Thesis: *Development of cannabidiol orodispersible tablets*
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Pediatric drug therapy has always been a challenge for researchers in pharmaceutical sciences. Orodispersible preparations, such as orodispersible tablets (ODTs), oral lyophilizates, and orodispersible films represent medicinal products proper for compliance enhancement.

The thesis approaches multiple research directions however, its main aim is the development and evaluation of orodispersible tablets with cannabidiol (CBD-ODTs) for pediatric patients. The low production costs and the reduced time of the technological process are decisive in the selection of this pharmaceutical formulation.

The first part of the thesis includes the state of art underlying the subsequent experimental studies. Relevant data regarding the CBD and the proposed excipients' properties were presented, including the analytical methods that can be used to assay the active pharmaceutical ingredient from the medicinal product.

For a proper excipient selection, the first research directions included in the *Personal Contribution* chapter, include three preformulation studies:

- Including CBD in a fast-release pharmaceutical formulation. As an innovative tool, the SeDeM-ODT expert system was used to select the suitable excipients for the development of new orodispersible tablets used in the pediatric field;
- The API: excipients compatibility study using two different methods (DSC, FTIR);
- The CBD concentration and excipient type influence on the compressibility, compactibility, and tabletability profiles.

The first study uses the SeDeM-ODT expert system, the main objectives being the analysis of the active pharmaceutical ingredient (API) and some excipients with different roles: fillers (lactose, microcrystalline cellulose), sweeteners (mannitol and sorbitol), superdisintegrants (soy polysaccharides, sodium starch glycolate, and sodium croscarmellose), and co-processed excipients (Prosolv® ODT G2 - PODTG2, Prosolv® EasyTab sp - PETsp).

The incidence factors specific to a powder were verified. The obtained results showed that from all analyzed excipients, the co-processed ones have properties that need small adjustments – PODTG2, being the excipient that presented radius values belonging to the incidence factors higher than 5. The data generated through this study allowed to establish the quantities of the co-processed excipients needed to develop ODTs.

In a medicinal product, the compatibility between the API and the excipients is a very important element, therefore the main objective of **the second study** was the identification of the possible incompatibilities between the API and the selected excipients using thermal analysis - differential scanning calorimetry (DSC) and spectral analysis Fourier Transformed Infrared Spectroscopy (FTIR). No significant interactions were exhibited between the CBD and selected excipients; consequently, they were maintained in further studies.

The third study consisted of the evaluation of some excipients regarding the compressibility, compactibility, and tabletability profiles. Nine formulations were evaluated (C1-C9), where the concentration of CBD and the type of excipients used were varied. The mixtures underwent compression using the Gamlen D 500 tableting machine, applying three levels of compression mass (100, 300, and 500 kg). The dynamic compression analysis showed that the presence of CBD in the ODT composition conducted to a decrease in the mechanical resistance, porosity, and an increase in the solid fraction. The ejection and detachment stress were established for the nine formulations

proposed; observing values of this parameter lower than 5 MPa, meaning that there is a lower risk of decapping. This chapter completes the preformulation study realized in order to obtain ODTs that fulfill all the critical parameters selected.

The fourth research direction consisted of the development and formulation of CBD-ODTs, regarding Ph. Eur. 10 regulations: fast disintegration (<3 min), fast release, and friability (<1%).

Based on the results obtained during the preformulation studies considering the excipient selection, eight CBD-ODTs were developed, varying the following parameters: quantitative parameter (PLX407 concentration - two levels 0 and 10 %) and qualitative parameters (co-processed excipient type: PODTG2 and PETsp and the type of superdisintegrant: CCS and EMCS). A full factorial design was used to accomplish the critical quality parameters: friability < 1%, mechanical resistance in the proposed range, disintegration time < 180 s, and the amount of API released after 30 minutes > 80%. This experiment revealed the way that some factors are influencing the fabrication process of the ODTs.

Eleven formulations were obtained using the direct compression method (eight formulations belonging to the proposed design and three representing the central point). The tablets were evaluated in terms of dimensional characteristics (uniformity of mass, average diameter, average radius) and pharmacotechnical (friability, mechanical resistance, disintegration time, and API released after 1, 3, 5, 10, 15, and 30 minutes). The pharmacotechnical parameters represented the dependent variables analyzed through this formulation study. The results obtained were evaluated via *Modde 12.1 software* (Umetrics), generating the optimal composition and the theoretical values of the dependent variables.

The optimal CBD-ODT (O12) respects all the provisions from the in-force Ph. Eur., friability < 1%, mechanical resistance in the proposed range, disintegration time < 30 s, and an amount of API released of almost 100 % after 30 min.

The last study aims to quantify the CBD from the ODT matrices. In this regard, a chromatographic method was developed, validated, and transferred to two chromatographic systems (HPLC and UHPLC). The method was simple, specific, and precise, being successfully used to assay the CBD from the orodispersible formulations.

Originality

Nationally, there is no medicinal product with CBD available with a prescription (Rx) or Over-the-Counter (OTC), which is why the developed CBD-ODTs in this thesis can represent a starting point for future research regarding the patients with rare forms of epilepsy.

The main elements of originality of the thesis consist of:

- the use of SeDeM-ODT diagrams to select the suitable excipients for developing a new formulation of ODTs designed for pediatric therapy and including the CBD in a pharmaceutical formulation with a fast release.
- profiling the compatibilities between the API and the proposed excipients using two different analytical methods.
- the API and selected excipients influence on the compressibility, compactibility, and tabletability profiles.

To fulfill the actual trend regarding the orodispersible tablets, a natural excipient (Emcosoy®) was used, which proved to be a useful disintegrant. Currently, a reduced number of studies highlighted the disintegrant property of this excipient.

CBD-ODTs were obtained, with an improved water solubility for the API. The optimized formula, O12, satisfies all the proposed pharmacotechnical characteristics (disintegration time < 180

s, reduced friability < 1%, good crushing strength > 35 N), and also the uniformity of dosage (between 85-115 % of the declared amount). The amount of API released after 30 minutes is almost 100 %, the assay of the CBD being performed using the previously developed chromatographic method.