Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 611 - 612 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.295
Short communication

Development and characterization of tadalafil-loaded pharmacosomes incorporated into gel for topical administration

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Introduction

Tadalafil is a phosphodiesterase type-5 (PDE-5) inhibitor widely used for the treatment of erectile dysfunction. However, its oral administration may be associated with adverse effects, including headache, flushing, dyspepsia, and muscle pain, while its poor aqueous solubility can limit dissolution and bioavailability (Coward and Carson, 2008). Pharmacosomes, lipid-based vesicular systems formed through the interaction of drug molecules with phospholipids, have emerged as a promising strategy to enhance the solubility, stability, and controlled release of poorly water-soluble drugs. Incorporation of tadalafil-loaded pharmacosomes into a topical gel may improve local drug retention, provide sustained release, and reduce systemic exposure, thereby potentially enhancing therapeutic efficacy and minimizing adverse effects associated with oral therapy (Mohamed et al., 2023).

Therefore, the aim of this study was to develop and characterize tadalafil-loaded pharmacosomes incorporated into a topical gel system and to evaluate their potential for improved drug delivery performance.

Materials and methods

Preparation of Tadalafil-loaded pharmacosomes

Tadalafil-loaded pharmacosomes, T9 and T12, were prepared by the solvent evaporation method. Tadalafil, hydrogenated phosphatidylcholine and cholesterol (1:3:0.4 and 1:4.06:0.66, *w/w*, for T9 and T12, respectively). were dissolved in a chloroform and methanol mixture (2:1, *v/v*). The solvents were evaporated using a rotary evaporator (40 °C, 97 mbar, 50 rpm) to form a thin lipid film, which was hydrated with phosphate buffer (pH 6.8) through four cycles of shaking and ultrasonication at 50 °C. The resulting dispersion was homogenized at 24000 rpm for 5 min and stored at 4 °C.

Preparation of Tadalafil pharmacosomal gel

The gel was prepared using Carbopol as a gelling agent. Carbopol (0,2 g), glycerin (1 g), propylene glycol (1 g), ethanol (0.2 g), EDTA (0.01 g) and the pharmacosomal dispersion (2 g) were mixed under continuous stirring. The pH was adjusted to 6.5 with sodium hydroxide, and purified water was added to obtain the final formulation.

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Characterization

Mean particle size (d_{50}) and particle size distribution (Span) were determined using a Mastersizer 2000 (RI = 1.520, absorption = 0.001).

Entrapment efficiency (EE%) was determined by. Pharmacosomal dispersions were centrifuged (4500 rpm, 25°C, 30 min, Rotofix 32 - Hettich Zentrifugen, Germany) in Vivaspin 20 ultrafiltration cuvettes (100000 MWCO units, Sartorius, Germany) to separate the unentrapped drug. The resulting sediment was collected, appropriately diluted, and analyzed with UV–Vis spectrophotometry (225 nm) using a tadalafil calibration curve (1–100 µg/mL) prepared in phosphate buffer (pH 6.8).

The dissolution test was performed using an *in vitro* membrane dialysis method (MEMBRA-CEL® dialysis tubing, MWCO 7000 RC, Serva Feinbiochemica GmbH, Germany), with phosphate buffer (pH 6.8) as the receptor medium maintained at 37 °C. Four formulations were tested (T9 and T12 pharmacosomes, as well as GT9 and GT12 gels), where 500 µL of pharmacosomal dispersions or 5 g of gel were applied to the donor compartment. Samples of 5 mL were withdrawn from the receptor medium at 1, 2, 4 and 6 hours and replaced with fresh buffer. The absorbance was measured at 225 nm using UV spectrophotometry (Philippsen et al., 2017).

Rheological characterization of the gels was performed using amplitude sweep (linear viscoelastic region), flow curve (steady shear region), and three-interval thixotropy (rest, breakdown and recovery region) tests at 25 °C and 32 °C.

Results and discussion

Both pharmacosomal formulations exhibited a single, well-defined particle size distribution with a d_{50} of approximately 6.4 µm. The Span values indicated a narrow size distribution for both systems (<1.5). High entrapment efficiency was achieved for both formulations, with T9 reaching 97.8% and T12 93.0%, confirming efficient incorporation of Tadalafil within the pharmacosomal system. The incorporation of pharmacosomes into the gel influenced the release profile of tadalafil.

The incorporation of pharmacosomes into the gel matrix significantly modulated drug release behavior. GT9 exhibited 72.4% release compared to 45.1% from T9, while GT12 showed 44.1% release compared to 80.3% from T12. The overall slower and more controlled release from gel formulations is attributed to increased diffusion resistance within the polymeric network, as well as the requirement for drug partitioning from the pharmacosomal system into the hydrated gel structure prior to release. Such controlled release is particularly advantageous for topical Tadalafil administration, as it ensures sustained local availability of the drug at the application site over an extended period, thereby potentially enhancing localized PDE-5 inhibition and therapeutic response while reducing the need for frequent application.

Rheological analysis demonstrated that both gel systems exhibited dominant elastic behavior ($G' > G''$), shear-thinning properties, and thixotropic recovery, indicating good structural integrity during storage and easy spreadability under shear, followed by rapid structural recovery after application. These properties support prolonged retention at the application site, further contributing to sustained drug exposure.

Conclusion

Tadalafil-loaded pharmacosomes were successfully incorporated into a gel, achieving high entrapment efficiency, a uniform particle size and optimal rheological properties. These results confirm that the developed gel is a stable and effective system for the topical delivery of tadalafil, offering a potential alternative to oral administration with reduced systemic side effects.

References

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