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Fabrication and evaluation of poloxamer-facilitated, glyceryl monooleate-based tizanidine cubosomes

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ABSTRACT

Cubosomes are lipid-based, nanostructured aqueous dispersions formed through a highly organized, spontaneous self-assembly process. These dosage forms have demonstrated potential as effective drug carriers, enhancing therapeutic efficacy. In this study, cubosomes were developed in order to evaluate their suitability as nanocarriers for the transdermal delivery of tizanidine (TZN); a skeletal muscle relaxant with low oral bioavailability. Cubosomal vesicles were prepared through the thin-film hydration technique, by using glyceryl monooleate (GMO) as the lipid component and poloxamer 407 (P407) as the stabilizer. Vesicle properties were modulated by varying the surfactant-to-lipid ratio. The developed TZN-loaded cubosomes were characterized for vesicle size (113.5–182.6 nm), polydispersity index (0.049–0.301), and drug entrapment efficiency (41.39%–79.20%). The results indicate that TZN-loaded cubosomal dispersions may represent a promising approach to transdermal drug delivery.

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1. Introduction

Cubosomes are advanced drug delivery systems composed of hydrated surfactant structures capable of forming a bicontinuous liquid cubic crystal phase, thus achieving thermodynamic stability *via* self-association. These nanocarriers feature two internal aqueous channels and a three-dimensional honeycomb-like architecture built from curved, bicontinuous lipid bilayers. Cubosomes are typically synthesized through the self-assembly of amphiphilic lipids, such as glyceryl monooleate (GMO) and phytantriol, using poloxamer 407 (P407) as a stabilizing agent[1].

Tizanidine (TZN) is a centrally

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Table 1. Physicochemical characteristics of different tizanidine (TZN)-loaded cubosomes. In all formulations, TZN was 10 mg. Abbreviations used: EE%, encapsulation efficiency; GMO, glyceryl monooleate; P407, poloxamer 407; PDI, polydispersity index; PS, particle size.

Formulation	**GMO** (mg)	**P407** (mg)	**PS** (nm)	**PDI**	**EE%**
F1	100	6	165.0 ± 9.4	0.301 ± 0.061	69.04% ± 1.30%
F2	150	6	171.2 ± 7.0	0.135 ± 6.966	73.40% ± 4.35%
F3	200	6	182.6 ± 3.6	0.178 ± 0.007	79.20% ± 6.74%
F4	100	12	134.1 ± 5.0	0.119 ± 0.008	41.39% ± 2.50%
F5	150	12	141.7 ± 5.5	0.130 ± 0.530	59.56% ± 0.81%
F6	200	12	173.2 ± 0.4	0.141 ± 0.100	63.47% ± 2.56%
F7	100	24	113.5 ± 9.4	0.109 ± 0.022	67.09% ± 1.02%
F8	150	24	150.3 ± 7.0	0.049 ± 0.049	72.94% ± 3.41%
F9	200	24	160.9 ± 3.6	0.113 ± 0.006	76.80% ± 2.02%

acting muscle relaxant classified as a myotonolytic agent and a selective α_2-adrenoceptor agonist, indicated for the treatment of spasticity in patients with cerebral or spinal pathology. TZN exhibits antispastic efficacy comparable to baclofen, with a more favourable tolerance profile. Its reported half-life ranges from 2.1 to 4.2 h, and its oral bioavailability is approximately 34%–40% due to extensive first-pass metabolism[2,3]. Owing to its short half-life, TZN necessitates frequent administration. Numerous studies have explored formulation strategies aimed at enhancing bioavailability and reducing dosing frequency. Among these, novel drug delivery technologies have emerged in order to address pharmacokinetic limitations. Recent investigations suggest that the skin offers a viable route for systemic drug administration[4].

Vesicular carriers (including cubosomes) have garnered attention for their potential to facilitate transdermal drug delivery by improving permeation across the stratum corneum. Compared to oral delivery, transdermal administration offers several advantages: sustained release at a uniform rate, ease of termination by device removal, self-administration, and circumvention of hepatic first-pass metabolism, thereby reducing systemic side effects[5].

This study aimed at formulating TZN-loaded cubosomal nanovesicles stabilized with P407 and characterized by small particle size (PS), low polydispersity index (PDI), and high entrapment efficiency (EE%).

2. Methodology

The materials used included TZN, GMO, and P407 (Hyper Chem, China), polyvinyl alcohol (PVA; HiMedia, India), ethanol (HPLC grade), chloroform (AR grade; Chem-Lab, Belgium), potassium dihydrogen phosphate, and sodium hydroxide.

Cubosomes were prepared through the thin-film hydration method. Briefly, 10 mg of TZN were dissolved with variable amounts of GMO (100–200 mg) and P407 (6–24 mg), as detailed in Table 1, in a mixture of ethanol and chloroform (3 mL each). The organic solvent was removed by rotary evaporation under reduced pressure (Heidolph, Germany), yielding a thin film of GMO and P407. This film was hydrated with 10 mL of phosphate buffer containing 1.25% w/v PVA at 70°C ± 2°C. The resulting dispersion was subjected to probe sonication (Bandelin Electronic, Germany) in pulse mode (2-sec off, 2-sec on) for 2 min. The dispersion was then stirred for 2 h and was cooled to ambient temperature. Samples were transferred into glass vials and stored at room temperature for further analysis[6].

Cubosomal PS and PDI were assessed *via* dynamic light scattering by using a Zetasizer (Malvern, UK). Prior to measurement, samples were diluted tenfold with deionized water[7]. EE% was determined by ultrafiltration, quantifying the unencapsulated drug in the supernatant. Specifically, 2 mL of the dispersion were placed into a microcentrifuge filter tube (Am-

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icon Ultra, Ireland; 10-kDa cutoff) and were centrifuged at 6,000 rpm for 10 min. The filtrate was diluted appropriately with ethanol[8], and absorbance was measured at 319 nm using a Shimadzu VR ultraviolet spectrophotometer. Blank cubosomes (without TZN) served as controls. EE% was calculated using the following equation:

EE% = [(total drug added – free drug) / total drug added] ×100

Data were expressed as mean ± standard deviation. Statistical analysis employed one-way ANOVA, with $p<0.05$ considered as significant.

3. Results and Discussion

PS was significantly influenced by the concentrations of both GMO and P407 ($p<0.05$). Increasing the levels of P407 led to reduced size distribution of cubosomes. GMO was positively correlated with higher EE%, whereas P407 exerted a negative impact. Notably, the P407 concentration significantly reduced PS ($p<0.05$), thereby corroborating with the findings by Alkawak *et al.*[9]. This reduction likely stems from P407's surfactant capacity to lower surface tension, thereby diminishing the surface energy and inhibiting particle aggregation.

Surfactant concentration plays a dual role: facilitating emulsification and preventing droplet coalescence; the observed effects of P407 on PS distribution likely follow similar reasoning. Additionally, by increasing the lipid phase concentration one can elevate the dispersion viscosity, which may hinder a fragmentation of bicontinuous structures into smaller particles[10].

The decrease in EE% with elevated P407 concentrations may reflect an enhanced solubility of TZN in the external medium, leading to drug leakage. Conversely, by reducing the P407 concentration while increasing lipid concentration appeared to accelerate solidification of cubosomal nanoparticles, potentially attributable to increased viscosity. This phenomenon may restrict drug migration to the external phase, thereby enhancing the EE%[9].

4. Conclusion

The study demonstrates that TZN-loaded cubosomal dispersions, formulated with GMO and stabilized by P407, possess favourable physicochemical characteristics for transdermal delivery. These nanocarriers may serve as promising vehicles for the improvement of the bioavailability and the reduction of the dosing frequency of TZN.

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Conflicts of interest

None exist.

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