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DESIGN AND EVALUATION OF A SPANLASTIC-BASED TRANSDERMAL PATCH OF DONEPEZIL HYDROCHLORIDE MONOHYDRATE FOR ALZHEIMER'S DISEASE THERAPY

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder that predominantly affects memory and cognitive function in older adults. Donepezil hydrochloride monohydrate, a reversible acetylcholinesterase inhibitor, is a first-line therapy for Alzheimer's disease, but its oral administration is limited by extensive hepatic first-pass metabolism, variable bioavailability, and gastrointestinal side effects that compromise patient compliance. To address these limitations, the present study aimed to design and evaluate a spanlastic-based transdermal patch of donepezil hydrochloride monohydrate as an alternative delivery strategy. Spanlastic vesicles were prepared by the ethanol injection method using Span 60 as the vesicle-forming agent and Tween 80 as the edge activator, and the optimized dispersion was incorporated into a hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP K-30) polymeric matrix to fabricate transdermal patches by solvent evaporation. The formulation was characterized for drug-excipient compatibility, particle size, zeta potential, entrapment efficiency, and in vitro cytotoxicity, and the resulting patches were evaluated for their physicomechanical properties. The optimized formulation produced nanosized vesicles with a mean particle size of 399 nm and a zeta potential of +1.8 mV, and entrapment efficiency reached 77 ± 5.29%, indicating satisfactory drug encapsulation. Fourier-transform infrared (FTIR) spectroscopy confirmed the absence of chemical interaction between donepezil hydrochloride and the formulation excipients. Cytotoxicity assessment on SK-N-SH human neuroblastoma cells by the MTT assay confirmed good biocompatibility across the tested concentration range, and the fabricated patches showed acceptable thickness, weight uniformity, folding endurance, surface pH, and drug content. Collectively, these findings suggest that spanlastic-based transdermal patches represent a promising, non-invasive alternative to oral donepezil therapy for the management of Alzheimer's disease and warrant further evaluation through ex vivo permeation and in vivo pharmacokinetic studies.

KEYWORDS: Donepezil hydrochloride monohydrate; Spanlastics; Transdermal patch; Alzheimer's disease; Cytotoxicity; Nanovesicles

1. INTRODUCTION

Alzheimer's disease is a chronic, progressive neurodegenerative disorder and the most common cause of dementia in older adults, characterized by a gradual decline in memory, reasoning, and the ability to perform everyday activities [1]. As the disease advances, affected individuals increasingly struggle with recent recall, independent living, and social engagement, placing a substantial and growing burden on patients, caregivers, and healthcare systems worldwide. Because Alzheimer's disease has no curative treatment, sustained and consistent pharmacological management remains central to symptom control and quality of life.

Donepezil hydrochloride monohydrate is among the most widely prescribed agents for Alzheimer's disease. It acts as a selective, reversible inhibitor of acetylcholinesterase, thereby increasing synaptic acetylcholine levels in the brain and partially compensating for the cholinergic deficit associated with the disease [2]. Despite its established efficacy, donepezil is conventionally administered by the oral route, which subjects the drug to extensive hepatic first-pass metabolism, reducing the fraction reaching systemic circulation and contributing to inter-patient variability in plasma levels [2,3]. Oral therapy is further complicated by gastrointestinal adverse effects and the need for repeated daily dosing, both of which can compromise adherence in an elderly and often cognitively impaired patient population.

Transdermal drug delivery has emerged as an attractive alternative for drugs such as donepezil that are compromised by oral administration. By delivering the drug across the skin directly into the systemic circulation, transdermal systems bypass hepatic first-pass metabolism, maintain steadier plasma drug concentrations, and reduce the frequency of administration, which together may improve both therapeutic consistency and patient compliance [3,4]. Indeed, a donepezil transdermal system has already reached clinical use for Alzheimer's disease, underscoring the clinical relevance of this delivery route for this drug [5]. However, the principal barrier to transdermal delivery remains the stratum corneum, whose densely packed lipid architecture restricts the passive permeation of most therapeutic molecules, including donepezil.

Vesicular nanocarriers have been widely explored to overcome this permeability barrier. Among these, spanlastics are elastic, surfactant-based nanovesicles first described by Kakkar and Kaur, composed of a non-ionic surfactant such as Span 60 together with an edge activator, typically a polysorbate such as Tween 80 [6]. The incorporation of an edge activator destabilizes the vesicle bilayer and confers a high degree of deformability, allowing spanlastic vesicles to squeeze through the intercellular channels of the stratum corneum more readily than conventional, rigid vesicular systems such as liposomes or niosomes [7]. This elasticity, combined with the biodegradability and chemical stability conferred by their non-ionic surfactant composition, makes spanlastics a particularly promising carrier for enhancing the transdermal penetration of drugs with otherwise limited skin permeability.

Building on this rationale, the present study was designed to develop donepezil hydrochloride monohydrate-loaded spanlastic vesicles and to incorporate the optimized vesicular dispersion into an HPMC/PVP K-30-based polymeric matrix to fabricate a transdermal patch. The formulation was systematically characterized for drug-excipient compatibility, vesicle size and surface charge, drug entrapment efficiency, and in vitro cytotoxicity on SK-N-SH neuroblastoma cells, and the resulting patches were assessed for the physicomechanical attributes relevant to transdermal application. The overall objective was to establish a spanlastic-based transdermal platform capable of improving the delivery of donepezil hydrochloride monohydrate for the management of Alzheimer's disease.

2. MATERIALS AND METHODS

2.1 Materials

Donepezil hydrochloride monohydrate was received as a gift sample from a pharmaceutical manufacturer. Span 60 and Tween 80 were procured from HiMedia Laboratories Pvt. Ltd. (Mumbai, India). Polyvinylpyrrolidone (PVP K-30), used as a film-forming polymer, was obtained from Loba Chemie Pvt. Ltd. (Mumbai, India). Polyethylene glycol and propylene glycol were used as plasticizers. Ethanol and all other solvents were of analytical grade and were purchased from S D Fine Chemicals Ltd. (Mumbai, India). All chemicals and reagents were used as received, without further purification.

2.2 Drug-Excipient Compatibility Study

Compatibility between donepezil hydrochloride monohydrate and the formulation excipients was assessed by Fourier-transform infrared (FTIR) spectroscopy. FTIR spectra of the pure drug and of the optimized spanlastic formulation were recorded and compared to identify any characteristic peak shifts or disappearances indicative of a chemical interaction.

2.3 Preparation of Donepezil Hydrochloride Monohydrate-Loaded Spanlastic Vesicles

Spanlastic vesicles were prepared by the ethanol injection method [6]. Span 60 and donepezil hydrochloride monohydrate were co-dissolved in ethanol to form the organic phase, which was then injected slowly, under continuous magnetic stirring, into an aqueous phase containing Tween 80 as the edge activator. Stirring was continued to allow complete vesicle formation, after which the resulting dispersion was subjected to mild sonication to reduce vesicle size and yield a uniform colloidal dispersion.

2.4 Particle Size and Zeta Potential Analysis

The mean particle size and zeta potential of the optimized spanlastic dispersion were determined using a dynamic light scattering-based particle size analyzer. Samples were appropriately diluted with distilled water prior to analysis, and measurements were performed at room temperature.

2.5 Determination of Entrapment Efficiency

The entrapment efficiency of donepezil hydrochloride monohydrate within the spanlastic vesicles was determined by the centrifugation method. An aliquot of the spanlastic dispersion was centrifuged at 5000 rpm for 30 minutes to sediment the vesicles and separate the unentrapped drug. The supernatant was suitably diluted, and its absorbance was measured at 230 nm using a UV-visible spectrophotometer. The concentration of free drug was calculated from a pre-established calibration curve, and entrapment efficiency (EE%) was calculated using the equation:

EE (%) = [(Total drug − Free drug) / Total drug] × 100

2.6 In Vitro Cytotoxicity Study

The cytotoxicity of the optimized formulation was evaluated by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay on human neuroblastoma SK-N-SH cells. Cells were seeded in 96-well plates and exposed to formulation concentrations ranging from 10 to 100 µg/mL. Following incubation, MTT reagent was added, and the resulting formazan crystals were solubilized in dimethyl sulfoxide (DMSO). Absorbance was recorded on a microplate reader, cell viability was calculated relative to untreated controls, and the half-maximal inhibitory concentration (IC_{50}) was derived from the concentration-viability profile. Cellular morphology was additionally examined under a phase-contrast microscope to corroborate the viability data.

2.7 Preparation of the Spanlastic-Based Transdermal Patch

Transdermal patches were fabricated by the solvent evaporation technique. HPMC and PVP K-30 were dissolved in a suitable solvent system to obtain a clear polymeric solution, to which the optimized spanlastic dispersion was added slowly under continuous stirring to ensure homogeneous distribution of the vesicles within the polymer matrix. The resulting casting solution was poured into a glass Petri dish and allowed to dry at room temperature until complete solvent evaporation. The dried patches were then carefully removed and stored in a desiccator until further evaluation.

2.8 Evaluation of the Spanlastic-Based Transdermal Patch

The fabricated patches were evaluated in triplicate for physical appearance, thickness, weight variation, folding endurance, surface pH, and drug content uniformity using standard pharmacopoeial methods, to assess their suitability for transdermal application. Data are expressed as mean ± standard deviation (n = 3).

3. RESULTS AND DISCUSSION

3.1 FTIR Analysis

FTIR spectroscopy was performed to evaluate the compatibility between donepezil hydrochloride monohydrate and the excipients used in the formulation. The spectrum of the pure drug displayed characteristic absorption bands corresponding to its principal functional groups, confirming its identity (Fig. 1, Table 1). The spectrum of the donepezil-loaded spanlastic dispersion retained all of the major characteristic peaks of the drug, with only minor shifts in peak position (Fig. 2, Table 2). No disappearance of diagnostic peaks was observed, indicating that these minor shifts most likely reflect physical mixing of the drug with the excipients rather than covalent or strong chemical interaction. Taken together, the FTIR data indicate that donepezil hydrochloride monohydrate remained chemically stable within the spanlastic system and was compatible with the selected formulation components.

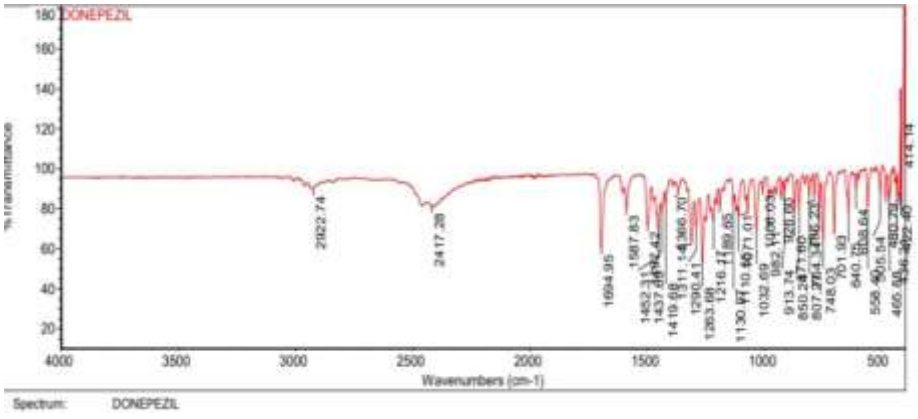


Fig. 1. FTIR spectrum of pure donepezil hydrochloride monohydrate.

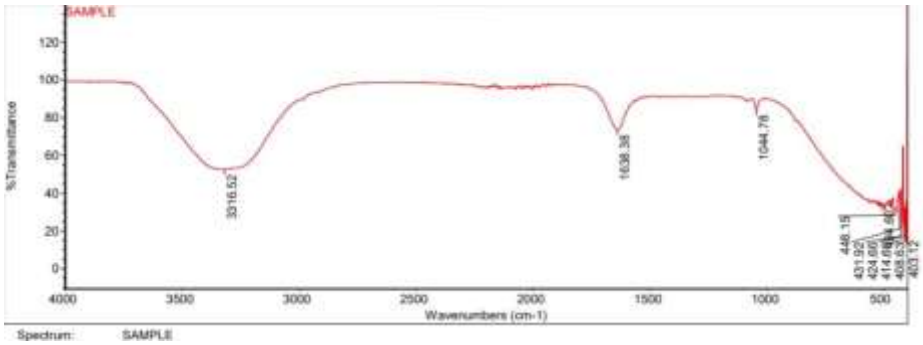


Fig. 2. FTIR spectrum of the donepezil hydrochloride monohydrate-loaded spanlastic dispersion.

Table 1. Characteristic FTIR absorption bands of pure donepezil hydrochloride monohydrate.

Observed peak (cm^{-1})	Functional group
3495–3460	O–H stretching
2922	C–H stretching
2174	C≡N stretching
1685	C=O stretching
1587	Aromatic C=C

Table 2. Characteristic FTIR absorption bands of the donepezil-loaded spanlastic dispersion.

Observed peak (cm^{-1})	Functional group
3316	Broad O–H
2920–2930	C–H stretching
2168–2175	C–N stretching
1683	C=O stretching

3.2 Particle Size Analysis

Particle size analysis of the optimized spanlastic formulation revealed a mean vesicle size of 399 nm (Fig. 3), confirming that the ethanol injection method combined with mild sonication yielded vesicles within the nanometre range and with a uniform size distribution. A vesicle size in this range is generally considered favourable for transdermal delivery, since sufficiently small, elastic vesicles are better able to penetrate the intercellular lipid channels of the stratum corneum than larger or more rigid particulate systems [7].

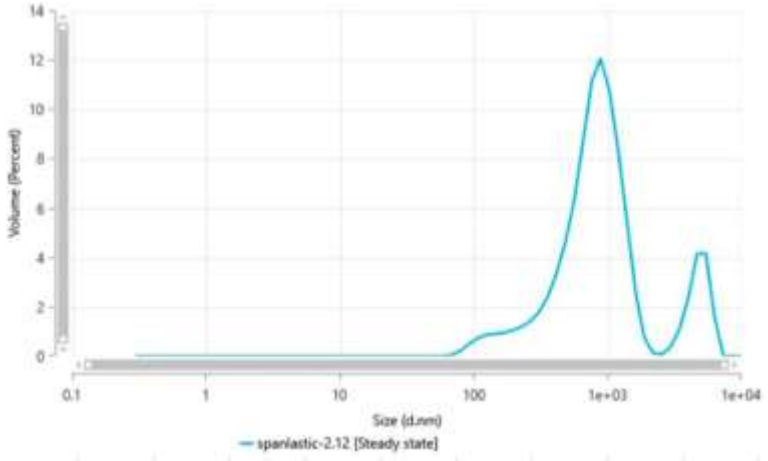


Fig. 3. Particle size distribution of the optimized spanlastic formulation.

3.3 Zeta Potential Analysis

The zeta potential of the optimized formulation, measured to characterize the net surface charge of the vesicles, was found to be +1.8 mV (Fig. 4). Although this value is numerically low, spanlastic vesicles are stabilized primarily through steric hindrance rather than electrostatic repulsion, since Span 60 and Tween 80 are non-ionic surfactants whose hydrophilic polyoxyethylene chains form a protective corona around the vesicle surface [6,7]. The low, slightly positive zeta potential recorded here is therefore consistent with the expected surface characteristics of a predominantly non-ionic, sterically stabilized vesicular system, although longer-term physical stability studies would help confirm the durability of this stabilization.

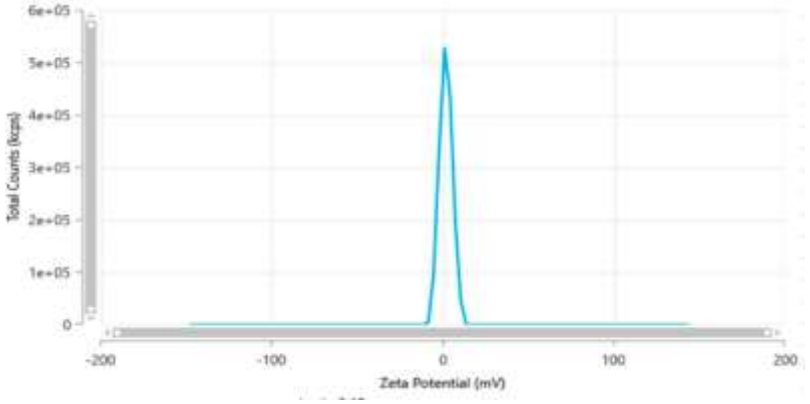


Fig. 4. Zeta potential distribution of the optimized spanlastic formulation.

3.4 Entrapment Efficiency

Entrapment efficiency was determined to quantify the proportion of donepezil hydrochloride monohydrate successfully incorporated within the spanlastic vesicles. Among the three formulations screened, entrapment efficiency ranged from 73% to 83% (Table 3, Fig. 5), and the optimized formulation achieved an entrapment efficiency of 77 ± 5.29%. This level of drug entrapment indicates efficient encapsulation and suggests that the Span 60:Tween 80 vesicular system provides an adequate hydrophobic domain and bilayer architecture for accommodating the drug during vesicle formation.

Table 3. Entrapment efficiency of the screened spanlastic formulations.

Formulation	Entrapment efficiency (%)
F1	73
F2	75
F3	83

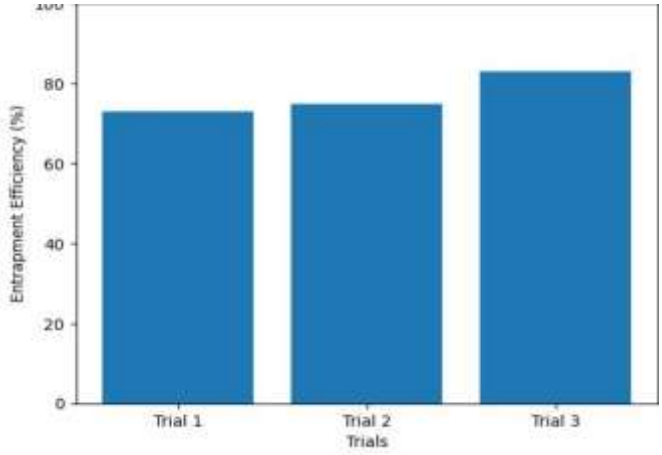


Fig. 5. Entrapment efficiency (%) of formulations F1–F3.

3.5 In Vitro Cytotoxicity Study

Cytotoxicity of the optimized formulation was assessed by the MTT assay on SK-N-SH human neuroblastoma cells across a concentration range of 10–100 µg/mL. Cell viability, calculated from the absorbance of the formazan product, was used to derive the IC_{50} of the formulation (Fig. 6). Phase-contrast microscopy of treated cells showed that the control group displayed normal, intact cellular morphology, and that cells exposed to concentrations of 70–100 µg/mL did not exhibit significant morphological alterations or cell shrinkage relative to the control (Fig. 7a–e). Together, these findings indicate that the spanlastic formulation was well tolerated by SK-N-SH cells across the tested concentration range and support the biocompatibility of the developed carrier system for neuronal applications relevant to Alzheimer's disease therapy.

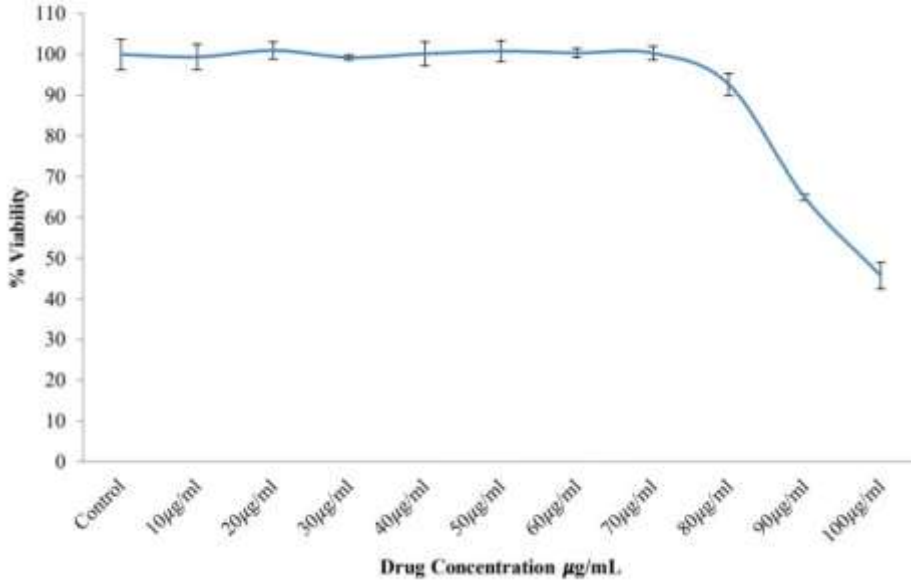
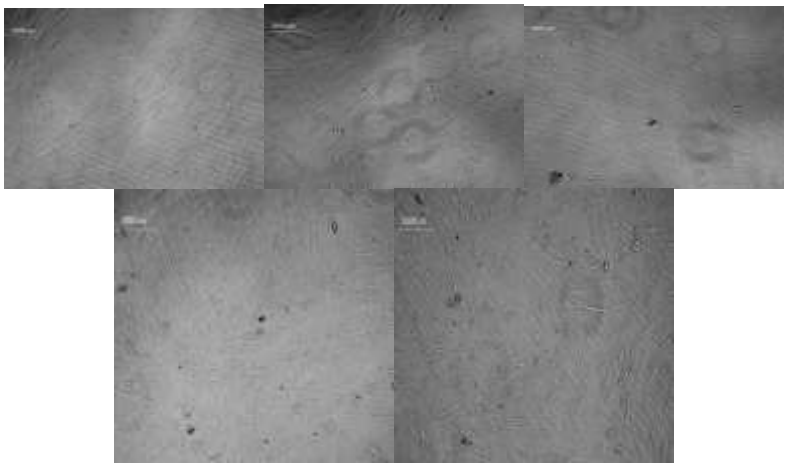


Fig. 6. Cell viability of SK-N-SH cells determined by the MTT assay.



(a) Control (b) 70 µg/mL (c) 80 µg/mL (d) 90 µg/mL (e) 100 µg/mL

Fig. 7. Phase-contrast micrographs of SK-N-SH cells following treatment with the optimized formulation at increasing concentrations.

3.6 Evaluation of the Spanlastic-Based Transdermal Patch

The fabricated transdermal patches were evaluated for their physical, mechanical, and chemical properties. Thickness, weight variation, and folding endurance were assessed in triplicate (Table 4), while surface pH, drug content, and physical appearance were evaluated across three independent trials (Table 5). The patches exhibited a mean thickness of 0.21 ± 0.01 mm, a mean weight of 126 ± 1.73 mg, and a mean folding endurance of 112 ± 3.61 folds, with low variation among trials indicating consistent and reproducible patch fabrication. The surface pH of the patches (6.7 ± 0.1) was close to the physiological pH of the skin, suggesting good compatibility and a low likelihood of skin irritation upon application. Drug content uniformity was high (97.5 ± 0.65%), and the patches were uniform and smooth in

physical appearance across all trials, further supporting the reproducibility of the solvent evaporation method used for patch fabrication.

Table 4. Physicomechanical properties of the spanlastic-based transdermal patch (mean ± SD, n = 3).

Parameter	Trial 1	Trial 2	Trial 3	Mean ± SD
Thickness (mm)	0.20	0.22	0.21	0.21 ± 0.01
Weight (mg)	124	127	127	126 ± 1.73
Folding endurance	108	115	113	112 ± 3.61

Table 5. Physicochemical evaluation of the spanlastic-based transdermal patch (mean ± SD, n = 3).

Parameter	Trial 1	Trial 2	Trial 3	Mean ± SD
Surface pH	6.6	6.7	6.8	6.7 ± 0.1
Drug content (%)	96.8	98.1	97.6	97.5 ± 0.65
Physical appearance	–	–	–	Uniform & smooth

4. CONCLUSION

In this study, donepezil hydrochloride monohydrate-loaded spanlastic vesicles were successfully prepared by the ethanol injection method and incorporated into an HPMC/PVP K-30-based transdermal patch by solvent evaporation. The optimized formulation produced nanosized, elastic vesicles with satisfactory entrapment efficiency, and FTIR analysis confirmed the absence of any adverse chemical interaction between the drug and the formulation excipients. The fabricated patches demonstrated consistent thickness, weight, folding endurance, surface pH, and drug content across trials, indicating a reproducible fabrication process. Furthermore, MTT-based cytotoxicity assessment on SK-N-SH neuroblastoma cells confirmed that the formulation maintained cell viability across the tested concentration range, supporting its biocompatibility. Taken together, these findings suggest that the spanlastic-based transdermal patch of donepezil hydrochloride monohydrate developed in this study may serve as a promising, non-invasive alternative to conventional oral therapy for Alzheimer's disease. Further ex vivo skin permeation studies and in vivo pharmacokinetic and pharmacodynamic evaluations are warranted to confirm the clinical translatability of this delivery system.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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