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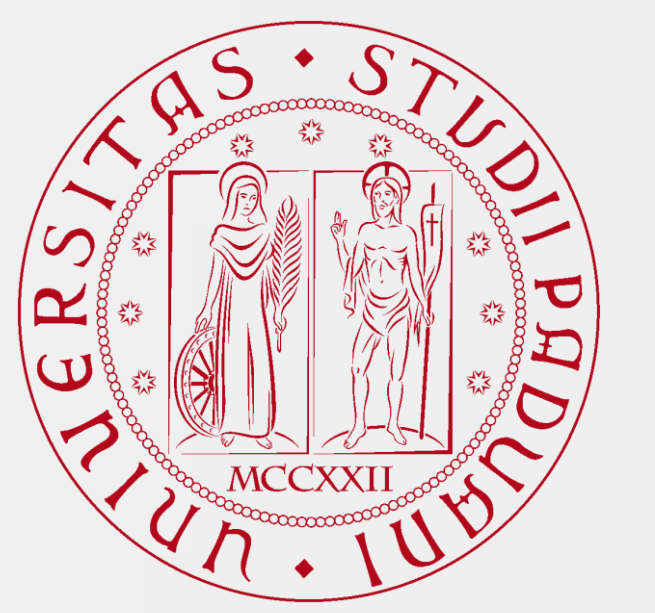
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# VESICULAR TRANSDERMAL DELIVERY SYSTEMS FOR CANNABINOIDS

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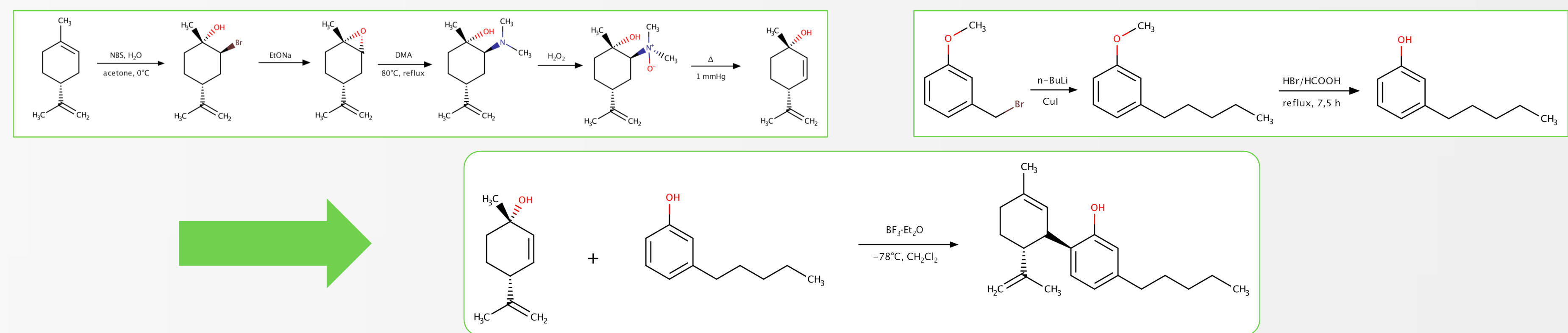
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During the last years, *Cannabis* and cannabinoids have gained increasing interest despite their disputed clinical applications.<sup>1</sup> The difficulty in guaranteeing a well-defined administered dose is one of the factors that leads to greater uncertainty in the study of these products. The development of new pharmaceutical forms, using a model molecule mimicking the solubility behavior of THC, the psychoactive component, is currently being studied in this project. Desoxy-CBD (DH-CBD), synthesized in the laboratory of Medicinal Chemistry, and CBD are the active ingredients selected for the development of transdermal vesicular systems, and subsequently included in hydrogels.

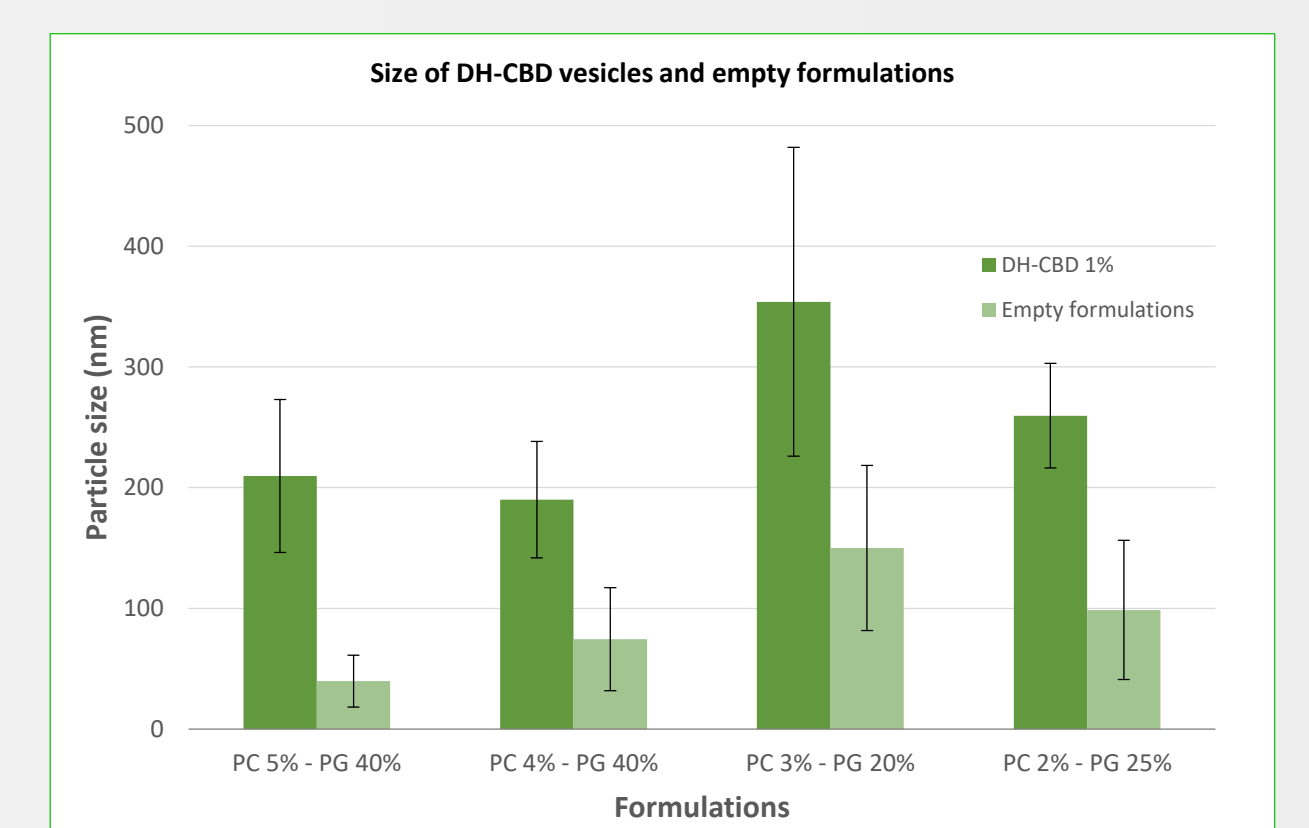
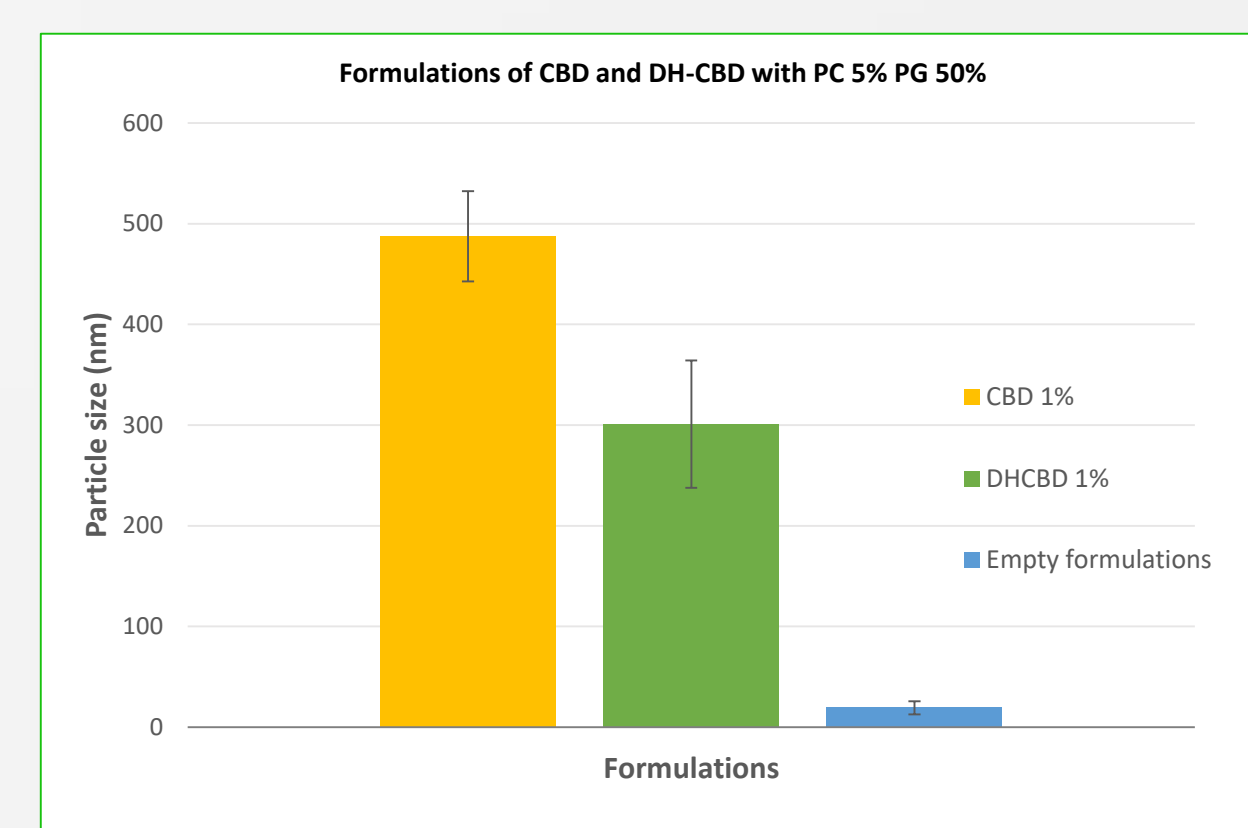
## DESOXY-CBD PRODUCTION



Desoxy-CBD is a non-psychoactive synthetic cannabinoid not easily available on the market. In this work, DH-CBD was synthesized by condensation of *p*-mentha-2,8-dien-1-ol and *m*-pentylphenol. The first synthon was obtained from a non-expensive material, *R*-(+)-limonene, modifying the Wilkinson-Price-Kassiou pathway<sup>3</sup>, while the second was synthesized treating 3-methoxybenzyl bromide with *n*-butyllithium and CuI. The condensation of the two synthons was performed with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  at  $-78^\circ\text{C}$  and the product was purified with flash chromatography.

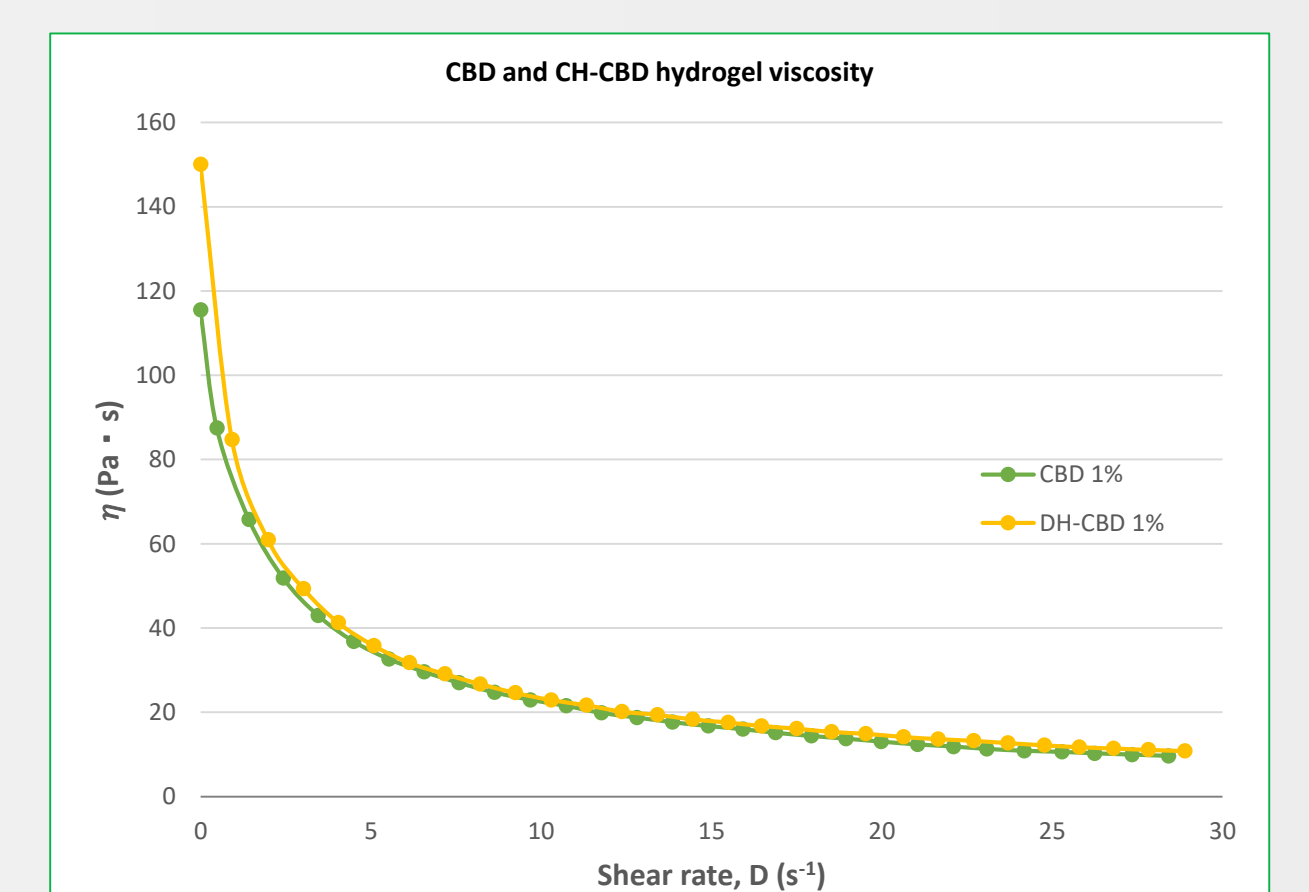
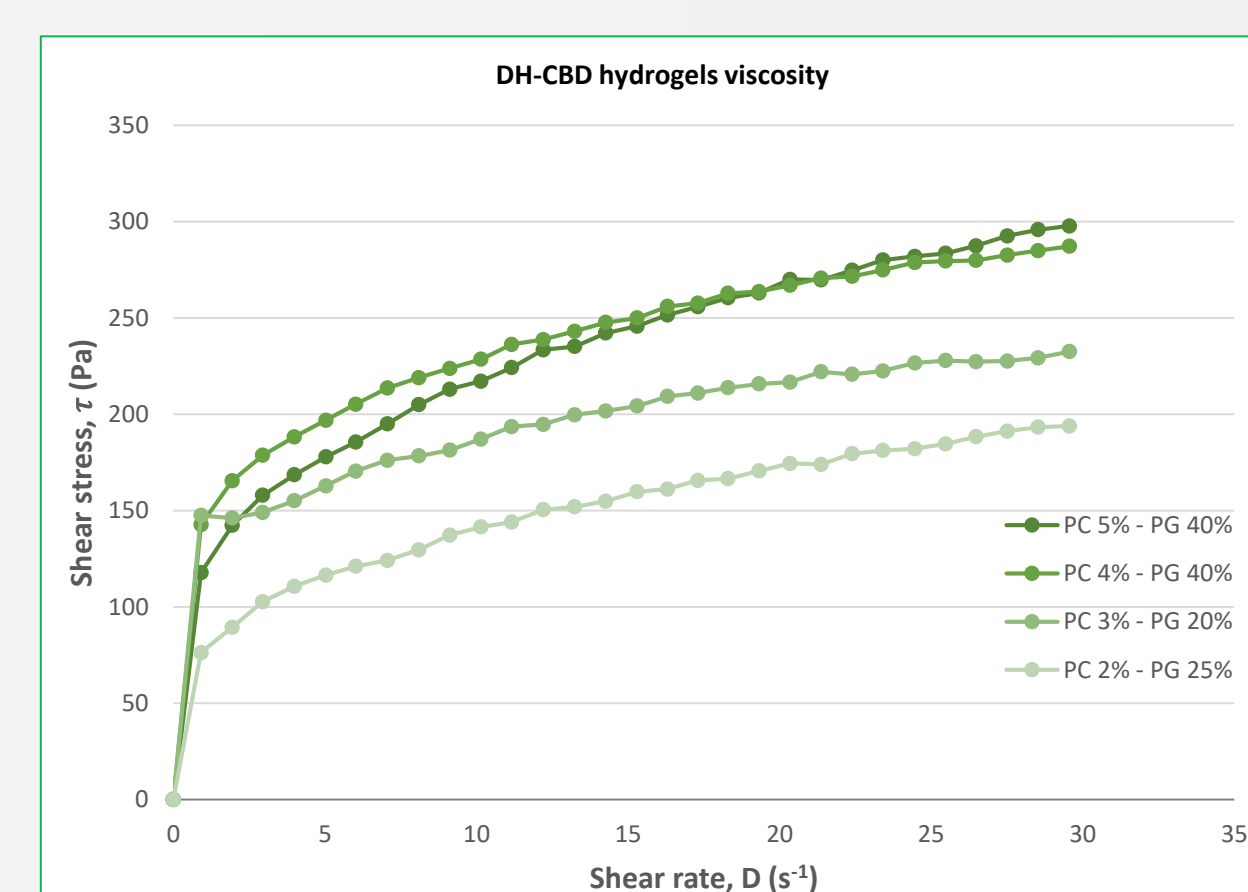
Soft vesicular systems composed of phosphatidyl-choline and ethanol have been developed in the last decades, starting from "Ethosomes"<sup>2</sup>. Each ingredient affects size,  $\zeta$ -potential, stability, and skin permeability.

## VESICLES CONTAINING DESOXY-CBD



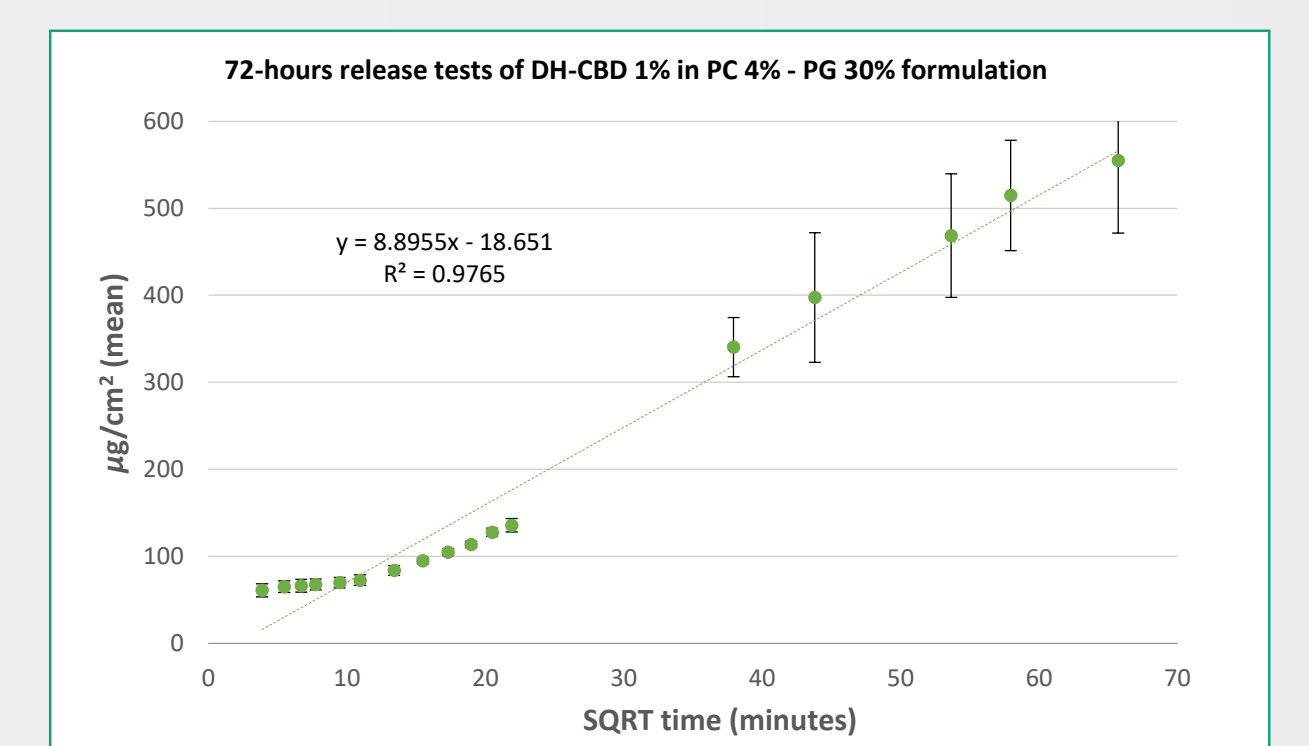
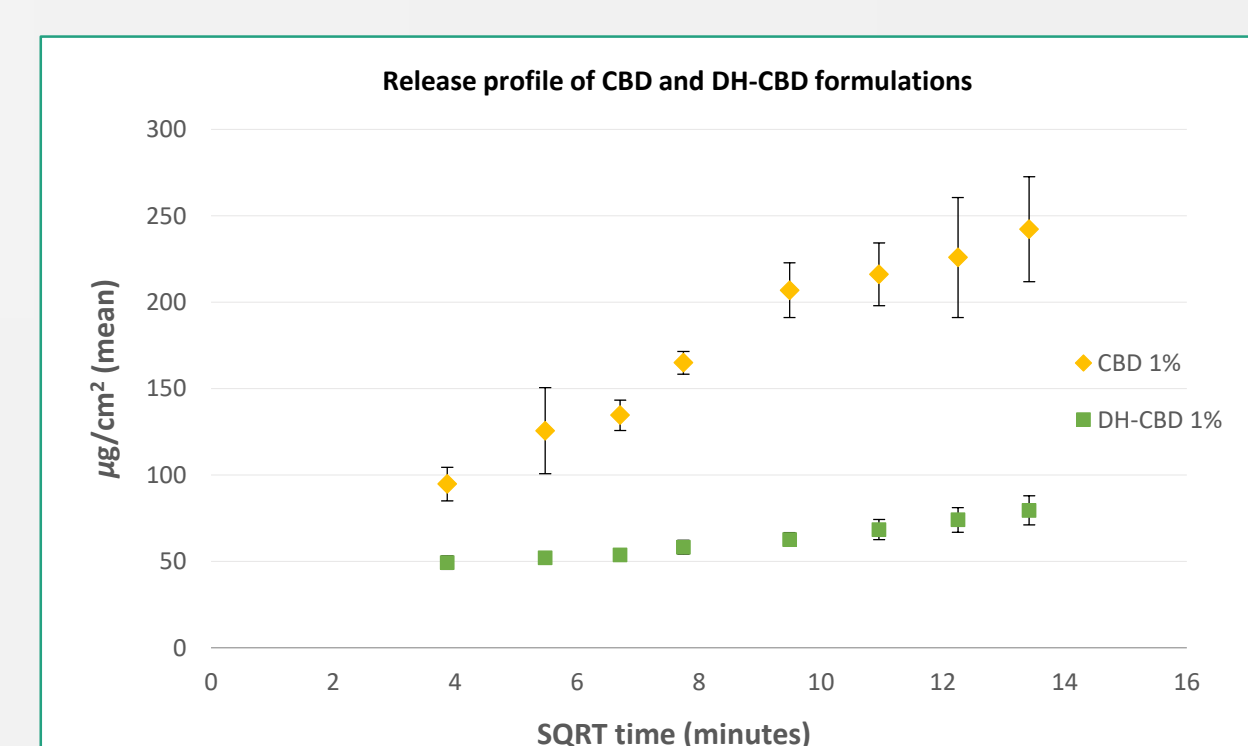
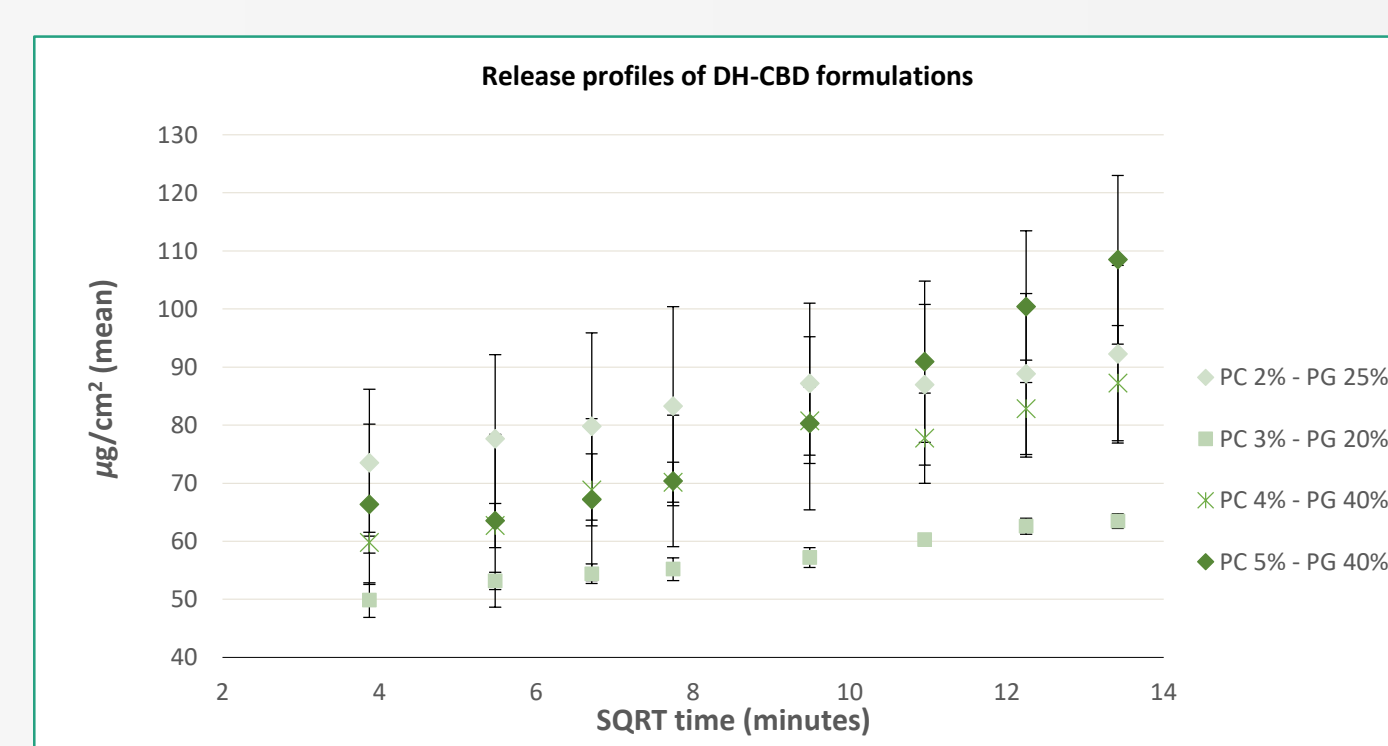
Vesicles containing DH-CBD or CBD were prepared by simple mixing method with a mechanical stirrer<sup>4</sup>. The effect of variable concentrations of propylene glycol (PG) ranging from 20 to 50% in systems containing DH-CBD were observed. Particle size was measured by DLS and optimal results were generally given by formulations with 40% PG, in which vesicle size was maintained at around 200 nm.

## HYDROGELS CONTAINING VESICLES



Loaded dispersions were incorporated 1:1 in hydrogel with 0,75% Carbopol Ultrez 10. Gels were stored at  $+4^\circ\text{C}$ . CBD and DH-CBD loaded gels composed by 1% drug, 5% PC, 20% ethanol, 50% PG, and water, were compared. The rheological behavior was observed with a rheometer, showing an optimal thixotropy in all the formulations. A relevant difference in terms of critical resolved shear stress was registered between CBD and DH-CBD formulations.

## RELEASE STUDIES OF DESOXY-CBD



Release studies were performed using Perspex cells and cellulose nitrate synthetic membranes. The highest DH-CBD release profile was achieved with 5% PC – 30% PG formulation, with  $117,51 \mu\text{g}/\text{cm}^2$ . The formulation composed by 4% PC – 30% PG showed a good overall profile in terms of particle size, stability in time, and entrapment efficiency. As compared to the equivalent DH-CBD formulation, hydrogels containing CBD showed a very high release profile, reaching  $242,28 \mu\text{g}/\text{cm}^2$ , but higher variability over time. The release of this formulation was tested over 72 hours, resulting  $508,36 \mu\text{g}/\text{cm}^2$ , with a desirable continuous and linear release profile, suitable for a prolonged transdermal delivery.

## CONCLUSIONS

Desoxy-CBD (DH-CBD) resulted a promising molecule that improves the design of transdermal delivery systems as binary ethosomes. DH-CBD formulations showed lower dimensions and a higher entrapment efficiency than the CBD formulations. The smaller dimensions of DH-CBD ethosomes can be an advantage for the transdermal drug delivery. Further studies on the diffusion and release properties will be made, and further analysis will show the potential transdermal delivery of the cannabinoids performed by these vesicular systems.

## REFERENCES

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