

Cannabidiol based borderline products – from development to registration processes

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Introduction

Cannabidiol (CBD) is the second most abundant phytocannabinoid structure in *Cannabis sativa* L., Cannabaceae family. It contains a bicyclic 21-carbon skeleton with a double bond in the terpene ring (Jacobs et al., 2016). Cannabidiol based products have been used mainly for additional treatment of pain, depression and anxiety in cancer suffering patients as well as immunostimulatory agents. They are used for treatment of nausea and vomiting, especially during chemotherapy or radiation therapy. Their effects are exerted through the endocannabinoid system through multiple receptors, including cannabinoid receptors (CBRs), opioid and serotonin receptors, adrenergic receptors, and G protein-coupled receptors (Pertwee & Cascio, 2014). At high doses can modulate the intoxicating effects of THC through CB1-dependent mechanisms despite having low CB1 binding affinity (Jacobs et al., 2016). In Republic of North Macedonia, the production, use and sale of registered cannabis products are regulated by the Law of Use of Narcotic Drugs and Psychotropic Substances (Official Gazette of R.M no. 37/2016). A borderline product is a product that contains: (1)probiotics; (2)active components of plant origin and it is classified as a food supplement in at least one member state of the European Union, and according to the special regulations applied in the Republic of Macedonia, it cannot be classified as a food supplement; (3)vitamins and minerals in quantities greater than the permitted prescribed in accordance with the special regulations applied in the Republic of Macedonia, if it is classified as a food supplement in at least one member state of the European Union and there is no registered product with the same strength in the Republic of Macedonia (Official Gazette of R.M no. 203/2015). According to the second term of this law CBD products are still registered as borderline products in our country.

Materials and methods

In our experimental conditions following materials were used in production processes: dry hemp biomass (DH-BM) (obtained from Bioherbalist, Czech Republic); medium-chain triglycerides oil (MCT oil) Type V, Ph. Eur. 10.0 (obtained from GustavHeess, Germany), hemp seed oil, refined (HSOr) (obtained from GustavHeess, Germany); ethanol 96% v/v Ph. Eur. 10.0 (EtOH) (obtained from Alkaloid AD, North Macedonia). All materials were provided with certificates of quality from the supplier, according to the pharmacopeial requirements. The ethanol extraction (EE) line consist of chillers, solvent extractors, centrifugal filters, buffer filtering equipment (BFE), falling film concentration equipment (FFCE), vacuum spherical concentration equipment (VSCE), filter separator, vacuum pumps and solvent recovery system.

Ethanol extraction of the DH-BM was done with appropriate EE line. First, a cold maceration of the DH-BM was performed with cold ethanol, with a ratio of DH-BM: EtOH=1:10 (w/v) for 1 h. After centrifugation of the mixture, ethanol extract was filtered and placed in thin-layer (film) distillation took in the FFCE at temperature of 78°C. By these methods the ethanol extract was obtained and afterward filtered through BFE. Concentration and ethanol evaporation of the extract were performed in VSCE, at the temperature of 80°C with homogenization. By these procedures, crude cannabis oil (CCO) was obtained.

Decarboxylation of CCO was performed in Double Jacketed Glass Reactor at a temperature of 140°C, followed by a short path distillation in order to purify and separate cannabinoids in cannabis extract.

Production of oil solutions – oil solutions of standardized cannabis extract (SE-CBD) were prepared in two types: (1)oil solutions in MCT oil and (2)oil solutions in HSOr. The mixing of the oil solution took place in a

magnetic stirrer at a temperature of 65°C with 200 rpm for 45 minutes.

Results and discussion

The reported technologies were used to finally obtain a high-purity and superior quality concentrate that can be processed into a variety of final products. In this way, we obtained an SE-CBD product with a total of CBD=70.6% (w/w) and total THC=0.17% (w/w), after in process control (IPC). Additionally, HPLC method for all IPC procedures were performed, and the final products were analyzed by a validated HPLC method with UV detector.

Three batches of each of the two types of oil solutions were made. The first batch contained 5% (w/w) CBD, the second batch 10% (w/w) CBD and the third batch 20% (w/w) CBD. All batches were packed in bulk of 200 ml in dark glass bottles. The received certificates for physico-chemical and microbiological tests were in accordance with the set specifications for the quality of the finished product. Registration procedure for classification of the products into borderline products was initiated. This process was supported with following documentation: (1) Request for product classification, in which the name of the product, the manufacturer, the country of origin, the agent, or the importer of the product have been specified; (2) A sample of the product for which classification is requested in final packaging; (3) Exact qualitative and quantitative composition of the product and certificates for product analysis; (4) Patient Information Leaflet (PIL) if not an integral part of the product's outer packaging; (5) List of countries in which the sale of the product is approved with its classification; (6) Product classification certificate issued by a competent authority from a member state of the European Union; (7) Free Sales Certificate, and (8) Negative opinion from AHV if the product comes from abroad and is registered as a dietary supplement. Oil solutions (final products) were packaged in 10 mL and 20 mL dark glass bottles with droppers. Secondary packaging for the products, was also designed as well as labels for labeling the contact (primary) packaging. All the required specimens and documentation by MALMED, for registration of CBD-based borderline products were delivered and processed for further registration procedures. After the completed procedure for registration of CBD-based borderline products, MALMED adopted Decisions approving the borderline products and allowed them to be entered in the Register of Borderline products. By issuing a registration number for each product, twelve CBD-based borderline products were registered. Six of them contained MCT oil, and the other six were with HSO, as excipients. Borderline products contain different concentrations of CBD (5% w/w, 10% w/w and 20% w/w) and are packaged in dark glass

bottles (with dropper) of 10 ml and 20 ml. These products can be dispensed and/or sold without a prescription (Over-the-counter medicines, OTC).

Due to the positive effects of using CBD, these oil preparations are proposed in: stress, anxiety, neurosis, depression, Parkinson's disease, Alzheimer's disease, some forms of epilepsy, multiple sclerosis, muscle spasms, muscle relaxant, nausea and vomiting as a result of chemotherapy or radiation therapy in the treatment of malignant tumors, unbalance of intestinal flora, chronic pain related to the nervous system–neuralgia and phantom pain (Larsen & Shahinas, 2020). The product in the form of oil solution (drops) ensures easy and fast absorption in the body after administration by dropping under the tongue (sublingual administration). Sublingual administration allows direct absorption of CBD and faster delivery of higher concentrations of CBD into the systemic circulation. Another advantage of this route administration is the possibility of easier dosing by gradually increasing the dose when necessary.

Conclusion

CBD oil solutions in different concentrations have been largely used in many countries and these preparations that can be found in our pharmaceutical market are an essential borderline product especially for cancer patients. The importance of technological processes must be emphasized in order to obtain high quality and safety products for our patients.

References

- [Jacobs, D.S., Kohut, S.J., Jiang, S., Nikas, S.P., Makriyannis, A., Bergman, J. 2016. Acute and chronic effects of cannabidiol on Δ^9 -tetrahydrocannabinol-induced disruption in stop signal task performance. *Exp. Clin. Psychopharmacol.* 24, 320–330. <https://doi.org/10.1037/pha0000081>
- Larsen, C., Shahinas, J. 2020. Dosage, Efficacy and Safety of Cannabidiol Administration in Adults: A Systematic Review of Human Trials. *J. Clin. Med. Res.* 12(3), 129–141. doi: 10.14740/jocmr4090
- Pertwee, R.G., Cascio, M.G. 2014. *Handbook of Cannabis*. Pertwee, R., editor. Oxford Scholarship Online; Oxford, UK, pp. 115–136.
- Official Gazette of R.M no. 203/2015. Rulebook on the closer conditions for borderline products, the method of approval and the necessary documentation. Agency for Medicines and Medical Devices-MALMED. Skopje, 2015.
- Official Gazette of R.M no. 37/2016. Law on amending and supplementing the law on the control of narcotic drugs and psychotropic substances. Ministry of Health. Skopje, 2016.]