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Short communication

Early-stage formulation development and characterization of Tadalafil-loaded pharmacosomes for topical administration

Tamara Ivanoska[1*], Elena Stefova Mitrovska[1], Dushko Shalabalija[2], Ljubica Mihailova[2], Lina Livrinska[2], Marija Glavash Dodov[2]

[1]*Research & Development, Alkaloid AD-Skopje, Blvd. Aleksandar Makedonski 12, 1000 Skopje, N. Macedonia*
[2]*Faculty of Pharmacy, Ss Cyril and Methodius University in Skopje, Majka Tereza 47, 1000 Skopje, N. Macedonia*

Introduction

Topical application of drugs is becoming increasingly relevant and is favored over oral administration whenever possible, due to a large number of advantages. In this way, systemic exposure to the active pharmaceutical ingredient (*API*) is avoided, a high local concentration of the *API* at the site of action is achieved and systemic side effects that the drug may cause are reduced.

Tadalafil (*TDL*) is a newer, highly potent, and highly selective phosphodiesterase-5 inhibitor, with vey poor solubility, used as an oral therapy for erectile dysfunction (Mohamed et al., 2023). Recently, increasing attention has been given to evaluating alternative routes of drug administration in order to enhance drug efficacy, reduce side effects, and improve patient acceptability. Pharmacosomes can be defined as amphiphilic lipid vesicular systems composed of drug–phospholipid complexes, capable of encapsulating poorly soluble hydrophilic and lipophilic active substances, like *TDL*. The main requirement for pharmacosome formation is that the *API* must possess an active hydrogen atom (-COOH, -OH, -NH_2) to allow esterification with the lipid component. (Semalty et al., 2009). Taking the above into consideration, the aim of this study was to evaluate the possibility of formulating *TDL* in the form of pharmacosomes for topical application.

Materials and methods

Following materials were used in this study: *TDL* (Alembic Pharmaceuticals Ltd, IN); Soy Lecithin (*SL*, National Lecithin, US), Lipoid S Hydrogenated Phosphatidylcholine (*PL*, Lipoid, DE), Ethanol, absolute (*EtOH*, Merck, DE), Chloroform (*CH*, Merck, DE), Methanol, (*MetOH*, Merck, DE).

Pharmacosomes containing *TDL* were prepared using the solvent evaporation method. Briefly, *TDL* and *SL* or *PL* were dissolved in *EtOH* or a mixture of *CH* and *MetOH* (2:1). Subsequently, the solvent was evaporated using a rotary evaporator (Rotavapor R-300, Buchi, CH), in a round-bottom flask resulting in the formation of a thin film. Hydration of the lipid film was carried out according to the method of Shalabalija et al. (2021), with certain modifications.

*tivanoska1@alkaloid.com.mk

Four formulations were prepared (*sample* T1-molar ratio *TDL*:*SL*=1:2 with *EtOH*; *sample* T2-molar ratio *TDL*:*PL*=1:2 with *EtOH*; *sample* T3-molar ratio *TDL*:*SL*=1:2 with *CH*:*MetOH* and *sample* T4-molar ratio *TDL*:*PL*=1:2 with *CH*:*MetOH*).

The particle size and size distribution (*PSD*) of pharmacosomes were measured using a Mastersizer 2000 (Malvern Instruments Ltd., UK).

Infrared spectra of *TDL*, *SL* and pharmacosomes were recorded using an FTIR spectrometer (Nicolet iS50 FT-IR, Thermo Scientific., US). DSC curves of *TDL*, *SL* and pharmacosomes were recorded using a NETZSCH DSC 204 F1 Phoenix instrument (Netzsch, DE).

Results and discussion

Results obtained from *PSD* measurement showed that d50 ranged from 20 to 111 μm, depending on formulation composition, which is not in the usual acceptable range for pharmacosomes (d50 < 300 nm) (Danaei et al., 2018). Formulations prepared with absolute ethanol, as a volatile and safer solvent showed larger particle sizes (>30 μm), lower uniformity and additionally the mixture was not completely dissolved and tended to precipitate upon standing, indicating that *EtOH* is not the most suitable solvent for producing pharmacosomes. On the other side, mixture of *CH* and *MetOH* as solvent (T3 and T4) gave better results that should be optimized. The formation of the complex can be confirmed using infrared spectroscopy by comparing the spectrum of the complex with the spectra of the individual components. In the region of 1750–1650 cm^{-1}, the characteristic carbonyl band of *TDL* changes in the complex, i.e., its intensity is reduced and it is broadened. This broadening and loss of intensity of the peaks in this region indicate that the carbonyl group of *TDL* is involved in intermolecular interactions (most likely hydrogen bonding) with the polar groups of *SL/PL* (choline, ethanolamine, inositol). In the region of 1250–1040 cm^{-1} decrease in peak intensity is observed in the complex, whereas in pure *SL/PL* these appear as typical sharp peaks characteristic of *SL/PL*. The decrease in intensity and broadening of this peak suggest interaction between the polar groups of *TDL* and the phosphate groups of the phospholipids in *SL/PL*, which is the most common binding site in drug–phospholipid complexes. From the above, it can be concluded that observed shifts and reductions in peak intensity indicate the formation of a complex, as a confirmation of pharmacosome formation. Obtained DSC analysis showed that pure *TDL* exhibited a characteristic sharp endothermic peak corresponding to its melting point, confirming its crystalline nature. In contrast, this characteristic endothermic peak was absent in the *SL/PL* complexes. The disappearance of the sharp melting endotherm of *TDL* indicates that the drug is no longer present as a distinct crystalline phase within the complex. This behavior suggests successful complex formation, likely due to molecular dispersion and/or amorphization of the drug, as well as strong drug-lipid interactions.

Conclusion

The generated results provide a solid basis for further formulation development, where through the use of design of experiments, the levels of lecithin and phosphatidylcholine would be varied as formulation variables. Additionally, process parameters such as mixing time and sonication should be optimized, and an additional high-speed homogenization step would be introduced in order to reduce particle size and achieve the target particle size (d50 < 300 nm).

References

Danaei, M. et al., 2018. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics 10, 57. https://doi.org/10.3390/pharmaceutics10020057

Mohamed, S.A. et al., 2023. Proniosomal gel-loaded phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil): prospects for topical penile therapy of tadalafil for treatment of erectile dysfunction. Gels 9, 597. https://doi.org/10.3390/gels9080597

Semalty, A. et al., 2009. Pharmacosomes: the lipid-based new drug delivery system. Exp. Opin. Drug Del. 6, 599-612. https://doi.org/10.1517/17425240902967607

Shalabalija, D. et al., 2021. Formulation and optimization of bioinspired rosemary extract-loaded PEGylated nanoliposomes for potential treatment of Alzheimer's disease using design of experiments. JDDST 63, 102434. https://doi.org/10.1016/j.jddst.2021.102434