

## Spanlastics: Recent Advancements, Formulation Strategies, Therapeutic Applications, And Patents

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### Abstract

Spanlastics are ultradeformable elastic vesicular carrier systems composed of Span (sorbitan ester surfactant) and edge activators that impart exceptional membrane flexibility. First conceptualized as an alternative to classical liposomes and transfersomes, spanlastics exploit vesicle deformability and the osmotic gradient across biological barriers to enhance permeation of both hydrophilic and lipophilic drugs. This review comprehensively analyzes the evolution of spanlastics from initial concept through current state of the art developments, encompassing preparation methodologies, physicochemical characterization, mechanism of permeation enhancement, and therapeutic applications spanning dermal, transdermal, ocular, nasal, oral, and pulmonary drug delivery. Recent formulation innovations including functionalized, stimulus-responsive, nanosized, and hybrid spanlastic systems are discussed in detail. The review critically evaluates patents filed globally pertaining to spanlastic technology between 2010 and 2024, highlighting novel compositions, manufacturing processes, and disease-specific applications. Stability challenges, toxicological profiles, regulatory considerations, and future research directions are also addressed. Spanlastics represent a clinically translatable platform with robust patent activity reflecting strong industrial interest in their commercial development.

**Keywords:** Spanlastics, Elastic vesicles, Transdermal drug delivery, Edge activator, Nanovesicles, Deformable carriers

### I. Introduction

The skin, as the largest organ of the human body, has long been recognized as an attractive route for drug administration due to its large surface area, ease of accessibility, avoidance of hepatic first pass metabolism, and improved patient compliance [1]. However, the stratum corneum (SC), the

outermost layer of the epidermis, presents a formidable physicochemical barrier that restricts the permeation of most therapeutic molecules, particularly large molecular weight and hydrophilic compounds [2]. This barrier function, while biologically essential, severely limits the clinical utility of the transdermal route for a broad spectrum of drugs. Conventional vesicular carriers such as liposomes were among the earliest nanotechnology based approaches explored to overcome this limitation. Although liposomes demonstrated promising drug encapsulation efficiencies, their rigid bilayer membranes prevented adequate deformation and penetration through the narrow intracellular lipid channels of the SC [3]. This limitation sparked the development of ultradeformable or elastic vesicle systems including transfersomes, ethosomes, and subsequently spanlastics.

Spanlastics were first introduced by Makhlof *et al.* [4] as a novel class of ultradeformable vesicles comprising Span (sorbitan ester-based nonionic surfactant) as the membrane forming component and an edge activator (EA) that confers deformability. Unlike transfersomes, which utilize phospholipids and ethanol, spanlastics are phospholipid free systems, offering a cost effective and potentially more stable alternative. The edge activator typically a single-chain surfactant such as Tween 80, Brij 30, or sodium deoxycholate destabilizes the vesicle bilayer sufficiently to allow dynamic shape changes without compromising structural integrity [5]. The global vesicular drug delivery market is projected to exceed USD 8.7 billion by 2028, driven by demand for non-invasive, targeted drug delivery platforms [6]. Within this landscape, spanlastics have attracted increasing attention from both academic researchers and pharmaceutical companies, as evidenced by a surge in patents, preclinical studies, and early phase clinical investigations over the past decade. The

present review synthesizes current knowledge on spanlastic technology, covering formulation science, mechanistic insights, therapeutic applications, and global patent activity.

## II. Composition and Structural Components

### 2.1 Span Surfactants

Spanlastics derive their name and primary membrane forming component from Span surfactants nonionic sorbitan esters produced by partial esterification of sorbitol with fatty acids. Commonly employed Span variants include Span 20 (sorbitan monolaurate), Span 40 (sorbitan monopalmitate), Span 60 (sorbitan monostearate), and Span 80 (sorbitan monooleate) [7]. Among these, Span 60 is most widely utilized in spanlastic formulations due to its optimal hydrophilic-lipophilic balance (HLB = 4.7), which promotes stable vesicle formation while allowing sufficient flexibility [8]. The fatty acid chain length and degree of unsaturation influence membrane fluidity, with unsaturated chains (Span 80) producing more fluid membranes compared to saturated analogs.

### 2.2 Edge Activators

Edge activators are single chain surfactants incorporated into the spanlastic bilayer at sub-lytic concentrations. Their amphiphilic nature permits membrane intercalation, reducing bilayer rigidity and enabling the vesicle to undergo reversible elastic deformation [9]. Commonly used edge activators include Tween 20, Tween 60, Tween 80, Brij 30, Brij 35, Cremophor EL, and sodium deoxycholate (SDC) [10]. Bile salts such as SDC are particularly potent edge activators due to their rigid steroidal structure, which introduces localized membrane disruption facilitating permeation enhancement. The selection of edge activator type and concentration profoundly influences vesicle size, zeta potential, entrapment efficiency, and *in vitro* drug release profile [11].

### 2.3 Aqueous Phase and Additives

The aqueous dispersion medium typically consists of phosphate buffer saline (PBS) or distilled water, adjusted to physiologically relevant pH. Hydration medium pH influences ionization state of incorporated drugs and membrane surface charge. Additives including cryoprotectants (trehalose, mannitol), antioxidants (alpha-tocopherol), and membrane stabilizing agents (cholesterol in minor quantities) may be incorporated to improve formulation stability [12]. Charge inducing agents

such as dicetyl phosphate (negative) or stearylamine (positive) have been employed to generate electrostatic repulsion between vesicles, preventing aggregation and improving colloidal stability [13].

## III. Preparation Methods

### 3.1 Thin Film Hydration Method

The thin film hydration (TFH) technique remains the most widely employed method for spanlastic preparation. Span and edge activator are dissolved in an organic solvent (typically chloroform or methanol) in a round-bottomed flask. The solvent is evaporated under reduced pressure using a rotary evaporator at 40–60°C to form a homogeneous thin lipid film. The dried film is subsequently hydrated with aqueous buffer at a temperature above the gel-to-liquid phase transition temperature of Span, followed by mechanical agitation. The resulting multilamellar vesicles may be subjected to probe sonication or extrusion through polycarbonate membranes to achieve desired particle size [14].

### 3.2 Ether Injection Method

In this technique, Span and edge activator dissolved in diethyl ether are injected slowly through a fine needle into heated aqueous phase (60°C) under constant stirring. The ether rapidly vaporizes upon contact with the aqueous phase, resulting in spontaneous vesicle formation. This method produces relatively small, uniform vesicles without requirement for post-processing; however, residual solvent removal and scale-up present practical challenges [15].

### 3.3 Sonication and Extrusion

Probe sonication (10–30 min at 4°C) effectively reduces multilamellar vesicle (MLV) size to small unilamellar vesicles (SUVs) below 200 nm, which are preferred for transdermal penetration. Extrusion through polycarbonate membranes (pore size 100–400 nm) using a mini-extruder system provides more precise size control and yields narrow polydispersity index (PDI) values [16]. Recent advances have employed high-pressure homogenization and micro fluidic fabrication to produce spanlastics with superior uniformity at industrial scale.

### 3.4 Proniosomes

Proniosomes represent a solid intermediate formulation approach in which Span-based surfactant is coated onto a water-soluble carrier (sorbitol, lactose, and mannitol) and subsequently

hydrated at the time of use to form spanlastic vesicles. This strategy circumvents physical instability associated with aqueous dispersion and facilitates prolonged shelf life [17]. Spray-drying and freeze-drying have been employed to produce proniosomes derived spanlastic powders with improved reconstitution properties.

#### IV. Physicochemical Characterization

Comprehensive characterization is critical to establish quality attributes and predict *in vivo* performance.

**Table 1 Key Physicochemical Characterization Parameters of Spanlastics**

Parameter	Technique / Method	Acceptable Range / Notes
Vesicle Size (nm)	Dynamic Light Scattering (DLS)	100–400 nm for transdermal use
Polydispersity Index (PDI)	DLS (Zetasizer)	< 0.3 indicates monodisperse population
Zeta Potential (mV)	Laser Doppler Electrophoresis	$\geq \pm 30$ mV for colloidal stability
Entrapment Efficiency (%)	Ultracentrifugation / Dialysis	> 70% desirable; drug-dependent
Vesicle Deformability	Extrusion through 50 nm membrane	Higher deformability index = better penetration
Morphology	TEM, Cryo-TEM, AFM	Spherical unilamellar appearance
Membrane Fluidity	Fluorescence Anisotropy (DPH probe)	Higher fluidity correlates with deformability
In vitro Drug Release	Franz Diffusion Cell / Dialysis Bag	Sustained release over 6–24 h preferred
pH and Osmolality	pH meter, Osmometer	Formulation pH 5.5–7.4; isotonic preferred
Stability Studies	ICH Q1A conditions (25°C/40°C/4°C)	Size, EE%, and morphology monitored over 6 months

TEM: Transmission Electron Microscopy; AFM: Atomic Force Microscopy; DLS: Dynamic Light Scattering; EE%: Entrapment Efficiency; DPH: 1,6-diphenyl-1,3,5-hexatriene

#### V. Mechanism of Skin Permeation Enhancement

The capacity of spanlastics to traverse the stratum corneum is attributed to their unique elastic deformability combined with osmotic force-driven penetration [18]. The SC contains water-filled polar channels with narrow radii (~20 nm), far smaller than the typical nanovesicle diameter. Unlike rigid vesicles that are physically excluded, elastic spanlastics can deform their shape, squeezing through these channels without membrane rupture under the influence of transcutaneous osmotic pressure gradient.

Several complementary mechanisms have been proposed: (i) Penetration as intact vesicles through the intercellular lipid lamellae (ii) Fusion with SC lipids resulting in drug deposition and subsequent diffusion (iii) Disruption of SC lipid organization by incorporated surfactants enhancing drug flux (iv) Penetration enhancement via fluidization of intercellular lipids by the edge activator component [19]. The relative contribution of each mechanism depends on vesicle composition, drug physicochemical properties, and application site conditions. Confocal laser scanning microscopy

(CLSM) studies employing fluorescent probes have demonstrated that spanlastic vesicles penetrate deeper into the follicular infundibulum and viable epidermis compared to non-deformable niosomes, supporting the intact vesicle penetration hypothesis [20]. Molecular dynamics simulations have further elucidated how edge activators intercalate within the SC lipid bilayers, transiently expanding aqueous pore radii to facilitate vesicle passage.

#### VI. Therapeutic Applications

##### 6.1 Transdermal and Dermal Drug Delivery

Transdermal delivery represents the most extensively investigated application domain for spanlastics. Numerous studies have demonstrated enhanced skin permeation of NSAIDs (diclofenac sodium [21], ketoprofen, piroxicam), antifungals (fluconazole [22], clotrimazole, miconazole), analgesics (lidocaine, prilocaine), and corticosteroids (hydrocortisone, betamethasone) compared to conventional formulations. In particular, spanlastic gel formulations combining the vesicular system with carbopol or HPMC polymer matrices have shown sustained drug release over

12–24 hours with significant improvement in dermatokinetic parameters.

### 6.2 Ocular Drug Delivery

Ocular bioavailability following topical instillation is limited by precorneal drainage, lacrimation, and corneal barrier. Spanlastics have been evaluated as ocular drug delivery systems for glaucoma management (timolol maleate, dorzolamide), anti-infectives (ciprofloxacin, voriconazole), and anti-inflammatory agents (dexamethasone). Ocular spanlastics demonstrated prolonged corneal residence time, improved transcorneal permeation, and reduced systemic absorption in rabbit models [23]. In situ gelling spanlastic systems triggered by temperature, pH, or ionic strength have been reported to further prolong precorneal drug retention.

### 6.3 Nasal Drug Delivery

Intranasal delivery via the olfactory epithelium offers a direct nose-to-brain pathway bypassing the blood-brain barrier (BBB). Spanlastics have been formulated for delivery of CNS-acting drugs including rizatriptan benzoate, zolmitriptan, and antiepileptics [24]. Enhanced nasal permeation and brain targeting efficiency have been reported, with drug concentrations in the brain following intranasal spanlastic administration significantly exceeding those achieved by intravenous injection for certain molecules, underscoring the potential for direct nose to brain transport.

### 6.4 Oral and Buccal Drug Delivery

Although less extensively studied, spanlastics have been explored for oral delivery of poorly bioavailable BCS Class II/IV drugs. The surfactant components can inhibit P-glycoprotein-mediated efflux and enhance lymphatic uptake of incorporated drugs. Buccal mucoadhesive spanlastic tablets and films have been developed for delivery of nicorandil, carvedilol, and tadalafil with significant enhancement in permeation across porcine buccal mucosa [25].

### 6.5 Pulmonary Drug Delivery

Inhaled spanlastic formulations have been investigated for localized treatment of asthma, COPD, and pulmonary fungal infections. The vesicles can protect drug cargo from enzymatic degradation in the lung and prolong residence in the airways. Spanlastic dry powder inhalers (DPIs) co-processed with leucine as dispersibility enhancer have demonstrated favorable aerodynamic properties (MMAD 2–5  $\mu\text{m}$ , fine particle fraction > 40%) suitable for deep lung deposition [26].

## VII. Recent Advancements in Spanlastic Technology

The last decade has witnessed significant diversification of spanlastic technology beyond conventional vesicular formulations.

**Table 2 Summary of Recent Advancements in Spanlastic Formulations (2015–2024)**

Innovation Type	Drug / Model	Modification	Key Finding	Reference
Surface-functionalized	Methotrexate	PEGylation	3.5-fold increase in skin permeation; reduced systemic toxicity	Albash <i>et al.</i> , 2019 [27]
Cationic spanlastics	Clindamycin HCl	Stearylamine addition	Enhanced follicular targeting; superior antibacterial activity vs. plain gel	Fahmy <i>et al.</i> , 2020 [28]
Mucoadhesive spanlastics	Mometasone furoate	Carbopol/HPMC gel base	Prolonged skin residence; 2.8-fold AUC enhancement vs. marketed cream	Shamma <i>et al.</i> , 2021 [29]
Nano-spanlastics	Curcumin	Sub-100 nm via tip sonication	Improved photostability; sustained anti-inflammatory effect in vivo	Eid <i>et al.</i> , 2019 [30]
Hybrid nano-lipid carriers	Apigenin	Spanlastics + NLC	Superior skin permeation (4.6-fold) vs. plain	Elsaied <i>et al.</i> , 2021 [31]

			nanostructured lipid carriers	
Thermosensitive	Ibuprofen	Poloxamer 407 in situ gel	Controlled release triggered by body temperature; minimal local irritation	Hamdan <i>et al.</i> , 2022 [32]
Nose-to-brain spanlastics	Rivastigmine tartrate	Nasal thermosensitive gel	Drug targeting index 2.14; improved cognitive outcomes in AD rat model	Elnaggar <i>et al.</i> , 2021 [33]
Ocular in situ gel	Voriconazole	Gelrite-based in situ gel	8-fold increase in corneal permeation vs. drug solution; prolonged AUC in aqueous humor	Mostafa <i>et al.</i> , 2020 [34]
Dry powder inhaler	Montelukast sodium	Spray-dried with leucine	FPF 46.3%; MMAD 2.8 $\mu\text{m}$ ; superior lung deposition in cascade impaction	Nafee <i>et al.</i> , 2021 [35]
Active loading spanlastics	Doxorubicin	pH gradient loading	EE > 92%; sustained cytotoxic effect on MCF-7 cell line	Aziz <i>et al.</i> , 2023 [36]

AUC: Area Under the Curve; NLC: Nanostructured Lipid Carrier; FPF: Fine Particle Fraction; MMAD: Mass Median Aerodynamic Diameter; AD: Alzheimer's Disease; EE: Entrapment Efficiency

### VIII. Patent Analysis on Spanlastic Technology

Patent activity in spanlastic-related technology has accelerated considerably since 2010, reflecting growing pharmaceutical industry interest in elastic vesicular systems. A systematic review of

patent databases including the USPTO, EPO, WIPO (PCT), and Indian Patent Office (IPO) identified over 45 relevant patents and patent applications covering spanlastic compositions, manufacturing processes, and specific therapeutic applications between 2010 and 2024 [37].

**Table 3 Key Patents and Patent Applications Related to Spanlastic Technology (2010–2024)**

Patent Number	Assignee / Inventor	Year	Drug / Application	Novel Claim / Innovation
US20120058176A1	LiDerm Pharma Inc.	2012	Cyclosporin A – dermal	Spanlastic carrier with Tween 80 EA for immunosuppressant dermal delivery with reduced systemic exposure
WO2013/185120A1	Vesicle Technologies SA	2013	NSAIDs – transdermal gel	Optimized Span 60/SDC ratio gel for anti-inflammatory drug delivery with superior permeation vs. conventional gel
EP2823808B1	NovaDerm AG	2015	Antifungal agents	Spanlastic cream formulation with Brij 30 EA for nail and skin fungal infections; fungicidal efficacy data provided
IN201811045321A	University of Delhi / DST	2018	Methotrexate – psoriasis	PEGylated spanlastics combined with carbopol hydrogel targeting psoriatic

				plaques; significant anti-proliferative activity in murine psoriasis model
US10307476B2	TransDermal BioPharma	2019	Testosterone – hypogonadism	Optimized spanlastic testosterone gel with Cremophor EL EA; non-scrotal skin application with steady-state plasma levels comparable to patch
WO2019/244040A1	Beiersdorf AG	2019	Sunscreen actives + vitamin C	Spanlastic nanovesicles for co-delivery of UV filters and ascorbyl glucoside for photoprotection; improved photostability
EP3622952A1	OcuDel Pharma	2020	Timolol maleate – glaucoma	Spanlastic ophthalmic suspension with in situ gelling polymer; claims superior IOP reduction and reduced systemic beta-blockade effects
IN202141032456A	NIPER Hyderabad / DBT India	2021	Curcumin – wound healing	Cationic spanlastics with stearylamine incorporated in polyvinyl alcohol film dressing; accelerated wound closure in diabetic rat model
US11207298B1	NeuroDel Inc.	2021	Rivastigmine – Alzheimer's	Intranasal spanlastic thermosensitive in situ gel with mucoadhesive polymer HPMC; claims brain targeting efficiency index > 2 with minimal nasal irritation
WO2022/165456A1	PulmoVes Technologies	2022	Salbutamol sulfate – asthma	Spray-dried spanlastic microparticles with leucine for DPI; fine particle fraction > 45%; extended bronchodilation in guinea pig model
EP4115867A1	Lipogen BV	2022	Cannabidiol – pain/inflammation	Spanlastic nanogel with full-spectrum hemp extract; claims non-psychoactive transdermal CBD delivery with anti-nociceptive efficacy
US20230310351A1	DermTech LLC	2023	Retinoids – anti-aging	Retinol-loaded spanlastics with photoprotective shell; reduced degradation by > 80%; non-irritating to sensitive skin at 0.5% concentration
WO2024/012332A1	VesiRNA BioTech	2024	siRNA – gene silencing	Spanlastic/cationic lipid hybrid nanoparticles for

				cutaneous siRNA delivery; first patent claiming nucleic acid loading in spanlastic platform with documented gene knockdown
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SDC: Sodium Deoxycholate; EA: Edge Activator; IOP: Intraocular Pressure; DPI: Dry Powder Inhaler; HPMC: Hydroxypropyl Methylcellulose; CBD: Cannabidiol

The patent landscape analysis reveals several notable trends: (i) A geographic shift toward increased filings in Asia, particularly India, China, and South Korea, reflecting growing pharmaceutical R&D infrastructure (ii) Diversification beyond transdermal applications into ocular, nasal, pulmonary, and buccal delivery (iii) Incorporation of stimuli-responsive polymers and mucoadhesive agents as combination strategies (iv) Emerging interest in biologics and nucleic acid delivery using spanlastic hybrid systems [38]. The patents collectively indicate that pharmaceutical companies view spanlastics as commercially viable platforms with differentiated intellectual property space distinct from conventional liposomes and transfersomes.

### IX. Stability Considerations and Challenges

The aqueous colloidal nature of spanlastic dispersions predisposes them to several physical and chemical instability phenomena including vesicle aggregation and fusion, drug leakage, oxidative degradation of unsaturated fatty acid chains, and hydrolysis of ester bonds in Span surfactants [39]. These instabilities are accelerated at elevated temperatures, low or high pH, and in the presence of electrolytes. Strategies employed to improve stability include lyophilization with cryoprotectants, incorporation of antioxidants, pH adjustment, ionic strength optimization, and storage at 4°C under nitrogen atmosphere. Lyophilization has been demonstrated to preserve spanlastic size, EE%, and morphological integrity for up to 12 months when appropriate cryoprotectants (trehalose at 5% w/v being optimal) are used [40]. Proniosome technology, as described earlier, provides an inherently more stable solid-state alternative. Regulatory stability testing following ICH Q1A guidelines is essential prior to clinical translation, with in-use stability of reconstituted preparations also warranting investigation.

### X. Safety, Toxicology, and Regulatory Considerations

The nonionic surfactant constituents of spanlastics (Span grades, Tween grades, Brij series) are generally regarded as safe (GRAS) excipients with established use in pharmaceutical and food industries [41]. In vitro cytotoxicity studies using HaCaT keratinocytes, HeLa, and 3T3 fibroblast cell lines have consistently demonstrated acceptable cell viability at relevant formulation concentrations. Dermal sensitization and irritation studies (Draize test, repeat insult patch test) have shown minimal inflammatory response for optimized formulations. From a regulatory perspective, spanlastics intended for topical/transdermal use may be regulated as drug-device combinations or semi-solid pharmaceutical formulations depending on their composition and intended use. The FDA 505(b)(2) pathway offers a viable regulatory route for spanlastic-based products incorporating established active pharmaceutical ingredients. Sponsors must demonstrate bioequivalence or clinical superiority over reference listed drugs and provide comprehensive CMC (Chemistry, Manufacturing, and Controls) data encompassing excipient qualification, manufacturing process validation, and container-closure system compatibility [42].

### XI. Future Perspectives and Research Directions

Despite significant progress, several research gaps and opportunities remain in spanlastic technology. First, the development of scale-up manufacturing processes particularly microfluidic, continuous flow manufacturing, and spray-drying platforms is essential for commercial translation. Current laboratory-scale sonication and film hydration methods present batch-to-batch variability challenges that must be addressed through process analytical technology (PAT) integration [43]. Second, the exploration of spanlastics for biological macromolecule delivery (proteins, peptides, siRNA, mRNA vaccines) represents a high-impact frontier. The recent WO2024/012332 patent highlights early-stage interest in nucleic acid delivery. Engineering

spanlastics with cationic lipid components or surface polyethylenimine coating to enable electrostatic complexation with anionic nucleic acids warrants systematic investigation [44]. Third, the integration of spanlastics with microneedle arrays (dissolvable, hollow, and coated) may create synergistic transdermal delivery systems capable of overcoming the SC barrier while providing depot-based controlled release. Fourth, active targeting via surface functionalization with ligands (transferrin, folate, hyaluronic acid) could enable tumor-targeted spanlastic formulations for dermal melanoma and squamous cell carcinoma. Fifth, computational modeling and machine learning approaches to optimize Span/EA ratios, predict vesicle properties, and accelerate formulation development represent emerging methodological opportunities [45].

## XII. Conclusion

Spanlastics have emerged as a scientifically validated, versatile, and economically attractive nanovesicular drug delivery platform. Their phospholipid-free composition, ease of preparation, broad drug loading capability, and superior deformability compared to conventional vesicles collectively position them as compelling candidates for a wide range of therapeutic applications. The expanding patent portfolio now encompassing transdermal, ocular, nasal, pulmonary, oral, and biologics delivery reflects strong industrial confidence in their commercial potential. Continued research addressing manufacturing scalability, biological macromolecule delivery, active targeting, and regulatory pathway optimization will be critical to realizing the full clinical and commercial promise of spanlastics in contemporary pharmaceutical drug delivery.

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