Case study 3: Cannabidiol

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Background

127. Cannabidiol (CBD) is a highly hydrophobic molecule known to be of relatively low oral bioavailability, with reports suggesting an average of approximately 6% (Millar *et al*., 2020). Moreover, a large degree of inter-individual variation exists in the absorption of CBD (Millar *et al*., 2018) and

absorption is modified by feeding state (Silmore *et al*., 2021; Mozaffari *et al*., 2021).

128. Preparation of CBD also affects its bioavailability. For instance, Williams *et al*. (2021) demonstrated that oral bioavailability differed between five different CBD formulations. A preparation comprising 5% CBD concentrated liquid (containing medium-chain triglyceride (MCT) oil, gum arabic, and citric acid in reverse osmosis water) evoked the shortest Tmax, highest Cmax, and largest AUC0-4h, whilst CBD powder suspended in reverse osmosis water had the lowest oral bioavailability.

129. The most bioavailable CBD preparation in Williams *et al*.'s (2021) study was formulated with medium-chain triglyceride (MCT) oil, citric acid, and gum arabic in reverse osmosis water. The authors suggested that the presence of gum Arabic and medium-chain triglyceride (MCT) oil may have aided CBD solubilisation in the GI tract and therefore enhanced absorption.

130. However, whilst formulation type can affect the bioavailability of CBD, questions remain as to how this translates into the supplement market and the precise products to which consumers might be exposed. CBD is widely consumed as a supplement in the UK and is available in a variety of formulations, for instance as oils, tinctures, capsules, in beverages, and in food. It is potentially misrepresentative, therefore, to speak of a 'standard' formulation of CBD.

131. However, a preliminary analysis conducted by the Secretariat of 51 CBD supplements available from the online market suggests a large portion of CBD supplements (29/51) are formulated with medium-chain triglyceride (MCT) oil as a carrier. The most common delivery method is oral oil drops: 25 out of the 51 products are formulated as oral oil drops, 19 of which use medium-chain triglyceride (MCT) oil as a carrier, with the remainder using either hemp seed oil or rice brain oil. Gummies are the second most common formulation (12/50) whilst oral sprays and capsules comprise the remainder.

132. One entry for micellar CBD was found. The proprietary formulation of this product was NovaSOL®, and the pharmacokinetics of curcumin formulated in this way have been studied in control settings (see above section). There were no other indications for CBD formulated in ways to increase oral bioavailability on a preliminary search of the online market, but a further general internet search identifies several possible products on the market.

Studies investigating the oral pharmacokinetics of CBD formulations

133. Alternative formulations have been designed to increase oral CBD bioavailability and alter its pharmacokinetic profile. Owing to potential application of CBD to treat symptoms of disease, a large amount of this research has been based on development for pharmaceutical indications. Unlike curcumin, however, there are currently only a few clear examples of novel formulation products available on or destined for the supplement/nutraceutical market (or to wholesalers/white label who supply this market).

134. However, some of the CBD formulations in development as academic and/or pharmaceutical projects have used food-grade ingredients to design preparations that could conceivably be adopted by supplement manufacturers. Additionally, owing to the regulatory status of CBD, some of these applications and/or products occupy a grey area between the pharmaceutical and supplement markets, and their penetrations into either space is possible.

135. Based on this reasoning, the following paragraphs summarise key studies investigating formulations of CBD with increased bioavailability in human subjects. The studies are selected to indicate possible formulations that might increase bioavailability and offer a ‘horizon scanning’ perspective on formulations that, owing to their formulation characteristics, might conceivably penetrate the CBD supplement market in the future.

136. Hobbs et al. (2020) investigated the relative oral bioavailability of two commercially available CBD formulations: ‘water-soluble’ and ‘lipid-soluble’ powders in 10 healthy subjects in a randomised parallel arm study. Volunteers were administered 30 mg CBD, which was suggested to be a ‘standard’ dose based on available products. The water-soluble powder had Cmax of 2.82 ng/mL and a Tmax of 90 min. The abstract to this study states that the water-soluble powder was approximately 4.5-fold more bioavailable than the lipid-soluble form.

137. De Prá *et al*. (2021) prepared a self-emulsifying drug delivery system (SEDDS) designed to increase the oral delivery of CBD. As described in the above section, SEDDS are lipid-based preparations of active ingredients formulated with lipids, surfactants, and/or co-surfactants that self-emulsify upon contact with the aqueous conditions of the GI tract to form mixed micelles and potentially increase absorption of lipophilic compounds (Pouton and Porter, 2008). The CBD SEDDS was prepared with polyoxyl 40 castor oil as the emulsifier and polyethylene glycol

400 as the co-emulsifier, both of which are food-grade ingredients.

138. The De Prá *et al*., (2021) study also investigated the effects of partially hydrolysed long-chain triglycerides (GML) as an excipient on the oral bioavailability of CBD. GML is composed of a mixture of mono-, di-, and triglycerides, which may improve the solubility of CBD via promoting mixed micelle formation. CBD formulated with medium-chain triglyceride (MCT) oil was used as the reference preparation. *In vitro* digestion studies demonstrated that the majority of CBD from the SEDDS remained partitioned in the aqueous phase post-digestion, suggesting a complete solubilisation under these conditions. Only a low percentage of CBD from the other two preparations, however, was recovered in the aqueous phase.

139. The preparations were investigated in a controlled trial comprising 11 (analysed) subjects. The trial was designed as a three-arm crossover study with 7-day washout periods between administration of subsequent formulations. These human pharmacokinetic studies demonstrated that SEDDS CBD formulation led to an increased Cmax and AUC0-12h versus the medium-chain triglyceride (MCT) formulations (2 and 1.5-fold, respectively). GML preparation also increased the Cmax and AUC0-12h by 1.9-and 1.3-fold, respectively. Both the SEDDS and GML formulations also decreased the Tmax of plasma CBD levels (1.7 and 1.6 hours, respectively, versus 4.3 hours). The authors concluded that the “bioavailability of [CBD] is significantly influenced by the physicochemical characteristics of [excipient] lipids, the length of the fatty acid chain, and its susceptibility to digestion.”

140. Knaub *et al*. (2019) also investigated the effect of a SEDDS on the oral pharmacokinetics of CBD. Their SEDDS was based on the VESIsorb® technology, a proprietary SEDDS system for which commercial ubiquinol formulations are already available on the market. The VESIsorb® SEDDS is comprised of “food emulsifiers, edible vegetable oils and fatty acids.”

141. Bioavailability was studied in sixteen healthy volunteers who were administered 25 mg CBD either formulated with medium-chain triglyceride (MCT) oil or with the SEDDS in a cross-over study design. SEDDS-CBD significantly increased oral bioavailability as indicated by increases in the Cmax and AUC0-24h of 4.4- and 1.7-fold, respectively (p0.0001 and p=0.0021). Tmax was also reduced from 3h to 1h with the SEDDS versus medium-chain triglyceride (MCT) oil CBD.

142. In interpreting their findings, Knaub *et al*., (2019) suggested that the increased oral bioavailability of CBD formulated with a SEDDS is due to the formation of droplets that solubilise CBD in the GI tract that deliver the molecule to enterocytes for absorption. Moreover, lymphatic transport, which bypasses the first-pass effect known to limit oral bioavailability of CBD, may also play a role.

143. Izgelov *et al*. (2020) compared the oral bioavailability of 90 mg CBD powder (no dissolution vehicle), CBD dissolved in sesame oil, and CBD formulated in a self-nano-emulsifying drug delivery system (SNEDDS) in a three-way crossover trial in 12 healthy subjects. The SNEDDS was composed of ethanol, soy lecithin, and surfactants (Tween 20, Span 80, and Kolliphor RH40).

144. CBD formulated in lipid-based systems was more bioavailable than CBD powder: Cmax was increased 22.5-fold and 17.5-fold with the SNEDDS and sesame oil CBD preparations, respectively, whilst AUC0-24h was increased approximately 8-fold for each formulation compared to the CBD powder. The SNEDDS also reduced Tmax and its associated variability (2 hours, versus 4 hours and 8.4 hours for sesame oil CBD and powder CBD, respectively). Sub-analysis of the sesame oil CBD time-concentration curves suggested the existence of two absorption behaviours in different groups of subjects; an ‘early’ and ‘delayed’ absorption population. Izgelov *et al*., (2020) suggested that the SNEDDS CBD formulation provided a less variable absorption profile owing to the consistent physicochemical parameters of the resultant emulsion compared to the sesame oil CBD preparation.

145. Patrician *et al*. (2019) investigated the oral bioavailability of a novel CBD formulation called ‘TurboCBD’ in a double-blinded, placebo controlled cross-over design with 12 participants. 45 mg or 90 mg CBD was administered. circulating CBD levels were higher with the TurboCBD 90 mg group at both 90 and 120 minutes compared with the 90 mg control (p0.05). Total area under the curve tended to be higher with TurboCBDTM 90 mg compared with 90 mg standard dose but did not reach statistical significance (10,865 ng/mL vs. 7,114 ng/mL; p=0.088). The authors concluded that TurboCBD had a higher bioavailability than a standard CBD preparation.

146. A pilot study from Blair (2020) reported on the pharmacokinetics of liposomal CBD in a cross-over trial with 15 healthy subjects compared to a control non-liposomal formulation. Ten mg of CBD were administered, and CBD blood levels were measured at 1-hour post-ingestion. Mean plasma CBD levels were higher with administration of liposomal versus non-liposomal CBD (1.77 ng/ml versus 0.24 ng/ml). Moreover, whilst CBD in plasma was detected in 6/15

participants administered non-liposomal CBD, it was detected in all of those (15/15) receiving liposomal CBD.

147. In summary, several bioavailable formulations of CBD appear to be emerging in academic research, and a number of these are tied to commercial interest for supplement formulation. A summary of the effects of the CBD formulations on the Cmax and AUC in the studies discussed above is presented in Table 7.

Table 7. Effects of CBD formulations on AUC and Cmax in healthy human subjects.

Bioavailable formulation	**Reference formulation**	**Cmax positive fold difference**	**AUC0-n positive fold difference**	**Study**
Water-soluble CBD	Lipid-soluble CBD	n.r.[a]	4.5	Hobbs *et al*. (2020)
GML CBD	MCT CBD	1.8	1.3	De Prá *et al*. (2021)
SEDDS CBD	MCT CBD	2.0	1.5	De Prá *et al*. (2021)
SEDDS CBD (VESIsorb®)	MCT CBD	4.4	1.7	Knaub *et al*. (2019)
Sesame oil CBD	Powder CBD	17.5	8.3	Izgelov *et al*. (20200
SNEDDS CBD	Powder CBD	22.5	7.6	Izgelov *et al*. (2020)
Liposomal CBD	‘non-liposomal’ CBD	7.4[b]	7.4[b]	Blair (2020)

AUC and Cmax fold differences were calculated by the secretariat based on presented data. AUC fold differences were calculated from the longest defined time period. [a] Abstract only retrieved. [b] from baseline-1 hour only (i.e., ‘Cmax’ by definition, but only one time point tested).