8025. DOI: 10.7150/thno.38587.
18. Dhuria SV, Hanson LR, Frey WH. Novel vasoconstrictor formulation to enhance intranasal targeting of neuropeptide therapeutics to the central nervous system. J Pharmacol Exp Ther. 2009;328(1):312-20.
19. Md S, Khan RA, Mustafa G, et al. Bromocriptine loaded chitosan nanoparticles intended for direct nose to brain delivery: pharmacodynamic, pharmacokinetic and scintigraphy study in mice model. Eur J Pharm Sci. 2013; 48: 393–405.
20. Patharapankal EJ, Ajiboye AL, Mattern C., & Trivedi, V. . Nose-to-Brain (N2B) Delivery: An Alternative Route for the Delivery of Biologics in the Management and Treatment of Central Nervous System Disorders. In Pharmaceutics .2024 ; 16(1) :66 . Multidisciplinary Digital Publishing Institute (MDPI).
21. Zhang W, Sigdel G, Mintz KJ, Seven ES, Zhou, Y, Wang C, & Leblanc RM. Carbon dots: A future blood–brain barrier penetrating nanomedicine and drug nanocarrier. In International Journal of Nanomedicine . 2021 ; 16 : 5003–5016). Dove Medical Press Ltd.
22. Pimentel E, Sivalingam K, Doke M, &Samikkannu, T. Effects of Drugs of Abuse on the Blood-Brain Barrier: A Brief Overview. In Frontiers in Neuroscience. 2020 ; 14 . Frontiers Media SA.
23. Kumar A, Ahmad A, Vyawahare A, & Khan R. Membrane Trafficking and Subcellular Drug Targeting Pathways. In Frontiers in Pharmacology , 2020 ;11. Frontiers Media SA.
24. Thomas LM, & Khasraghi AH . Nanotechnology-based topical drug delivery systems for management of dandruff and seborrheic dermatitis: An overview. In Iraqi Journal of Pharmaceutical Sciences .2020 29 (1) : pp. 12–32). University of Baghdad - College of Pharmacy.
25. Tamer MA., & Kassab, H J. The development of abrain targeted mucoadhesive amisulpride loaded nanostructured lipid carrier . Farmacia

.2023; 71(5), 1032–1044. https://doi.org/10.31925/farmacia.2023.5.18

26. Emad, N. A., Ahmed, B., Alhalmi, A., Alzobaidi, N., & Al-Kubati, S. S. Recent progress in nanocarriers for direct nose to brain drug delivery. In Journal of Drug Delivery Science and Technology . 2021; 64. Editions de Sante. https://doi.org/10.1016/j.jddst.2021.102642.

27. Formica, M. L., Real, D. A., Picchio, M. L., Catlin, E., Donnelly, R. F., & Paredes, A. J. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. In Applied Materials Today . 2022; 29. Elsevier Ltd. https://doi.org/10.1016/j.apmt.2022.101631.

28. Ren, Y., Nie, L., Zhu, S., & Zhang, X. Nanovesicles-Mediated Drug Delivery for Oral Bioavailability Enhancement. In International Journal of Nanomedicine . 2022 ; 17: 4861–4877. Dove Medical Press Ltd. https://doi.org/10.2147/IJN.S382192.

29. Ali, S. K., & Al-Akkam, E. J. . Effects of Different Types of Bile Salts on the Physical Properties of Ropinirole-Loaded Bilosomes. Al-Rafidain Journal of Medical Sciences. 2023; 5: 134–142. https://doi.org/10.54133/ajms.v5i.176

30. Naji, G. H., & al Gawhari, F. J.. Study the Effect of Formulation Variables on Preparation of Nisoldipine Loaded Nano Bilosomes. Iraqi Journal of Pharmaceutical Sciences .2023 ; 32 :271–282. https://doi.org/10.31351/vol32issSuppl.pp271-282

31. Younus Alkwak, R. S., & Rajab, N. A. . Lornoxicam-Loaded Cubosomes: - Preparation and In vitro Characterization. Iraqi Journal of Pharmaceutical Sciences . 2022; 31(1): 144–153. https://doi.org/10.31351/vol31iss1pp144-153

32. Albash, R., Al-Mahallawi, A. M., Hassan, M., & Alaa-Eldin, A. A. . Development and optimization of terpene-enriched vesicles (terpesomes) for effective ocular delivery of fenticonazole nitrate: In vitro characterization and in vivo assessment. International Journal of Nanomedicine. 2020; 16: 609–621. https://doi.org/10.2147/IJN.S274290.

33. 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. Scientia Pharmaceutica . 2021: 89(2). https://doi.org/10.3390/scipharm89020024 .

34. Alaaeldin, E., Abou-Taleb, H. A., Mohamad, S. A., Elrehany, M., Gaber, S. S., & Mansour, H. F. Topical nano-vesicular spanlastics of celecoxib: Enhanced anti-inflammatory effect and down-regulation of tnf-α, nf-κb and cox-2 in complete freund's adjuvant-induced arthritis model in rats. International Journal of Nanomedicine . 2021; 16: 133–145.

35. Albash R, Fahmy AM, Hamed MI, Darwish K. , & E -Dahmy, RM . Spironolactone hyaluronic acid enriched cerosomes (HAECs) for topical management of hirsutism: in silico studies, statistical optimization, ex vivo, and in vivo studies. Drug Delivery . 2021; 28(1); 2289–2300.

36. Albash R, Yousry C, Al-Mahallawi AM, & Alaa-Eldin AA . Utilization of PEGylated cerosomes for effective topical delivery of fenticonazole nitrate: in-vitro Characterization, statistical optimization, and in-vivo assessment. Drug Delivery . 2021; 28(1): 1–9.

37. Fareed NY, & Kassab HJ. Diacerein Loaded Novasome for Transdermal Delivery: Preparation, In-Vitro Characterization and Factors Affecting Formulation. Iraqi Journal of Pharmaceutical Sciences . 2023 ; 32: 214–224.

38. Salih O, & Muhammed E. Preparation, Evaluation, and Histopathological Studies of Ondansetron-Loaded Invasomes Transdermal Gel. Journal of Research in Pharmacy . 2024; 28(1), 289–303.

39. Mosallam S, Ragaie MH, Moftah NH, Elshafeey, AH, & Abdelbary AA. Use of novasomes as a vesicular carrier for improving the topical delivery of terconazole: In vitro characterization, in vivo assessment and exploratory clinical experimentation. International Journal of Nanomedicine . 2021; 16: 119–132.

40. Noor AD, & Rajab NA . Formulation and characterization of niosomes for controlled delivery of tolmetin. Journal of Pharmaceutical Negative Results . 2022 ; 13(4): 159–169.

41. Naji GH, & al Gawhari, FJ . Study the Effect of Formulation Variables on Preparation of Nisoldipine Loaded Nano Bilosomes. Iraqi Journal of Pharmaceutical Sciences . 2023 ; 32: 271–282.

42. Qais Abdulkafi A, Nazar Abdal-Hammid S, Alwan LA, & Nazar Abd Alhammid S. A modern method for the delivery of nanovesicular drugs, spanlastics . International Academic and Research Journal of Pharmacy . 2023 ; 4(1) : 1-10.

43. Al-Sawaf OF, & Jalal F . Novel Probe Sonication Method for the Preparation of Meloxicam Bilosomes for Transdermal Delivery: Part One. In Journal of Research in Medical and Dental Science .2023; 11(6) :15-20 .

44. Kakkar S, Kaur IP. Spanlastics -A novel nanovesicular carrier system for ocular delivery. Int J Pharm. 2011;13(10):202–210.

45. Sharma A, Pahwa S, Bhati S, Kudeshia P. Spanlastics: a Modern Approach for

Nanovesicular Drug Delivery System. Int J Pharm Sci Res. 2020;11(3):1057-1065

46. Ren Y, Nie L, Zhu S, Zhang X. Nanovesicles-Mediated Drug Delivery for Oral Bioavailability Enhancement. Int J Nanomedicine. 2022;17:4861-4877 .

47. Chauhan MK, Verma A. Spanlastics-Future of Drug Delivery and Targeting. Verma al World J Pharm Res. 2017;6(12):429-446.

48. Almuqbil RM., Sreeharsha N, & Nai AB. Formulation-by-Design of Efinaconazole Spanlastic Nanovesicles for Transungual Delivery Using Statistical Risk Management and Multivariate Analytical Techniques. Pharmaceutics . 2022 ; 14(7).

49. Alhammid SN, Kassab H J , Hussein LS , Haiss MA , Hussein k Alkufi HK. Spanlastics Nanovesicles: An Emerging and Innovative Approach for Drug Delivery . MA'AEN JOURNAL FOR MEDICAL SCIENCES . 2023; 2:100e107 .

50. Chauhan MK, Verma A. Spanlastics-Future of Drug Delivery and Targeting. Verma al World J Pharm Res. 2017;6(12):429-446.

51. Jadhav KR, Pawar AY, Bachhav AA, Ahire SA. Proniosome: A novel non-ionic provesicules as potential drug carrier. Asian J Pharm. 2016; 10(3): 210–222.

52. Aziz D, Mohamed SA, Tayel S, Makhlouf A. Enhanced Ocular Anti-Aspergillus Activity of Tolnaftate Employing Novel Cosolvent-Modified Spanlastics: Formulation, Statistical Optimization, Kill Kinetics, Ex Vivo Trans-Corneal Permeation, In Vivo Histopathological and Susceptibility Study. Pharmaceutics. 2022; 29(1) :1-21.

53. Elhabak M, Ibrahim S, Abouelatta SM. Topical delivery of l-ascorbic acid spanlastics for stability enhancement and treatment of UVB induced damaged skin. Drug Deliv. 2021; 28(1):445–453.

54. Abdelmonem R, Nabarawi M, Attia A. Development of novel bioadhesive granisetron hydrochloride spanlastic gel and insert for brain targeting and study their effects on rats. Drug Deliv. 2018;25(1):70–77.

55. Kamath K, & Ramakrishna Shabaraya, A.Spanlastics: amodern formulation approach in drug delivery . European journal of pharmaceutical and medical research . 2023 ; 10(4) : 96-102 .

56. Ahmed Al-Zubaidi, labeeb, & Salih Al-Rubaie, M. . Multi Lamellar Vesicles (Mlvs) Liposomes Preparation by Thin Film Hydration Technique. In Eng. &Tech.Journal . 2014 ; 32(3).

57. Al-mahallawi AM, Khowessah OM, Shoukri RA. Enhanced non invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles: Fabrication, in-vitro characterization, and comparative ex-vivo permeation studies. Int J Pharm. 2017; 157-164.

58. Ansari MD, Saifi Z, Pandit J, Khan I, Solanki P, Sultana Y, Aqil M. Spanlastics a Novel Nanovesicular Carrier: Its Potential Application and Emerging Trends in Therapeutic Delivery. AAPS PharmSciTech. 2022 ; 11;23(4):112. doi: 10.1208/s12249-022-02217-9. PMID: 35411425.

59. 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;6249–6261.

60. Mekkawy AI, Eleraky NE, Soliman GM, Elnaggar MG, Elnaggar MG. Combinatorial Therapy of Letrozole- and Quercetin-Loaded Spanlastics for Enhanced Cytotoxicity against MCF-7 Breast Cancer Cells. Pharmaceutics. 2022;14(7) :1-21.

61. Paecharoenchai O, Teng L, Yung BC, Teng L, Opanasopit P, Lee RJ. Nonionic surfactant vesicles for delivery of RNAi therapeutics. Nanomedicine (Lond). 2013 ;8(11):1865-73. doi: 10.2217/nnm.13.155. PMID: 24156490; PMCID: PMC3971008.

62. Singh S, Vardhan H, Kotla N, Maddiboyina B, Sharma D, Webster T. The role of surfactants in the formulation of elastic liposomal gels containing a synthetic opioid analgesic. Int J Nanomedicine. 2016;11:1475-1482 .

63. El Maghraby GM, Williams AC, Barry BW. Interactions of surfactants (edge activators) and skin penetration enhancers with liposomes. Int J Pharm. 2004;276(1-2):143-61. doi: 10.1016/j.ijpharm.2004.02.024. PMID: 15113622.

64. Moqejwa T, Marimuthu T, Kondiah PPD, Choonara YE. Development of Stable Nano-Sized Transfersomes as a Rectal Colloid for Enhanced Delivery of Cannabidiol. Pharmaceutics. 2022;14(4):703. doi: 10.3390/pharmaceutics14040703. PMID: 35456536; PMCID: PMC9032849.

65. 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;6249–6261.

66. Elmowafy E, El-Gogary RI, Ragai MH, Nasr M. Novel antipsoriatic fluidized spanlastic nanovesicles: In vitro physicochemical characterization, ex vivo cutaneous retention and exploratory clinical therapeutic efficacy. Int J Pharm. 2019;26(4):1-9.

67. Almuqbil, RM, Sreeharsha N, & Nair AB. Formulation-by-Design of Efinaconazole Spanlastic Nanovesicles for Transungual

Delivery Using Statistical Risk Management and Multivariate Analytical Techniques. Pharmaceutics . 2022; 14(7).

68. Badria F, Mazyed E. Formulation of Nanospanlastics as a Promising Approach for Improving the Topical Delivery of a Natural Leukotriene Inhibitor (3-Acetyl-11-Keto-β-Boswellic Acid): Statistical Optimization, in vitro Characterization, and ex vivo Permeation Study. Drug Des Devel Ther. 2020;14:3697-3721 .

69. Kaur IP, Rana C, Singh M, Bhushan S, Singh H, Kakkar S. Development and evaluation of novel surfactant-based elastic vesicular system for ocular delivery of fluconazole. J Ocul Pharmacol Ther. 2012;28(5):484–496.

70. 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;6249–6261.

71. Hussein JK, & Khalid Kadhem AK. Formulation and Evaluation of Idebenone Microemulsion as a Potential Approach for the Transmucosal Drug Delivery Systems. Iraqi Journal of Pharmaceutical Sciences . 2024 ; 33(1): 79–88. https://doi.org/10.31351/vol33iss1pp79-88

72. Farghaly DA, Aboelwafa AA, Hamza MY, Mohamed MI. Topical Delivery of Fenoprofen Calcium via Elastic Nano-vesicular Spanlastics: Optimization Using Experimental Design and In Vivo Evaluation. AAPS PharmSciTech. 2017;18(8):2898–2909.

73. Shamma Rehab Nabil, et,al. Enhanced skin targeting of retinoic acid spanlastics: in vitro characterization and clinical evaluation in acne patients. Journal of liposome research . 2019;5(2): 283-290.

74. Al Hazzaa, SA, & Rajab NA. Cilnidipine Nanocrystals, Formulation and Evaluation for Optimization of Solubility and Dissolution Rate. Iraqi Journal of Pharmaceutical Sciences. 2023; 32: 127–135.

75. Allah AKA, & Hussein AA. Preparation and evaluation of darifenacin hydrobromide loaded nanostructured lipid carriers for oral administration. Iraqi Journal of Pharmaceutical Sciences . 2018 ; 27(1): 53–68.

76. Jaber SH., & Rajab NA. Preparation, In-vitro, Ex-vivo, and Pharmacokinetic Study of Lasmiditan as Intranasal Nanoemulsion-based In Situ Gel. Pharmaceutical Nanotechnology. 2024 ; 12.

77. Ali MM, Shoukri, RA., & Yousry C. Thin film hydration versus modified spraying technique to fabricate intranasal spanlastic nanovesicles for rasagiline mesylate brain delivery: Characterization, statistical optimization, and in vivo pharmacokinetic evaluation. Drug Delivery and Translational Research. 2023; 13(4): 1153–1168.

78. Mekkawy AI, Eleraky NE, Soliman GM, Elnaggar MG, Elnaggar MG. Combinatorial Therapy of Letrozole- and Quercetin-Loaded Spanlastics for Enhanced Cytotoxicity against MCF-7 Breast Cancer Cells. Pharmaceutics. 2022;14(7) :1-21.

79. Farghaly DA, Aboelwafa AA, Hamza MY, Mohamed MI. Topical Delivery of Fenoprofen Calcium via Elastic Nano-vesicular Spanlastics: Optimization Using Experimental Design and In Vivo Evaluation. AAPS PharmSciTech. 2017;18(8):2898–2909.

80. Sezgin-Bayindir Z, Antep MN, Yuksel N. Development and characterization of mixed niosomes for oral delivery using candesartan cilexetil as a model poorly water-soluble drug. AAPS PharmSciTech. 2015 ;16(1):108-17. doi: 10.1208/s12249-014-0213-9. Epub 2014 Sep 10. PMID: 25204859; PMCID: PMC4309817.

81. Abdelbary G, El-Gendy N. Niosome-encapsulated gentamicin for ophthalmic controlled delivery. AAPS PharmSciTech. 2008;9(3):740-7. doi: 10.1208/s12249-008-9105-1. Epub 2008 Jun 18. PMID: 18563578; PMCID: PMC2977028.

82. Ali MM., Shoukri RA, & Yousry C. Thin film hydration versus modified spraying technique to fabricate intranasal spanlastic nanovesicles for rasagiline mesylate brain delivery: Characterization, statistical optimization, and in vivo pharmacokinetic evaluation. Drug Delivery and Translational Research . 2023; 13(4): 1153–1168.

83. Agha OA, Girgi G N S., El-Sokkary MMA, & Soliman O A. Spanlastic-laden in situ gel as a promising approach for ocular delivery of Levofloxacin: In-vitro characterization, microbiological assessment, corneal permeability and in-vivo study. International Journal of Pharmaceutics . 2023 ; 6 (12) . https://doi.org/10.1016/j.ijpx.2023.100201

84. Alharbi WS, Hareeri RH, Bazuhair M, Alfaleh, M. A., Alhakamy, N. A., Fahmy, U. A., Alamoudi, A. A., Badr-Eldin, S. M., Ahmed, O. A., AlGhamdi, S. A., & Naguib, M. J.

85. Spanlastics as a Potential Platform for Enhancing the Brain Delivery of Flibanserin: In Vitro Response-Surface Optimization and In Vivo Pharmacokinetics Assessment. Pharmaceutics . 2022; 14(12).

السبانلاستك كنظام لتوصيل الأدوية للجهاز العصبي المركزي

رجاء عباس دهش *، [1] و موفق محمد غريب[2]

[1] وزارة الصحة والبيئة ، بغداد ، العراق.

[2] فرع الصيدلانيات ، كلية الصيدلة، جامعة بغداد ، بغداد ، العراق.

الخلاصة

العديد من المركبات الدوائية الموجودة الان في السوق غير فعالة في علاج اضطرابات الدماغ فهي لا تصل الى الدماغ بالتركيز المطلوب ليكون لها تأثير دوائي نظرا لوجود العديد من العوائق مثل حاجز الدم في الدماغ والبروتين فهذه بعض الاليات التي تحمي الدماغ من الظروف الضارة. هذه الأنظمة وخاصة حاجز الدم في الدماغ تعيق التدخلات العلاجية للعديد من الادوية , وبالتالي فأن غالبية الادوية لا تعطي التأثير المطلوب لانها لا تستطيع اختراق الدماغ لذلك لا فائدة منها في علاج امراض الدماغ . ونتيجة لذلك ظهرت العديد من الاستراتيجيات التي يمكن ان تعزز توصيل الدواء الى الدماغ . ونتيجة لذلك ظهرت العديد من الاستراتيجيات التي يمكن ان تعزز توصيل الدواء الى الدماغ , وهكذا حققت أجهزة توصيل الدواء الحويصلية تقدما مهما في تكنولوجيا النانو وتعتبر هذه الأنظمة مفيدة لتجنب العديد من المشاكل المتعلقة بأشكال الجرعات التقليدية و حيث اثبتت الجسيمات الشحمية والجسيمات النانوية والسبانلاستك انها اكثر فعالية في توصيل الدواء . السبانلاستك هي طريقة توصيل الدواء مرنة قائمة على المواد المخفضة للتوتر السطحي والتي تحبس الدواء ضمن طبقة ثنائية وهي تقدم كلا من الادوية المحبة للماء والكارهة للماء والتي يتم استخدام عامل تخفيض التوتر السطحي ومنشط الحافة والايثانول لتحضير السبانلاستك ويمكن استخدام العديد من الطرق لتحضير هذه الحويصلات

الكلمات المفتاحية: الدماغ , نانوتكنولوجي , الحويصلات النانوية , سبانلاستك , المواد الخافضة للتوتر السطحي.