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Review Paper

Intranasal Spanlastics Nanocarriers: Advancing Nose to Brain Drug Delivery

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ABSTRACT

Intranasal drug delivery is a noninvasive approach for directly targeting the brain through the olfactory and trigeminal pathways, effectively bypassing the blood–brain barrier. However, its efficacy is constrained by mucociliary clearance and limited permeability. Spanlastics, elastic nanovesicles made from non-ionic surfactants and edge activators, have emerged as promising carriers to address these issues. Their remarkable deformability and adaptable bilayer structure facilitate mucosal penetration and extend the nasal residence time, thereby enhancing drug absorption and bioavailability. Spanlastics can encapsulate both hydrophilic and lipophilic drugs and are generally produced using techniques such as ethanol injection and thin-film hydration, resulting in stable nanosized vesicles with high entrapment efficiency. Recent developments, including surface modification and mucoadhesive strategies, have further improved targeting efficiency. In summary, intranasal spanlastics constitute an effective and versatile platform for nose-to-brain drug delivery for the treatment of neurological disorders...

INTRODUCTION

Intranasal drug delivery has gained considerable attention as a noninvasive and efficient route for targeting the central nervous system (CNS) [3,14]. This approach facilitates the direct transport of therapeutic agents to the brain via the olfactory and trigeminal neural pathways, thereby bypassing the blood–brain barrier (BBB) and minimizing systemic side effects [3,14]. Despite these advantages, conventional intranasal formulations are associated with several limitations, including rapid mucociliary clearance, enzymatic degradation, limited drug permeability, and poor

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retention in the nasal mucosa, which collectively compromise their therapeutic efficacy [2,4].

To overcome these challenges, advanced nanocarrier systems have been extensively studied. Among these, spanlastics have emerged as a novel class of elastic nanovesicles composed of non-ionic surfactants and edge activators [1,12]. These vesicles exhibit enhanced deformability compared to conventional vesicular systems, such as liposomes and niosomes, enabling improved penetration across biological membranes [1,6]. Their flexible bilayer structure supports efficient drug encapsulation, enhances physicochemical stability, and enables the delivery of both hydrophilic and lipophilic therapeutic agents [1,5]. Spanlastics can be fabricated using various techniques, including ethanol injection and thin-film hydration, allowing precise control over the vesicle size, entrapment efficiency, and surface characteristics [6,12]. The incorporation of edge activators imparts elasticity to the vesicles, facilitating their transport through narrow intercellular spaces within the nasal epithelium [1,5]. Moreover, their nanoscale size and high surface area contribute to enhanced drug absorption and prolonged residence time in the nasal cavity [5,7].

Furthermore, spanlastics can be functionalized with mucoadhesive polymers and targeting strategies to enhance nasal retention and improve brain-targeting efficiency [8,10]. These modifications promote stronger interactions with the nasal mucosa and enable sustained drug release. Owing to these advantages, spanlastics have gained significant attention as a promising platform for nose-to-brain drug delivery, particularly in the treatment of neurological disorders, such as neurodegenerative diseases, epilepsy, and brain tumors [3,14].

Overall, spanlastics represent a versatile and efficient drug delivery system capable of overcoming the limitations of conventional intranasal formulations, thereby offering significant potential for brain-targeted therapies.

BUILDING BLOCKS OF SPANLASTICS

Spanlastics are composed of carefully selected components that collectively form flexible and efficient nanovesicular systems. The primary structural elements include non-ionic surfactants, typically from the Span series (e.g., Span 60 or Span 80), which constitute the bilayer framework of the vesicles [1,12]. These surfactants are combined with edge activators, commonly Tween surfactants (such as Tween 20 or Tween 80), which impart elasticity and deformability by disrupting the tightly packed lipid bilayer structure [1,5,15].

An aqueous phase, usually distilled water or a suitable buffer system, is essential for vesicle formation and its stabilization [6]. In several preparation methods, organic solvents such as ethanol are employed to dissolve surfactants prior to vesicle assembly, facilitating uniform dispersion and controlled vesicle formation [6,12]. In some formulations, cholesterol is incorporated to enhance membrane stability and reduce permeability; however, its concentration is typically optimized to preserve the elastic nature of spanlastics [5,7]. Additionally, functional excipients such as charge-inducing agents or mucoadhesive polymers may be included to improve vesicle stability, enhance interaction with biological membranes, and prolong residence time at the site of administration [8,10].

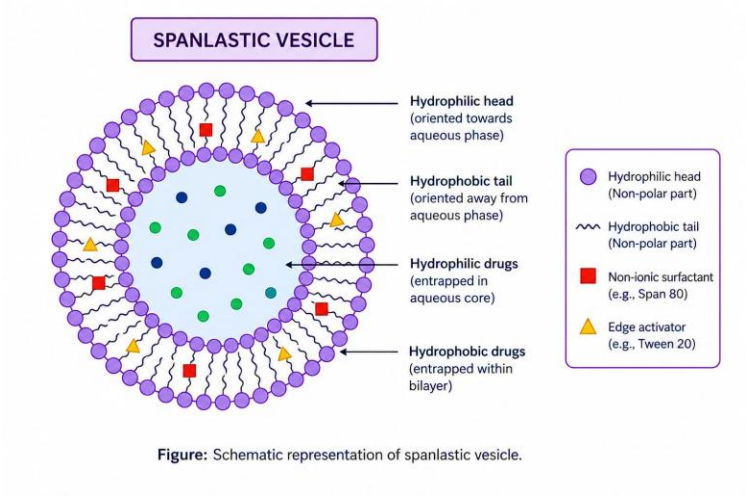

Fig1: Schematic diagram of spanlastics vesicle

MECHANISM OF ENCHANCED PERMEATION BY SPANLASTICS

Spanlastics enhance drug permeation through a combination of physicochemical and biological mechanisms attributed to their elastic vesicular structure and surfactant composition [1,12]. The incorporation of edge activators disrupts the regular packing of the vesicular bilayer, increasing membrane fluidity and imparting high deformability [1,5]. This enables spanlastic vesicles to traverse intercellular spaces and narrow pores within epithelial barriers without structural rupture, thereby facilitating enhanced permeation [5,6].Additionally, non-ionic surfactants interact with the lipid components of biological membranes, leading to transient disruption of epithelial lipid organization and increased membrane permeability [5,7]. Spanlastics may also promote paracellular transport by modulating tight junction integrity, thereby enhancing drug diffusion across the epithelial layers [6,10]. Their nanoscale size allows close contact with the mucosal surface, improving adhesion and prolonging the residence time at the absorption site [5,8].Furthermore, spanlastics function as drug reservoirs, providing sustained release and maintaining a concentration gradient that drives diffusion across the biological membranes [1,12]. Collectively, these mechanisms contribute to improved drug penetration, enhanced absorption, and increased bioavailability compared with conventional delivery systems [1,6].

TYPES OF PREPARATION METHODS

Two commonly employed preparation methods have been reported for spanlastics, each significantly influencing the vesicle size, entrapment efficiency, and overall stability [6,12].

1. Ethanol Injection Method

In this method, a non-ionic surfactant and edge activator are dissolved in ethanol and subsequently injected into an aqueous phase under continuous stirring [6,12]. Upon contact with an aqueous medium, spontaneous vesicle formation occurs owing to the rapid diffusion of ethanol, leading to the formation of nanosized and relatively uniform spanlastic vesicles [6].This technique is simple, reproducible, and widely utilized for laboratory-scale preparation, as it allows for better control over the vesicle size distribution and minimizes aggregation [6,12]. Additionally, rapid solvent diffusion promotes the formation of stable vesicles with satisfactory entrapment efficiency [1,6].

2. Thin-Film Hydration Method

The thin-film hydration method, also known as the rotary evaporation technique, is widely employed for preparing spanlastics [6,12]. In this method, non-ionic surfactants and edge activators are dissolved in an organic solvent, followed by solvent evaporation under reduced pressure to form a thin lipid film on the inner wall of a round-bottom flask [6]. The resulting film is subsequently hydrated with an aqueous phase under continuous agitation, leading to the formation of multilamellar vesicles, which can be further reduced to nanosized vesicles by sonication or extrusion [6,12].

CHARACTERIZATION OF SPANLASTICS

Spanlastics are characterized using various physicochemical techniques to confirm vesicle formation, stability, and performance [1,5].

Morphological analysis using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) revealed spherical, smooth, nanosized vesicles with a relatively uniform distribution [5,7]. Particle size, polydispersity index (PDI), and zeta potential were determined using dynamic light scattering (DLS), indicating nanoscale dimensions, homogeneity, and colloidal stability of the formulation [1,5].

Fourier-transform infrared spectroscopy (FTIR) was employed to assess drug–excipient compatibility, confirming the absence of significant chemical interactions [1,12]. Thermal and crystallinity analyses using differential scanning calorimetry (DSC) and X-ray diffraction (XRD) demonstrated reduced crystallinity or amorphous dispersion of the drug within the vesicular system, indicating successful encapsulation [5,9].

Entrapment efficiency is evaluated to determine the drug-loading capacity of the vesicles, while in vitro release studies assess the drug release profile, often demonstrating controlled and sustained release behavior [1,6]. Stability studies further confirm that spanlastics maintain their physicochemical integrity under appropriate storage conditions, supporting their suitability for drug delivery applications [5,12]

INTRANASAL DELIVERY AND BRAIN TARGETING

Intranasal drug delivery offers several advantages as a noninvasive route for systemic and brain-targeted drug delivery [3,14]

- Provides a non-invasive administration route through the nasal cavity, improving patient compliance [3]
- Avoids first-pass metabolism, thereby enhancing drug bioavailability [3,14]
- Ensures rapid onset of action due to the rich vascularization of the nasal mucosa [3]
- Enables direct brain delivery via
  - Olfactory pathway
  - Trigeminal nerve pathway [3,14]
- Effectively bypasses the blood–brain barrier (BBB), allowing efficient CNS targeting [3,14]
- Requires low dose volume and is convenient for administration [2]
- Enhances therapeutic efficiency while reducing systemic side effects [3,14]

APPLICATIONS

- Intranasal delivery has been widely explored for various therapeutic applications, particularly in brain targeting and systemic delivery [3,14].
- Delivery of drugs for central nervous system (CNS) disorders [3]
- Management of neurodegenerative diseases, such as:
  - Alzheimer's disease
  - Parkinson's disease
- Treatment of epilepsy and psychiatric disorders [3,14]

- Pain management and migraine therapy [3]
- Delivery of peptides, proteins, and vaccines via the nasal route [14]
- Potential application in systemic delivery of poorly bioavailable drugs [2,14]

ADVANTAGES OF SPANLASTICS VESICLES OVER CONVENTIONAL VESICULAR CARRIERS [1,5,12]

PARAMETER	SPANLASTICS	CONVENTIONAL VESICULAR CARRIERS
Vesicle flexibility	Highly elastic and deformable due to edge activators	Rigid and less flexible bilayer
Permeation ability	Enhanced permeation	Limited permeation
Entrapment efficiency	Higher	Moderate
Bioavailability	Significantly improved due to better absorption	Moderate

LIMITATIONS OF SPANLASTICS

Despite their promising advantages, spanlastics are associated with several limitations that may affect their practical application in drug delivery systems.

- Physical instability: Spanlastic vesicles may undergo aggregation, fusion, or deformation during storage, potentially affecting their size distribution and performance [5,12].
- Drug leakage: The highly elastic bilayer structure can sometimes lead to drug leakage, especially during prolonged storage [1,5].
- Surfactant-related toxicity: High concentrations of non-ionic surfactants and edge activators can cause irritation or toxicity, particularly in sensitive biological tissues such as the nasal mucosa [2,4].
- Formulation complexity: Precise optimization of the surfactant type and ratio is required to achieve the desired vesicle characteristics, making formulation development challenging [6,12].
- Limited clinical and scalability data: Most studies are confined to laboratory or preclinical levels, with insufficient data on large-scale production and clinical translation [3,14].

FUTURE PERSPECTIVES:

- **Integration of Artificial Intelligence (AI) in Formulation Design**
- Application of Artificial Intelligence and Machine Learning to optimize formulation parameters
- Prediction of optimal surfactant ratios, particle size, and entrapment efficiency
- Reduction in trial-and-error experimentation, accelerating formulation development
- Development of predictive models for permeation behavior and stability enhancement
- **Personalized and Advanced Drug Delivery Systems**
- Design of patient-specific intranasal dosage forms tailored to nasal anatomy

- Utilization of 3D Printing for fabricating nasal inserts and gels
- Enables controlled, localized drug release with improved dosing precision and reproducibility
- **Surface Modification Strategies for Targeted Delivery**
- Functionalization of spanlastics with targeting ligands and polymers
- Use of mucoadhesive polymers such as Chitosan to enhance nasal retention and permeation
- Improved interaction with biological membranes leading to enhanced brain targeting efficiency [16,17,18]

CONCLUSION

Intranasal drug delivery is a promising noninvasive approach for rapid drug absorption and efficient brain targeting by bypassing the blood–brain barrier (BBB). Spanlastics significantly enhance drug permeation, retention, and bioavailability compared to conventional delivery systems owing to their elastic and nanosized vesicular structures.

Recent advancements, including the integration of Artificial Intelligence-based formulation design, 3D printing of nasal delivery systems, surface modification techniques, and targeted delivery strategies, have further improved formulation efficiency and enabled personalized therapeutic approaches. These innovations contribute to optimized drug delivery and enhanced clinical potential.Despite existing challenges, such as physical instability, scalability issues, and limited clinical validation, ongoing research and technological advancements continue to address these limitations. Overall, spanlastics demonstrate significant potential as an advanced platform for intranasal drug delivery, particularly for brain-targeted therapies, and are expected to play a crucial role in the future of nanomedicine-based CNS drug delivery systems.

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