Poster

Crystal Structure of Cannabidiol Inclusion Complexes in Native and Methylated beta-Cyclodextrins

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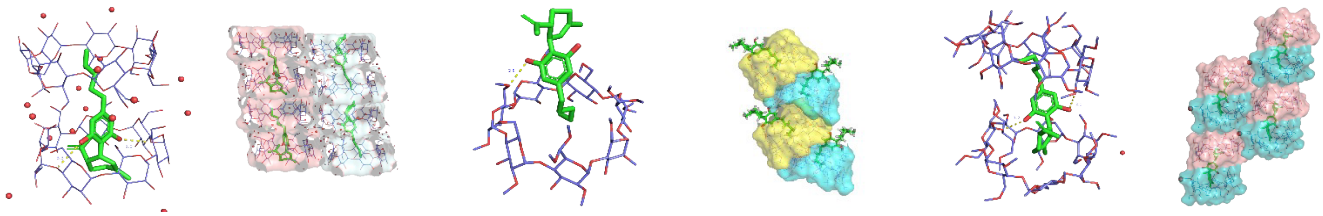
Cannabidiol (CBD), a non-psychoactive compound found in cannabis, has been extensively studied for its potential to alleviate anxiety, chronic pain, inflammation, and epilepsy [1]. Encapsulating CBD in cyclodextrins (CDs) significantly enhances its solubility, stability, and bioavailability. This leads to more consistent and efficient delivery, thereby enhancing its therapeutic efficacy. Additionally, cyclodextrin complexes can mask the bitter taste of CBD, making it more palatable for oral consumption [2].

This study aims to elucidate the crystal structure of CBD inclusion complexes in β-cyclodextrin (β-CD), 2,6-di-O-methyl-β-cyclodextrin (DM-β-CD) and 2,3,6-tri-O-methyl-β-cyclodextrin (TM-β-CD). Single crystal X-ray diffraction data at 100 K were collected at the EMBL Beamline MX1 - P13 (PETRA III storage ring, DESY, Hamburg, Germany) in the first case and on a Bruker D8-Venture diffractometer in the latter two cases. Full data sets up to 0.81, 0.99, and 0.89 Å resolution respectively, were obtained and processed with XDS or Bruker SAINT software. The crystal structures were determined with ShelxD and refined with ShelxL program to final R values of 0.086, 0111 and 0.06, respectively. CIF files were deposited with the CCDC (deposition numbers: 2287491, 2098419 and 2094890).

The CBD/β-CD complex crystallizes in the C2 space group with a 2:1 host:guest stoichiometry, featuring a CBD molecule enclosed by two β-CDs arranged in a "tail-to-tail" manner (Fig. 1a). This inclusion mode justifies the low solubility of the complex observed in many studies, as it indicates that multiple hydrogen bonds can be formed between the wide rim ("head") of the host β-CDs of adjacent complex units, leading to the formation of self-assemblies and subsequent precipitation. The CBD/DM-β-CD complex, crystallizing in the $P2_12_12_1$ space group, has a 1:1 stoichiometry. The aliphatic chain of CBD is entrapped in the hydrophobic cavity whereas its limonene and benzenediol groups protrude from the narrow rim of the host, filling the interspace between the adjacent complex units that are arranged in a "herring bone" mode along the crystallographic b-axis (Fig. 1b). The CBD/TM-β-CD complex crystallizes in the monoclinic $P2_1$ space group, with a 2:1 host:guest stoichiometry. In this case, the CBD is encapsulated in a "head-to-head" dimeric cavity formed by two TM-β-CD molecules. Although the formation of this kind of dimer is very common in native β-CD inclusion complexes, this is the first time it has been observed for a TM-β-CD inclusion complex, indicating CBD's ability to tether the host molecules in such a manner [2] (Fig. 1c).

The structural information on CBD inclusion in CDs provided in this work may be useful for engineering modified guest-host preparations with optimized pharmacological properties and shaping future therapeutic strategies.



(a) **(b)** **(c)**

Figure 1. The CBD inclusion complex in (a) native, (b) dimethylated and (c) permethylated β-CD, along with the respective crystal packing of each complex case.

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We acknowledge Hempoil® for the kind offer of pure CBD crystals. We also acknowledge support of this work by the project "INSPIRED-The National Research Infrastructures on Integrated Structural Biology, Drug Screening Efforts and Drug Target Functional Characterization" (Grant MIS 5002550), which is implemented under the Action "Reinforcement of the Research and Innovation Infrastructure", funded by the Operational Programme "Competitiveness, Entrepreneurship and Innovation" (NSRF 2014–2020) and co-financed by Greece and the European Union (European Regional Development Fund)