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Formulation and evaluation of flunarizine-loaded spanlastic nanovesicles for treating migraine

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ABSTRACT

This study investigates the use of spanlastic nanovesicles in order to enhance the solubility and bioavailability of flunarizine. Flunarizine-loaded spanlastics were prepared using the ethanol injection method, and were subsequently evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, and deformability index. The optimized formulation exhibited a particle size of 185 nm, a polydispersity index of 0.2134, a zeta potential of -17 mV, an entrapment efficiency of 68.01%, and a relative deformability of 8.32 g. The findings support spanlastic nanovesicles as a viable delivery system for improving the solubility and enhancing the bioavailability of flunarizine.

1. Introduction

Migraine is a major, yet under-recognized, public health concern that imposes substantial financial burdens on individuals and society. Affecting over one billion people across geographical, cultural, and socioeconomic boundaries, migraine is a chronic condition with a high prevalence and a demonstrable impact on quality of life. The migraine pathophysiology involves dysregulation of brainstem neurons that mediate vascular control, in conjunction with the trigeminovascular nociceptive system[1,2].

Spanlastics are surfactant-based nanovesicular elastic carriers composed of Span 60 and an edge activator (EA). These flexible vesicles have been employed in order to improve the solubility and bioavailability of both lipophilic and hydrophilic pharmaceutical agents[3,4]. Flunarizine is effective in migraine therapy by mitigating the intracellular Ca^{2+} overload induced

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Table 1. Overview of the findings of the undertaken experimental trials of the developed flunarizine-loaded spanlastic nanoformulations. Abbreviations used: DI, deformability index; EA, edge activator; EE%, entrapment efficiency percentage; PDI, polydispersity index; PS, particle size.

Formulation	**Type of EA**	**Span : EA ratio**	**Sonication time** (min)	**PS** (nm)	***PDI***	**EE%**	**DI**
F1	Tween 20	9:1	0	487.7	0.5317	64.51%	1.02
F2			3	436.9	0.4534	61.21%	1.36
F3			6	358.8	0.392	57.78%	1.79
F4	Tween 20	7:3	0	342.1	0.4224	70.76%	4.89
F5			3	185.8	0.2134	68.01%	8.32
F6			6	149.3	0.3024	60.82%	10.7
F7	Tween 20	5:5	0	199.4	0.413	62.31%	9.24
F8			3	151	0.2767	54.92%	11.97
F9			6	92.65	0.1857	51.61%	13.84

by cerebral hypoxia. However, flunarizine is practically insoluble in water, necessitating the use of cosolvents for injectable formulations; an approach associated with an increased risk of adverse effects. Consequently, existing formulations are suboptimal for severely ill patients due to poor bioavailability and absorption. This study aimed at developing a novel nanovesicular system in order to enhance the solubility and bioavailability of flunarizine.

2. Methodology

2.1. Materials

Flunarizine dihydrochloride was obtained from Hyperchem, China. Span 60 and Tween 20 were also sourced from Hyperchem, China. All additional reagents and solvents were of analytical grade and used without further purification.

2.2. Preparation of flunarizine-loaded spanlastic nanovesicles

Flunarizine-loaded spanlastic nanovesicles were prepared *via* the ethanol injection method, using Span 60 and Tween 20 in varying ratios. Briefly, the vesicle-forming agent and flunarizine were dissolved in ethanol. This ethanolic solution was then slowly injected, with stirring, into an aqueous phase containing the EA, preheated to 70°C. The resulting mixture was continuously stirred at 70°C, cooled to 5°C, and stored pending further analysis[4,5].

3. Results and Discussion

3.1. Particle size (PS), polydispersity index (PDI), and zeta potential (ZP)

Table 1 presents the particle size measurements of the formulated spanlastics, which ranged from 92.65 to 487.7 nm. The selected formulation, sonicated for 3 min with a Span 60 to Tween 20 ratio of 70:30, exhibited a notably reduced particle size. It was evident that by lowering the Span 60 and by increasing the EA concentrations, one yielded smaller vesicles, likely due to reduced interfacial tension that facilitates particle division and formation of smaller nanostructures[6]. All formulations demonstrated a substantial decrease in particle size following sonication, regardless of the sonication duration[7]. The recorded zeta potential (ZP) was -20 mV, thereby suggesting low aggregation propensity among the resulting spanlastics.

3.2. Vesicle elasticity measurement

Table 1 indicates that the deformability index (DI) of the nano-spanlastics ranged from 1.02 to 13.84 g. Increasing the EA percentage improved the DI relative to the Span 60 to EA ratio, potentially due to a bilayer fluidization induced by the EA enrichment. This enhancement likely reflects the EA in-

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corporation into the vesicular membrane structure. Moreover, longer sonication times corresponded with greater DI values[8].

3.3. The impact of formulation variables on the EE% of flunarizine-loaded spanlastic nanovesicles

As shown in Table 1, flunarizine entrapment within the spanlastics varied between 51.61% and 70.76%. The data clearly indicate that a 30% drug loading yielded the highest EE%, influenced by the Span 60 to EA ratio. A reduced bilayer fluidization at optimal EA levels may improve drug retention and minimize leakage. However, the excessive EA compromised the EE%, likely due to increased membrane fluidity leading to drug leakage. Additionally, the extended sonication times significantly diminished the EE% in flunarizine-loaded spanlastics[9].

4. Conclusion

The developed flunarizine-loaded spanlastic nanovesicles effectively enhanced drug solubility, thereby addressing limitations stemming from poor aqueous solubility and extensive first-pass metabolism. Our study's findings suggest that an encapsulation in spanlastic carriers presents a viable nanoscale delivery approach for improving flunarizine bioavailability.

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Conflicts of interest

None exist.

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