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REVIEW OF THERAPEUTICS

Food effects on the formulation, dosing, and administration of cannabidiol (CBD) in humans: A systematic review of clinical studies

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Abstract

Cannabidiol (CBD), a non-psychotropic phytocannabinoid from the Cannabis plant, is increasingly being pursued as a treatment for differing ailments. The bioavailability and pharmacokinetics of CBD are not well understood, and proper dosing schemes have not been adequately developed for its clinical use. CBD is a lipophilic molecule and exhibits low water solubility, so its formulation expectedly impacts its gastrointestinal absorption and subsequent blood plasma concentrations. In this review article, the food effects on CBD pharmacokinetics were analyzed. Clinical trials focusing on the performance of Epidiolex, the FDA-approved CBD formulation, were found in several databases and systematically analyzed in terms of administration method, dosing schedules, and patient characteristics. 44 data sets from clinical trials were found to be useful in the quantitative analysis. Following the normalization of all the pharmacokinetic data sets by dose and patient weight, CBD exhibited a much greater bioavailability in fed patients. For Epidiolex, administration in the fed state led to lower interindividual variability and more predictable pharmacokinetics. Considering all the different oral formulations of CBD, further analysis points to the main excipient of oral CBD formulations (refined sesame seed oil) as a major contributor to the dose-dependent variations in CBD pharmacokinetics, especially affecting the fasted state. We discuss the implications of these results on the downstream pharmacodynamics of endocannabinoid receptor modulation and its broad physiological implications.

KEYWORDS
cannabidiol, drug absorption, Epidiolex, food effects, pharmacokinetics, Sativex

1 | INTRODUCTION

Cannabidiol (CBD) is a non-psychotropic cannabinoid found in the Cannabis plant, as opposed to the psychoactive cannabinoid: tetrahydrocannabinol (THC).[1,2] CBD is found to have a very low oral bioavailability of approximately 9%–13%, which has contributed to major difficulties in drug development.[3] In terms of the timing and importance of this review article, CBD products derived from hemp (Cannabis sativa plants with no parts containing more than 0.3% THC by dry weight) are no longer designated as scheduled products under the 2018 Farm Bill, which removed CBD products from a Schedule I substance designation under the Controlled Substances Act. Further, CBD is the active pharmaceutical ingredient of Epidiolex, which is manufactured by GW Pharmaceuticals and is the first and only Food and Drug Administration (FDA)–approved CBD drug product in the United States.[2] Epidiolex is an oral solution with CBD that is formulated as a 100 mg/ml solution in sesame oil as the primary vehicle with dehydrated alcohol, strawberry flavoring, and sucralose excipients.[2]

Epidiolex is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.[2] Epidiolex is recommended to be taken in 2.5 mg/kg doses or greater twice daily. Epidiolex, other oral solutions of CBD, and CBD-containing products such as Sativex (THC-CBD combination drug approved by the European Medicines Agency for use in Europe) have been increasingly used in clinical trials to test therapeutic efficacy, assess adverse events, and further advance understanding of the mechanisms of action of CBD.[4] There is also an abundance of information available about how food consumption affects the measured peak blood concentrations of the active pharmaceutical ingredients (C_{max}) and the time to reach C_{max} after oral administration (T_{max}) of CBD.[2]

Overall, the factors that influence the pharmacokinetics of CBD have not been thoroughly evaluated, and what data are available shows large interpatient variability. While this review is focused on oral drug product bioequivalence, the FDA considers understanding and controlling the systemic pharmacokinetics of a drug product as the critical parameter for drug product regulation.[5,6] Furthermore, there are no standard recommendations for dosing and administration of CBD. This is because current published clinical trials have not provided sufficient evidence to generate recommendations about such regimens that assess the food effect on CBD bioavailability. To begin to address this deficit in knowledge, we performed a systematic review of clinical studies conducted to date on the impact of food on CBD pharmacokinetics. We considered drug formulations, dosing schemes, and patient demographics. To combine available raw data from the existing literature, we examined the reported C_{max}, T_{max}, and area under the concentration versus time curve ($AUC_{0-\infty}$) in relation to the expected pharmacokinetic behavior of CBD as captured by a population pharmacokinetic model.[5-7]

By investigating CBD bioavailability under different fasted and fed-state conditions using clinical trial data, we developed models that could be used to better guide evidence-based recommendations regarding CBD dosing and administration. Accordingly, the quantitative analysis on drug formulation, dosing schemes, and varying patient conditions conducted in this review article will help establish the importance of developing food-effect guidelines for CBD that will greatly benefit patients and clinicians in achieving their desired therapeutic aims. A possible mechanism of the effect of food on CBD is that fat and the caloric content of food can delay gastric emptying time, bile flow stimulation, and luminal metabolism.[1] This review article also points to areas in which greater attention is needed to improve patient responses and better control key formulation and administration variables that exert the greatest effect on the biopharmaceutical performance of orally administered CBD.

2 | METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.[8] Database searches using the a priori criteria were conducted in PubMed (from July 1980 to October 2020), clinicaltrials.gov (from September 18, 2014, to October 1, 2020), and the University of Michigan database (from July 1980 to December 2019). Additionally, a search was conducted with Google Scholar to identify other studies that were found to fit study criteria. A thorough search of all references was also conducted to find the greatest number of clinical trials that would fit within the scope of the review's subject matter.

The search study was conducted by the lead author (L.S.). Keywords and heading titles found within accepted search criteria included Bioavailability, CBD, Cannabidiol, Cannabinoids, duodenum, epilepsy, food effect, gastric emptying, humans, lipid-based drug delivery, lipid excipient, liver function, lymphatic absorption, metabolism, oral drug delivery, and pharmacokinetics. For detailed descriptions of data compiled from each reference, please refer to Table 1. L.S. screened all titles, abstracts, and full text to determine viability for quantitative and qualitative use within the review article.

A total of 44 data sets from 14 publications that met search criteria were included in the review's analysis.[3,4,9-20] Clinical trials that were multi-crossover or parallel-group, open-label, randomized, double-blinded, and/or placebo-controlled that met the following search criteria were included (a) CBD oral administration in human subjects, (b) amount of dose or doses given with administration methods and information on drug product used, (c) pharmacokinetic data for CBD from blood plasma, which included C_{max}, T_{max}, and $AUC_{0-\infty}$, and (d) a description of patient conditions in fed or fasted states.

2.1 | Risk of bias assessment

Possible bias in the included clinical trials was analyzed with the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) assessment tool (Table 2).[21] Biases were defined as those due to (a) confounding, (b) selection of participants into the study, (c) misclassification of intervention bias, (d) deviations from interventions, (e) missing data, (f) bias in outcome measurement, and (g) selection of reported results.[21] Each classification of bias was assessed by low, medium, high, and critical risk of bias per ROBINS-I.[21] All studies scored low for risk of bias in selection, misclassification of intervention, missing data, and outcome measurement except for one study that did not include enough information.[4] One study had a moderate risk of bias for confounding due to the stratification of individuals based on the severity of hepatic impairment.[10] Another study had a moderate risk of bias for deviations from intervention because one subject needed to decrease their dosage by 100 mg based on subject characteristics.[11] Two studies had a moderate risk of bias for selection of results due to knowledge of interventions that would be adequate for a non-randomized trial, but not comparable to a randomized control trial.[10,12]

2.2 | Study selection

A total of 6,409 studies were found from searches in PubMed, the University of Michigan library database, and clinicaltrials.gov. One

TABLE 1 Administration methods and meal contents

Data points	Drug	Fasted/Fed	Administration Time	FDA guidance	Caloric content (kcal)	Fat content (g)	Published	Nation	Reference
A1-A3	Epidiolex	Fasted	Dose given after an overnight fast	Yes	0	0	3-Oct–18	Canada	17
B1-B3	Epidiolex	Fed	Dosed 30 min after meal, evening dose given 12 h after	Yes	574	26.4	21-Feb–19	Netherlands	15
C	Oral capsule	Fed	Dosed 30 min after light meal following an overnight fast	Yes	450	12.5	10-Feb–16	USA	18
D1	Oral capsule	Fed	Dosed 4 h and 8 h after meal	No	574	26.4	28-Nov–17	Israel	3
D2	Sativex	Fed	Dosed 4 h and 8 h after meal	No	574	26.4	28-Nov–17	Israel	3
E1 - E2	Oral capsule	Fed	Dosed 2 h after a light breakfast	No	450	12.5	1-May–15	USA	19
F1-F3	Sativex	Fasted	24-h fast pre-dose with no food 15 min before and after morning dose	No	0	0	4-Nov–03	UK	12
F4	Oral capsule	Fasted	24-h fast pre-dose with no food 15 min before and after morning dose	No	0	0	4-Nov–03	UK	12
G	Sativex	Fasted	Fasted conditions	No	0	0	16-Jun–10	UK	4
H1-H5	Epidiolex	Fasted	Overnight fast of at least 10 h	Yes	0	0	30-Oct–18	Netherlands	9
H6	Epidiolex	Fed	Overnight fast of at least 10 h, high-fat breakfast given 30 min before dose	Yes	918	62	30-Oct–18	Netherlands	9
H7-H8	Epidiolex	Fasted	Overnight fast before first dose, 2-h fast before evening dose (6 days), single dose on 7th day	Yes	0	0	30-Oct–18	Netherlands	9
I1-I4	Oral capsule	Fed	Light low-fat breakfast 1–2 h before dose, snack 4 h after dose	No	450	12.5	12-Sep–19	USA	24
J1-J2	Oral capsule	Fed	Standard meal 30 min before dose, after overnight fast	Yes	574	26.4	10-Nov–17	Israel	16
J3	Sativex	Fed	Standard meal 30 min before dose, after overnight fast	Yes	574	26.4	10-Nov–17	Israel	16
K1-K3	Sativex	Fasted	Fasted 10 h overnight and 4 h post-dose	Yes	0	0	22-Nov–12	UK	13
K4-K6	Sativex	Fasted	Fasted 10 h overnight and 4 h post-dose	Yes	0	0	22-Nov–12	UK	13
L1-L4	Epidiolex	Fed	Low-protein breakfast 2 h before dose after an 8-h overnight fast	No	450	12.5	28-Mar–19	Hungary, Czech Republic, Slovakia	10
M1	Epidiolex	Fasted	Fasted overnight for 10 h, meal given 4 h after dose	Yes	0	0	27-Jun–19	USA	11
M2	Epidiolex	Fed	Fasted overnight 10 h, high-fat breakfast burrito given 30 min before dose	Yes	850	60	27-Jun–19	USA	11
N	Sativex	Fed	36-h fast before dose, standard low-fat breakfast 30 min before dosing, and standard meals 4 h and 10 h post-dose +digestive biscuits	Yes	450	12.5	15-Apr–05	UK	18

Data point nomenclature is as follows: Assigned letter corresponds to the publication, and numbers (if any) correspond to individual studies within the publication

TABLE 2 ROBINS-I results

Study	Confounding	Selection Bias	Misclassification of Intervention	Deviations from Intervention	Missing Data	Outcome Measurement	Selection of Results
15	Low	Low	Low	Low	Low	Low	Low
3	Low	Low	Low	Low	Low	Low	Low
14	Low	Low	Low	Low	Low	Low	Moderate
4	Low	NI	NI	NI	NI	NI	NI
10	Moderate	Low	Low	Low	Low	Low	Moderate
11	Low	Low	Low	Moderate	Low	Low	Low

All risk of biases were scored as low, moderate, high, critical, or no information (NI)

additional study was found in a search for the package insert of Sativex on Google,[4] but no other studies were identified from the references that were not already found in the initial database search. After duplicate studies were removed, 374 studies were screened for eligibility of the search criteria, which were made up of 98 studies from PubMed, 275 studies from the University of Michigan library database, and one study from the Sativex package insert (Figure 1).[4,6]

After screening, 272 studies were removed due to one or more of the following: absence of human subjects, review or pharmacology-based article, and not performed with CBD. Of the 102 articles that were deemed eligible, 30 were used for the preliminary analysis because the other trials lacked pharmacokinetic data and measurements for CBD, did not use oral administration methods, did not report dosing schemes and/or dose, and/or did not report patient demographic data. 14 publications that met all quantitative search criteria were reviewed based on abstract and title, which were deemed eligible.[3,4,9-20] A full-text screening was done on each publication, and all 14 were included in the quantitative analysis. The screening flow diagram can be found in Figure 1.6

Of the 14 studies assessed, there were five publications from Phase I clinical trials,[9,10,12-14] six publications that were open-label,[10-13,15,16] five publications that were crossover designs,[3,12,14,16] six publications that were double-blind,[9,12,14,17,18,20] and five publications that included a placebo.[9,14,17,19,20] There were 527 subjects in total that were accounted for in the quantitative analysis of this review article. Five publications assessed GW Pharmaceuticals' drug Epidiolex,[9-11,15,17] six publications assessed the CBD combination drug Sativex,[3,4,12-14,16] and six publications used oral capsule formulations containing CBD.[3,12,16,18-20] Additionally, one study assessed the drug-drug interactions with Epidiolex and three anti-epileptic drugs.[15] One publication analyzed Epidiolex on subjects with varying levels of hepatic impairment,[10] but all other included publications used healthy volunteers in their studies.

2.3 | Assessing CBD pharmacokinetics and the impact of food based on a PopPK modeling approach

To assess whether the behavior of CBD in clinical trials conformed to predicted behavior, three population pharmacokinetic (PopPK) models were used to compare raw data blood CBD concentration data from clinical trials with the predicted pharmacokinetic values (Figures S1 and S3).[6] Dose- and patient weight–normalized averages for Epidiolex under fed and fasted conditions were calculated using Equation (1).

$$\text{Normalized Value} = \frac{x}{\left(\frac{\text{Raw dose}}{\text{PopPK } \textit{mod} \text{ el Epidiolex mg/kg}}\right)} \quad (1)$$

where raw C_{max} or AUC given in a study is defined as x

Graphical schematics of PopPK models in the fasted (Figure S1) and fed state (Figure S3) were created with GraphPad Prism 9, version 9.0.0, by the lead author (L.S.). The dose- and patient weight–normalized fasted and fed averages for Epidiolex were plotted alongside the fasted and fed PopPK models using the GraphPad Prism 9 (Figure S4).

A root mean squared error (RMSE) equation was used to determine the degree of similarity between raw data from clinical trials and the values predicted with the PopPK models for the C_{max} and T_{max} of Epidiolex and is shown in Equation (2).

$$RMSE = \sqrt{(T_p - T_a)^2 + (C_p - C_a)^2} \quad (2)$$

where C_a is C_{max} actual, C_p is C_{max} predicted, T_a is T_{max} actual, and T_p is T_{max} predicted

A modified root mean squared error (normalized RMSE) equation was used to calculate the deviation, expressed as a fraction, of the clinical trial pharmacokinetic averages from the predicted PopPK models (Equation 3). The normalized RMSE equation placed an even weight on the C_{max} and T_{max} averages, which accounted for the C_{max} having a greater numerical value than the T_{max}.

$$\text{Normalized RMSE} = \sqrt{\left(\frac{T_a}{T_p} - 1\right)^2 + \left(\frac{C_a}{C_p} - 1\right)^2} \quad (3)$$

where C_a is C_{max} actual, C_p is C_{max} predicted, T_a is T_{max} actual, and T_p is T_{max} predicted

2.4 | Construction of a scientific literature–derived PopPK model

A three-compartment PopPK model was built based on a similar model used for analyzing THC concentrations in humans under fasted

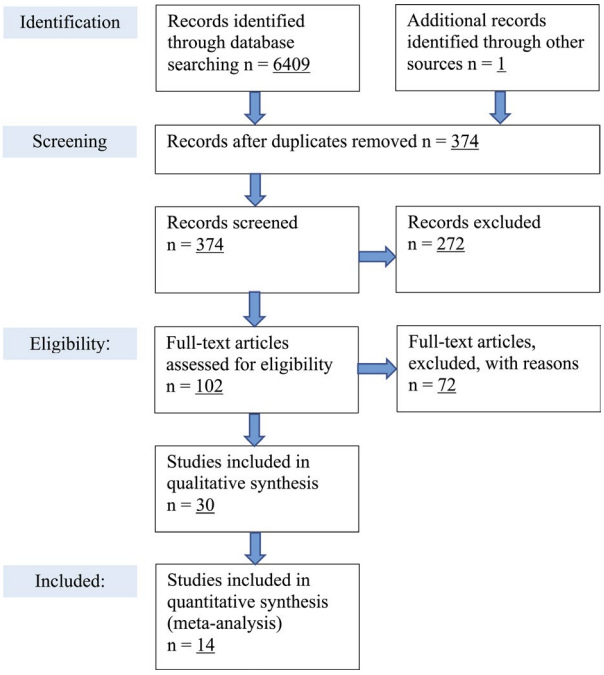

FIGURE 1 PRISMA flow diagram showing database search results, exclusions, and inclusions for this reviews analysis

conditions (Figures S1 and S3).[13,22,23] The PopPK model consisted of a single oral (PO) dose under fasted conditions. Moreover, the CBD PopPK model assumed the same absorption (k_a) and distribution parameters as the THC PopPK model due to CBD and THC early concentration profiles having a similar pattern when administered as a co-formulated product.[23] THC and CBD possess very similar chemical structures and physicochemical properties (eg, lipophilicity, molecular weight, charge, solubility).[23] Parameters including volume of distribution in the central compartment (V_2), oral bioavailability (FPO), and elimination rate constant in the central compartment (k_{20}) were modified to match the predicted behavior of CBD for a single dose of Epidiolex (2.5 mg/kg for a 75 kg adult). All modified parameter values are written in the code for the fasted (Script S1) and fed (Script S2) PopPK models. Raw NONMEM data for the fasted and fed PopPK models were transposed into a set number of time and blood plasma concentration values using RStudio, version 1.3.1073 (Figures S1 and S3).

2.5 | Assessing the effect of food on CBD pharmacokinetics using GW pharmaceuticals' PopPK pharmacokinetic model

A two-compartment PopPK model was used by GW Pharmaceuticals in the New Drug Application (NDA) submission for Epidiolex.[6] GW Pharmaceuticals' PopPK model was based on an Epidiolex clinical trial, which included a single ascending dose phase (SAD), multiple ascending dose phase (MAD), and food-effect phase on healthy subjects.[9] The food-effect phase consisted of a single dose of 1500 mg of Epidiolex, which was given to 12 healthy subjects in a fasted state following an overnight fast, and 12 healthy subjects in a fed state following an overnight fast and high-fat breakfast.[9] GW Pharmaceuticals' PopPK model was based on zeroth-order absorption, which increased CBD blood plasma concentration in proportion to the dose of Epidiolex.[6]

3 | RESULTS

3.1 | General considerations regarding Epidiolex pharmacokinetics

Pharmacokinetic parameters for all Epidiolex studies, as well as Sativex and oral capsule publications, were dose- and patient weight–normalized to make a proper comparison between values. A pharmacokinetic analysis was performed using quantitative data collected from the five publications that administered Epidiolex to subjects.[9-11,15,17] Three pharmacokinetic measurements were utilized in the analysis: (a) peak concentration of CBD in the plasma (C_{max}), (b) time to peak concentration of CBD in the plasma (T_{max}), and (c) area under the curve from zero to infinity ($AUC_{0-\infty}$). Further information regarding the number of subjects, dose, number of doses, age, body mass index (BMI), primary race, patient conditions, and time of administration was collected and can be viewed in Table 3.

In the five publications that administered Epidiolex, a total of 20 studies were performed with varying dose strengths, subject conditions, number of doses, and timing of dose. Each study was dose- and patient weight–normalized with Equation (1) to correspond to a single starting dose of Epidiolex (2.5 mg/kg) recommended for a standard adult (75 kg).[2] Thus, each pharmacokinetic measurement was normalized to a dose of 187.5 mg of Epidiolex for a 75 kg patient and is shown in Table 4.

To ensure the inclusion of other methods of administrations and formulations for the comparison with Epidiolex, the remaining nine publications were analyzed under the same methods and separated by the administration of either oral capsule drug products or Sativex in each study.[3,4,12-14,16,18-20] There were six publications that administered Sativex to subjects for a total of ten studies.[3,4,12-14,16] There were six publications that administered an oral capsule formulation of CBD for a total of 11 studies.[3,12,16,18-20]

3.2 | Assessing the effects of food on Epidiolex pharmacokinetics

Upon comparison of fasted and fed pharmacokinetic values for Epidiolex, the fed state was observed to have a significantly larger maximum blood plasma concentration (C_{max}) than the fasted state based on an unequal variances t test ($p = 0.0003$). Dose-normalized and patient weight–normalized data from 20 studies collected for Epidiolex were further separated based on whether subjects were held under a fasted or fed condition upon administration and blood plasma collection. Nine total studies of Epidiolex were performed under fed conditions,[9-11,15] while the remaining 11 studies were

TABLE 3 Raw pharmacokinetic parameters and subject specifics

Drug	Subjects (n)	Primary Sex	Primary race(s)	Median BMI (kg/m^2), (SD)	Median Age (yrs), (SD)	Total dose (mg)	No. of doses	Time of administration	C_{max} (ng/ml), mean (CV%)	T_{max} (h)	AUC(0-∞) (h*ng/ml), mean (CV%)
Epidiolex											
A1	38	M	Caucasian	25.9 (2.7)	37.7 (8.9)	750	1	Morning	336.2 (46.7)	5.116	1683.3 (46.7)
A2	39	M	Caucasian	25.9 (2.7)	37.7 (8.9)	1500	1	Morning	524.5 (64.9)	6.133	2713 (64)
A3	40	M	Caucasian	25.9 (2.7)	37.7 (8.9)	4500	1	Morning	426.9 (112.8)	4.067	2290.3 (104.1)
B1	15	M	Caucasian/Multiple	24.81 (3.52)	27.7 (8.2)	1500	2	Morning & Evening	840 (61.1)	5	–
B2	12	M/F	Caucasian	25.71 (3.52)	35.1 (12.9)	1500	2	Morning & Evening	852 (57.3)	4.5	–
B3	14	M	Caucasian	23.21 (2.22)	29.9 (10.5)	1500	2	Morning & Evening	838 (39.8)	5	–
H1	6	M/F	Caucasian	23.73 (2.45)	26 (3.2)	1500	1	Morning	292.4 (87.9)	4	1618 (74.6)
H2	6	M/F	Caucasian	23.15 (2.33)	25 (4.7)	3000	1	Morning	533 (35.1)	5	2802 (35.5)
H3	6	M/F	Caucasian	21.38 (1.71)	25.8 (7.9)	4500	1	Morning	722.1 (52.3)	5	3426 (48.3)
H4	6	M/F	Caucasian	23.6 (2.53)	22.8 (3.2)	6000	1	Morning	782 (83)	5	3900 (79.3)
H5	12	M/F	Caucasian	23.34 (1.9)	25.1 (6.2)	1500	1	Morning	335.4 (81.3)	3.5	2198 (48.2)
H6	12	M/F	Caucasian	23.34 (1.9)	25.1 (6.2)	1500	1	Morning	1628 (51.4)	3	8669 (33.9)
H7	9	M/F	Caucasian	22.28 (3.03)	28.6 (8.5)	750	13	Morning and Evening (6 days), Morning dose on 7th day	Day 1 am: 290.8 (86.3), Day 1 pm: 732.4 (39.4), Day 7 am: 330.3 (40.8)	Day 1 am: 5, Day 1 pm: 2.5, Day 7 am: 3	–
H8	9	M/F	Caucasian/Multiple	22.23 (2.33)	25.1 (4.8)	1500	13	Morning and Evening (6 days), Morning dose on 7th day	Day 1 am: 361.8 (105.8), Day 1 pm: 1385 (52.4), Day 7 am: 541.2 (53.7)	Day 1 am: 5, Day 1 pm: 4, Day 7 am: 3	–
L1	8	M/F	Caucasian	25.8 (5.7)	57.5 (8.1)	200	1	Morning	233 (70.5)	2.8	699 (44.2)
L2	8	M/F	Caucasian	29.6 (3.8)	55.6 (11.1)	200	1	Morning	354 (42.3)	2	1163 (39.9)
L3	6	M/F	Caucasian	30.0 (4.7)	52.7 (6.9)	200	1	Morning	381 (52.5)	2.5	2439 (29.5)
L4	8	M/F	Caucasian	29.4 (3.2)	55 (10)	200	1	Morning	148 (65)	2.3	474 (73.8)
M1	8	M/F	Caucasian/Black	90 kg	49	300	1	Morning	9.0 (33.33)	3.2	159 (49.06)
M2	8	M/F	Caucasian/Black	90 kg	49	300	1	Morning	135 (66.67)	2.4	771 (62.26)
Oral Capsule											
C	8	M/F	Black/Caucasian/ Mixed	–	29.1 (9.1)	800	1	Morning	77.9	3	–
D1	9	M	–	–	25	10	1	Dosed 4 h and 8 h after meal	0.5 (20)		3.1 (12.90)
E1	6	M/F	Black/Caucasian	–	38.5 (2.2)	400	1	Morning	181.2 (21.96)	3	7040 (40.2)
E2	6	M/F	Black/Caucasian	–	38.5 (2.2)	800	1	Morning	221.1 (16.10)	3	8670 (35.06)

(Continues)

TABLE 3 (Continued)

Drug	Subjects (n)	Primary Sex	Primary race(s)	Median BMI (kg/m^2), (SD)	Median Age (yrs), (SD)	Total dose (mg)	No. of doses	Time of administration	C_{max} (ng/ml), mean (CV%)	T_{max} (h)	AUC(0-∞) (h*ng/ml), mean (CV%)
F4	12	M/F	Caucasian	24.33 (1.8)	36.5 (8.38)	10	1	Morning	2.47	1.267	362.04
I1	12	M	–	25 (2)	24 (4)	45	1	Morning	16.8 (66.67)	1.883	2252 (45.49)
I2	12	M	–	25 (2)	24 (4)	90	1	Morning	54.6 (43.04)	2.05	7115 (41.86)
I3	12	M	–	25 (2)	24 (4)	45	1	Morning	21.2 (45.75)	2.167	2860 (45.49)
I4	12	M		25 (2)	24 (4)	90	1	Morning	77.6 (52.32)	1.833	10,865 (58.19)
J1	13	M	Caucasian	24.8	30.7	10	1	Morning	3.22 (39.62)	3	10.31 (40.14)
J2	13	M	Caucasian	24.8	30.7	100	1	Morning	47.44 (42.35)	3.5	153.04 (22.67)
Sativex											
D2	9	M	–	–	25	10	1	Dosed 4 h and 8 h after meal	2.1 (19.05)	1	6.9 (18.84)
F1	12	M/F	Caucasian	24.33 (1.8)	36.5 (8.38)	10	1	Morning	2.5	1.633	427.33
F2	12	M/F	Caucasian	24.33 (1.8)	36.5 (8.38)	10	1	Morning	3.02	2.8	407.79
F3	12	M/F	Caucasian	24.33 (1.8)	36.5 (8.38)	10	1	Morning	2.61	2.05	496.98
G	12	M/F	–	–	–	10	1	–	5.4 (57.3)	1	–
J3	13	M	Caucasian	24.8	30.7	10	1	Morning	2.05 (53.83)	3.5	7.81 (35.96)
K1	6	M	Caucasian/Black/Asian	23.5	32	5	1	Morning	0.39 (20.51)	1	1.66 (30.72)
K2	12	M	Caucasian/Black/Asian	23.5	32	10	1	Morning	1.15 (64.35)	1.39	5.64 (72.52)
K3	6	M	Caucasian/Black/Asian	23.5	32	20	1	Morning	2.17 (56.68)	1	13.28 (96.84)
K4	6	M	Caucasian/Black/Asian	23.5	32	5	9	Morning, 9 days	0.49 (42.86)	1.64	2.52 (28.97)
K5	12	M	Caucasian/Black/Asian	23.5	32	10	9	Morning, 9 days	1.14 (75.44)	1.27	6.66 (46.55)
K6	6	M	Caucasian/Black/Asian	23.5	32	20	9	Morning, 9 days	3.22 (59.01)	2	20.34 (35.84)
N	24	M	–	24.5	34	10	1	Morning	3.33	4.22	43107.6

All data collected from clinical trials and categorized by Epidiolex, Sativex, or oral capsule.

TABLE 4 Normalized Pharmacokinetic Parameters to 2.5 mg/kg for 75 kg

Data points	Raw dose (mg)	Dose-normalized dose (mg)	Dose-normalized C_{max} (ng/ml)	T_{max} (h)	Dose-normalized AUC(0-∞) (h*ng/ml)
Predicted Fasted	187.5	187.5	81.723	0.5	–
Predicted Fed	187.5	187.5	300.63	2.5	–
A1	750	187.5	84.05	5.12	420.83
A2	1500	187.5	131.13	6.13	339.13
A3	4500	187.5	106.73	4.07	95.43
B1	1500	187.5	210	5	–
B2	1500	187.5	213	4.5	–
B3	1500	187.5	209.5	5	–
C	800	187.5	18.26	3	–
D1	10	187.5	39.38	1	58
D2	10	187.5	9.38	3	129
E1	400	187.5	84.94	3	3300
E2	800	187.5	51.82	3	2032
F1	10	187.5	46.94	1.63	8012
F2	10	187.5	56.63	2.8	7646
F3	10	187.5	48.94	2.05	9318
F4	10	187.5	46.31	1.27	6788
G	10	187.5	26.34	1.38	–
H1	1500	187.5	36.55	4	202.25
H2	3000	187.5	33.31	5	175.13
H2	4500	187.5	30.09	5	142.75
H4	6000	187.5	24.44	5	121.88
H5	1500	187.5	41.93	3.5	274.75
H6	1500	187.5	203.5	3	1083.63
H7	750	187.5	82.58	3	–
H8	1500	187.5	67.65	3	–
I1	45	187.5	70	1.88	–
I2	90	187.5	113.75	2.05	–
I3	45	187.5	88.33	2.17	–
I4	90	187.5	161.67	1.83	–
J1	10	187.5	60.38	3	193.31
J2	100	187.5	88.95	3.5	286.95
J3	10	187.5	38.44	3.5	146.44
K1	5	187.5	14.63	1	62.25
K2	10	187.5	21.56	1.38	105.75
K3	20	187.5	20.34	1	124.5
K4	5	187.5	18.38	1.64	–
K5	10	187.5	21.38	1.27	–
K6	20	187.5	30.19	2	–
L1	200	187.5	218.44	2.8	655.31
L2	200	187.5	331.88	2	1090.31
L3	200	187.5	357.19	2.5	2337.19
L4	200	187.5	138.75	2.33	444.38
M1	300	187.5	5.63	3.2	353.77
M2	300	187.5	84.38	2.4	481.88
N	10	187.5	62.44	4.22	808267.5

Dose- and patient weight–normalized values correspond to the population pharmacokinetic (PopPK) plot generated by E.C. and transposed by A.W.

performed under fasted conditions.[9,11,17] Two of the studies that were performed under fasted conditions administered multiple doses of Epidiolex to subjects, but only the primary pharmacokinetic parameters from a single dose were included in the analysis to ensure consistency.[13] In addition, three studies for Sativex were performed under fed conditions,[3,16] and ten studies were performed under fasted conditions.[4,12-14] A total of ten studies of oral capsule formulations were performed under fed conditions,[3,16,18-20] and one study was performed under a fasted condition.[12]

The mean $C_{max,}$ $T_{max,}$ $AUC_{0-\infty,}$ and all corresponding standard deviations and coefficient of variation (CV%) measurements were calculated for the fasted and fed groups of Epidiolex using Microsoft Excel, version 16.42, and RStudio, version 1.3.1073 (Table 5). The same methods were performed among all studies of Sativex and oral capsule formulations (Table 5). Epidiolex had a dose- and patient weight–normalized C_{max} of 218.51 ng/ml with a 36.4% coefficient of variation, a T_{max} of 3.28 h with a 34.6% coefficient of variation, and $AUC_{0-\infty}$ of 1015.5 h*ng/ml with a 63.54% coefficient of variation under fed patient conditions. The C_{max} of Epidiolex under fed patient conditions (218.51 ng/ml) was nearly a fourfold increase from Epidiolex under fasted patient conditions (58.55 ng/ml). Thus, a fed patient state will lead to a significantly larger maximum blood plasma concentration of CBD. The T_{max} of Epidiolex under fed patient conditions (3.28 h) was shorter than fasted patient conditions (4.27 h). Yet, the T_{max} is less indicative of the predicted pharmacokinetic mechanisms of CBD based on the inability to dose- and patient weight–normalize the measurement. The unequal variances *t* test was not statistically significant for T_{max} ($p = 0.069$), showing that the T_{max} was less important in the comparison of Epidiolex under fasted and fed conditions. The dose- and patient weight–normalized mean $AUC_{0-\infty}$ for Epidiolex under fed conditions (1015.5 h*ng/ml) was over fourfold greater than the mean $AUC_{0-\infty}$ under fasted conditions (236.21 h*ng/ml). The unequal variances *t* test was statistically significant for $AUC_{0-\infty}$ ($p = 0.04$). However, there was less certainty in the comparison among fasted and fed groups for $AUC_{0-\infty}$ because the value was not reported in three of the fasted Epidiolex studies and three of the fed Epidiolex studies.

The coefficient of variation (CV%) was used to assess the degree of interindividual variability among fasted and fed Epidiolex averages. All coefficient of variation values for the dose- and patient weight–normalized $C_{max,}$ $T_{max,}$ and $AUC_{0-\infty}$ measurements can be found in Table 5. The coefficient of variation for the C_{max} of Epidiolex in a fed state (36.37%) was much lower than in the fasted state (60.52%), indicating that there was less interindividual variability among fed studies. Furthermore, the coefficient of variation for the T_{max} of Epidiolex in the fed state (34.64%) was slightly larger than the fasted state (23.25%), and the coefficient of variation for $AUC_{0-\infty}$ in the fed state (63.54%) was larger than the fasted state (46.05%). As C_{max} was the only statistically significantly different value between fasted and fed conditions, which included all 20 studies, the comparison between the coefficient of variation values for C_{max} was the most significant in our analysis. A smaller interindividual variability among fed Epidiolex studies indicates that the fed state had a more predictable behavior for the concentration of CBD in the blood plasma.

3.3 | Assessing how meal content affects Epidiolex pharmacokinetics

When assessing the studies that utilized a food effect in combination with Epidiolex administration, there was a considerable difference in the type of meal given, and a lack of information about meal contents. The FDA recommends several guidelines for food-effect studies, with both high-fat/high-calorie and low-fat/low-calorie meals.[5] The FDA states that a food-effect study with a high-fat/high-calorie meal must contain between 800 and 1000 total kcal, 55–65 g of fat, which is equivalent to 500–600 kcal, 50% fat content within the meal, 150 kcals from protein, and 250 kcals from carbohydrates.[5] An example of a high-fat/high-calorie meal consists of two fried eggs in butter, two strips of bacon, two slices of toast with butter, four ounces of hash browns, and eight ounces of whole milk.[5] In contrast, the FDA notes that a food-effect study with a low-fat/low-calorie meal must contain between 400 and

TABLE 5 Normalized pharmacokinetic parameters to 2.5 mg/kg for 75 kg

Drug	C_{max} (ng/ml), (CV%)	T_{max} (h), (CV%)	Dose-Normalized AUC(0-∞) (h*ng/ml), (CV%)	No. of studies	Dose- and Weight–normalized RMSE	RMSE	Studies included
Epidiolex							
Fed	218.51 (36.37)	3.28 (34.64)	1015.45 (63.54)	9	0.41	82.12	B1-B3, H6, L1-L4, M2
Fasted	58.55 (60.52)	4.27 (23.25)	236.21 (46.05)	11	7.55	23.48	A1-A3, H1-H5, H7, H8, M1
Sativex							
Fed	36.75 (59.04)	3.57 (14.01)	404206.97 (99.96)	3	0.98	263.88	D2, J3, N
Fasted	30.53 (46.03)	1.62 (32.35)	4211.42 (98.43)	10	2.33	51.21	F1-F3, G, K1-K6
Oral capsule							
Fed	77.75 (49.27)	2.44 (29.96)	240.13 (19.5)	10	0.74	222.88	C, D1, E1, E2, I1-I4, J1, J2
Fasted	46.31 (0)	1.27 (0)	6788 (0)	1	1.6	35.42	F4

Mean dose- and patient weight–normalized values correspond to the population pharmacokinetic (PopPK) plot generated by E.C. and transposed by A.W.

500 total kcal, 11–14 grams of fat, which is equivalent to 100–125 kcal, and 25% fat content in the meal.[5] An example of a low-fat/low-calorie meal would contain eight ounces of 1% milk, one boiled egg, and one packet of instant oatmeal.[5] Furthermore, the FDA notes that a high-fat/high-calorie meal can likely delay gastric emptying, stimulate bile flow, change gastrointestinal pH, increase splanchnic bile flow, change luminal metabolism of a drug substance, and physically or chemically interact with a dosage form or a drug substance administered.[5] Biopharmaceutics Class System (BCS) class II drugs, such as CBD, with high permeability and low solubility, will likely undergo an increased bioavailability upon administration with a high-fat/high-calorie meal.[24] Thus, it is vital to understand how co-administration with food will impact the drug's pharmacokinetics, which will determine the clinical success of Epidiolex.

Information on the meal contents in fed studies for Epidiolex was collected and is summarized in Table 1. Fed studies for Sativex and oral capsule drug products were also included in Table 1 for comparison. Among the studies that listed the caloric content and fat content of the meal(s) given, data were entered and converted into standard units. For fed studies that did not provide information about specific caloric content or the percentage of fat, the average numbers for high- or low-fat/calorie FDA recommendations were implemented.[5] For studies that did not give any indication of whether the meal was high- or low-fat/calorie, a mean imputation technique was performed for a standard meal, which contained 574 kcal with 26.4 g of fat. For all studies that co-administered Epidiolex with a meal, two included a high-fat/high-calorie meal,[11,25] three included the standard meal from mean imputation,[15] and four included a low-fat/low-calorie meal.[10] Table 6 includes all information regarding meal contents co-administered with Epidiolex, Sativex, and oral capsule drug products in fed studies. Conclusions cannot be made based on the small number of acceptable food-effect studies found in the database search.

3.4 | Assessing how sesame oil vehicle mimics the fed state and mainly affects the pharmacokinetics of CBD in the fasted state

The food effect on CBD is largely correlated with the pharmacokinetics and pharmacodynamics of CBD. Following the breakdown of caloric and fat content within meals co-administered in fed patient studies, the oil content for the formulation of Epidiolex is hypothesized to mimic a fed state in the body at high doses.[26] The main excipient (non-active pharmaceutical ingredient) in Epidiolex consists of a highly lipophilic substance, which has a high concentration of oil.[2] 736 mg of sesame seed oil and 100 mg of CBD are included per 1 ml of Epidiolex.[2,27] The recommended starting dose of 2.5 mg/kg/dose in a human adult would include 0.02 ml/kg/dose of oil excipient.[2] The largest oral dose of Epidiolex given to patients in clinical trials was 6 g per day, which is equivalent to approximately 44.2 ml of sesame seed oil excipient.[9] Based on the caloric content of sesame oil, the ~44.2 ml amount of sesame seed oil excipient was equivalent to approximately 353 calories.[2,9,28] Research is lacking for the exact effect food has on the bioavailability of CBD, so a survey of published literature on the bioavailability of CBD under varying patient conditions, doses, and drug formulations was deemed to be crucial.

The total sesame seed oil volume was calculated, in ml, for each study that administered Epidiolex to patients. In addition, the amount of oil derived from fat in the meals given in fed studies was added to the oil volume of sesame oil in the corresponding dose. The sum of oil from the sesame seed oil excipient of Epidiolex and the meal(s) consumed was defined as the total amount of oil in a specific study. The total oil volume consumed in Epidiolex studies, as well as Sativex and oral capsule formulation studies, can be found in Table 7.

The highest total volume of oil consumed in a study for Epidiolex was 73 ml, with 62 ml of the total oil coming from 62 g of fat in the co-administered meal.[11] The lowest total volume of oil, 2.2 ml, was in a fasted study for Epidiolex.[11] Therefore, the total amount of the oil consumed was from the sesame seed oil excipient in a single 300-mg dose of Epidiolex.[11] A human gastrointestinal and physiology study found that long-chain fatty acids as little as 2 milliliters were found to stimulate gall bladder contraction and stimulate increased secretion of bile salts, phospholipids, and cholesterol in the intestine.[26] The effect of increased bile salts and phospholipids is found to contribute to enhanced absorption of drugs with a low solubility.[26] Fatty acid excipients have also been linked to an improved uptake of CBD, which may bypass first-pass liver metabolism and lead to increased absorption and bioavailability.[20] Therefore, it is possible that a dose of Epidiolex of 272 mg or more will mimic a positive food effect on CBD, even under fasted patient conditions.[2] It is of great importance

TABLE 6 Fed study meal breakdown

Drug	Meal type	Studies included	Mean caloric content (kcal)	Mean fat content (g)	Mean normalized C_{max} (ng/ml)	Mean normalized T_{max} (hours)	Mean normalized AUC (h*ng/ml)
Epidiolex	High-fat	H6, M2	884	61	72.51	3.61	782.75
Epidiolex	Standard	B1-B3	574	26.4	146.92	4.17	–
Epidiolex	Low-fat	L1-L4	450	12.5	208.36	2.51	1131.80
Sativex	Standard	D2, J3	574	26.4	49.78	2	137.91
Sativex	Low-fat	N	450	12.5	62.44	4.22	808267.5
Oral capsule	Standard	D1, J1, J2	574	26.4	45.59	3.33	179.46
Oral capsule	Low-fat	I1-I4	450	12.5	90.49	2.06	–

TABLE 7 Oil volume in food and excipients

Drug	Excipients	Excipient oil volume (ml)	Oil from meal (ml)	Total amount of oil (ml)
Epidiolex				
A1	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	5.52	0	5.52
A2	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	0	11.04
A3	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	33.12	0	33.12
B1	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	26.4	33.12
B2	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	26.4	33.12
B3	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	26.4	33.12
H1	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	0	11.04
H2	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	22.08	0	22.08
H3	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	33.12	0	33.12
H4	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	44.16	0	44.16
H5	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	0	11.04
H6	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	62	73.04
H7	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	5.52	0	5.52
H8	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	11.04	0	11.04
L1	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	1.472	13.54	15.012
L2	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	1.472	13.54	15.012
L3	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	1.472	13.54	15.012
L4	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	1.472	13.54	15.012
M1	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	2.208	0	2.208
M2	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	2.208	60	62.208
Oral capsule				
C	Dehydrated alcohol, refined sesame oil, strawberry flavor, sucralose	8	12.5	20.5
D1	Piperine, tween, span, polyoxyl 40-hydroxy castor oil, lecithin, tricaprin, ethyl lactate	0.22	26.4	26.62
E1	Corn Oil	–	12.5	–
E2	Corn Oil	–	12.5	–
F4	Granulated Lactose	–	0	–
I1	Multi-spectrum organic hemp oil CO_2 extract	162.9	12.5	175.4
I2	American ginseng, Gingko Biloba, multi-spectrum organic hemp oil CO_2 extract	325.8	12.5	338.3
I3	Multi-spectrum organic hemp oil CO_2 extract	162.9	12.5	175.4
I4	American ginseng, Gingko Biloba, multi-spectrum organic hemp oil CO_2 extract	325.8	12.5	338.3
J1	Gelatin	–	26.4	–
J2	Gelatin	–	26.4	–
Sativex				
D2	Ethanol, propylene glycol, peppermint oil	0	26.4	26.4
F1	Ethanol, propylene glycol, peppermint oil	0	0	0
F2	Ethanol, propylene glycol, peppermint oil	0	0	0
F3	Ethanol, propylene glycol, peppermint oil	0	0	0
G	Ethanol, propylene glycol, peppermint oil	0	0	0
J3	Ethanol, propylene glycol, peppermint oil	–	26.4	–
K1	Ethanol, propylene glycol, peppermint oil	0	0	0
K2	Ethanol, propylene glycol, peppermint oil	0	0	0

(Continues)

TABLE 7 (Continued)

Drug	Excipients	Excipient oil volume (ml)	Oil from meal (ml)	Total amount of oil (ml)
K3	Ethanol, propylene glycol, peppermint oil	0	0	0
K4	Ethanol, propylene glycol, peppermint oil	0	0	0
K5	Ethanol, propylene glycol, peppermint oil	0	0	0
K6	Ethanol, propylene glycol, peppermint oil	0	0	0
N	Ethanol, propylene glycol, peppermint oil	0	12.5	12.5

1 ml of Epidiolex contains 736 mg refined sesame oil and 100 mg CBD.

to understand the exact amount of sesame seed oil excipient in a certain dose of Epidiolex that will contribute to a positive food effect with or without consumption of a meal.

3.5 | Pharmacokinetic considerations for multi-dose regimens of CBD

Only single-dose administrations of Epidiolex and other CBD-containing drug products were used in the analysis, as only two publications performed multi-dose regimens.[9,13] One study administered Epidiolex in two doses of either 750 or 1500 mg per day for 6 days, and a single dose on the seventh day.[9] The C_{max} and T_{max} with respective coefficient of variation (CV%) values for the first dose of either 750 or 1500 mg were 290.8 ng/ml (86.3) at 5 h and 361.8 ng/ml (105.8) at 5 h, respectively.[9] Subsequently, the C_{max} and T_{max} for the last single dose of either 750 mg or 1500 mg on the seventh day were 330.3 ng/ml (40.8) at 3 h and 541.2 ng/ml (53.7) at 3 h, respectively.[9] Because the two studies that performed multiple-dose regimens were only conducted under fasted patient conditions, the results cannot be included in the review's analysis. Further clinical trials and research on multiple doses of CBD under fasted and fed patient conditions are needed for the consideration of how multi-dose regimens may impact the bioavailability of CBD.

3.6 | Assessing the effects of food on circulating CBD concentrations using a scientific literature–derived 3-compartment PopPK model

Using a three-compartment PopPK model based on published pharmacokinetic data, the predicted C_{max} and T_{max} under fasted conditions were 81.72 ng/ml at 30 min (Figure S1).[13,22,23] Additionally, the code written by Dr. Capparelli in NONMEM provided the modified absorption rate constant (k_a) and oral bioavailability (FPO) for the predicted fed state (Script S1). The fed-state absorption rate constant (ka) and oral bioavailability (FPO) were implemented and transposed into the corresponding time and plasma concentration values by co-author (A.R.W) (Script S2).[23] The predicted C_{max} and T_{max} under fed conditions were 300.63 ng/ml at 2.5 h (Figure S3). Average dose- and patient weight–normalized Epidiolex C_{max} and T_{max} values for clinical trial data under fasted and fed conditions were compared with the respective PopPK models and predicted C_{max} and T_{max} (Figure S4). The RMSE and normalized RMSE calculations were used to determine whether data from clinical trials followed the predicted behavior of CBD in the respective PopPK model. All RMSE calculations pertaining to the fasted and fed PopPK models for a single dose of Epidiolex (2.5 mg/kg for a 75 kg adult) can be found in Table 5. The RMSE in the fed state was 82.12, and the normalized RMSE in the fed state was 0.41. For the fasted state, the RMSE was 23.48 and the normalized RMSE was 7.55. Because RMSE Equation (1) does not equally weigh the C_{max} and T_{max} values, the C_{max} will mainly account for the result. The normalized RMSE calculations from Equation (2) were expressed as evenly weighted percentages of error from the predicted values, which were more indicative of how accurate the PopPK models predicted the behavior of CBD in clinical trials. The PopPK model for the fed state is found to be more accurate in its comparison with the pharmacokinetic data collected from clinical trials of Epidiolex. This shows that the fed state will be highly beneficial for future dosing regimens and predictions regarding the expected behavior of CBD in the patient population.

3.7 | Assessing the effects of food on circulating CBD concentrations using GW pharmaceutical's PopPK model

Raw data were not accessible for the PopPK model provided in the Epidiolex NDA, which was obtained from the FDA filings and submitted by GW Pharmaceuticals.[9] However, the clinical trial data used to generate the model can be analyzed to assess its accuracy.[9] According to the clinical trial data used for the PopPK model of Epidiolex, the C_{max}, T_{max}, and $AUC_{0-\infty}$ for the fasted state were 335.4 ng/ml, 3.5 h, and 2198 h*ng/ml, respectively. Consequently, the C_{max}, T_{max}, and $AUC_{0-\infty}$ for the fed state were 1628 ng/ml, 3 h, and 8669 h*ng/ml, respectively.[9] Dose- and patient weight–normalized values for clinical trial data can be found in Table 8. According to GW Pharmaceuticals' PopPK model, the bioavailability of CBD was much greater in the fed state and is shown to increase by a 0.52 fractional change from non-fed conditions.[6] RMSE and normalized RMSE calculations were performed for dose- and patient weight–normalized Epidiolex averages for a 1500-mg dose and a 75 kg adult under fasted and fed conditions (Table 9). The RMSE for Epidiolex under fed conditions was 1116.4, and the normalized RMSE was 3.89. The RMSE under fasted conditions

TABLE 8 Normalized PK parameters to GW pharmaceuticals' PopPK model (1500 mg)

Data points	Dose-normalized C_{max} (ng/ml)	T_{max} (h)	Dose-normalized AUC(0-∞) (h*ng/ml)
Predicted Fasted	335.4	3.5	2198
Predicted Fed	1628	3	8669
A1	672.4	5.12	3366.6
A2	524.5	6.13	2713
A3	142.3	4.07	763.43
B1	840	5	–
B2	852	4.5	–
B3	838	5	–
C	146.063	3	–
D1	75	1	465
D2	315	3	1035
E1	679.5	3	26400
E2	414.56	3	16256.25
F1	375	1.63	64099.5
F2	453	2.8	61168.5
F3	391.5	2.05	74547
F4	370.5	1.27	54306
G	810	1.38	–
H1	292.4	4	1618
H2	266.5	5	1401
H2	240.7	5	1154
H4	195.5	5	975
H5	335.4	3.5	2198
H6	1628	3	8669
H7	581.6	3	–
H8	361.8	3	–
I2	560	1.88	75066.67
I2	910	2.05	118583.33
I3	706.67	2.17	95333.33
I4	1293.33	1.83	181083.33
J1	483	3	1546.5
J2	711.6	3.5	2295.6
J3	307.5	3.5	1171.5
K1	117	1	498
K2	172.5	1.38	846
K3	162.75	1	996
K4	147	1.64	–
K5	171	1.27	–
K6	241.5	2	–
L1	1747.5	2.8	5242.5
L2	2655	2	8722.5
L3	2857.5	2.5	18292.5
L4	1110	2.33	3555
M1	45	3.2	795
M2	675	2.4	3855
N	499.5	4.22	6466140

Dose- and patient weight–normalized values correspond to the population pharmacokinetic (PopPK) plot generated by GW Pharmaceuticals.

was 250.9, and the normalized RMSE was 8.14. As previously mentioned, the normalized RMSE calculations were a better indicator of how accurate the PopPK model was in predicting the behavior of CBD in patients. The normalized RMSE for Epidiolex under fed patient conditions was much smaller than fasted conditions, meaning that the GW Pharmaceuticals' PopPK model for Epidiolex yielded similar conclusions as those obtained with the three-compartment alternative model that was generated for the present review, based on previously published data from academic research laboratories.

4 | DISCUSSION

In accordance with the Epidiolex and Sativex drug package inserts, CBD pharmacokinetics were more accurate and efficacious in terms of lower interindividual variability and significantly greater bioavailability in the presence of food.[2,4] CBD has poor solubility and high permeability, meaning that the bioavailability in the fasted state was observed to be quite low, especially in orally administered products.[2] Because CBD is categorized as a BCS II drug, and concomitant food administration has been reported to increase the bioavailability of CBD,[2] we hypothesized that the fed state will alter drug absorption in the gastrointestinal tract and possibly influence first-pass metabolism.[1] Although the FDA recommends that food-effect bioavailability and bioequivalence studies are conducted under the administration of a high-calorie (800–1000 calories) and high-fat meal (50% of caloric content), only a fraction of food-effect studies on CBD have abided by the FDA's guidelines.[5] Knowing that a meal will significantly increase the maximum concentration of CBD, while reducing the interindividual variability of the CBD concentration in the plasma, is of great importance for future recommendations regarding dosing and administration schemes. An example of a dosing scheme would follow the assumption that there will be a larger amount of CBD absorbed in the body at the maximum concentration, and therefore greater bioavailability, and thus, all patients should be advised to take Epidiolex with a meal. Any patient that may not need a high plasma concentration of CBD could take a reduced dose in the presence of food to achieve the desired therapeutic effect.

Based on the pharmacokinetic behavior of CBD in clinical trial data in relation to the PopPK models, a fed state was observed to achieve the current pharmacokinetic predictions more accurately (Figure S4).[6] Both a low (187.5 mg) and high (1500 mg) dose of Epidiolex under fed conditions were found to have a more accurate behavior of CBD in comparison with the respective PopPK models.

TABLE 9 Interindividual variability of normalized PK parameters in GW pharmaceuticals' PopPK model

Drug	C_{max} (ng/ml), (CV%)	T_{max} (h), (CV%)	Dose-Normalized AUC(0-∞) (h*ng/ml), (CV%)	No. of studies	Dose- and Weight-normalized RMSE	RMSE	Studies included
Epidiolex							
Fed	1467 (52.66)	3.28 (34.65)	8056.08 (62.36)	9	3.89	1166.37	B1-B3, H6, L1-L4, M2
Fasted	332.55 (52.61)	4.27 (23.25)	1664.89 (51.65)	11	8.14	250.86	A1-A3, H1-H5, H7, H8, M1
Sativex							
Fed	374 (23.74)	3.57 (14.01)	2156115.5 (141.35)	3	0.49	73.38	D2, J3, N
Fasted	304.13 (66.53)	1.62 (32.35)	33692.5 (98.43)	10	3.52	222.41	F1-F3, G, K1-K6
Oral capsule							
Fed	597.97 (56.42)	2.44 (29.96)	57447.78 (105.16)	10	0.99	297.34	C, D1, E1, E2, I1-I4, J1, J2
Fasted	370.5 (0)	1.27 (0)	54306 (0)	1	3.85	288.78	F4

Mean dose- and patient weight–normalized values correspond to the PopPK plot created by GW Pharmaceuticals.

The low dose of Epidiolex had a much smaller normalized RMSE value (0.41) than that of the high dose (3.9).

Higher doses of Epidiolex, such as 1500 mg, contain a substantially larger amount of oil from excipients alone. A 1500-mg dose of Epidiolex includes approximately 11 ml of oil, whereas a 187.5-mg dose of Epidiolex would contain approximately 1.4 ml of oil.[28] As previously mentioned, an oil volume as low as 2 milliliters has been reported to stimulate increased bile salt secretion, elevate levels of phospholipid and cholesterol in the intestine, and trigger gall bladder contraction.[26] Thus, CBD drug product excipients are likely contributing to the increased interindividual variability in fasted state studies—especially with higher doses as greater oil volumes may largely affect the gastrointestinal mechanisms in digestion as the high doses are administered in conjunction with large amounts of sesame oil vehicle.

It is expected that the effect of food on CBD pharmacokinetics is also poised to have an impact on endocannabinoid receptor signaling pharmacodynamics as exemplified by current research.[29] The molecular signaling mechanisms that are perturbed by CBD, THC, and other phytocannabinoids are part of the biochemical pathways involved in inflammation, wound healing, and regeneration. Food effects are not only important in understanding the pharmacokinetics of Epidiolex, Sativex, Marinol, and other FDA-approved prescription drugs, but can also offer mechanistic insights into the possible health benefits of phytochemical cannabinoid receptor modulators present in hemp-derived nutritional supplements that are now sold in most health food stores across the United States. The interplay between endocannabinoid receptor modulation and greater amounts of amino acid and L-carnitine metabolites in the circulation, together with food-effect considerations, reveals an entirely new field centered on the interaction between phytocannabinoids, nutrition, organismic physiology, health, and disease.[29]

5 | CONCLUSIONS

This review article outlines the necessity for factoring in patient food effects in the therapeutic treatment and subsequent dosing and administration regimens of CBD. This review is of great importance due to the widespread availability of CBD products. Companies developing CBD drug products and supplements can use the findings in this review and the PopPK model analysis to help provide more accurate recommendations. Based on a thorough analysis of the data found in published clinical trials, Epidiolex is shown to have a statistically significant increase in maximum concentration in the plasma when taken with a meal. Furthermore, oil content in excipients and meal content should be considered when generating dosing regimens, as many drug products for CBD contain large amounts of oil excipients. Thus, dosing CBD in the presence of a meal leads to much improved, predictable pharmacokinetics, which should translate to improved pharmacodynamics in terms of any observed efficacy and side effects. To our knowledge, this is the only study addressing how high doses of a drug formulated in sesame oil, such as Epidiolex, can lead to a situation resembling a fed state based on the excipients alone.[2] Moving forward, PopPK models for CBD should be modified to include the amount of vehicle and its impact on the food effect, especially in the case of multi-dose regimens, to achieve the most predictable pharmacotherapeutic outcomes in humans. Of noteworthy significance, the magnitude of the effect of food on the increase in C_{max} and $AUC_{0-\infty}$ is well beyond the range that is typically observed with other FDA-approved drugs and is more akin to the effect of food on the absorption of vitamins.[30,31] This suggests that CBD absorption may be mediated by specific transport pathways involved in the uptake of nutrients into the body.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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